EMERGING TECHNOLOGY FOR MONITORING AND TREATMENT IN CRITICAL CARE

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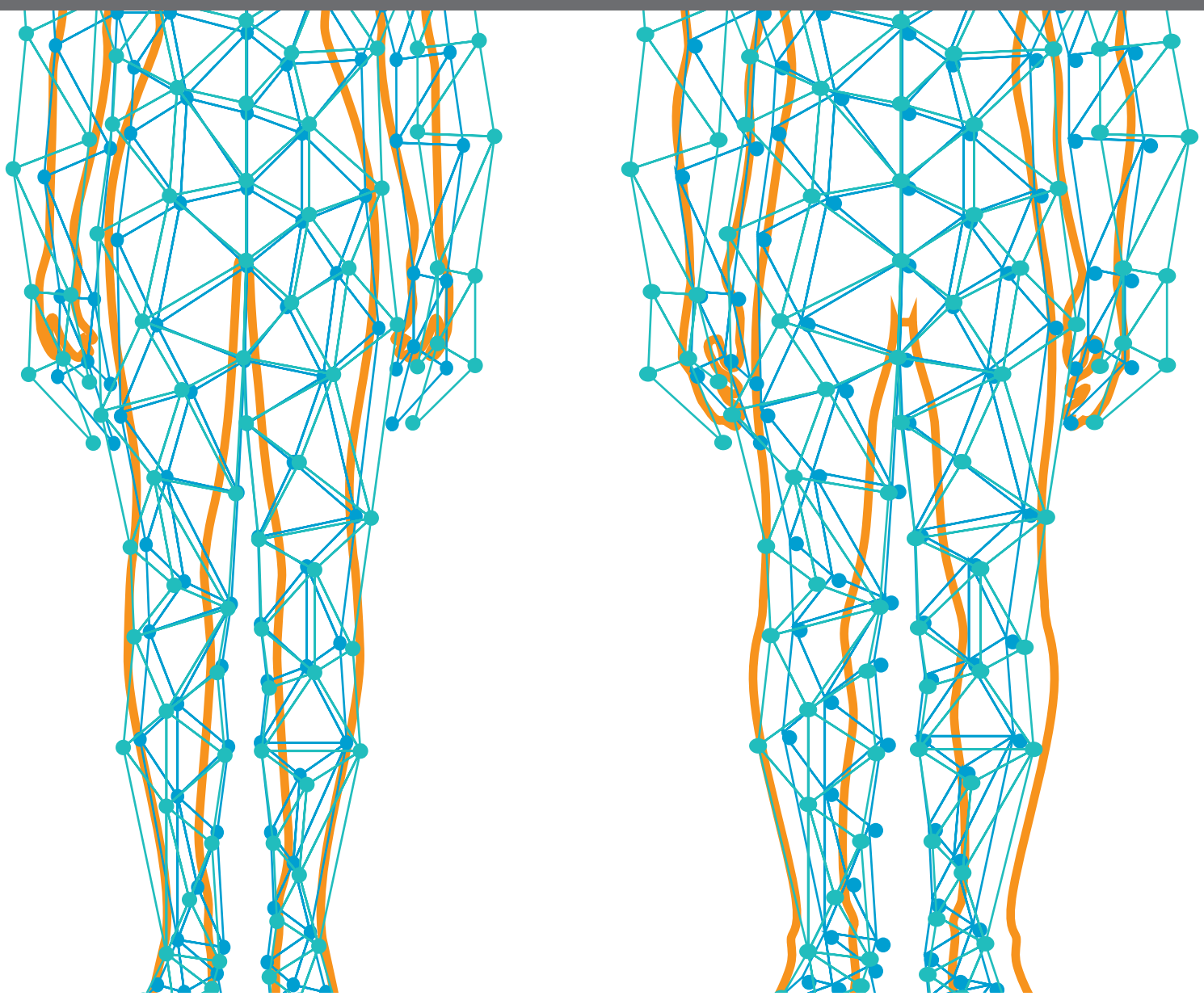

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EMERGING TECHNOLOGY FOR MONITORING AND TREATMENT IN CRITICAL CARE

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REVIEW
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Near-Infrared Spectroscopy Assessments of Regional Cerebral Oxygen Saturation for the Prediction of Clinical Outcomes in Patients With Cardiac Arrest: A Review of Clinical Impact, Evolution, and Future Directions

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Despite three decades of advancements in cardiopulmonary resuscitation (CPR) methods and post-resuscitation care, neurological prognosis remains poor among survivors of out-of-hospital cardiac arrest, and there are no reliable methods for predicting neurological outcomes in patients with cardiac arrest (CA). Adopting more effective methods of neurological monitoring may aid in improving neurological outcomes and optimizing therapeutic interventions for each patient. In the present review, we summarize the development, evolution, and potential application of near-infrared spectroscopy (NIRS) in adults with CA, highlighting the clinical relevance of NIRS brain monitoring as a predictive tool in both pre-hospital and in-hospital settings. Several clinical studies have reported an association between various NIRS oximetry measurements and CA outcomes, suggesting that NIRS monitoring can be integrated into standardized CPR protocols, which may improve outcomes among patients with CA. However, no studies have established acceptable regional cerebral oxygen saturation cut-off values for differentiating patient groups based on return of spontaneous circulation status and neurological outcomes. Furthermore, the point at which resuscitation efforts can be considered futile remains to be determined. Further large-scale randomized controlled trials are required to evaluate the impact of NIRS monitoring on survival and neurological recovery following CA.

Keywords: cardiac arrest, cardiopulmonary resuscitation, near-infrared spectroscopy, cerebral oxygen saturation, brain oximetry, ROSC, neurological outcome, prognostication

BACKGROUND

Out-of-hospital cardiac arrest (OHCA) remains a major public health challenge worldwide. The global report on OHCA has described that the estimated incidence of OHCA treated *via* emergency medical services (EMS) was 47.3, 40.6, 45.9, and 51.1 per 100,000 person-years in North America, Europe, Asia, and Australia, respectively (i.e., ∼4 million cases each year) (1). Despite advances in treatment, such as routine application of targeted temperature management (TTM), neurological prognosis remains poor among survivors of OHCA (2), and there are no reliable methods for predicting neurological outcomes in patients with cardiac arrest (CA) and post-cardiac arrest syndrome (PCAS). International guidelines recommend a multimodal approach for determining prognosis. However, these guidelines are neither universally accepted nor universally implemented, and prognostication may be delayed up to 72 h after restoration of normothermia (3–5).

Physiologically, a prolonged "no-flow" interval during CA followed by low cerebral perfusion during resuscitative management (i.e., "low-flow" status) leads to hypoxic ischemia–reperfusion brain injury—the primary cause of disability after successful resuscitation (6). Near-infrared spectroscopy (NIRS) can be used to obtain continuous, non-invasive measurements of regional cerebral oxygen saturation (rSO_2) in real time, which may aid in monitoring oxygen metabolism in the brain during this ischemia–reperfusion process. Measurements of rSO_2 are considered to reflect the balance between cerebral oxygen delivery and consumption in the area of the brain located beneath the device (7). NIRS has been applied in patients with circulatory shock (8), acute brain injury (9, 10), those undergoing perioperative cardiac surgery (11, 12) or carotid endarterectomy (13–15), and during veno-arterial extracorporeal membrane oxygenation in the intensive care unit (ICU) (16–18). Several recent studies have highlighted the feasibility of NIRS for brain monitoring during cardiopulmonary resuscitation (CPR) and after the return of spontaneous circulation (ROSC) in patients with CA (19–24). There are two theoretical uses for NIRS brain monitoring and it is important to understand both. Application of NIRS monitoring may aid in predicting patient outcomes, which may in turn aid clinicians in determining whether to continue or halt resuscitation efforts based on the patient's chance of survival. Alternatively, NIRS measurements may aid in determining the most appropriate resuscitation therapies. For example, patients with low initial NIRS values may benefit from more aggressive resuscitation efforts (e.g., improved CPR, pharmacological treatment, circulatory support). Unfortunately, no previous studies have validated the use of NIRS for either of these purposes. Furthermore, the cut-off rSO_2 value for predicting good vs. poor clinical outcomes in patients with CA remains to be determined. Publicly available studies have also varied with regard to the timing of NIRS (during CPR or post-ROSC), the clinical setting (prehospital, emergency department [ED], or ICU), and the types of NIRS readings analyzed (initial, mean, highest, or changes in rSO_2 values over the course of CPR or the ICU stay). Thus, further studies are required to determine the predictive value of NIRS monitoring and its potential for guiding treatment strategies in patients with OHCA (25). In the present review, we discuss the development and evolution of NIRS technology, as well as the potential usefulness of rSO_2 during CA and post-resuscitation care.

Abbreviations: OHCA, out-of-hospital cardiac arrest; EMS, emergency medical services; TTM, targeted temperature management; PCAS, post-cardiac arrest syndrome; rSO_2, regional cerebral oxygen saturation; NIRS, near-infrared spectroscopy; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; ED, emergency department; $ETCO_2$, end-tidal CO_2; AUC, area under the curve; ROC, receiver operating characteristic curve; CPC, Glasgow–Pittsburgh Cerebral Performance Category.

A BRIEF REVIEW OF NIRS TECHNOLOGY

In 1977, Jöbsis provided the first evidence that NIRS can be used to monitor tissue metabolism *in vivo* (26). Notably, they intended to develop an optical technique for measuring *in vivo* redox changes in the mitochondrial enzyme cytochrome c oxidase (27). They discovered that near-infrared light penetrates deeper into tissues due to its higher tissue transparency, enabling real-time monitoring of changes in the concentrations of light-absorbing molecules within the tissue. Given that hemoglobin chromophores are present in higher concentrations than cytochrome c oxidase, numerous studies have focused on the use of NIRS to measure levels of oxygenated, deoxygenated (or redox/"reduced"), and total hemoglobin (28). In 1985, Ferrari et al. utilized NIRS for continuous, non-invasive monitoring of the human brain (29). In 1995, Müllner et al. provided the first preliminary report regarding the use of NIRS in patients with OHCA, demonstrating that higher median rSO_2 values during continuous CPR in the ED were associated with better 1-week survival (19). In 2004, Newman et al. demonstrated the feasibility of continuous, non-invasive cerebral oximetry measurements obtained using NIRS and suggested a possible role for NIRS in evaluating the adequacy of CPR methods (20).

Given the physics of light in the near-infrared spectral region (600–900 nm) within the brain, tissue absorption is mainly determined based on levels of oxygenated and reduced hemoglobin, with smaller contributions from water, lipids, and cytochrome c oxidase. Cerebral saturation is measured using a light source fixed to the head, which transmits infrared and red spectrum light through the skin, skull, connective tissues, and brain. Quantification is then performed using a light detector. The separation between the source and detector is an important parameter of the NIRS system, as it determines the depth of penetration (i.e., ∼2–2.5 cm with current systems) (30, 31). Values are thus measured from a "banana-shaped" volume of tissue (32, 33). Furthermore, the intence of near-infrared light is also important because the larger source-detector distance, the deeper the photon reaches inside the brain layer, but the intensity of the detected light decreases more strongly (34, 35).

rSO_2 values can be affected by various factors, such as extracranial contamination, skin pigmentation (36, 37), and physiological conditions. Changes in physiological conditions may in turn lead to changes in cerebral blood flow or oxygen content. Among the factors known to influence

these parameters are cardiac output, acid–base status, major hemorrhage, obstructions of arterial inflow/venous outflow, hemoglobin concentration, hemoglobin saturation, pulmonary function, inspired oxygen concentration, and drug use (e.g., phenylephrine) (38–41).

Currently, there are several commercially available NIRS devices (12, 16, 34, 36, 42–45). These devices differ with regard to the wavelengths and frequencies used, the timing of light transmission, the distance between the light source and detector, and the primary principle of measurement [e.g., Beer-Lambert law (46), spatial-resolved spectroscopy law (47), or time-resolved absorption spectroscopy law (46)]. Thus, the algorithms used to derive hemoglobin saturation from the inputs received also differ for each device. It has been reported that values for rSO_2 typically range from 55 to 80%, and rSO_2 <50% or a 20% reduction from the individual baseline is generally considered indicative of the need for intervention (48). However, it is noted that the threshold of the normal range is not clearly defined due to the characteristics of the equipment, and the range of normal values actually varies among the equipment (37). As most clinical NIRS devices assume a venous/arterial distribution in cerebral cortical tissue of ∼70/30 or 75/25%, based in part on the results of positron emission tomography studies (39), rSO_2 values are primarily influenced by cerebral venous oxygen saturation (49). However, previous studies have reported that the venous/arterial distribution of the cerebral cortex varies among individuals (37, 50, 51), suggesting that rSO_2 values are also variable (50). Previous studies have reported that the absolute values, or different degrees of variability in rSO_2 due to several factors, vary between NIRS devices under various conditions (36, 37, 45, 52). Given that rSO_2 values also vary based on physiological conditions, some authors have suggested that relative changes in rSO_2 from baseline are more appropriate for guiding resuscitative efforts than absolute values (53, 54).

SEARCH STRATEGY

To review articles regarding NIRS brain monitoring in patients with CA, we searched PubMed, Web of Science, and Google Scholar for relevant studies. There was no language restriction. We developed a search strategy using the combination of keywords and Medical Subject Heading (MeSH) terms, which were "(Near-infrared spectroscopy [MeSH] OR (regional cerebral oxygen saturation) OR (brain oximetry)) AND ((Heart arrest [MeSH]) OR (cardiac surgery) OR prehospital)" for PubMed and Web of Science, and ["Near-infrared spectroscopy," "cardiac arrest," "regional saturation"] for Google Scholar. The main findings of the included studies are summarized in **Table 1**.

USE OF NIRS FOR EARLIER DETECTION OF RE-ARREST IN PREHOSPITAL SETTINGS

While ROSC is often successful in pre-hospital settings, many patients subsequently develop circulatory instability and experience re-arrest (i.e., a loss of pulse after sustained ROSC) (74). Since re-arrest before reaching the hospital is among the potential barriers to survival in patients with OHCA (74), early recognition of re-arrest is crucial for ensuring prompt re-activation of resuscitation protocols, including CPR and early defibrillation. Many EMS systems routinely use pulse oximetry measurements; however, pulse oximetry depends on the presence of a peripheral pulse, and the technique is unreliable when used during CA because pulsatile blood flow is inadequate in peripheral tissue beds under such conditions (75, 76). Using a finger pulse oximeter is problematic during CA because any resultant values likely reflect the pulsation of venous blood. Thus, although the presence of a plethysmograph waveform on pulse oximetry is potentially valuable in detecting ROSC, the main purpose of pulse oximetry is to ensure appropriate oxygenation after ROSC, and its use is limited during CPR (76).

In contrast to pulse oximetry, NIRS can measure tissue oxygenation in the absence of pulsatile flow, without the need to interrupt chest compressions (55, 57, 62). Since NIRS values are affected by ambient light (52, 77), some devices cannot be used outside. Nonetheless, rSO_2 monitoring may aid in the early detection of ROSC and re-arrest in patients with CA (55–57, 62). Meex et al. observed that rSO_2 values immediately increased after ROSC and that new episodes of ventricular fibrillation were immediately detected as sudden decreases in rSO_2. These findings suggest that decline in rSO_2 values can reflect life-threatening situations such as pulseless arrhythmia or severe cerebral hypoperfusion, both of which indicate an urgent need for CPR (55). Additional studies have reported that ROSC is associated with increases in NIRS values, while re-arrest is associated with decreases in NIRS values (56, 57). Notably, these studies showed the decrease in rSO_2 at the re-arrest episode, which is difficult to find re-arrest without pulse check. It may be useful to be aware of re-arrest immediately without pulse check. Another study reported that NIRS monitoring can aid in assessing perfusion and guiding interventions during transport (78). Some authors have suggested that low NIRS readings highlight the need for additional lifesaving interventions such as fluid resuscitation and/or vasopressors (40, 41, 79). Therefore, NIRS monitoring may enable early recognition of re-arrest, especially in PEA, and poor cerebral circulation during EMS resuscitation protocol. Since vital signs and the results of physical assessments can be influenced by environmental factors (e.g., pre-hospital settings, ambulance transport), further clinical studies are required to determine the value of NIRS in various settings.

FEASIBILITY OF NIRS FOR THE ASSESSMENT OF CPR QUALITY

Well-performed CPR has been associated with higher rates of ROSC (80, 81), better cerebral perfusion (82), and improved cerebral oxygenation (83). Several large-scale studies have demonstrated that high-quality CPR improves survival and neurological outcomes among patients with CA (84–86). However, monitoring the adequacy of circulation and cerebral oxygenation during CPR remains challenging. To date, studies

TABLE 1 | Summary of main findings in the included studies.

Author	Year	Type of cerebral oximeter	Type of CA	Clinical setting	Conclusion	Reference
EARLIER DETECTION OF RE-ARREST						
Frisch	2012	InSpectra	OHCA	Prehospital	A decline in rSO_2 level may correlate with re-arrest.	(24)
Meex	2013	FORE-SIGHT	OHCA		Re-arrest was accompanied with sudden drop in rSO_2	(55)
Schewe	2014	EQANOX 7600	OHCA	Prehospital-VT	rSO_2 decreased prior to re-arrest.	(56)
Nomura	2016	HAND ai TOS	OHCA	Prehospital-PEA	Re-arrest PEA was accompanied with sudden drop in rSO_2	(57)
ASSESSMENT OF CPR QUALITY						
Paarmann	2010	INVOX 5100	IHCA	In-hospital	rSO_2 may be a non-invasive alternative for the assessment of the adequacy of oxygen transport (i.e. CPR efforts).	(58)
Kämäräinen	2012	INVOS 5100c	IHCA	In-hospital	High quality CPR and improving CPR technique was not significantly reflected in rSO_2 as quantified.	(59)
Meex	2013	FORE-SIGHT/EQUANOX advance	IHCA/OHCA	In-hospital	Decrease in rSO_2 during interruption of CPR Increase in rSO_2 due to improved resuscitation efforts	(55)
Schewe	2014	Equanox 7600	OHCA	Prehospital (mechanical CPR)	rSO_2 during mechanical CPR was higher compared to manual compression	(56)
Parnia	2014	Equanox 7600	IHCA	In-hospital (mechanical CPR)	Mechanical CPR was significantly associated with higher rSO_2 compared with manual chest compression.	(60)
Ogawa	2015	TOS-OR	OHCA	ER (mechanical CPR)	LDB-CPR significantly increased rSO_2 value compared with manual CPR.	(61)
PREDICTION OF ROSC						
Asim	2014	INVOS 5100c	OHCA	ER	ROSC was established in the patients with rise in rSO_2.	(62)
Sanfilippo	2015	N/A	IHCA/OHCA		Both initial and average rSO_2 values were significantly higher in the ROSC group than in the non-ROSC group.	(63)
Cournoyer	2016	N/A	IHCA/OHCA		Mean NIRS value were higher in patients experiencing ROSC than in their respective counterparts.	(53)
Schnaubelt	2018	N/A	IHCA/OHCA		Both mean rSO_2 and ΔrSO_2 were higher in the ROSC group than in the non-ROSC group.	(64)
Takegawa	2019	TOS-OR	OHCA	ER	The combination of baseline rSO_2 with the amount of maximum rise in rSO_2 over time is better predictor of ROSC.	(65)
PREDICTION OF FAVORABLE NEUROLOGICAL OUTCOMES						
Meex	2013	FORE-SIGHT	OHCA	ICU-During TTM	rSO_2 value was significantly lower in non-survivors compared with survivors at 3 h after induction of TTM.	(66)
Storm	2014	INVOS 5100c	IHCA/OHCA	ICU-During TTM	rSO_2 within the first 40 h after ROSC is significantly lower in patients with poor neurological outcome.	(67)
Genbrugge	2016	FORE-SIGHT	OHCA	ICU-During TTM	The mean rSO_2 in the rewarming phase was significantly higher among patients with CPC scores of 1–2.	(68)
Cournoyer	2016	N/A	IHCA/OHCA		Mean NIRS value or combined initial and mean NIRS values were higher in patients with good neurologic outcomes.	(53)
Bougle	2016	INVOS	OHCA	ICU-During TTM	rSO_2 within 48 h after ICU admission does not allow discriminating patients with good or bad outcome.	(69)
Schnaubelt	2018	N/A	IHCA/OHCA		ROC analysis could not confirm a significant discriminatory power for mean rSO_2 values.	(64)
Saritas	2018	INVOS	CA	ICU-During TTM	There was no significant correlation between rSO_2 values and neurologic outcomes.	(70)
Nakatani	2018	INVOS 5100c	OHCA	ER/ICU-During TTM	TTM at 32–34°C effectively decreased all-cause mortality in comatose OHCA patients with rSO_2 41–60% on arrival.	(71)
Jakkula	2019	INVOS 5100c	OHCA	ICU	No association between rSO_2 and NSE at 24, 48, 72 h after OHCA or good neurological outcomes at 6 months.	(72)
Sakurai	2020	INVOS 5100c	OHCA	ICU- During TTM	There was no significant difference in rSO_2 values between prognosis groups at any time point.	(73)

CA, Cardiac arrest; OHCA, Out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; rSO_2, regional cerebral oxygen saturation; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; CPC, cerebral performance category; ER, emergency room; ICU, intensive care unit; LDB, load distributing band; NSE, neuron specific enolase; ROC, receiver operating characteristic; TTM, targeted temperature management; N/A, not available.

investigating the use of NIRS devices to assess the quality of CPR have yielded conflicting results (55, 58, 59).

To assess the quality of CPR, Kämäräinen et al. measured rSO_2 using an INVOS 5100c device and simultaneously monitored indicators of CPR quality. Compression depth, the rate and release of compressions, and ventilation rate were monitored during CPR with automated real-time audiovisual feedback (59). Data related to the quality of CPR and rSO_2 were measured at 30-s intervals until ROSC (59). The authors observed that cerebral oxygenation remained low throughout high-quality CPR (59), in contrast to the previous findings that cerebral rSO_2 decreases due to circulatory arrest during cardiac surgery but increases during CPR (87) or cardiopulmonary bypass (88). However, the rSO_2 data recorded in this study were unreliable in many cases, as 59% of the 30-s intervals exhibited artifacts that precluded quantification of rSO_2 (59). In contrast, Meex et al. observed parallel increases in systolic arterial pressure and rSO_2 during CPR (55), suggesting a positive effect of CPR on these two parameters. In addition, switching CPR providers resulted in a measurable increase in cerebral oxygen saturation. An rSO_2 decreased to values between 30 and 35% after cessation of CPR. The authors further stated that rSO_2 monitoring allows for both the continuous estimation of cerebral oxygenation without ROSC and the assessment of CPR efficacy (55). Previous research has indicated that mechanical chest compression, which is thought to provide adequate compression over long periods of time without fatigue or interruption, significantly increases rSO_2 values in patients with OHCA, in contrast to manual chest compression (61). Although their sample sizes were small, other studies have also noted that mechanical CPR is associated with significantly higher rSO_2 values than manual CPR (56, 60).

The abovementioned findings indicate that dynamic rSO_2 monitoring may be more useful than static assessments of rSO_2 during CPR, as such monitoring can provide quantitative information regarding cardiac output and cerebral perfusion during chest compressions. Application of NIRS for the assessment of CPR quality and oxygen delivery to the brain may thus help to improve clinical outcomes following CA. Further studies are required to determine how NIRS monitoring can be integrated into standardized CPR protocols.

PREDICTION OF ROSC AND FAVORABLE NEUROLOGICAL OUTCOMES

International guidelines recommend end-tidal CO_2 ($ETCO_2$) monitoring for the assessment of CPR quality, noting that a sudden increase in $ETCO_2$ is likely to represent an early indicator of ROSC (89). The potential value of $ETCO_2$ for optimizing resuscitation efforts is discussed elsewhere (89). However, $ETCO_2$ readings are influenced by mechanical ventilation settings, the tidal volume of ventilation, many drugs administered during resuscitation, and by different lung pathologies. In addition, $ETCO_2$ monitoring does not provide data related to cerebral circulation. Thus, $ETCO_2$ monitoring is distinctly different from NIRS monitoring. In a recent prospective study by Engle et al., $ETCO_2$ assessments and cerebral oximetry were performed simultaneously during CPR in the ED (90). The authors observed that both $ETCO_2$ and rSO_2 were good predictors of ROSC. However, logistic regression analysis of the simultaneously collected data revealed that rSO_2 was superior to $ETCO_2$ in predicting ROSC (90).

A 2015 systematic review and meta-analysis reported that both initial and average rSO_2 values were significantly higher in the ROSC group than in the non-ROSC group (63). An extensive 2016 meta-analysis including 20 studies demonstrated that mean NIRS values were higher in patients experiencing ROSC, surviving to discharge, and surviving with good neurologic outcomes than in their respective counterparts (53). The authors further reported that combined initial and mean NIRS values were higher in patients who survived to discharge and in those who experienced good neurological outcomes than in their counterparts (53). In the most recent systematic review and meta-analysis of 26 studies, Schnaubelt et al. demonstrated that both mean rSO_2 and ΔrSO_2 (i.e., the difference between the initial value and the value at ROSC, or the difference between the initial value and the value at the end of CPR) were higher in the ROSC group than in the non-ROSC group (64). ROSC was not observed when mean rSO_2 remained $<26\%$. An rSO_2 threshold of 36% predicted ROSC with a sensitivity of 67% and specificity of 69%, while a ΔrSO_2 of 7% predicted ROSC with a sensitivity of 100% and a specificity of 86% [area under the curve (AUC) = 0.733 and 0.893, respectively] (64).

However, given that baseline values vary among patients (54), comparisons of static values obtained using different devices may be methodologically problematic (91, 92). Importantly, all studies in these meta-analyses focused on averages obtained from static values, rather than on changes in NIRS readings within the same patient. Thus, it is difficult to determine the absolute cut-off value for discontinuing CPR based on the currently available data, as some patients experienced ROSC even with rSO_2 values lower than the suggested cut-off values. Furthermore, some authors have suggested that dynamic assessments of rSO_2 obtained throughout resuscitation are more appropriate than static assessments for evaluating outcomes in patients with CA (22). In a single-center retrospective study, Takegawa et al. evaluated the association between the probability of ROSC and the degree of rSO_2 increase during CPR among 90 patients with OHCA, 35 (38.9%) of whom achieved ROSC (65). Receiver operating characteristic curve (ROC) analysis revealed that the amount of maximum rise in rSO_2 value (i.e., the difference between maximum and baseline values) over a 16-min measurement period yielded an AUC of 0.75 for differentiating between the ROSC and non-ROSC groups. In addition, the best AUC value was achieved by the combination of the amount of maximum rise and baseline rSO_2, rather than by the amount of maximum rise alone (AUC = 0.91) (65). The authors suggested that discontinuation of CPR may be indicated in patients with low initial values who do not exhibit an appropriate increase in rSO_2, resulting in a low mean value. Taken together, the available data suggest that average rSO_2 and ΔrSO_2 values during CPR may aid in determining the likelihood of achieving ROSC in patients with CA. Given that it is difficult to measure mean rSO_2 during on-going CPR in real-world settings, it is reasonable to

focus on the combination of baseline rSO_2 and ΔrSO_2 during CPR. Further large-scale, prospective, multicenter studies are required to assess the ability of ΔrSO_2 to predict ROSC.

Previous studies have reported good neurologic outcomes following CA in patients with both high initial rSO_2 values and high mean rSO_2 values (53). In the most recent meta-analysis, the calculated averaged mean rSO_2 values were higher in patients with favorable neurological outcomes (Glasgow–Pittsburgh Cerebral Performance Category [CPC]: 1 or 2) than in those with poor neurological outcomes (rSO_2: 47 vs. 38%, $P = 0.018$) (64). CPC scores of 1 or 2 were not observed in patients with mean rSO_2 values $\leq 30 \pm 17\%$. Mean rSO_2 values in patients with favorable neurological outcomes were significantly above 30%. However, ROC analysis for neurological outcomes could not confirm a significant discriminatory power for mean rSO_2 values (AUC = 0.770, $P = 0.098$), likely due to the small sample size (64). The authors concluded that mean rSO_2 and ΔrSO_2 values have good predictive value for ROSC but not for favorable neurological outcomes (64). Moreover, in a *post hoc* analysis of a randomized clinical trial, Jakkula et al. observed no association between cerebral rSO_2 (median rSO_2 during the first 36 h) and concentrations of neuron-specific enolase (a marker of neurological injury) at 24, 48, and 72 h after OHCA or good neurological outcomes at 6 months (72). Despite the promising trends suggested by the available evidence, clear cut-off values of rSO_2 for predicting favorable outcomes after CA are yet to be established.

USE OF NIRS DURING TTM

Given that induction of hypothermia affects cerebral oxygen metabolism and changes the balance between oxygen supply and demand (93), several studies have examined the role of NIRS monitoring during TTM (66–71, 73). Although some small-scale studies have applied NIRS monitoring during and after TTM in patients with PCAS, meta-analyses or systematic reviews on NIRS monitoring during TTM have been extremely limited. Meex et al. evaluated serial changes in rSO_2 during TTM in 28 patients with OHCA who underwent hypothermia at 33°C for 24 h after ROSC (66). Values for rSO_2 decreased significantly within 3 h after the onset of TTM, indicating that the balance between oxygen supply and demand may have been adversely affected. After 3 h, rSO_2 gradually increased again even during hypothermia, increasing further during the 12-h rewarming period. Although there was no significant difference in rSO_2 between the survival and non-survival groups, the decrease in rSO_2 observed during the early stages of hypothermia was significantly greater in the non-survival group than in the survival group (66). Other studies have also reported a general trend that rSO_2 values decrease after the onset of hypothermia, increasing during and after rewarming (68, 70). These results were contrary to the expectation that rSO_2 values should increase due to reductions in brain metabolism/oxygen consumption and the effects of hypothermic conditions on the affinity of hemoglobin for oxygen (66). Therefore, the contrary results were likely due to increases in cerebrovascular resistance and decreases in cerebral blood flow.

There are several possible explanations for decreases in rSO_2 during the early phase of TTM. Some investigators have suggested that cerebral blood flow and rSO_2 are influenced by cardiac output, use of α-adrenergic vasoconstrictor agents (40, 41, 94), use of anesthetic agents, or other confounding factors. Some studies have also reported that rSO_2 values during TTM are associated with neurological prognosis (67, 68, 71). Storm et al. evaluated the association between rSO_2 values and neurological outcomes at hospital discharge and 6 months later in 60 patients with in-hospital cardiac arrest and OHCA. Continuous measurements of cerebral rSO_2 were obtained for 40 h (i.e., from the onset of hypothermia to rewarming). Median rSO_2 values at all time points (i.e., at the start of measurement; upon reaching 33°C; and at 4, 12, 24, and 40 h) were persistently higher in patients with CPC scores of 1–2 than in patients with CPC scores of 3–5 (median rSO_2: 68 vs. 58%, $P < 0.01$) (67). However, rSO_2 levels largely overlapped between outcome groups, suggesting that the potential of rSO_2 to aid in predicting outcomes is limited (67). Genbrugge et al. reported that the mean rSO_2 value during rewarming following hypothermia was significantly higher among patients with CPC scores of 1–2 than among those with CPC scores of 3–5 (70 ± 1 vs. $68 \pm 1\%$, $P = 0.046$) (68). However, they also mentioned that significant

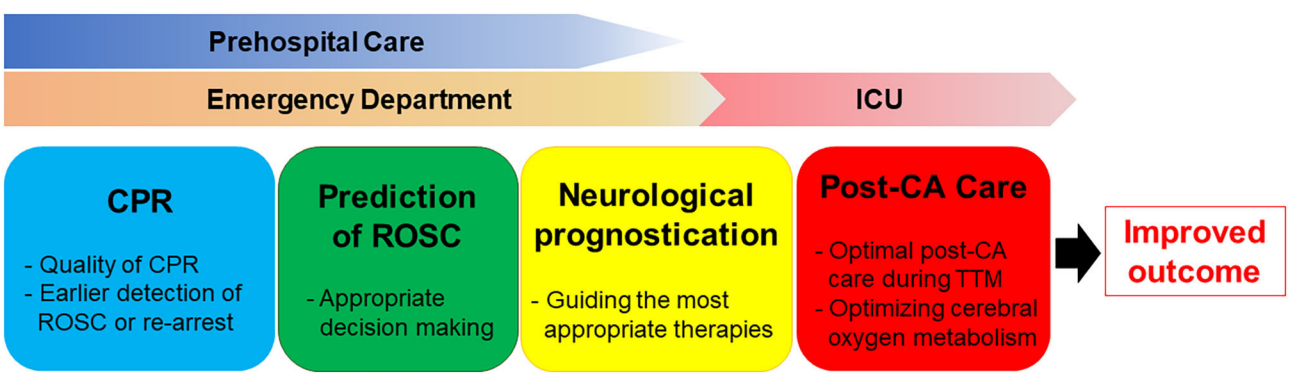

FIGURE 1 | The clinical relevance of NIRS brain monitoring as a predictive tool in both pre-hospital and in-hospital settings.

differences in rSO_2 in their study were unlikely to be clinically meaningful given that such data are not available at the bedside. Moreover, given the small sample size of the study, their data cannot be used to determine cutoff rSO_2 values for predicting outcomes (68). In contrast, other studies have reported no significant differences in rSO_2 values between prognosis groups, even when changes in rSO_2 values over time were investigated (69, 70, 73).

Given the available evidence, further studies are required to validate the efficacy of rSO_2 values during the early stages of TTM in predicting outcomes in patients with PCAS. Stratifying patients according to severity based on rSO_2 values (71) may aid in distinguishing which patients would benefit from hypothermia. Further large-scale, prospective, multicenter studies are required to elucidate the potential of rSO_2 during TTM for predicting neurological outcomes following CA.

CONCLUSION

In the present review, we summarized the development, evolution, and potential application of near-infrared spectroscopy (NIRS) in adults with CA, highlighting the clinical relevance of NIRS brain monitoring as a predictive tool in both pre-hospital and in-hospital settings (**Figure 1**). To date, no studies have established acceptable rSO_2 cut-off values for differentiating patient groups based on ROSC status and neurological outcome. Furthermore, the extent of decrease in rSO_2 from baseline that constitutes an abnormal finding in patients with CA remains to be determined. Additional studies are required to determine the point at which resuscitation efforts can be considered futile. Nonetheless, the available evidence indicates that rSO_2 may aid not only in predicting outcomes among patients with CA, but also in optimizing CPR strategies and guiding neuroprotective interventions. Further large-scale randomized controlled trials are required to evaluate the impact of NIRS monitoring on survival and neurologic recovery. Moreover, additional studies should evaluate NIRS-guided resuscitative strategies, using improvements in NIRS values to optimize resuscitation efforts, post-resuscitation care, and patient outcomes.

AUTHOR CONTRIBUTIONS

RT and KH: concept, design, and drafting manuscript. DR, TL, SM, MO, TS, and LB: critical revision of the manuscript for important intellectual content. All authors: have read and approved the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.587930/full#supplementary-material

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REVIEW
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Advances in the Approaches Using Peripheral Perfusion for Monitoring Hemodynamic Status

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Measures of peripheral perfusion can be used to assess the hemodynamic status of critically ill patients. By monitoring peripheral perfusion status, clinicians can promptly initiate life-saving therapy and reduce the likelihood of shock-associated death. Historically, abnormal perfusion has been indicated by the observation of pale, cold, and clammy skin with increased capillary refill time. The utility of these assessments has been debated given that clinicians may vary in their clinical interpretation of body temperature and refill time. Considering these constraints, current sepsis bundles suggest the need to revise resuscitation guidelines. New technologies have been developed to calculate capillary refill time in the hopes of identifying a new gold standard for clinical care. These devices measure either light reflected at the surface of the fingertip (reflected light), or light transmitted through the inside of the fingertip (transmitted light). These new technologies may enable clinicians to monitor peripheral perfusion status more accurately and may increase the potential for ubiquitous hemodynamic monitoring across different clinical settings. This review will summarize the different methods available for peripheral perfusion monitoring and will discuss the advantages and disadvantages of each approach.

Keywords: capillary refill time, shock, sepsis, medical device, peripheral perfusion, optics, monitoring, hemodynamic status

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INTRODUCTION

Hemodynamic instability creates an imbalance between oxygen delivery and consumption and is an important contributor to organ failure (1). Hemodynamic monitoring is crucial to identify inadequate tissue perfusion in order to prevent organ dysfunction and death (2). Both global and peripheral biomarkers of tissue perfusion are used clinically as proxies for hemodynamic status. Global measurements often require invasive techniques, and the extent to which they reflect tissue oxygenation has been questioned (3).

Blood is diverted from less vital to more vital organs in response to circulatory failure (3–5). Compared to central organs, the peripheral, non-vital organs are the first to reflect hypoperfusion during shock and the last to reperfuse during resuscitation (6). As a result, clinicians shift from global to peripheral perfusion monitoring to promptly recognize deteriorating clinical status and to assess the effectiveness of resuscitation therapy (7). Measures of peripheral tissue perfusion have emerged as important tools to monitor the hemodynamic status of critically ill patients. Efforts have

been made to determine the ideal method for assessing peripheral perfusion status, which should be non-invasive, rapid, reproducible, and easily measured.

Shock is the clinical manifestation of acute circulatory failure. It is characterized by signs of tissue hypoperfusion (8) and leads to impairments in cellular oxygen delivery (9, 10). Septic shock is a form of distributive shock that results from dysregulations in the host inflammatory response to infection (11). As a leading healthcare burden, septic shock accounts for one-third to one-half of all deaths occurring in hospital settings (12), with roughly 32 million sepsis cases per year (13). Given that peripheral perfusion status can be used to quickly assess shock severity (14), hemodynamic monitoring can allow clinicians to promptly initiate therapy, evaluate the effectiveness of interventions, and assess the patient throughout their recovery.

The monitoring of peripheral perfusion status is a central element to patient care. Methods to perform this measurement are of interest and can be complicated. Major modalities that are used to measure peripheral perfusion status include capillary refill time (CRT) and temperature. New technologies have been developed to calculate CRT. These devices measure either light reflected at the surface of the fingertip (reflected light), or light transmitted through the inside of the fingertip (transmitted light). These new approaches can enable clinicians to non-invasively monitor hemodynamic status with more accuracy than traditional measurements and may become a very valuable aspect of clinical medicine. This review will discuss the pros and cons of the available methods to monitor peripheral perfusion in critically ill patients. The available techniques will be grouped according to their mechanism of monitoring perfusion status, including reflected light, transmitted light, and temperature. Within these categories, the techniques will be further delineated as either subjective or objective methods of monitoring. This review therefore provides a novel schema for classifying the available methods of monitoring peripheral perfusion (**Table 1**).

METHODS TO MONITOR PERIPHERAL PERFUSION

Capillary Refill Methods

Capillary refill time is the time it takes for the color of a distal capillary bed to return to baseline after applying enough pressure to cause blanching. Delayed CRT is defined as >2 s (46) and indicates abnormal circulatory status (47). CRT is used clinically to assess peripheral circulation for signs of shock and dehydration (21).

Abbreviations: CRT, Capillary refill time; AUC, area under the curve; SOFA, sequential organ failure assessment; ICC, interclass correlation; RBC, red blood cell; DCRT, digitally measured capillary refill time; N, newton; SDF, sidestream dark field; NIRS, near infrared spectroscopy; PPI, peripheral perfusion index; $PtcO_2$, transcutaneous carbon dioxide tensions; OCT, 10 min-oxygen challenge test; OCI, oxygen challenge index; Q-CRT, quantified CRT; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; BRT, blood refill time; CRI, capillary refill index; StO_2, peripheral tissue oxygen saturation; VOT, vascular occlusion test; TLI, total light intensity; Tc-toe, central-to-toe; Tskin-diff, forearm-to-fingertip; LDF, laser doppler flowmetry.

Reflected Light and Surface Color Changes

Subjective Measures

Clinicians routinely measure CRT using the naked eye. The value of these measurements in hemodynamic monitoring has been widely studied. Ait-Oufella et al. (15) examined septic shock patients 6 h after resuscitation. The investigators found that prolonged CRT was a strong predictive factor of 14-day mortality. Hernandez et al. (4) studied a mixed severe sepsis/septic shock population 6 h after resuscitation. The authors found that CRT <4 s was associated with correction of hyperlactatemia at 24 h. van Genderen et al. (16) examined the diagnostic accuracy of different peripheral perfusion measures in identifying surgical patients at high risk of developing post-operative complications. The investigators reported that CRT displayed the highest diagnostic accuracy [area under the curve (AUC) 0.91] and was independent of systemic hemodynamics. Hernandez et al. (17) compared organ dysfunction in septic shock patients 72 h after different methods of resuscitation. The authors reported that peripheral perfusion–targeted resuscitation was associated with less organ dysfunction compared to lactate-targeted resuscitation [mean sequential organ failure assessment (SOFA) score 5.6 vs. 6.6]. Peripheral perfusion–targeted resuscitation also trended toward reduced 28-day mortality, but did not reach the proposed statistical significance threshold ($p = 0.06$). Zampieri et al. (48) reassessed the results of this trial using both a *post-hoc* Bayesian analysis and a mixed logistic regression analysis. The authors reported a very high probability that peripheral perfusion–targeted resuscitation results in lower mortality and faster resolution of organ dysfunction than lactate-targeted resuscitation strategies. These findings highlight the prognostic value and therapeutic potential of the manual CRT-test.

Subjective CRT measurements are quick, convenient, non-invasive, and inexpensive methods of measuring hemodynamic status. However, there are important limitations. Measurements can be confounded by ambient (49–51), skin (49, 52, 53), and core temperature (50), ambient lighting (54), gender and age (50–52). Clinicians may interpret surface color changes differently, which raises concerns about the reliability of the CRT-test. Ait-Oufella et al. (15) found that CRT is very reproducible with an excellent inter-rater concordance (80%: index finger; 95%: knee). van Genderen et al. (16) reported a good overall agreement for inter-rater reliability of CRT between different examiners on different post-operative days ($\kappa = 0.74$–0.91). However, Alsma et al. (55) reported that inter-observer agreement on CRT is moderate at best, and higher for the distal phalanx ($\kappa = 0.40$) than for the sternum ($\kappa = 0.30$). Brabrand et al. (56) found only moderate inter-observer reliability ($\kappa = 0.56$) when observers categorized CRT as normal or abnormal. When CRT was measured in seconds, the investigators found an acceptable interclass correlation (ICC) of 0.62. Quantitative measures of CRT with clearly defined cut-offs appear to reduce discrepancies between observers (57).

It is possible that training may improve the reproducibility of the CRT-test. In our laboratory, we analyzed CRT measurements made by observers with varying training levels (58). We found that the mean intra-observer reliability was higher in clinicians

TABLE 1 | Summary of the available methods used to monitor peripheral perfusion.

Method	Subjective measures	Objective measures
Reflected light	Manual CRT (4, 15–17) – Quick, convenient, non-invasive, and inexpensive – Results in lower mortality and faster resolution of organ dysfunction than other resuscitation strategies (i.e., lactate) – Confounded by ambient/skin/core temperature, ambient lighting, gender, and age – Debatable interrater reliability	DCRT (18) – More accurate than clinical assessment – Limited in populations with darker skin Polarization spectroscopy (19) – Measurements correspond with the clinical definition of manual CRT – Time-consuming – Limited in chaotic clinical settings Novel device that adjusts for pressing strength/time (20) – Allows for standardized protocols – Limited in populations with darker skin Automated, pneumatic device (21) – Continuous measurements – May reduce clinician burden and inter-observer variability SDF (22–26) – Low cost, good portability, high sensitivity – Assesses deep sublingual arterioles – Time-consuming – Limited data utilization
Transmitted light	N/A	NIRS (27–30) – Non-invasive, easily monitored, reproducible – Time-consuming and expensive PPI (31–35) – Unambiguous, noninvasive, and continuous evaluations of perfusion status – Correlates with other variables of peripheral perfusion (pulse pressure, systolic blood pressure, calf blood-flow, oxygen delivery) – Predicts impending shock and mortality in septic patients status post-resuscitation – Limited in patients with hypothermia, embolism, or local vasospasm Q-CRT/BRT/CRI (14, 36–40) – Quick, non-invasive, and reproducible measurements – Predicts sepsis with same accuracy as lactate and qSOFA/SIRS scores – May promptly identify abnormal peripheral perfusion and allow for expedited treatment
Temperature	Clinical estimates of cool extremities (41–43) – Performed quickly and easily – Provides valuable insight on perfusion status – Large degree of inter-observer variability – May be confounded by ambient temperature	Body temperature gradients (4, 44, 45) – Greater accuracy and reproducibility than subjective assessments – Limited in anesthetized and cardiac surgical patients – May be confounded by ambient temperature

CRT, capillary refill time; DCRT, digitally measured capillary refill time; SDF, sidestream dark field; NIRS, near infrared spectroscopy; PPI, peripheral perfusion index; Q-CRT, quantified CRT; BRT, blood refill time; CRI, capillary refill index; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome.

than non-clinicians (0.46 vs. 0.25). It was also the highest in attending physicians and physician assistants, followed by residents, nurses, and non-clinicians. Standardization of compression strength may also improve reproducibility. Ait-Oufella et al. (15) reported excellent inter-rater concordance using 15 s of firm pressure. Alsma et al. (55) found only slightly higher inter-observer correlation using 15 s of pressure compared to 5 s. Considering practicality in emergent settings, investigators recommend the use of 5 s of moderate, firm pressure to perform CRT measurements (55, 57). Standardization of the protocol may help overcome the shortcomings in routinely measuring CRT.

Objective Measures

Technology has been developed to objectively calculate CRT. These devices also measure reflected light, but eliminate the variability that exists when clinicians manually measure CRT. Shavit et al. (18) introduced the concept of digitally measured CRT (DCRT). DCRT is calculated as the time between the release of fingertip compression and the recovery frame. In children with gastroenteritis, DCRT was more accurate at assessing the presence of significant dehydration than overall clinical assessment by experienced pediatric ED physicians (AUC 0.99 vs. 0.88). Kawaguchi et al. (20) developed a device that adjusts for pressing strength and time to determine the characteristics of the optimal fingernail compression. The authors reported that fingernail compressions <2 s resulted in unreliable CRT measurements. They found significant differences in CRT at pressing strengths of 1 newton (N) and 3 N, but no significant differences between 3, 5, and 7 N. The investigators therefore recommended compressions using 3–7 N of pressure for 2 s. Development of devices that uniformly apply these compression settings may improve the precision of hemodynamic monitoring

in clinical settings. Using an automated, pneumatic device, Blaxter et al. (21) reported a statistically significant increase in CRT in the majority of patients who underwent forearm cooling. As the device provides continuous measurements, it can repeatedly monitor hemodynamic status while reducing clinician burden and inter-observer variability. John et al. (19) used video mode polarization spectroscopy to quantify changes in red blood cell (RBC) concentration. The authors found that tRtB1 (rapid return of RBC concentration to baseline after release of fingertip pressure) corresponds best with the clinical definition of visually inspected CRT. However, clinicians may actually measure t_{pk} (onset of hyperemia after resolution of blanching) when they perform the test. The naked eye alone may therefore be incapable of capturing the fundamentals of the CRT test. Implementation of this software into clinical care may allow clinicians to monitor perfusion status and guide clinical decision-making with more accuracy. However, this technology is limited in chaotic clinical settings, where recorded video data can be shaky and unfocused (36). In contrast to fingertip assessments, certain technologies evaluate perfusion status via analysis of reflected light at different areas of the peripheral surface. Investigators have used sidestream dark-field (SDF) imaging (22, 23) to assess peripheral perfusion via evaluation of the sublingual microcirculation. In critically ill patients, Klijn et al. (24) reported that SDF assessed tissue perfusion and oxygenation was not inferior to invasive hemodynamic measurements in monitoring fluid responsiveness. SDF provides clear capillary imaging and can evaluate deep sublingual arterioles (22, 25). However, a large amount of data is discarded due to image quality artifacts and manual tracing of the vessels is too time consuming to be practical for clinical use. The development of automated devices would increase the clinical utility of SDF measurements (26).

Objective CRT measurements provide detailed data, improve reproducibility, and minimize observer bias. There are also disadvantages. Technology that assesses skin color changes (18, 20) is limited in populations with darker skin. The current design of these devices is impractical for routine use in clinical settings (18) and the procedures are time-consuming (19). Future research should focus on making adjustments that reduce procedural time and allow these devices to be easily implemented into patient care.

Transmitted Light and Spectrophotometric Methods

New technologies measure peripheral perfusion by analyzing light transmitted through the inside of the fingertip. Since visual assessments cannot be performed, there are no subjective measures of peripheral perfusion using this methodology.

Near infrared spectroscopy (NIRS) analyzes spectra in the near-infrared range to quantify oxyhemoglobin and deoxyhemoglobin levels in order to assess peripheral tissue oxygen saturation (StO_2) (27, 28). The utility of NIRS for monitoring critically ill patients remains uncertain (28). Lima et al. (29) investigated the relationship between thenar StO_2 during a vascular occlusion test (VOT) to the peripheral perfusion status and clinical outcome of critically ill patients. The authors reported a significantly lower baseline StO_2 and StO_2 recovery rate in patients with abnormal peripheral perfusion compared to patients with normal peripheral perfusion (72 vs. 81 and 1.9 vs. 3.2, respectively). These findings were independent of disease condition and hemodynamic status. In a follow-up study, Lima et al. (28) investigated the effect of peripheral vasoconstriction on thenar StO_2. After body surface cooling, the authors reported a significant decrease in StO_2 (82–72%) and StO_2 recovery rate (3.0–1.7%/s). Together, these findings suggest that peripheral tissue oxygenation varies according to peripheral circulation status. StO_2 measurements should therefore be interpreted in the context of other markers of peripheral circulation, such as skin temperature. Given that perfusion status continually changes in critically ill patients, clinicians must carefully consider peripheral circulatory status when using NIRS for hemodynamic monitoring. Although NIRS can non-invasively evaluate perfusion, it is limited by the fact that the measurements are time consuming and expensive (30).

Peripheral perfusion index (PPI) has been investigated for its use in hemodynamic monitoring. Using pulse oximetry, PPI is calculated from the ratio between the pulsatile and non-pulsatile signals of absorbed light (31) and provides insight on the circulatory status of vital organs during shock (32). In a study on healthy newborn infants, Zaramella et al. (32) compared the relationship between foot PPI and variables of peripheral perfusion measured by NIRS on the calf. The authors reported a significant correlation between foot PPI and both calf blood flow ($r = 0.32$) and oxygen delivery ($r = 0.32$). In a study on 100 children undergoing hemodynamic monitoring, Sivaprasath et al. (33) reported that PPI had a good correlation with pulse pressure and systolic blood pressure in all age groups, and a weak correlation with mean arterial blood pressure and diastolic blood pressure. The authors concluded that a 57% reduction in PPI from baseline may predict impending shock in children. He at al. (34) explored the prognostic value of PPI in septic patients. The authors reported that PPI was significantly correlated with baseline transcutaneous carbon dioxide tensions ($PtcO_2$), 10 min-oxygen challenge test (OCT) and oxygen challenge index (OCI). The authors also found significantly lower PPI, 10 min-OCT, and OCI values in non-survivors compared to survivors. These variables predicted ICU mortality with similar accuracy to arterial lactate level. PPI therefore appears to be a simple yet powerful predictor of mortality in septic patients status post-resuscitation. The results of these studies support the use of PPI for unambiguous, non-invasive, and continuous evaluations of global resuscitation status and outcome. However, PPI is limited in patients with hypothermia, embolism, or local vasospasm (35). Additional studies are necessary to support the routine monitoring of PPI as a parameter to detect impending shock and improve clinical outcomes.

Recent research has focused on the development of new technology that quantifies CRT using a pulse oximeter, which investigators have called quantified CRT (Q-CRT). Morimura et al. (14) first introduced this method. The authors analyzed the infrared transmitted light intensity (TLI) emitted from a pulse oximeter senor. They defined Q-CRT as the time in seconds from the release of fingertip compression to TLI reaching 90%

of baseline. The authors reported that Q-CRT was significantly correlated with blood lactate levels in ICU patients ($r_s = 0.681$). Q-CRT has also been correlated with venous blood lactate levels in ED patients (37). Together, these results suggest that Q-CRT might be an effective measure of insufficient global tissue perfusion and shock in both the ICU and ED. In ED patients with suspected infection, Yasufumi et al. (38) investigated the ability of Q-CRT to predict sepsis compared with quick sequential organ failure assessment (qSOFA) and systemic inflammatory response syndrome (SIRS) scores. The authors reported that the accuracy of Q-CRT in predicting sepsis was comparable to qSOFA scores, SIRS scores, and lactate level. Q-CRT may therefore be a quicker and non-invasive alternative to evaluate patients with suspected sepsis.

In our laboratory, we modified the TLI calculation used to measure Q-CRT. We modeled the curve fitting the recovery phase of the TLI waveform as an exponential decay using the least squares method, and measured the time at which the fitting curve returned to 90% (**Figure 1**). This improved measurement was named blood refill time (BRT) (39, 40) and later referred to as capillary refill index (CRI) (36). In a healthy volunteer (39), we found that our device successfully detected prolonged BRT (5.8 s) after fingertip cooling to 22.8°C. In 30 healthy volunteers (40), we measured BRT at room temperature, after immersion in cold water, and after re-warming by warm water. We reported that the "cold" group had significantly longer BRT (4.67 s) than the "room temperature" (1.96 s) and "re-warm" groups (1.96 s). Our data suggests a causal relationship between temperature and peripheral blood perfusion. Healthcare providers routinely encounter patients with cool fingertips when performing bedside evaluations of CRT. Our results suggest that clinicians should interpret these measurements with caution when performed in the setting of unknown fingertip temperature.

We compared the accuracy of CRI to CRT calculated via software analysis of recorded fingertip compression videos (36). We measured CRT and CRI at room temperature, after immersion in cold water, and after re-warming by warm water. To avoid procedural variability in compression, the fingertips were compressed pneumatically for both CRI and CRT at the same pressure and duration. We found that there was a strong correlation between CRI and CRT ($r = 0.89$). We performed a validation study in the ED to clinically evaluate the accuracy of our device (36). We reported a strong correlation between CRI and CRT ($r = 0.76$). Given the use of software analysis, we believe our study provides reliable evidence that the CRI algorithm is representative of the CRT measurements performed in clinical practice. We also reported higher CRI and CRT in ED patients compared to healthy volunteers at room temperature. Using a Bland-Altman analysis, we found that CRI was consistently higher than CRT (difference $= +1.01$). Although CRI and CRT measurements both represent peripheral perfusion status, this data suggests that the absolute value of the measurements may not be equal. Because CRI was associated with a systematic bias rather than random errors, we recommend it as a reliable and objective alternative to the manual CRT-test.

Q-CRT/CRI minimizes observer variability and provides immediate and reproducible data regarding the circulatory status of critically ill patients. Given that resuscitation strategies rooted in peripheral perfusion monitoring result in lower mortality, faster resolution of organ dysfunction, and decreased fluid requirements (17, 48), Q-CRT/CRI may have tremendous clinical potential. However, future research is necessary in populations of critically ill patients in order to evaluate the efficacy of Q-CRT/CRI in lowering mortality and reducing individual requirements (i.e., vasopressor, mechanical ventilation, and renal replacement therapies). With further clinical support, this technology may be a promising alternative for continuous monitoring and spot check measurements of peripheral perfusion.

TEMPERATURE

Body temperature is distributed both centrally (body core) and peripherally (body shell and environment) (59). Thermoregulatory status provides insight about the clinical condition of patients in intensive/critical care units. In response to shock, blood flow is restricted to central/vital organs at the expense of peripheral organs. Peripheral temperature is therefore used as an indicator of hemodynamic status (16, 60). Septic shock is divided into two categories: "cold" and "warm" shock (41, 61). Some authors believe that this distinction might confuse the interpretation of perfusion state (62). Regardless, studies show that peripheral temperature is still useful in differentiating well-perfused from hypo-perfused patients (63).

Subjective Measures (Clinical Estimates)

Healthcare providers use clinical judgment to estimate peripheral body temperature in order to quickly evaluate hemodynamic status. In ICU patients, Kaplan et al. (42) compared clinician assessment of distal extremity skin temperature (warm or cool) to objective markers of hypoperfusion. The authors found that patients with cool extremities had significantly higher serum lactate levels and lower cardiac index compared to patients with warm skin temperature. Hasdai et al. (43) reported that the presence of cold and clammy skin was an independent predictor of 30-day mortality in cardiogenic shock patients. 48 h after resuscitation, Lima et al. (41) found that ICU patients with cool extremities had significantly higher rates of organ failure compared to patients with normal skin temperature (SOFA score 9 vs. 7).

Peripheral temperature measurements can be performed quickly and easily while providing valuable insight on perfusion status. However, there is a large degree of variability, since what is considered "cool" to one clinician may not always be consistent. Changes in ambient temperature may also affect clinical estimates of skin temperature (41).

Objective Measures (Temperature Gradients)

Body temperature gradients provide objective measures of peripheral perfusion status. The gradients are created by calculating the temperature difference between two points, such as central-to-toe (Tc-toe), forearm-to-fingertip (Tskin-diff), and peripheral-to-ambient. Skin temperature can be measured using

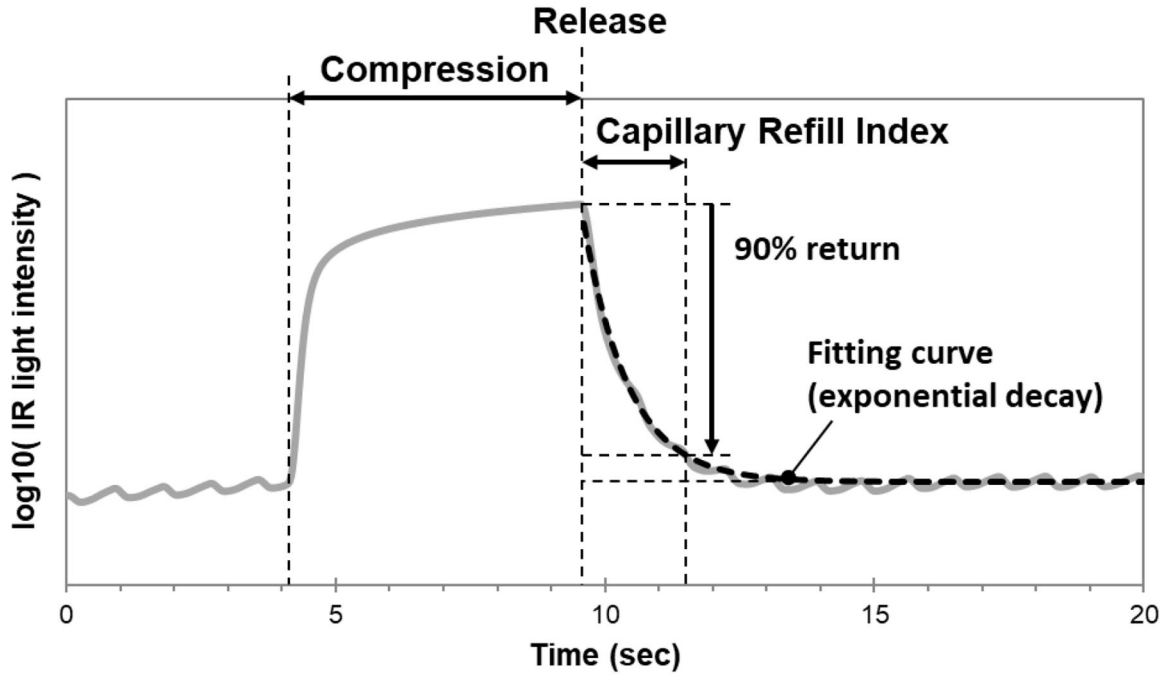

FIGURE 1 | Mechanism of the CRI monitoring device. The curve fitting the recovery phase of the TLI waveform is modeled as an exponential decay using the least squares method. CRI is measured as the time at which the fitting curve returns to 90% of baseline.

infrared thermometer (59), thermocouple disposable probes (64), or infrared thermography (65). Regardless of the modality used, these gradients provide non-invasive, accurate measures of thermoregulatory peripheral vasoconstriction (66). In response to shock, there is a reduction in fingertip blood flow in order to maintain perfusion of vital organs. This causes Tskin-diff and Tc-toe gradients to increase in the presence of constant environmental conditions (60). Peripheral-to-ambient gradients decrease during shock (3), despite some limitations that exist from this interpretation and from using ambient temperature as a marker.

In critically ill patients, Joly et al. (44) reported a significantly lower toe-to-ambient gradient in non-survivors (0.9°C) than in survivors (3.4°C). In septic patients, Hernandez et al. (4) found that return of Tc-toe to normal within the first 6 h of resuscitation was independently associated with successful resuscitation. It was also predictive of hyperlactatemia normalization at 24 h. In septic patients, Bourcier et al. (45) reported significant decreases in toe-to-room temperature gradients in patients who died from multiple organ failure (−0.2°C) compared to survivors (+3.9°C). Toe-to-room temperature gradient was also significantly correlated with other measures of tissue perfusion, including urine output, arterial lactate level, knee CRT, and mottling score.

Body temperature gradients provide better reproducibility than clinical estimates of cool hands/feet (67) and are more accurate reflections of peripheral blood flow than skin temperature alone (3, 68, 69). Abnormal gradients can be used as early indicators of abnormal perfusion, while therapeutic efficacy can be monitored by normalization of the gradient (70). As most critically ill adult patients undergo invasive monitoring, the use of body temperature gradients provides a non-invasive, economic, and effective alternative to monitor circulatory status (59). However, body temperature gradients are limited in certain populations, including anesthetized (71) and cardiac surgical patients (72). Differences in ambient temperature between the two measurement sites may also influence Tc-toe and Tskin-diff gradients. However, any fluctuations in ambient temperature should affect both sites similarly and minimize any potential confounds (41).

RECOMMENDATIONS AND CONCLUSIONS

In order to promptly initiate life-saving clinical interventions and improve outcomes, an early recognition of shock is key. Many authors therefore recommend peripheral perfusion measures to continuously assess the hemodynamic status of critically ill patients. However, current sepsis bundles suggest the need for the reassessment of resuscitation guidelines. It appears that the use of therapies guided by peripheral perfusion measurements result in favorable clinical outcomes. It is important to acknowledge that our review does not discuss all of the available technologies that may be used to evaluate peripheral perfusion status, such as laser doppler flowmetry (LDF), infrared thermography (73), and PulseCam technology (74). Nevertheless, clinicians should choose among the available techniques with an understanding of

the pros and cons of each approach (**Table 1**). Newer technologies that measure CRT, such as the objective CRI device used in our laboratory, meet many of the important criteria of assessing peripheral perfusion and are promising tools to monitor shock status at the bedside. Future studies focused on peripheral perfusion should further define the clinical implications of these devices, including their utility in modulating response to treatment. Adjustments should also be made to make the devices more practical for routine clinical use. The ability of these technologies to provide uniform/reproducible measurements across different clinical settings, decrease the use of hospital resources, and improve clinical outcomes would strengthen the role of peripheral perfusion monitoring in the bedside evaluation of hemodynamic status.

AUTHOR CONTRIBUTIONS

KSh and JF designed the conception of the work. JF drafted. KSh and KSa edited the manuscript. LB supervised and enabled the work. All authors added intellectual content, interpretations of the work, critically revised the paper, and gave final approval of the version to be published.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cutting-Edge Technology for Rapid Bedside Assessment of Capillary Refill Time for Early Diagnosis and Resuscitation of Sepsis

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Sepsis currently affects over 30 million people globally with a mortality rate of ∼30%. Prompt Emergency Department diagnosis and initiation of resuscitation improves outcomes; data has found an 8% increase in mortality for every hour delay in diagnosis. Once sepsis is recognized, the current Surviving Sepsis Guidelines for adult patients mandate the initiation of antibiotics within 3 h of emergency department triage as well as 30 milliliters per kilogram of intravenous fluids. While these are important parameters to follow, many emergency departments fail to meet these goals for a variety of reasons including turnaround on blood tests such as the serum lactate that may be delayed or require expensive laboratory equipment. However, patients routinely have vital signs assessed and measured in triage within 30 min of presentation. This creates a unique opportunity for implementation point for cutting-edge technology to significantly reduce the time to diagnosis of potentially septic patients allowing for earlier initiation of treatment. In addition to the practical and clinical difficulties with early diagnosis of sepsis, recent clinical trials have shown higher morbidity and mortality when septic patients are over-resuscitated. Technology allowing more real time monitoring of a patient's physiologic responses to resuscitation may allow for more individualized care in emergency department and critical care settings. One such measure at the bedside is capillary refill. This has shown favor in the ability to differentiate subsets of patients who may or may not need resuscitation and interpreting blood values more accurately (1, 2). This is a well-recognized measure of distal perfusion that has been correlated to sepsis outcomes. This physical exam finding is performed routinely, however, there is significant variability in the measurement based on who is performing it. Therefore, technology allowing rapid, objective, non-invasive measurement of capillary refill could improve sepsis recognition compared to algorithms that require lab tests included lactate or white blood count. This manuscript will discuss the broad application of capillary refill to resuscitation care and sepsis in particular for adult patients but much can be applied to pediatrics as well. The authors will then introduce a new technology that has been developed through a problem-based innovation approach to allow clinicians rapid

assessment of end-organ perfusion at the bedside or emergency department triage and be incorporated into the electronic medical record. Future applications for identifying patient decompensation in the prehospital and home environment will also be discussed. This new technology has 3 significant advantages: [1] the use of reflected light technology for capillary refill assessment to provide deeper tissue penetration with less signal-to-noise ratio than transmitted infrared light, [2] the ability to significantly improve clinical outcomes without large changes to clinical workflow or provider practice, and [3] it can be used by individuals with minimal training and even in low resource settings to increase the utility of this technology. It should be noted that this perspective focuses on the utility of capillary refill for sepsis care, but it could be considered the next standard of care vital sign for assessment of end-organ perfusion. The ultimate goal for this sensor is to integrate it into existing monitors within the healthcare system.

Keywords: capillary refill, objective, device, sepsis 2, emergency care

INTRODUCTION

Sepsis is the leading cause of death in United States (US) hospitals (3, 4). Globally, sepsis affects 30 million people annually including 3 million children with a mortality rate of ∼30% (5–7). Furthermore, sepsis is the number 1 cause of both hospitalization and readmission in the U.S. with and approximate annual cost of $27 billion and $2 billion respectively (8). With sepsis currently affecting more than 1.7 million individuals in the US, technological advances to improve diagnosis and monitoring could save many lives (9). One particular area that can have a substantial impact is improved recognition in the early phases of sepsis as every hour delay in the diagnosis and treatment increases mortality by 8%.

Once sepsis has been detected it is key to resuscitate patients in a timely fashion. The current surviving sepsis guidelines have recommended fluid administration (30 mls per kilogram) to all patients within the first 3 h (10). This approach is suggested based on sepsis related decreases in end-organ perfusion with fluids helping optimize oxygen delivery. However recent studies have challenged this recommendation showing that over-resuscitation may in fact increase mortality (11). Therefore, the ability to individualize therapy and direct resuscitation at the bedside in real-time based on the patient physiology and response to therapeutic interventions is vital. The current standard of care focuses on following the surviving sepsis campaign recommendations and relies heavily on blood tests for end-organ function/perfusion; however, there may be better alternatives. The sepsis-3 definitions have shown more focus on clinical variables that can be obtained quickly and non-invasively which an additional measure like capillary refill could improve upon (12). One large clinical trial enrolled and randomized septic patients into two resuscitation arms; one whose treatment was managed via serial blood lactate levels or, the other, via serial capillary refill assessment (13, 14). If a patient did not have normalization of their capillary refill time or serum lactate they were given more fluids. Capillary refill-guided resuscitation demonstrated more favorable outcomes in terms of morbidity and mortality than the current standard, serum lactate.

Capillary refill is not a novel data point, it is well-known to medical providers and is taught routinely in nursing and medical schools. It is a physical finding that should be assessed and documented on every acutely ill patient as it is a marker of distal perfusion (15). The correlation between organ perfusion and peripherally measured capillary refill time has been well-studied (16, 17). One study of sepsis patients created a protocol to withhold further intravenous fluids in patients that had normalized their capillary refill times and found decreased end organ failure compared to those in the standard care arm (18). A follow up study compared therapeutic monitoring via capillary refill to metabolic parameters, including central venous oxygen saturation and found the presence of normalized capillary refill time at 6 h was independently and significantly associated with successful resuscitation (19). Recent trials have successively demonstrated the ability of capillary refill to dynamically reflect physiologic responses to fluid challenges in patients with various types of shock (20). Consequently, intensive care unit protocols are being developed with the aim of normalizing capillary refill as a guide to more targeted and individualized sepsis care (21). The difficulty to date with capillary refill is its subjective nature. Our group performed a study evaluating capillary refill in healthy subjects by board certified physicians with video and found statistically significant variability within and between providers (22).

Emergency and Critical Care physicians are key to the improved care of sepsis. One way to accomplish this is through innovation and fostering technology development within our specialty, capitalizing on the experience of bedside clinicians, rather than relying on industry. This type of work is critical to improve healthcare, and emergency physicians should be leaders in this area as we deliver care across multiple and varied care settings. Based on a recent publication in the American Journal of Emergency Medicine, our group followed a problem-based innovation approach to develop a new bedside technology for sepsis and other conditions to more effectively and reliably monitor distal tissue perfusion (23). This approach identifies a clinically relevant problem in the emergency department and

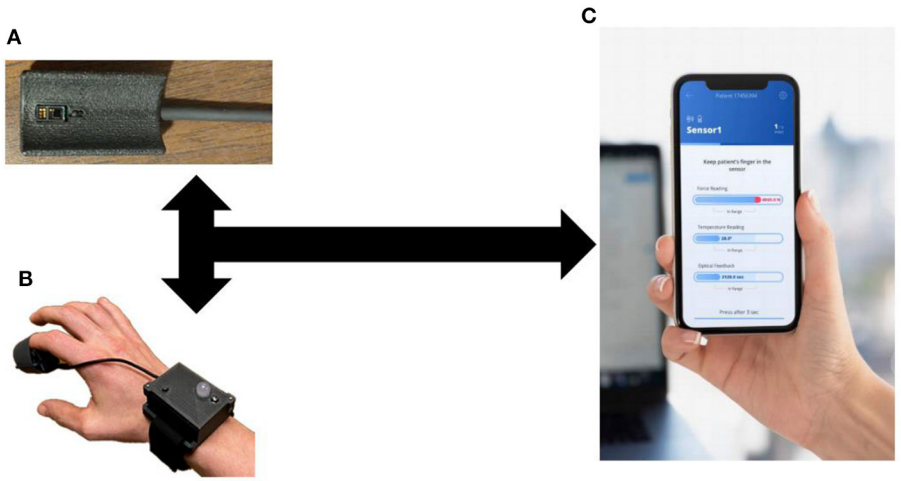

FIGURE 1 | Capillary Refill Technology. **(A)** Finger Sensor; **(B)** Sensor on a patient; **(C)** Mobile application to process real-time data collection.

then works to develop a solution. By defining the problem very well and specific the solution can be developed more robustly.

CUTTING-EDGE TECHNOLOGY

Flowsense is a capillary refill measurement system designed with clinical users in mind. This device was designed to optimize ease of use and data collection quality based on an innovation feedback cycle from two previous design and data collection study generations performed by our team. It is a wireless portable finger sensor with a streamlined application that guides users through the measurement process, and provides real-time feedback on measurement quality, requesting repeated measure when necessary. These features ensure reproducible, reliable data for timely critical interventions and medical decision making.

The Flowsense finger sensor is a battery-operated optical, temperature, and force measurement instrument which collects highly accurate real-time signals, provides user input and feedback through an operation button and multicolor LED, and allows wipe-down disinfection in between uses. This unit combines a highly integrated, lightweight and compact finger-mounted sensor stack with a wrist-mounted wireless transceiver and user control. This design minimizes motion and acceleration artifact at the finger during data collection, and provides a comfortable watch-like wrist mount for digital signal processing and control interface. The system workflow allows for simple initiation at the application level and 100% remote user operation of the wireless finger sensor without requiring app interaction while taking measurements.

Upon measurement completion, final results and data graphs are displayed to the user, and data is uploaded to a secure cloud server automatically for post-processing (**Figure 1**). This cloud-based platform will enable system integration with digital health records, physician user alerts, and a continuous process of capability improvement through enhanced clinical feature extraction enabled by machine learning and artificial intelligence techniques. A pilot cohort of patients in the emergency department were enrolled to compare the signal processing algorithms from this device to manual assessment of capillary refill (24). This study found that the algorithm for capillary refill assessment showed a good correlation to expert trained capillary refill assessment (Pearson coefficient 0.7).

Technical Detail

The current design focuses on a stand-alone technology for data collection. As can be seen from **Figure 1**, this technology can integrate into current medical monitors and be used routinely during vital sign assessment. In addition, the stand-alone device allows its use in the prehospital, outpatient or home environment.

Each finger sensor is calibrated and uniquely serialized, and has the ability to pair with any approved control unit. As such, pairing flexibility and system swap capability is maintained to ensure high clinical throughput and low down-time in case finger sensor or battery replacement is required. Together, these features make the Flowsense system the only system capable of accurately measuring capillary refill, with a design oriented toward clinical use and low electronics parts cost (∼$15), enabling future home use as well. Prior reports and research have examined methods to assess capillary refill mainly with the use of standard pulse oximetry waveforms (25, 26). This has shown significant promise for capillary refill in its ability to correlate with blood lactate levels and detect sepsis earlier while monitoring critically ill adult patients (27, 28). The technology described in this report is unique and may be superior to prior technology in that it does not use transmitted pulse oximetry. Instead as described it utilizes reflected light with the ability to penetrate deeper into the capillary beds than infrared light with less signal-to-noise ratio. The pressure application is through a simple manual method rather than an expensive pneumatic bladder. To increase the reproducibility, the accompanying application instructs the user to apply pressure for 3 s keeping

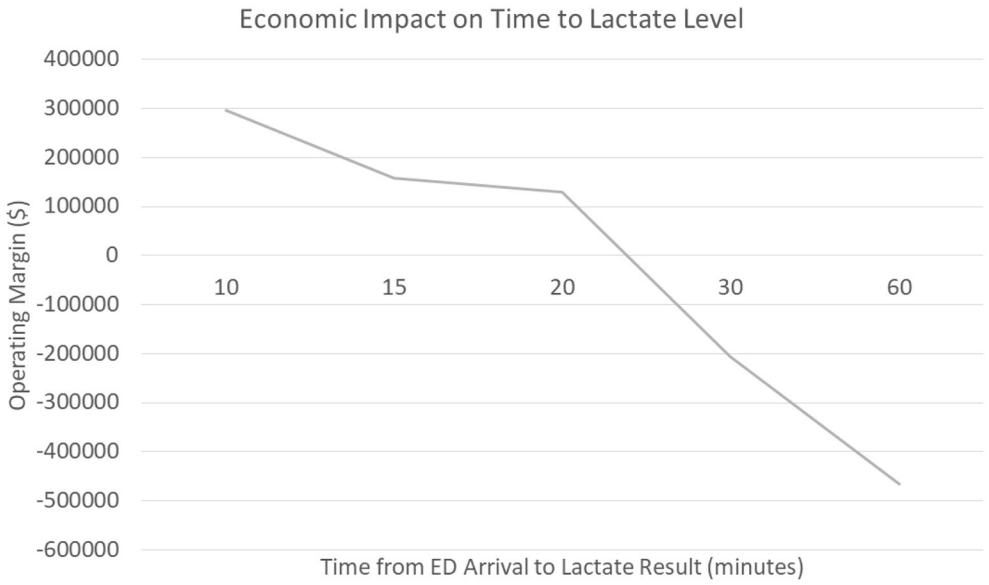

FIGURE 2 | Economic Impact of Emergency Department Sepsis Recognition.

it within a steady range. If the application senses a significant deviation, including too high or low of pressure, or that pressure was not rapidly released it will notify the user and help them troubleshoot. This expands the utility of the technology to providers with limited training to more experience.

ECONOMIC MODEL

As discussed earlier, sepsis care is costly to hospital systems (8). To further investigate the economic impact a technology to rapidly and accurately measure capillary refill could have, specifically in the emergency department, our group worked with a large academic medical center in the United States. This medical center cared for 2,606 patients with the final primary diagnosis of sepsis over a 2-year period (July 2018 through July 2020); we were able to obtain financial data on 1,571 patients. This data included revenue to the hospital, charges, and cost data calculated as direct and indirect costs. The operating margin was calculated as the difference in the revenue generated minus the direct/indirect costs the hospital incurred to provide the care. Over this time frame in the care for the ∼1,600 patients, hospital revenue was $82,726,206.93 while incurring $86,887,008.45 in costs. This resulted in a net ***negative*** operating margin of ∼$4,200,000 for sepsis care.

We hypothesize that delayed recognition in the emergency department could be a significant contributor to the negative margin associated with sepsis care. The data shows that patients who had a serum lactate drawn within the first 10 min generated a *positive* operating margin for the hospital (+$296,000) compared to patients who had their serum lactate within 60 min who generated a *negative* operating margin (-$466,000). Furthermore, when evaluating patients who presented to the emergency department at this medical center vs. direct admits, the data shows a significant trend that delays in serum lactate levels resulted in significant costs to the hospital; *an opportunity that non-invasive technology may improve* (**Figure 2**) The average time for drawing blood tests (lactate) related to sepsis diagnosis in the emergency department was ∼61 min, though non-invasive vital signs were performed on average within 8 min of emergency department arrival; a simple technology to measure capillary refill could be incorporated with existing monitors and be obtained in a very timely fashion. Our voice of customer work with providers showed the preference and ability to measure capillary refill time using our technology along with other routine vital signs. Therefore, our technology has the ability to be used during initial emergency department triage, within the first 10 min, and offers a significant opportunity to improve healthcare costs in addition to patient outcomes.

DISCUSSION

Through a problem-based approach, our group was able to develop a new technology for assessment of distal perfusion in the care of sepsis (23). Sepsis results in significant end-organ dysfunction due to distributive shock that shunts blood away from the capillary bed in the finger to preserve oxygenated blood for vital organs (29). Capillary refill assessment is very subjective and literature has shown that under ideal circumstances physicians have high variability in their assessment (22). Our technology increases the ability of personnel, with both advanced and limited training, to monitor patients in a variety of settings ranging from the ED, the intensive care unit, the prehospital setting and potentially even the home. The current device is primed for clinical research and undergoing testing in the both the ICU and ED setting to further validate its clinical evidence.

AUTHOR CONTRIBUTIONS

DS, AK, and MH developed the technology. DS prepared the first draft, critically revised, and approved final draft of manuscript. RC, MH, and AK critical reviewed and approved the final draft of the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Inhaled Gases as Therapies for Post–Cardiac Arrest Syndrome: A Narrative Review of Recent Developments

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Despite recent advances in the management of post–cardiac arrest syndrome (PCAS), the survival rate, without neurologic sequelae after resuscitation, remains very low. Whole-body ischemia, followed by reperfusion after cardiac arrest (CA), contributes to PCAS, for which established pharmaceutical interventions are still lacking. It has been shown that a number of different processes can ultimately lead to neuronal injury and cell death in the pathology of PCAS, including vasoconstriction, protein modification, impaired mitochondrial respiration, cell death signaling, inflammation, and excessive oxidative stress. Recently, the pathophysiological effects of inhaled gases including nitric oxide (NO), molecular hydrogen (H_2), and xenon (Xe) have attracted much attention. Herein, we summarize recent literature on the application of NO, H_2, and Xe for treating PCAS. Recent basic and clinical research has shown that these gases have cytoprotective effects against PCAS. Nevertheless, there are likely differences in the mechanisms by which these gases modulate reperfusion injury after CA. Further preclinical and clinical studies examining the combinations of standard post-CA care and inhaled gas treatment to prevent ischemia–reperfusion injury are warranted to improve outcomes in patients who are being failed by our current therapies.

Keywords: cardiac arrest, cardiopulmonary resuscitation, ischemia-reperfusion injury, neuroprotection, nitric oxide, xenon, molecular hydrogen (H_2), PCAS

INTRODUCTION

Cardiac arrest (CA) is a significant cause of death worldwide; ∼356,000 cases occur out-of-hospital (OHCA) (1), and 200,000 cases occur in-hospital (IHCA) (2) per year in the United States. In recent years, rates of layperson-initiated cardiopulmonary resuscitation (CPR) and layperson use of automated external defibrillators have increased over time (1). Despite such recent advances in social awareness and management of CA, the survival rate without neurologic sequelae after resuscitation remains very low, representing a public health challenge (1–5). To date, no specific pharmaceutical drugs are effective against post-CA syndrome (PCAS) (3–5).

Over the past decades, resuscitation guidelines have emphasized the lifesaving value of high-quality CPR methods and rapid defibrillation for achieving the return of spontaneous circulation (ROSC), as well as treatment strategies such as hypothermia for post-CA brain injury. In 2002, two randomized controlled trials (RCTs) showed that therapeutic hypothermia (TH) significantly improved long-term outcomes in patients with PCAS who presented with ventricular fibrillation (VF) as an initial rhythm, drawing attention to the multidisciplinary treatment approach for those patients (3, 4, 6, 7). However, a large European RCT conducted by Nielsen et al. in 2013, including 939 comatose patients after ROSC, showed no significant benefit of improving the neurological outcomes when TH cooled down to 33°C compared to the management at a near-normal temperature of 36°C (8). This report questioned the effectiveness of TH for PCAS, which has been recommended in the international guidelines for a decade. In light of this controversy, a large RCT conducted by Bernard et al. in 2016, including 1,198 OHCA patients, demonstrated that the induction of mild TH, using a rapid large-volume intravenous cold saline infusion during CPR, indeed decreased the rate of ROSC in adult patients with an initial shockable rhythm and did not improve the survival rate (9). Recent RCT conducted by Lascarrou et al. in 2019 has evaluated targeted temperature management (TTM) for comatose patients who had been resuscitated from CA with non-shockable rhythm. They concluded that moderate TH at 33°C for 24 h led to a higher survival with a favorable neurologic outcome at 90 days compared to targeted normothermia (10). Also, the latest American Heart Association guidelines recommended TTM for comatose adults after ROSC from OHCA and IHCA with any initial rhythm (11). Despite these evidences, many uncertainties within the topic of TTM remain, and therefore, the development of alternative approaches with or without TTM is an unmet medical need in improving the prognosis of PCAS.

Prolonged ischemia during CA results in a variety of cellular insults. After achieving ROSC, ischemia–reperfusion injury (IRI) causes oxidative stress in the reperfused tissues, leading to exacerbation of the cellular injury (12). Recently, it has been shown in several scientific publications that nitric oxide (NO) (13), molecular hydrogen (H_2) (14), xenon (Xe) (15), carbon monoxide (16), argon (17), and hydrogen sulfide (18) have protective effects against organ injuries related to IRI. In general, gases are small molecules; therefore, they have excellent diffusivity and easily permeate the cell membrane, targeting different organelles including the mitochondria and the nuclei. Especially, the cytoprotective effects of NO, H_2, and Xe have attracted much attention in PCAS in not only animal models but also clinical settings. Therefore, the scope of this review is to describe those selected gases that have transitioned from bench to bedside and that have been already administered in patients. Herein, we briefly introduce the pathophysiology of PCAS and present a review of recent biomedical research developments on NO, H_2, and Xe that have been proposed in recent literature.

POST-CA SYNDROME

PCAS is described as a unique and complex pathophysiological condition that involves (a) systemic IRI, (b) post-CA brain injury, and (c) post-CA myocardial dysfunction (3, 4). This condition is often complicated by a fourth component: the unsolved condition that caused the CA (3).

All clinical and biological manifestations associated with PCAS are putatively attributed to the IRI in vital organs including the brain and heart (3–5). The whole-body IRI with consequent oxygen debt causes a generalized activation of the cell-mediated immunologic response, vascular endothelial damage, hypercoagulability, and immunosuppression (3, 19–21). It has been observed that sharp increases in various cytokines occur in the bloodstream as early as 3 h after CA. Several cytokines have shown greater elevations in non-survivors than in survivors (20). Accordingly, it has been proposed that the pathophysiology of PCAS has several similar features as those of sepsis (19). The causes of post-CA organ damage may include increased activation of leukocytes, upregulated cytokines production, intracellular Ca^{2+} overload, mitochondrial dysfunction (22), and the generation of excessive reactive oxygen species (ROS) (23, 24). Excessive ROS production leads to DNA damage and lipid peroxidation, ultimately resulting in increased necrosis, apoptosis, and necroptosis (12, 25, 26). Compelling evidence has shown that mitochondria play a crucial role as effectors and targets of IRI (27–32). In fact, mitochondria are considered as one of the most susceptible subcellular targets of brain ischemia (33–35). A dysfunctional mitochondrial electron transport chain (METC) can result in an electron "leakage" phenomenon, reduced free oxygen, and the utilization of oxygen as an ubiquitous electron donor (substrate) to produce ROS (36). A body of evidence from preclinical studies has demonstrated that post-CA normoxic therapy improves neurological impairment, histological neuronal cell death, and cerebral metabolism (37–42).

Post-CA brain injury includes anoxic neuronal degeneration due to global ischemia during CA and/or shortly after ROSC, as well as delayed neurodegeneration, which can ensue within hours or several days after CA (43, 44). In a cohort study of 187 patients who underwent brain autopsy after CA, histopathologically determined severe hypoxic–ischemic encephalopathy was observed in patients with bilaterally absent cortical somatosensory-evoked potentials, gray–white matter ratio of brain computed tomographic imaging $<$ 1.10, highly malignant electroencephalographic patterns, and serum neuron-specific enolase concentration $>$ 67 μg/L (45). In response to the stress due to global ischemia, several cytokine/chemokines, adhesion molecules, and ROS are released by different cells, including leukocytes, endothelial cells, and activated platelets (46). Aberrant ROS generation causes damage to fatty acids in the cell membrane, leading to increased membrane permeability and disruption of the blood–brain barrier (BBB). Cell membrane damage and BBB disruption result in cell swelling and cerebral edema, which, in turn, leads to further exacerbation of brain ischemia. Hypoperfusion during CPR and/or shortly after ROSC leads to a mismatch between oxygen demand and supply, resulting in secondary hypoxia (47). The delayed neurodegeneration after ROSC involves complex and multiple mechanisms including cytotoxic free radical production, neuronal excitability, activation of apoptotic signaling pathways, intracellular Ca^{2+} overflow, and

mitochondrial dysfunction, among others (22, 28, 30, 48). Neuronal cell damage in the brain regions that are vulnerable to ischemia, such as the hippocampus and cerebral cortex, becomes irreversible within a few hours after the onset of ischemia, thus requiring early therapeutic interventions. Notably, some evidence suggests that the brain function after ROSC could be preserved indirectly, supporting the homeostasis of damaged organs other than the brain itself (49).

Most cases of PCAS exhibit a widespread left ventricular wall motion abnormality that is transient and reversible, in cases of normal or near-normal coronary flow or non-cardiomyopathy. This phenomenon is called post-CA myocardial stunning, which has been recently recognized as a leading cause of early death after a successful ROSC (3). In one study assessing the prevalence of coronary artery disease and acute coronary artery occlusion after resuscitation for OHCA presenting with VF as an initial rhythm, significant coronary artery lesions were found in 71% (50). Approximately 30% of patients had significant coronary artery lesions even in the absence of chest pain symptoms before CA and ST-segment elevation after ROSC (50). A meta-analysis focusing on studies for OHCA patients pointed out that acute coronary angiography should be strongly considered irrespective of electrocardiographic findings, due to the high prevalence of coronary artery disease in patients without an obvious non-cardiac etiology (51). Preexisting coronary artery disease exacerbates the myocardial damage associated with PCAS. The presence of myocardium stunning prolongs the recovery of wall motion through IRI (52), which includes excessive ROS production (53) and Ca^{2+} overload (54, 55), resulting in hemodynamics destabilization after ROSC. In addition, clinical studies have shown that right ventricular or biventricular dysfunction can contribute to poor outcomes after ROSC (56, 57). Therefore, hemodynamic stabilization is particularly important to maintain adequate cerebral blood flow and prevent late-onset neuronal damage.

RECENT DEVELOPMENTS IN GAS RESEARCH AS THERAPEUTIC AGENTS FOR PCAS

In light of the limited clinical evidence supporting TH and other conventional approaches, recent preclinical studies have been focusing on alternative strategies that could increase neuroprotection immediately after ROSC. Significant attention has been paid to the possible use of inhaled gases such as NO, H_2, and Xe, which have shown cytoprotective effects on organ injuries related to PCAS (13, 58–62). The main function of the lungs is to work as a gas exchanger, which allows oxygen to diffuse from the inhaled gas in the alveolus to the blood. The blood then carries and delivers oxygen to tissues to assist in the complex process of oxidative phosphorylation (63). Inhaled gas is a unique route of drug delivery, distinct from the intravenous or oral administration of medications, which allows for inhaled gaseous molecules to pass from the lung directly into the arterial circulatory system. Alternatively, it is conceivable that circulating cells are directly exposed to the gases as they pass through the pulmonary capillaries and may interact with or "pacified," by a certain mechanism of each inhaled gas before the cells reach the reperfused peripheral tissues including the brain and heart.

Nitric Oxide

The biological effects of NO are mediated through the activation of guanylyl cyclase (GC), followed by cyclic guanosine monophosphate (cGMP) production (GC pathway) (64). The biological effects of NO are also mediated through protein S-nitrosylation (SNO), which is the covalent attachment of NO to cysteine residues of target proteins (SNO pathway), by cGMP-independent mechanisms (65, 66). Both of these mechanisms have been implicated in the bioprotective effects of NO in IR disorders. Thus, several mechanisms that are responsible for the beneficial effects of NO on PCAS have been suggested (67). Potential mechanisms responsible for the beneficial effects of NO on the outcomes of PACS are shown in **Figure 1**. It has been reported that the administration of NO through inhalation (13, 58, 68, 69) or with an NO-donating compound (70) improves outcomes after CA in multiple species. Additionally, in mice lacking the NO synthase 3 gene, the protective effect of TH after CA/CPR is abolished (71), suggesting that NO may play an important role in TH. Furthermore, given the well-established pulmonary vasodilating effects of inhaled NO (72), it is conceivable that inhaled NO reduces the CA-induced pulmonary vascular resistance, thus enhancing the right-sided ventricular function and improving the outcomes of PCAS. Additionally, NO inhibits leukocyte adhesion (73) and migration (74), platelet activation (75), and acute inflammation (76). It has been reported that poor survival after CA/CPR is associated with leukocyte infiltration in the brain, heart, lung, liver, and kidney in mice (77, 78). It has also been demonstrated that NO is transported from the lung to the peripheral tissues through the hemoglobin, plasma protein SNOs, and nitrite ion generation and that NO in the periphery is released in the local ischemic region that exhibits acidosis where acid–base changes produce various physiological effects (79).

Minamishima et al. reported that NO breathing improves the outcomes after ROSC in mice by GC-dependent mechanisms (13). Wild-type mice were subjected to 7.5 min of potassium chloride–induced CA and subsequently resuscitated. One hour after CPR, mice were extubated and breathed air alone or air supplemented with 40 ppm NO for 23 h. The post-CA mice breathing air alone (air group) exhibited a poor 10-day survival rate (4 of 13 [30.7%]), depressed neurological and left ventricular function, increased caspase-3 activation, and cytokine driven inflammation in the brain. NO breathing attenuated the neurological and cardiac dysfunction 4 days after CA/CPR and markedly improved the 10-day survival rate (11 of 13 [84.6%]; $P = 0.003$ vs. air group) (13). They also found that GC-1α deletion abolished the ability of inhaled NO to inhibit the production of inflammatory cytokines in the brain and to improve the neurological function and survival rate after CA (13). These observations suggest that the protective effects of inhaled NO on outcomes after ROSC are largely mediated by GC-1α-dependent mechanisms. Another research group showed that NO inhalation starting at initiation of CPR until 30 min after

ROSC prevented myocardial injury and improved neurologic function and survival in rats (68). It was also shown that NO breathing, starting with the left ventricular assist device–supported CPR for 5 h, increased the transpulmonary blood flow by reducing the pulmonary artery pressure and improving neurological outcomes in pigs (69). Moreover, inhaled NO improved pulmonary artery relaxation pressure during CPR, coronary perfusion pressure during the postresuscitation phase, and short-term survival in a porcine model of CA. Interestingly, these benefits occurred despite fewer vasopressor doses and shallower chest compressions (80).

On the other hand, the protein SNO pathway has recently attracted considerable attention (65, 66, 81). Protein SNOs have demonstrated the capacity to inhibit mitochondrial proteins such as complex I in the electron transport chain, cytochrome c oxidase, and F1F0ATPase (complex V), as well as to modulate mitochondrial ROS production, influence calcium-dependent opening of the mitochondrial permeability transition pore, promote selective importation of mitochondrial proteins, and stimulate mitochondrial fission (65, 81). Furthermore, SNO proteins play a crucial role in intracellular Ca^{2+} handling, protein trafficking, and regulation of cellular defense against apoptosis and oxidative stress (65).

S-nitrosoglutathione (GSNO), which is the most abundant intracellular S-nitrosothiol in human tissue, plays an important role as a reservoir of NO bioactivity (82). GSNO has potent antioxidant and anti-inflammatory effects in animal models of IR (83, 84). In physiological conditions, GSNO and protein SNOs remain at equilibrium, whereas GSNO reductase (GSNOR) centrally regulates the reduction of GSNO (**Figure 2**) (85). GSNOR is normally expressed in all tissues including the brain, liver, vascular endothelium, and smooth muscle cells (86). As GSNOR reduces the intracellular level of protein SNO and NO bioavailability, the genetic deletion or pharmacological inhibition of GSNOR has been reported to increase the tissue levels of the protein SNO, as well as to induce vasodilation and reduce

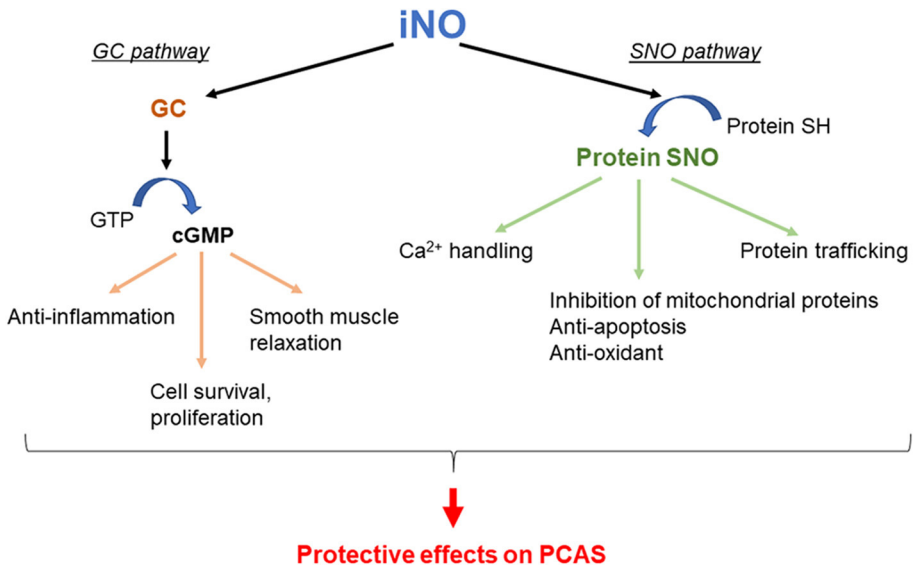

FIGURE 1 | Potential mechanisms by which inhaled nitric oxide (iNO) improves outcomes in post–cardiac arrest syndrome (PCAS). GC, guanylyl cyclase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; SNO, S-nitrosylation.

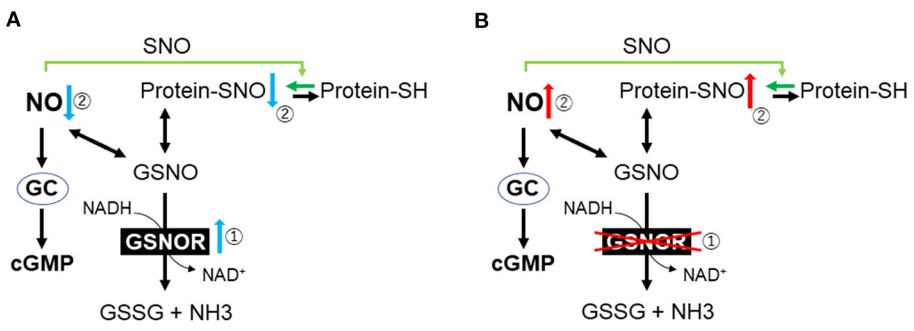

FIGURE 2 | Outline of nitric oxide metabolism. **(A)** Cardiac arrest and resuscitation increase the activity of GSNOR. **(B)** Genetic or pharmacological inhibition of GSNOR increases the tissue levels of protein SNO and NO bioavailability. GC, guanylyl cyclase; cGMP, cyclic guanosine monophosphate; SH, cysteine thiols; GSNO, S-nitrosoglutathione; GSNOR, GSNO reductase; GSSG, glutathione disulfide; NH3, ammonia; NO, nitric oxide; SNO, S-nitrosylation.

inflammation. Previous animal studies suggest that GSNOR inhibition may be beneficial for systemic and brain inflammation as well as for ischemic cardiomyopathy (87–89).

To determine the role of GSNOR in the outcomes after CA/CPR, Hayashida et al. evaluated the effects of both GSNOR inhibitors and GSNOR gene deletion on the survival and neurological outcomes after CA in mice (90). They found that GSNOR activity increased in the plasma and brain after CA/CPR and that protein SNO levels in the brain decreased after 6 h in the placebo group, whereas GSNOR inhibitors, administered 15 min after ROSC, attenuated the upregulated GSNOR activity and restored protein SNO levels in the brain (90). Additionally, in wild-type mice after CA/CPR, GSNOR inhibitors improved the neurological deficit score and survival rate (81.8 vs. 36.4%, $P = 0.031$). Similarly, GSNOR-deleted mice prevented the reduction of the brain protein SNOs, suppressed neuronal damage, and improved survival. Both GSNOR inhibitor and GSNOR deletion attenuated the disruption of the BBB after CA/CPR. In PCAS patients, it was found that plasma GSNOR activity was higher than that in preoperative cardiac surgery patients or healthy volunteers ($P < 0.0001$) (90). In another publication, they demonstrated that plasma NO consumption in post-CA patients was 3-fold greater than in healthy volunteers (91). Overall, these observations suggest that increased GSNOR activity and the subsequent NO consumption may play an important pathogenetic role after ROSC and that the inhibition of GSNOR is a novel molecular target to improve neurological outcomes after CA/CPR (**Figure 2**).

Dezfulian et al. conducted a single-center, randomized, double-blind pilot clinical study to determine the effect of low-dose (∼9.6 mg) intravenous sodium nitrate, a donor of NO, on OHCA patients (92). The patients were eligible to be enrolled in this study if the patient was successfully resuscitated from non-traumatic CA and survived to the intensive care unit (ICU) admission. Patients who had hypoxemia, hypotension, or inability to receive intravenous sodium nitrate within 12 h of onset were excluded. The results showed that there was no adverse effect on heart rate, systolic blood pressure, or blood methemoglobin level within 30 min of administration in the sodium nitrate group ($n = 7$) compared to the control group ($n = 4$). Plasma protein SNO and cGMP levels, which have protective effects on IRI (93), were elevated in the sodium nitrate group. The authors concluded that NO drug can be feasible for patients with PCAS and that further investigation is warranted (92). The same investigators are currently conducting a clinical trial to examine the effects of inhaled NO therapy on PCAS (ClinicalTrials.gov identifier: NCT04134078)[1]. Taken together, NO gas inhalation and NO-related drugs are currently one of the most promising pharmaceutical treatments for PCAS.

Molecular Hydrogen (H_2)

H_2 is a colorless, odorless, and non-toxic gas at room temperature. H_2 gas is explosive in air at a wide concentration range of 4.0–75.0% by volume, whereas in oxygen, the explosive limit is from 4.0 to 94.0% (94). The ignition point of H_2 (527°C) is higher than that of gasoline (500°C), and it is difficult to ignite it spontaneously at standard conditions of pressure. These lines of evidence suggest that H_2 is relatively safe in daily life when its concentration is < 4% (94, 95). H_2 is enzymatically metabolized as an energy source by providing electrons to METC. These enzymes catalyze the reversible redox reaction between H_2 and its constituent two protons and two electrons (96). The use of inhaled H_2 to diminish ischemic injury has been applied successfully in several rodent models, such as stroke (14, 97), acute myocardial infarction (MI) (98), and CA (60, 61). Consequently, clinical pilot studies have shown the beneficial effects of H_2 in patients with acute MI (99) and OHCA (100).

While the mechanism of H_2 protection has not been fully determined, many experts believe that its protective action is based on antioxidant properties with direct effects on ROS (101–104). Mitochondrial respiration chain, xanthine oxidase, uncoupling of NOS, and the family of nicotinamide adenine dinucleotide phosphate oxidases are significant sources of ROS (105). ROS includes superoxide anion radicals ($\bullet O_2^-$), hydrogen peroxide (H_2O_2), hydroxyl radical ($\bullet$OH), peroxynitrite ($ONOO^-$), and nitric oxide (NO$\bullet$). $\bullet O_2^-$ is putatively the primary ROS mostly generated by electron leakage from the METC (106–109). H_2O_2 is enzymatically converted from $\bullet O_2^-$ by superoxide dismutase. $\bullet$OH is a highly reactive, toxic ROS, and the major cause of oxidative stress (110); there is no detoxifying system for $\bullet$OH *in vivo*. $\bullet$OH is generated from H_2O_2 or $\bullet O_2^-$ through the Fenton or Weiss reaction in the presence of catalytically active metals such as Fe^{2+} and Cu^+ (111). $\bullet O_2^-$ reacts with $\bullet$NO to generate $ONOO^-$, which is a highly active nitrogen species (112). Oxidative stress caused by H_2O_2 and $\bullet$NO induces the production of enzymes involved in antioxidation and tolerance to protect the cells against oxidative stress, such as NF-E2–related factor 2 (113). Noteworthy, research has shown that many antioxidant supplements could not prevent cancer, MI, and atherosclerosis but rather, conversely, cause increased mortality (114–116); therefore, awareness of side effects is very important for developing an effective and safe antioxidant for ROS-related diseases. An ideal antioxidant should mitigate excessive oxidative stress without disturbing the redox homeostasis. In other words, an ideal molecule would simultaneously reduce strong oxidants such as $\bullet$OH, while maintaining signaling molecules such as H_2O_2 (95). Preclinical studies have shown that H_2 specifically quenches detrimental ROS such as $\bullet$OH and $ONOO^-$, while maintaining other less potent ROS (14). Potential mechanisms responsible for the beneficial effects of H_2 on PACS are shown in **Figure 3**. However, more precise mechanisms of the beneficial effects of H_2 remain elusive.

In 2007, Ohsawa et al. found that H_2 acts as an antioxidant by selectively reducing highly cytotoxic ROS, such as $\bullet$OH and $ONOO^-$ in cultured cells, and that 2–4% of H_2 has cytoprotective effects against IRI *in vivo* (14). Furthermore, it was demonstrated that H_2 did not react with stable, lowly active ROS, such as H_2O_2, $\bullet O_2^-$, and $\bullet$NO *in vitro* (14). In a rat model of MI, 2% H_2 inhalation starting 5 min after the ligation of a coronary artery and continued for 60 min after reperfusion reduced the infarct size and inhibited the left ventricular remodeling (98). The

[1]https://clinicaltrials.gov/ct2/show/NCT04134078.

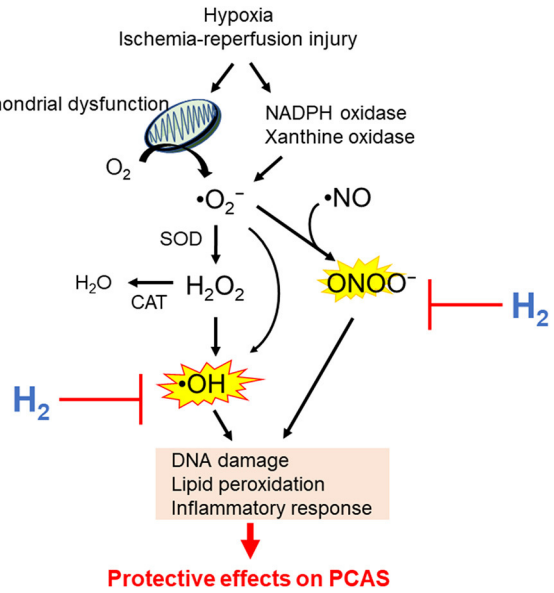

FIGURE 3 | Potential mechanisms by which hydrogen (H_2) inhalation improves outcomes in post–cardiac arrest syndrome (PCAS). NADPH, nicotinamide adenine dinucleotide phosphate; $•O_{2-}$, superoxide anion radicals; H_2O_2, hydrogen peroxide; •OH, hydroxyl radical; $ONOO^-$, peroxynitrite; •NO, nitric oxide; SOD, superoxide dismutase; CAT, catalase.

authors confirmed that H_2 diffuses into the myocardial ischemic tissues in a blood flow–independent manner, suggesting that H_2 rapidly dissolved into the blood immediately after the start of inhalation and has the potential advantage of excellent diffusion even into ischemic regions (98). Another research group reported the inhibitory effect of H_2 on myocardial IR damage in a dog model of acute MI (117). Moreover, the safety and efficacy of inhaled H_2 for the prevention of reperfusion injury in patients with acute MI undergoing percutaneous coronary intervention have been assessed (99). In a single-center, open-label, pilot study, inhalation of 1.3% H_2 did not reduce the infarct size during the acute phase after acute MI. However, the left ventricular stroke volumes assessed by magnetic resonance imaging (MRI) were improved at 6 months in comparison with 1 week after MI only in the H_2 inhalation group (99). This suggests that H_2 inhalation can be safely administered to patients with acute MI and can suppress adverse left ventricular remodeling at 6 months after infarction.

Hayashida et al. demonstrated that inhalation of 2% H_2 starting at the beginning of CPR and administered for 2 h after ROSC significantly improves the outcomes in a rat model of CA with VF (60). H_2 inhalation, but not TH, prevented an increase in the left ventricular end-diastolic pressure and myocardial injury and suppressed systemic inflammation after ROSC. The survival rate at 72 h after ROSC was 31% in the control group and 69% in both the TH and H_2 groups and was even higher at 77% in the combined therapy (inhaled 2% H_2 plus TH) group. Further, the same study group tested the benefit of H_2 administered after ROSC under a normoxic condition, which was considered essential for clinical application (61). In this study, inhaled 1.3% H_2 with 26% O2 was started 5 min after ROSC and continued for 2 h. The survival rates at 7 days were 38% in the control group, 71% in either the H_2- or the TH-alone groups, and 86% in the combined therapy of H_2 plus TH group. At 7 days after CA/CPR, H_2 improved the motor activity and special memory assessed by the Y-maze test. Immunohistochemistry studies showed that H_2 inhalation alone or in combination with TH inhibited neuronal injury in the hippocampus 7 days after ROSC. These results indicate that H_2 inhalation after ROSC is as effective as TH for improving the neurological prognosis in rats with PCAS, whereas combined therapy had an additive effect (61). Further, Nemeth et al. showed that, in a hypoxic–ischemic encephalopathy piglet model, treatment with 2.1% H_2 for 4 h reduced oxidative stress and improved neural recovery (118). Moreover, Cole et al. demonstrated the protective effects of inhaled H_2 on neurologic injury after cardiopulmonary bypass in a porcine model of neonatal circulatory arrest (119).

In a single-center, prospective, open-label, single-arm study, Tamura et al. demonstrated the safety and feasibility of H_2 inhalation after ROSC in comatose patients with a consciousness level $\leq$8 points on the Glasgow Coma Scale and a systolic blood pressure $\geq$90 mmHg (irrespective of vasopressor use) (100). In this study, the patients received 2% H_2 for 18 h using a ventilator in combination with TTM of 33–36°C. The rates of survival with Cerebral Performance Category (CPC) 1–2 were assessed at 90 days after CA. The rates of survival with CPC 1–2 were assessed at 90 days after CA. One CA patient with severe pneumonia and septic shock died of respiratory deterioration 22 h after the discontinuation of H_2 inhalation. An outcome of CPC 1 was achieved in 4 of all 5 eligible patients. The independent data monitoring committee concluded that no adverse event was attributable to inhaling hydrogen gas in this study. This study concluded that inhaled H_2 could be feasible and performed safely in patients with PCAS. Currently, a phase II, multicenter, prospective, randomized, double-blind, placebo-controlled trial to verify the efficacy of H_2 inhalation in patients with PCAS is underway (identifier: UMIN000019820) (120).

Xenon

Xe is one of the noble gases, which are the elements of group 18 on the periodic table. It has anesthetic properties, which were recognized ~50 years ago (121). It has the lowest blood–gas partition coefficient among anesthetic gases (122). It has the advantage of being non-flammable and non-teratogenic, and it has less cardiovascular effects and no adverse effects on cognitive function in animal models (123–126). In recent years, there has been increased interest in noble gases as novel treatments for ischemic and traumatic brain injury (127–129). Excessive activation of *N*-methyl-D-aspartate (NMDA)–type glutamate receptors is, in general, a key mechanism of excitotoxicity after brain injury (130, 131). During excitotoxicity, excessive glutamate release results in the activation of NMDA receptors, leading to calcium overload inside the neurons and the different types of neuroglia. This calcium overload triggers prodeath signaling pathways, ROS production, and mitochondrial damage (132–137), resulting in cell necrosis, apoptosis, and necroptosis (138). Additionally, the linkage of NMDA receptor and activation

of microglia has been suggested (139, 140). Interestingly, studies have shown that NMDA-mediated excitotoxicity occurs unequally in different brain cells because neuroglia such as astrocytes do not express NMDA receptors in the same way as neurons do, making astrocytes relatively resistant to NMDA toxic effects (141, 142). Xe is an antagonist of NMDA-type glutamate receptors (143), and subsequent animal studies have reported that Xe has neuroprotective properties in animal models of stroke (144) and CA (59, 62, 145, 146). Additionally, Xe exhibits neuroprotection by inhibiting the activation of microglia and attenuating neural damage in the hippocampus after experimental subarachnoid hemorrhage (147). In a porcine model of CA, Fries et al. demonstrated that a single inhalation of Xe started 1 h after ROSC and continued for 1 h significantly improved functional recovery and reduced neuronal damage in a porcine model of CA (146). Furthermore, they showed that administration of Xe as early as 10 min after ROSC (59) and extending up to 5 h (146) did not result in additional neuroprotection. Subsequently, they demonstrated that only the combination of Xe and mild TH provided significant and persistent improvements in functional recovery in a clinically relevant, porcine model of CA/CPR. In contrast to mild TH alone, this approach also preserved cardiac output in the early postresuscitation period (62). Potential mechanisms responsible for the beneficial effects of Xe on the outcomes of PACS are shown in **Figure 4**.

In 2013, Arola et al. reported that Xe inhalation in combination with TH can be safely applied to patients with PCAS (148). Subsequently, Laitio et al. demonstrated that Xe had a neuroprotective effect on PCAS in a randomized, single-blind phase 2 clinical trial (149). In this study, 110 patients with PCAS admitted to the ICUs were randomly assigned to receive either TH alone (control group) or inhaled Xe in combination with TH (33°C) for 24 h (Xe group). The main inclusion criteria were the presence of a witness, initial electrocardiogram waveform VF or non-perfused ventricular tachycardia, and ROSC ≤45 min after resuscitation. The primary endpoint was the severity of ischemic white matter brain injury as evaluated by fractional anisotropy from diffusion tensor MRI, which was scheduled at 36–52 h after ROSC. Xe inhalation was started within 4 h after ROSC, and the mean end-tidal Xe concentration was 48.2%. The fractional anisotropy was significantly lower in 41.7% of the voxels in the control group than in the Xe group (i.e., 58.3% of the voxels did not significantly differ between the groups), indicating that cerebral white matter and myelin damage were suppressed in the Xe group. Specifically, the mean global fractional anisotropy value adjusted for age, sex, and site factors was 3.8% higher in the Xe group than in the control group ($P = 0.006$). The adjusted radial diffusivity value was 3.9% lower in the Xe group than in the control group ($P = 0.03$). There were no significant differences in the secondary endpoints of 6-month survival and brain function outcomes between the two groups (27.8% in the Xe group vs. 34.5% in the control group; adjusted hazard ratio, 0.49, $P = 0.053$) (149). Given that myelin is required for the normal functioning of the central nervous system and its damage is related to neurocognitive dysfunction (150), this study suggested that Xe may protect the cerebral white matter by preventing brain myelin injury after ROSC (149). Although there was no significant difference in survival in this study, Xe can be potentially a novel treatment for PCAS. Subsequently, Arola et al. demonstrated that among comatose survivors of OHCA, in comparison with TH alone, inhaled Xe combined with TH resulted in significantly reduced release of troponin-T, which suggests that Xe results in less severe myocardial injury, supporting its cardioprotective effects (151). These two recent clinical trials suggest the translational potential of Xe inhalation for the management of PCAS (149, 151). These studies have demonstrated that Xe inhalation in combination with TH is safe and feasible. Currently, phase III, multicenter, prospective, randomized, single-blind, placebo-controlled trial to evaluate the efficacy of Xe inhalation on neurofunctional outcomes after OHCA is underway (identifier: NCT03176186)[2].

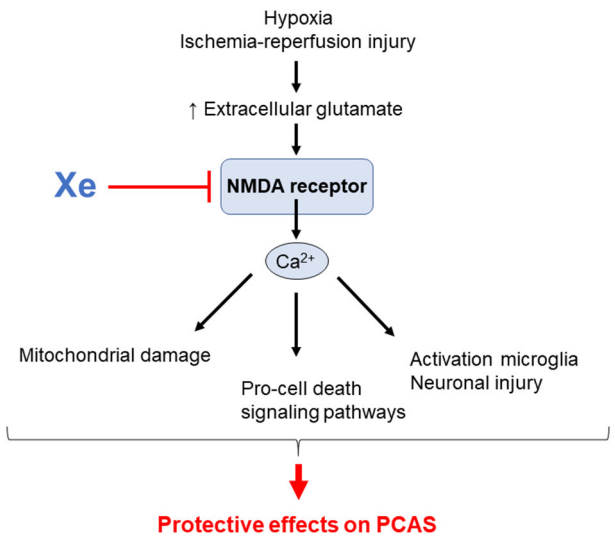

FIGURE 4 | Potential mechanisms by which xenon (Xe) inhalation improves outcomes in post–cardiac arrest syndrome (PCAS). NMDA; *N*-methyl-D-aspartate.

Xe has many properties as an ideal general anesthetic, and because the noble gases emit light when an electric field is applied, they are often used as gas lasers in medical applications such as surgery (152). However, Xe has not been widely used in clinical practice as it is rare and relatively expensive (152). Therefore, as a relatively large amount of gas is expected to be used for inhalation therapy for PCAS, the feasibility in terms of the cost has been regarded as a potential problem. Hence, further investigations for the clinical application of Xe will be required.

Other Considerations

NO is a toxic molecule (153) synthesized by NO synthases, which include three isoforms: neuronal NOS (NOS1), inducible NOS (NOS2), and endothelial NOS (NOS3) (154). In contrast to NO, mammalian cells do not have to produce intracellular Xe and H_2. Although Xe is non-toxic, many of its compounds are toxic because of their strong oxidative properties. Xe readily penetrates the BBB, offering rapid onset of action, and titration of dose

[2]https://clinicaltrials.gov/ct2/show/NCT03176186.

TABLE 1 | Summary table of the past and current clinical trials on inhaled gases as therapies for PCAS (as of 1st, Dec, 2020).

Intervention	Study title	Status	Locations	Identifier
Nitric oxide	Improving outcomes in cardiac arrest with inhaled nitric oxide	Recruiting	USA	NCT04134078[1]
Molecular hydrogen	Efficacy of inhaled hydrogen on neurological outcome following brain ischemia during post-cardiac arrest care: HYBRID II trial (Phase II)	Recruiting	Japan	UMIN000019820 (120)
Xenon	Xenon for neuroprotection during post-cardiac arrest syndrome in comatose survivors of an out of hospital cardiac arrest (XePOHCAS)	Recruiting	USA	NCT03176186[2]
Molecular hydrogen	The effect and safety of hydrogen inhalation on outcome following brain ischemia during post cardiac arrest care: HYBRID study	Completed	Japan	UMIN000012381 (100)
Xenon	Effect of xenon and therapeutic hypothermia, on the brain and on neurological outcome following brain ischemia in cardiac arrest patients (Xe-hypotheca)	Completed	Finland	NCT00879892 (148, 149)
Nitric oxide	Inhaled nitric oxide after out-of-hospital cardiac arrest	Terminated[a]	USA	NCT03079102

[a] *The study has stopped early because of slow enrollment and planned change of institution by a principal investigator and will not start again.*

and response are rapid because of a low blood–gas partition coefficient (122). H_2 has no known cytotoxicity even at high concentrations (155, 156).

As the primary target of NO, heme-based proteins play a central role. Integrated approaches revealed the physiological significance of NO on mitochondrial cytochrome c oxidase, a central mediator of mitochondrial respiration (157). Xe exerts neuroprotective effects by acting as an antagonist of the excitotoxic NMDA receptors (143). Excessive inflow of calcium mediated by NMDA receptors triggers complex biochemical cascades that ultimately lead to neuronal cell death (134). Although the molecular mechanisms of H_2 have not yet been clarified, it has been shown that H_2 does not reduce the oxidized heme of cytochrome c (14). In addition, a combined inhalation of NO plus H_2 during IRI reduced the infarct size, maintained cardiac function, and reduced the generation of myocardial nitrotyrosine, which is associated with NO inhalation (158). Therefore, the primary targets of these gases seem to differ from different standpoints. Moreover, the optimal timing, concentration, and therapeutic window may differ among these gases. The exact underpinning mechanisms of these therapies remain to be unveiled in future studies. Elucidation of the mechanism of action will accelerate the translation into clinical. Summary of the past and current clinical trials investigating the effects of gases on PCAS are shown in **Table 1**. Because these gases are colorless, odorless, and difficult to check visually, they require a pressure regulator and flowmeter and must be handled under the local high-pressure gas safety control act, in clinical translation. It is important to clarify and establish the safety, toxicity, flammability, operability, and cost, individually, for the clinical application. However, we would like to emphasize that gas inhalation therapy may not require extensive equipment or advanced medical technology and is relatively easy to be introduced in a large number of facilities. In addition, dedicated gas cylinders can be installed in public areas or on ambulances to provide earlier therapeutic interventions during CPR or immediately after ROSC.

CONCLUSION

We reviewed the developments in research on basic and clinical applications of NO, H_2, and Xe for PCAS. The discussed studies provide insights on new frontiers regarding the fact that gas therapy may bring promising improvements in the prognosis of patients after ROSC. Nevertheless, there are substantial differences in the mechanisms by which these gases modulate IRI after ROSC. Further preclinical and clinical studies examining the combinations of standard post-CA care plus inhaled gas treatment to prevent IRI are warranted to improve outcomes in patients who are being failed by our current therapies.

AUTHOR CONTRIBUTIONS

KH: concept, design, and drafting manuscript. SM, KS, RT, TY, DR, RC, SG, EM, and LB: critical revision of the manuscript for important intellectual content. All authors have read and approved the manuscript. All authors contributed to the article and approved the submitted version.

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Effects of Apparent Temperature on the Incidence of Ventricular Tachyarrhythmias in Patients With an Implantable Cardioverter–Defibrillator: Differential Association Between Patients With and Without Electrical Storm

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Background: Electrical storm (ES) has profound psychological effects and is associated with a higher mortality in patients with implantable cardioverter–defibrillator (ICD). Assessing the incidence and features of ES, is vital. Previous studies have shown winter peaks for ventricular tachyarrhythmia (VTA) in ICD patients. However, the effects of heat with a high relative humidity remain unclear. Thus, this study aimed to assess the nonlinear and lagged effects of apparent temperature [or heat index (HI)] on VTA among patients with and without ES after ICD implantation.

Methods: Of 626 consecutive patients who had ICDs implanted from January 2004 to June 2017 at our hospital, 172 who experienced sustained VTAs in ICD recording were analyzed, and their clinical records were abstracted to assess the association between VTA incidence and HI by time-stratified case-crossover analysis. Cubic splines were used for the nonlinear effect of HI, with adjustment for air pollutant concentrations.

Results: A significant seasonal effect for ES patients was noted. Apparent temperature, but not ambient temperature, was associated with VTA occurrences. The low and high HI thresholds for VTA incidence were $<15^{\circ}$ and $>30^{\circ}$C, respectively, with a percentage change in odds ratios of 1.06 and 0.37, respectively, per 1°C. Lagged effects could only be demonstrated in ES patients, which lasted longer for low HI (in the next 4 days) than high HI (in the next 1 day).

Conclusion: VTA occurrence in ICD patients was strongly associated with low HI and moderately associated with high HI. Lagged effects of HI on VTA were noted in patients with ES. Furthermore, patients with ES were more vulnerable to heat stress than those

without ES. Patients with ICD implantation, particularly in those with ES, should avoid exposure to low and high HI to reduce the risk of VTAs, improve quality of life and possibly reduce mortality.

Keywords: electrical storm, implantable cardioverter-defibrillator, incidence rate, relative humidity, ventricular tachyarrhythmia

INTRODUCTION

Ventricular tachyarrhythmias (VTAs) are associated with a greater risk of sudden death. Treatment with implantable cardioverter–defibrillators (ICDs) has become the standard intervention for patients at risk of life-threatening VTAs, including ventricular tachycardia (VT) and ventricular fibrillation (VF) (1). ICDs also provide detailed information about VTAs, which could help evaluate the nature and distribution of ventricular arrhythmias. Electrical storm (ES), which is defined as three or more separate VT/VF episodes leading to ICD therapy within 24 h, not only produces profound psychological morbidity but is also associated with increased mortality (2). Hence, clinical assessment of the incidence and features of ES is vital; however, ES is unpredictable (3). Studies in the United States (4), Germany (5), Switzerland (6), and Canada (7) found that VTA incidence peaks in winter. In some studies in Japan (8) and Korea (9), the peak incidence of ICD shocks occurs in spring and early summer in patients with Brugada syndrome. High temperature is also reported to cause sudden cardiac deaths and cardiovascular mortalities (10, 11).

Relative humidity (RH) in the aforementioned study areas of continental climate is generally low compared with that in subtropical or tropical areas, such as Southeast Asian countries. The climate in Taiwan, which is an island located in the western Pacific Ocean, is generally warm and humid (with a year-round RH of approximately 76%). Previous researches showed that there is a significant interaction effect of temperature and RH on cardiovascular mortality (12, 13). High RH inhibits body heat dissipation when ambient temperature is high and insulation when temperature is low; both augment the sensation of temperature. Thus, apparent temperature or heat index (HI), which is a composite index of ambient temperature and RH that could determine how the body perceives temperature, has been proposed to have a more eminent cardiovascular effect than ambient temperature alone (13). Hence, this study aimed to assess the nonlinear and delayed association between sustained VTAs and HI in patients with ICD implantation (both with and without ES) and quantify the risk of VTAs due to apparent temperature.

MATERIALS AND METHODS

Data

This retrospective cohort study included 626 consecutive patients who had ICD implantation at National Taiwan University Hospital from January 1, 2004, to June 30, 2017. Data on sex, age at index date, smoking status, place of residence, and medical history, including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, congestive heart failure, medication use, clinical diagnosis for defibrillator implantation, and initial left ventricular ejection fraction (LVEF), were extracted from medical records. The setting of ICD therapy for each patient, including VT zone, VF zone, antitachycardia pacing (ATP) therapy, and shock energy, was determined by the physician. This study was approved by the National Taiwan University Hospital Research Ethics Committee.

Ventricular Tachyarrhythmia Events

Information on each VTA event, including the date, timing, and duration of each arrhythmia, was extracted from the ICD device during the outpatient follow-up period. Two independent cardiologists reviewed the records to discriminate VTAs from supraventricular arrhythmia and determined whether the therapy was appropriate shock or inappropriate shock. Patients with inappropriate ICD shocks, including supraventricular tachycardias, double counting of R waves, oversensing of T waves as R waves, and an artifact or noise, and those with VTAs who experienced acute coronary syndrome were excluded in our study. We considered VTA that recurred within 5 min as the same episode as the preceding event regardless of the total number of ATP or shock therapy (2). **Figure 1** shows the flowchart of patient selection. Forty-five patients with ICD therapies experiencing ES and 127 patients with isolated appropriate ICD therapies were included in the final analysis.

Air Quality Data

We obtained hourly measurements of air pollutant concentrations ($PM_{2.5}$, PM_{10}, NO, NO_2, SO_2, O_3, and CO) from the air-monitoring stations of Taiwan Environmental Protection Agency from January 1, 2004, to June 30, 2017 and estimated the 24-h average concentrations at the patients' residence. Geographic information system was employed to determine the coordinates of the home address. We divided the residence of the patients into seven geographical areas across Taiwan for their spatial heterogeneity: North, Northern Central (NC), Central (C), Central South (CS), South (S), Northern East (NE), and East (E).

A generalized additive model for each area was applied to estimate the air pollutant exposures based on the measures from the monitoring stations. The model included three meteorological covariates (daily 24-h average temperature, wind speed, and RH) that influence pollutant dispersion. Township population density and traffic load (total counts of automobiles and motorbikes) near the monitoring station were also included as land use covariables in the model (14). We used cubic splines to model the meteorological covariables, population

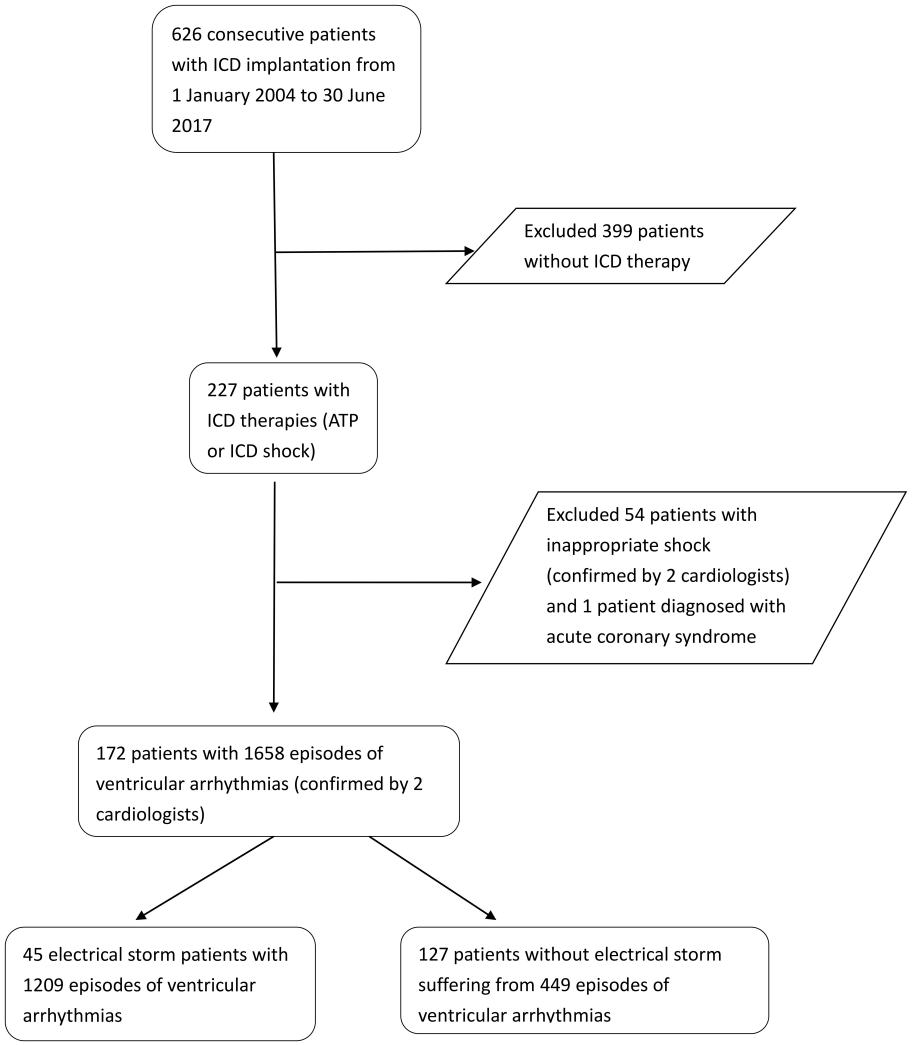

FIGURE 1 | Flowchart of patient selection.

density, and traffic load and validated the model using a cross-validation technique (15). For patients residing <1 km away from a monitoring station, the estimates of air pollutant exposures were obtained directly from the measures of that station. An ordinary kriging technique was applied to the model residuals for the spatially smoothed estimates across the study areas of western Taiwan (N, NC, C, CS, and S), which were the main residential areas with geospatial homogeneity.

Heat Index Data

We calculated the HI (°F) based on Steadman's formula or Rothfusz's full formula, depending on whether the calculated HI was </≥80°F, with adjustments according to different ranges of RH and temperature (16) (see **Supplementary Material**, for the detailed formula). The calculated HI in °F was converted to °C. We obtained the 24-h average temperature and RH from the air-monitoring station that is closest to the patients' residence.

Statistical Analysis

We used a bidirectional time-stratified case-crossover approach to assess the association between the incidence of sustained ventricular arrhythmia and HI. This design allowed for investigation of short-term environmental exposures, such as air pollution and temperature, by comparing the subject's exposure before the time of the event (case period) with the exposures at separate control periods. A conditional logistic regression was used to analyze the subject's event onset and the matched sets (control periods) for the differences of exposure status. Thus, each patient serves as his or her own control and adjusts for confounding by season, month, day of the week, time trend upon exposure, and individual characteristics. The case periods were the days of sustained VTA occurrences in patients with ICD. For each case period, the matched control periods (days) were the same weekdays of the same month. For preliminary analysis, we used a conditional logistic regression model to assess the statistical association between the incidence of sustained VTA

and the composite effects of ambient temperature and RH. We included composite weather condition based on temperature and RH (numbered 1–6) as a covariable; we categorized ambient temperature into low, medium, and high and RH into low and high. The cutoff values were determined using Youden's index based on the corresponding receiver operating characteristic curve. Other covariables adjusted in the model included estimated 24-h air pollutant concentrations and an indicator variable of whether an episode occurred on the previous day. Subsequently, we assessed the association between the incidence of ICD therapy and HI using cubic splines with three degrees of freedom to account for the nonlinear effect of low and high HI, after adjusting for air pollutant concentrations and previous-day incident.

To assess monthly and seasonal effects, we employed a generalized linear model with a logit link for recurrent VTA incidents of each patient during the follow-up period. Variations among the patients were treated as random effects. To assess the lagged effects of HI on ICD therapies, we fitted the conditional logistic models with different lag structures for the calculated HIs from the current day (lag 0) up to the sixth lagged day (lag 6). Moreover, we performed subgroup analysis by evaluating the differential effects of HI on VTAs between (1) ES group and non-ES group; (2) ischemic cardiovascular disease (CVD) group and non-ischemic CVD group. Because most of the patients were admitted for the management of ES. Therefore, some of the VTA episodes had occurred in the hospital where the temperature and humidity were well controlled. A sensitivity analysis was performed by excluding the patients who experienced in-hospital ES episodes. We calculated the relative risks (RRs) as the ratios of the corresponding estimated probabilities. The analyses were performed using the SAS software (version 9.4) (SAS Institute Inc., Cary, NC) and the R software (version 3.5.1) for statistical computing. A test statistics with a P value < 0.05 was considered statistically significant.

RESULTS

Study Population and Meteorological Data

Between January 1, 2004, and June 30, 2017, 1,659 ICD therapies (ATP or shock) were recorded in 172 patients with ICD during a median follow-up of 65 months. Mean age was 55.5 $\pm$ 18.0 years and mean LVEF was 49.7 (18.5%). The major causes of ICD implantation were ischemic cardiomyopathy (n = 64, 37.2%) and dilated cardiomyopathy (n = 44, 25.5%). Among the 172 patients with ICD therapy, 45 (26.2%) experienced ES, 69.2% used beta-blocker, and 77.3% received amiodarone (**Table 1**).

During the study period, the lowest and highest recorded 24-h average temperature was 7.7 and 33.6°C, respectively, with a median of 24.0°C, and the lowest and highest RH was 24.5 and 97.7%, respectively, with a median of 74.5%. The calculated 24-h average HI ranged from 6.7 to 41.4°C, with a median of 24.6°C. The estimated $PM_{2.5}$ (PM_{10}) concentration ranged from 4.2 (9.1) $\mu g/m^3$ to 107.4 (587.5) $\mu g/m^3$, with an interquartile range of 9.1 (20.1) $\mu g/m^3$. **Table 2** lists the exposure distributions of HI, temperature, RH, and estimated air pollutant concentrations for the 172 patients.

Monthly and Seasonal Pattern of Ventricular Tachyarrhythmia Events

Figure 2 shows the monthly incidence rates (IRs) for all, ES, and non-ES patients. The monthly overall IR of sustained VTA was highest in March (0.96% per person-month) and lowest in September (0.40% per person-month). The monthly IRs for patients with ES were generally much higher than those for non-ES patients, with the highest (1.80%) and lowest (0.23%) IRs noted in June and November, respectively. By contrast, the monthly difference in IRs for patients without ES were non-significant. As shown in **Figure 2**, sustained VTA occurred more frequently in spring and summer than in fall. A significant seasonal effect on VTA occurrence was observed in patients with

TABLE 1 | Clinical characteristics of ICD patients with confirmed sustained ventricular tachyarrhythmias.

	ICD patients with VTAs ***N*** **= 172**
Age, mean (SD), years	55.6 (17.8)
Male (%)	133 (76.9)
Hypertension (%)	87 (50.3)
Diabetes mellitus (%)	41 (23.7)
Dyslipidemia (%)	43 (24.9)
Smoking (%)	30 (17.3)
CAD (%)	79 (45.7)
CHF (%)	78 (45.1)
CVA (%)	17 (9.8)
Diagnosis at ICD implantation (%)	
Ischemic cardiomyopathy	65 (37.6)
Dilated cardiomyopathy	44 (25.4)
Hypertrophic cardiomyopathy	10 (5.8)
Arrhythmogenic right valve dysplasia	10 (5.8)
Long QT syndrome	7 (4.0)
Brugada syndrome	13 (7.5)
Congenital heart disease	5 (2.9)
Idiopathic	19 (11.0)
Indication of ICD implantation (%)	
Primary prevention	20 (11.6)
Secondary prevention	153 (88.4)
Ejection fraction (%)	
≧50	85 (49.4)
40–49	26 (15.0)
<40	62 (36.0)
Concomitant medication (%)	
β-blockers	119 (68.8)
Amiodarone	133 (76.9)
ACEi/ARB	86 (50.0)

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; ICD, implantable cardioverter–defibrillators; VTAs, ventricular tachyarrhythmias.

TABLE 2 | Distribution of the estimated air pollutant concentrations and weather data from January 1, 2004, to June 30, 2017.

Measure	No.of days	Min	5%	25%	50%	75%	95%	Max
Heat index (°C)	3,424	6.73	13.22	18.79	24.57	31.87	36.32	41.40
Temperature (°C)	3,424	7.72	13.75	18.88	24.04	28.38	30.83	34.05
Relative humidity (%)	3,424	24.54	58.61	68.00	74.46	81.04	88.92	97.70
$PM_{2.5}$ ($\mu g/m^3$)	3,424	4.17	13.63	19.44	23.97	30.41	44.75	107.38
PM_{10} ($\mu g/m^3$)	3,434	9.08	25.19	33.17	40.25	53.25	82.34	587.51
CO (ppm)	3,439	0.13	0.30	0.46	0.57	0.72	1.04	2.50
NO_2 (ppb)	3,432	1.96	10.36	16.93	20.65	24.74	32.10	54.54
O_3 (ppb)	3,397	6.14	16.06	20.56	24.62	29.64	39.45	81.20
SO_2 (ppb)	3,428	0.56	2.22	2.96	3.65	4.54	5.66	22.44

CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; SO_2, sulfur dioxide.

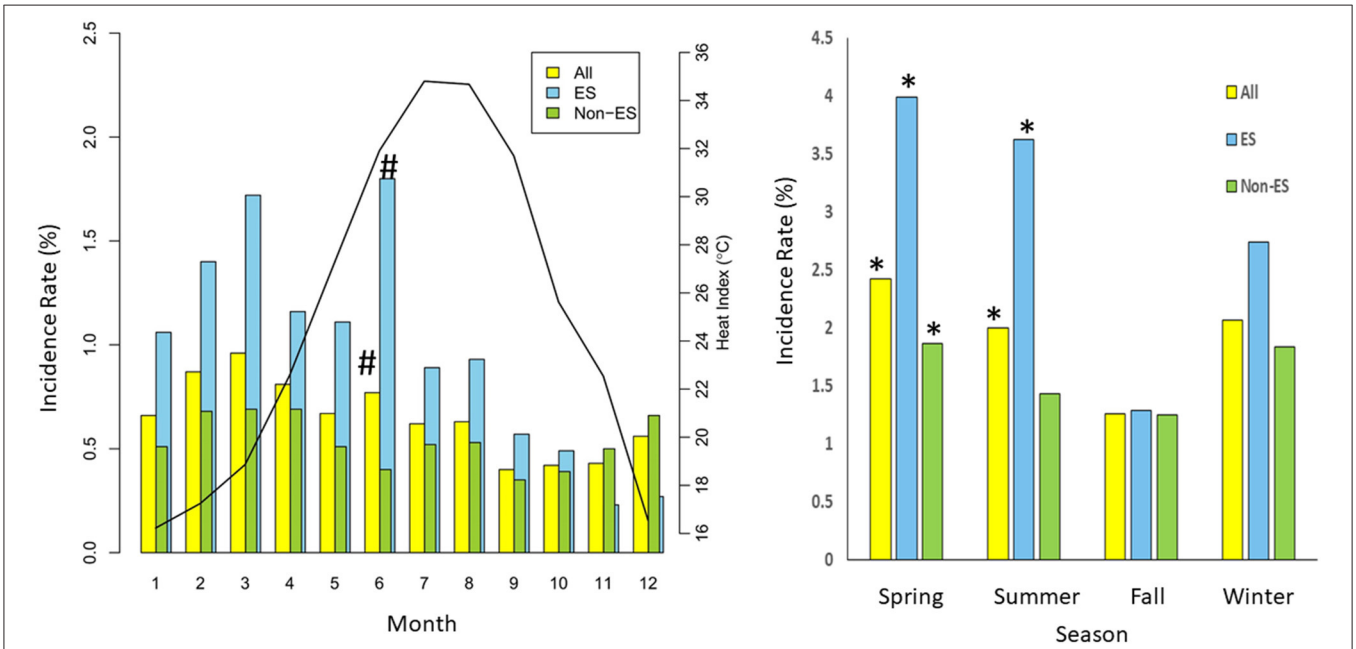

FIGURE 2 | Annual distribution of VTA incidence rate (per person-month) (vertical bar) of 172 patients with ICD (yellow), 45 patients with electrical storm (ES) (blue), and 127 non-ES patients (green). Solid line indicates mean monthly heat index between January 1, 2004, and June 30, 2017. *means $P < 0.05$ as compared with fall; # means $P < 0.05$ as compared with reference month.

ES in spring and summer; for non-ES patients, a significant effect was noted in spring.

Nonlinear and Delayed Associations Between HI and the ICD Therapy Incidence

For the association between the incidence of ICD therapy and the composite effect of temperature and RH, **Figure 3** shows that high RH (≥74%) had a significant increase in RR (i.e., >1) of VA in low (<13°C) and high (≥29°C) temperatures as compared with modest temperature (13–29°C) and low RH (<74%). These results suggested that RH could modify the relationship between temperate and VTA occurrence. Thus, we chose a HI (an index that combines temperature and RH) as an alternative indicator of ambient temperature and used a nonlinear model to analyze the combined effects of temperature and RH on VTA incidents.

Figure 4 shows the nonlinear and lag-specific RR of VTA incidence at different HIs from 0 to 6 days, with a reference HI at 24.5°C. RR increased with either higher or lower HI, with thresholds at 15°C for low HI and 30°C for high HI (lag 0). In patients with ES, the lag effects of low HI were long-lasting (in the next 4 days). However, for high HI, modest lag effects (in the next day only) were noted in patients with ES (**Figure 4B**), whereas the lag effect for non-ES patients was null (**Figure 4C**). Moreover, **Figure 5** shows the lag-specific percentage change in odds ratio (OR) for a 1°C decrease in HI at 15°C or increase at 30°C. In all patients, the OR increased by 1.06% (95% CI

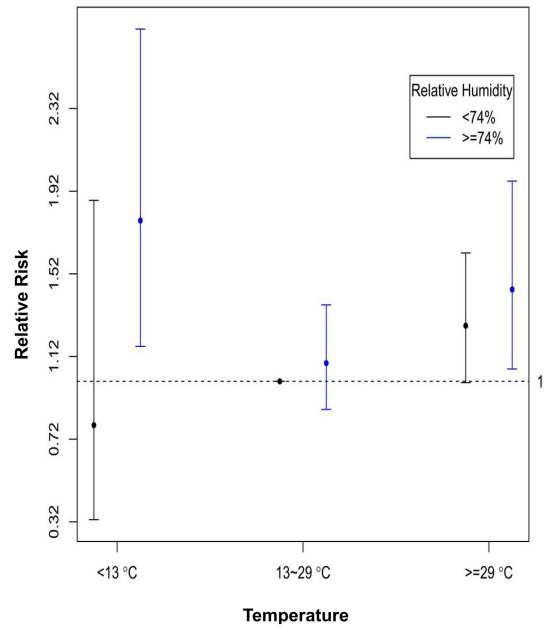

FIGURE 3 | Relative risks of VT incidence of composite conditions of temperature and relative humidity, with modest temperature (13–29°C) and low relative humidity (<74%) as the reference. The dots are the relative risks, and the bars are the corresponding 95% confidence intervals.

−0.12 to 2.20%) for a 1°C decrease at 15°C and 0.37% (95% CI 0.17–0.56%) for a 1°C increase at 30°C (lag 0) (**Figure 5A**). The percentage changes of OR in different lags were different between patients with ES and those without ES. In patients with ES, the percentage changes below 15°C were significantly >0 at lag 1 to lag 4, while the percentage changes above 30°C were also significantly >0 at lag 1 (**Figure 5B**). However, the percentage changes of OR for below 15°C and above 30°C were both non-significant at all lags in non-ES patients (**Figure 5C**). The acute and lagged effects of low and high HI on VTA incidents in patients with ES and those without ES are summarized in **Table 3**. We also found there is differential effects of HI on VTAs in different etiology of CVD. The effects of low HI on VTAs seemed more prominent in patients with ischemic CVD than those with nonischemic CVD. The percentage changes of VTA occurrences below 15°C were significantly larger at lag 0 to lag 1. Meanwhile, the nonlinear and delay effects of high HI on VTAs can only be demonstrated in patients with nonischemic CVD. These results are shown in **Figure 6**.

Besides, patients who had a VTA occurrence on the previous day had a high OR (6.80, 95% CI 4.97–9.30), which was consistent with the lag effects of HI on VTAs. Air pollutant $PM_{2.5}$ did not have a significant association with sustained VTA incidence (OR 0.993, 95% CI 0.982–1.004). Similarly, all the other air pollutants had no significant association with VTA incidence and had similar outcomes when adjusted in the model (data not shown). The sensitivity analysis showed the occurrence of VTAs were still significantly associated with both low HI and high HI after excluding the patients who experienced in-hospital ES episodes. Furthermore, the lagged effects of high HI on VTAs seem even longer (up to lag 3) in patients with ES. These results are shown in **Supplementary Figure 1**. Another sensitivity analysis excluding 10 patients with RV dysplasia and 13 patients with Brugada syndrome had similar outcomes.

DISCUSSION

Our data showed a significant seasonal effect in spring and summer among ICD patients with sustained VTAs, especially in patients with ES. In ES patients, monthly IR was highest in June and lowest in November. RH can modify the relationship between ambient temperature and the occurrence of VTAs in patients with ICD. A strong and modest nonlinear association between lower and higher HI, respectively, and sustained VTAs was found after adjusting for air pollutant concentrations. Patients with ICD had the lowest IR of sustained VTAs at a 24-h average HI of 24.5°C and had a higher IR either at a lower or higher HI. Moreover, lagged effects of HI on VTAs could only be demonstrated in patients with ES, which lasted longer for low HI (in the next 4 days) and were relatively shorter for high HI (in the next day only). Meanwhile, the lagged effects were more prominent than acute effects (lag 0) in patients with ES, especially for low HI. Furthermore, patients with ES were more vulnerable to heat stress than those without ES in both acute and lagged effects of high HI. To the best of our knowledge, this is the first study to evaluate the association between the occurrence of VTAs and apparent temperature in patients with an ICD living in a subtropical area.

Meteorological influences may activate pathophysiological mechanisms facilitating the occurrence of VTAs in susceptible patients. Cold weather conditions could contribute to the occurrence of arrhythmias through the activation of both the sympathetic nervous system and the coagulation system, which may reduce the ischemic threshold and in turn trigger VTA onset (17). Currently, several studies have examined the influence of temperature, mainly low temperature, on sustained VTAs. For every 1°C decrease in ambient temperature, the risk of ventricular arrhythmias is reportedly increased by 1.2% (18). Lower temperature and drier air are reportedly associated with an increased risk of ventricular arrhythmia onset among ICD patients (3). ICD shocks are reportedly 25% more common during extremely cold days and 8% more common during cold days (7). Despite the higher average minimum temperature in Taiwan, our study results were consistent with those of prior studies. The possible mechanism of sustained VTA occurrence during periods of thermal stress may be multifactorial (19). Increased skin blood flow and volume depletion due to sweating result in reduced coronary blood flow and a significant increase in blood viscosity. Heart rate and cardiac contractility are elevated during heat stress, which further worsens the myocardial oxygen supply–demand imbalance. Arterial thrombosis and disruptions in the autonomic nervous system may also pose a risk of VTAs (20). Moreover, extremely high temperature is associated with an increased risk of out-of-hospital cardiac arrest and cardiovascular death (10, 11). Most sudden deaths are caused by

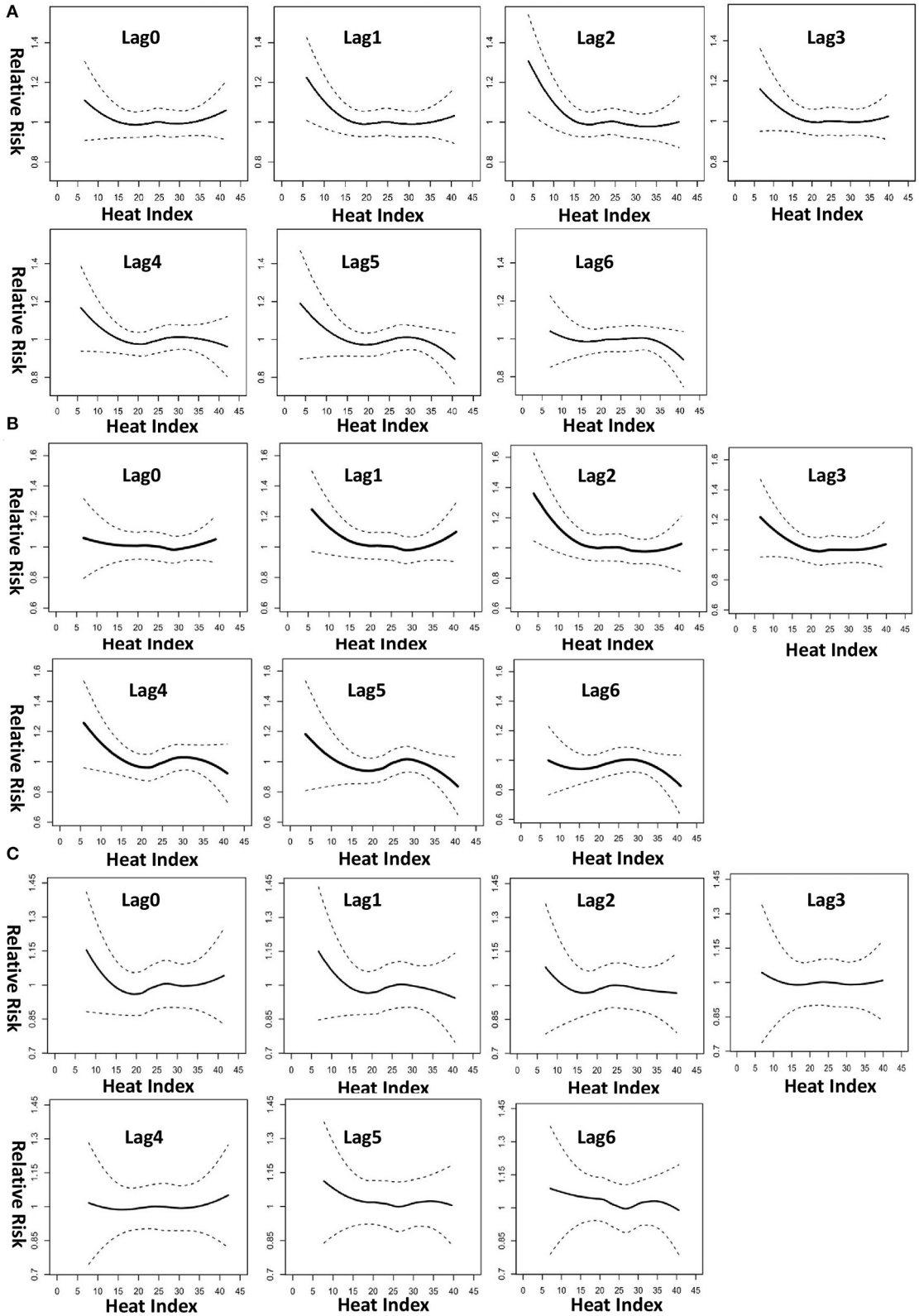

FIGURE 4 | Lag-specific relative risk of VT incidence at different heat indices, with reference at 24.5°C, for **(A)** all 172 patients, **(B)** 45 patients with ES, and **(C)** 127 non-ES patients. The plots were generated using locally weighted scatterplot regression from the output of conditional logistic regression model with cubic spline effect for heat index.

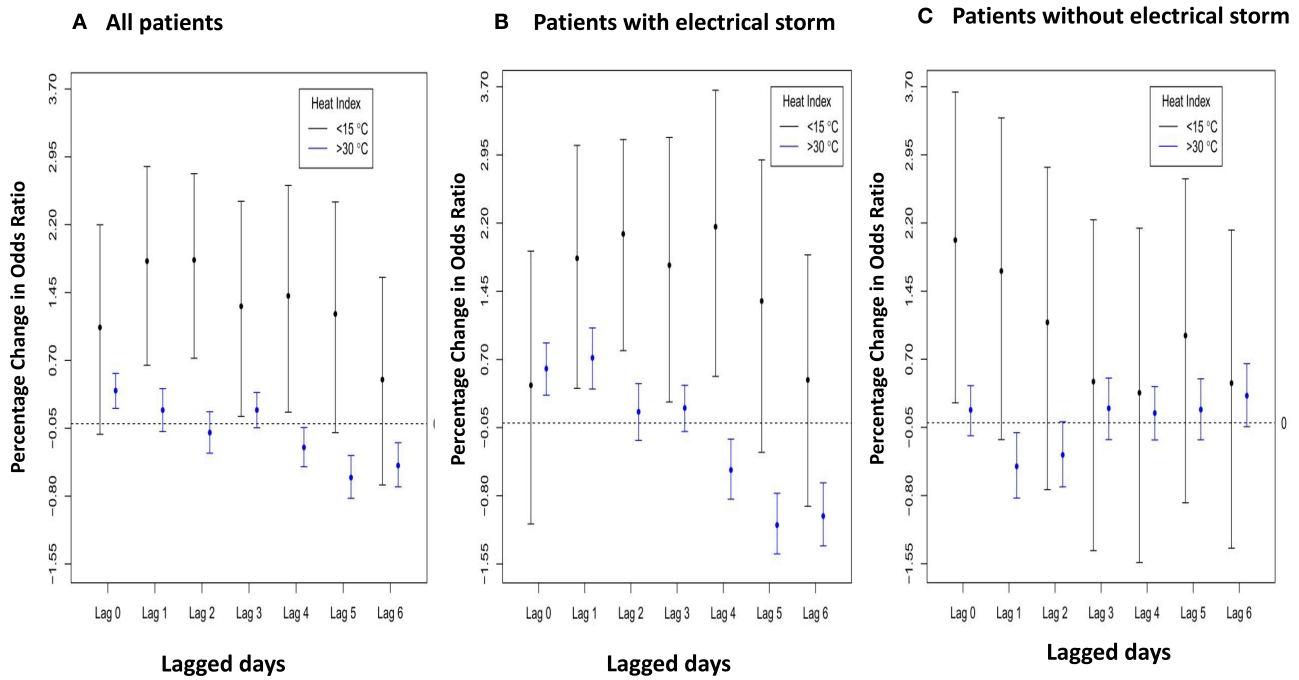

FIGURE 5 | Lag-specific percentage change in odds ratio per 1°C decrease (increase) when daily HI < 15°C (>30°C) for **(A)** all 172 patients, **(B)** 45 patients with ES, and **(C)** 127 non-ES patients.

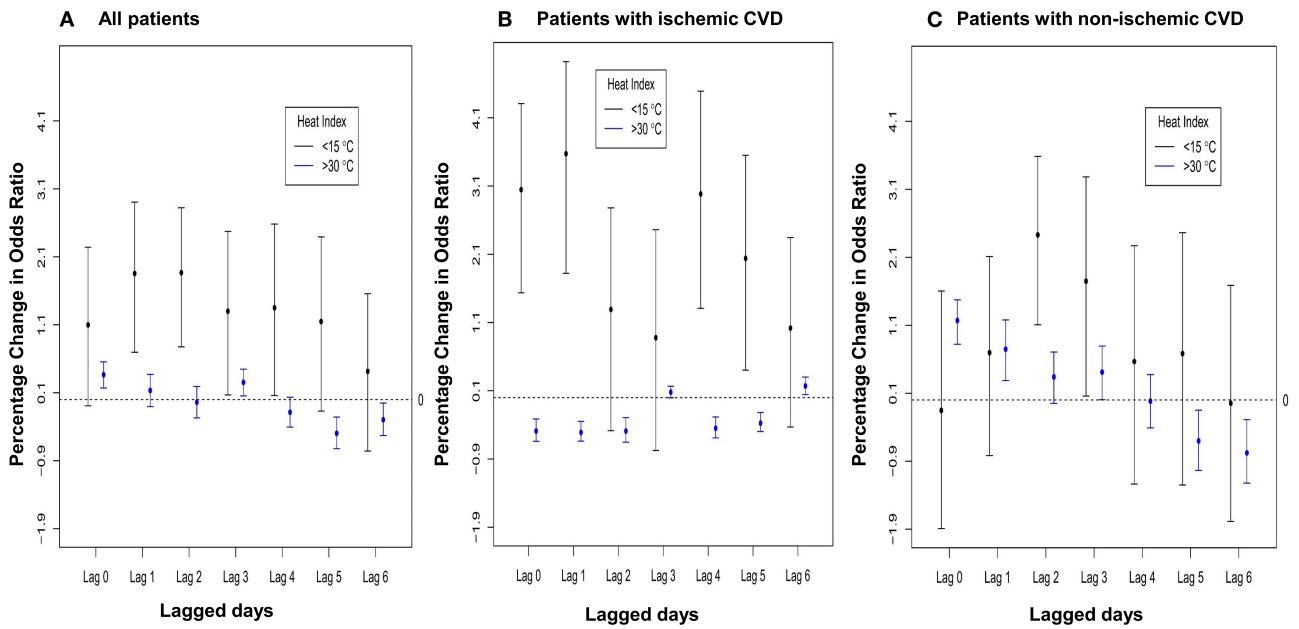

FIGURE 6 | Lag-specific percentage change in odds ratio per 1°C decrease (increase) when daily HI < 15°C (>30°C) for **(A)** all 172 patients, **(B)** patients with ischemic CVD and **(C)** patients with non-ischemic CVD.

VTAs, which may occur even in individuals without a known cardiac disease (21). Studies in Korea and Japan found that VTA attack peaks during summer in patients with RV dysplasia, Brugada syndrome, and early repolarization syndrome (8, 9). In our study, we found that a higher HI is associated with a greater incidence of sustained VTAs, even after excluding 10 patients

TABLE 3 | The acute and lagged effects of low and high HI on VTA incidents in patients with ES and those without ES.

	Association	All ICD	Patients with ES	Non-ES
		***N* = 172**	***N* = 45**	***N* = 127**
Cold effect	Acute	lag 0 (±)	lag 0 (–)	lag 0 (+)
(HI < 15C)	Delay	lag 1–4 (+)	lag 1–4 (+)	lag 1–4 (–)
Heat effect	Acute	lag 0 (+)	lag 0 (+)	lag 0 (–)
(HI > 30C)	Delay	lag 1 (–)	lag 1 (+)	lag 1–6 (–)

+ (–): significant (non-significant) association between VTAs and HI.

with arrhythmogenic RV dysplasia and 13 patients with Brugada syndrome. The different pathophysiology of cold and thermal stress may underlie the differential effects of HI on VTAs between patients with ischemic CVD and nonischemic CVD.

The association of cardiac arrhythmias with temperature is most likely influenced by the simultaneous effect of other atmospheric constituents. RH may also play a significant role in temperature-related arrhythmic effects, especially in the humid zones of places with subtropical and tropical climates. Low evaporation rate with high RH results in more heat retention in the body and heightens subjective hot sensation. Similarly, subjective cold sensation is heightened at a low temperature with high humidity. Fries et al. found a correlation of mean monthly felt temperature (including humidity) with frequency of VTAs (22), which is consistent with our results showing an association between HI and VTA incidence. Furthermore, using personal daily records, we have clarified the lag effects of low and high HI and the different associations in patients with ES and those without ES after adjusting for air pollutant concentrations. These lagged effects on VTAs are consistent with the effects of heat and cold on mortality (23). The lags for cold-related mortality were longer, and those for heat-related mortality shorter. In Taiwan, RH is high year-round, with an average of 76%. During the study period, the maximum temperature was 34°C, and the HI was augmented to 41°C because of high RH. By contrast, in countries like the UK, USA, Germany, and Switzerland, the RH is high in winter but is modest in summer (50–70%). This might account for the regional variations of study results related to the association between temperature and VTA.

ES is a state of electrical instability and is associated with high mortality. The cause of ES is a complex interaction between the autonomic nervous system, ischemia, and a predisposing electrophysiological substrate. However, data on ES predictors remain insufficient (24). ES incidence is reportedly not homogenous over time but seems to have a clustered pattern.

Significant adverse prognostic association of clustered VTAs is observable with even 2 VTA events within 3 months and increases with higher cluster density (25). An association between ES and an increase in monthly temperature variation had been reported (26). Our study is the first to show the association of HI with ES and the lagged effects of HI on VTA occurrence. Hence, in addition to cold weather, heat stress may play an important role in the incidence of ES. The combination effects of RH and temperature and the lagged effects of HI may partially explain the seasonal variation and clustered pattern of ES occurrence. However, the underlying mechanisms are unknown, and thus, further research is needed to clarify the interplay of heat stress and ES.

Recently, there has been a heightened awareness of the effects of extreme temperature due to global warming on health (24, 26), and such extreme temperature could also influence heat-related cardiac morbidity and mortality (11). However, relevant evidence in regions exposed to high HI, such as India and Southeast Asian countries where at least more than half of the world's population lives, remains limited. Our study showed a higher risk of sustained VTAs and ES with extremely high HI in patients with ICD in Taiwan, although the causality could not be confirmed because of the ecological study design. Nonetheless, precautions when dealing with extreme temperatures are recommended, and preparation for the reallocation of medical and social resources when facing climate changes would be vital in the near future.

The association between ambient air pollution and VTAs occurrence in patients with ICD remained inconclusive (27, 28). Our data showed no association between air pollutants, such as $PM_{2.5}$ and PM_{10}, and the incidence of sustained VTAs. This could be because the patients were advised to stay indoors during days with bad air quality, or they might have been at working places rather than at their residence when the incident occurred. Future studies are needed for the associations of VTAs with short-term air pollution exposure.

Several potential limitations should be noted in our study. First, we did not have the patients' individual meteorological exposure information. The study participants might have spent majority of their time indoors with air-conditioning during summer. Thus, nondifferential misclassification of exposure that likely attenuated the association toward the null for high HI was possible. The use of a heater in winter is not common in Taiwan; thus, the misclassification error for low HI is minimal in our study. Second, we did not have information on patients' socioeconomic status or occupation, which may have an effect on individual's VTA incidents. Nonetheless, the case-crossover analysis with patients serving as controls for themselves should have minimized the associated bias. Third, 87% of our study patients were secondary prevention ICD patients. Absence of uniform ICD programming in our patient population might affect the detection rate of VTAs. Most of ICD programming in our study was according to the characteristics of clinical VTAs and/or physician clinical experience. However, some slow VTs might be still und-detected in clinical scenario. Forth, patients who were lost-to-follow-up might lead to underestimate VTA episodes, which in turn could yield a bias on the study result as well. The case-crossover analysis with patients serving as controls for themselves could minimize this selection bias.

In conclusion, sustained VTAs of patients with ICD in Taiwan were strongly associated with low HI and modestly associated with high HI. Particularly, patients with ES were more vulnerable to heat stress than those non-ES patients, and the lagged effects of HI on VTAs could only be found in patients with ES. Avoiding exposure to low as well as high HI of those at risk of VTAs, especially those clustered VTAs, could improve the quality of life and may reduce mortality.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the study protocol was approved by the National Taiwan University Hospital Research Ethics Committee (study no. 201612133RINC). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

H-CH, Y-BL, and C-CC designed the study. P-CS, J-SL, and CC were responsible for data collection. J-SL and C-CC were responsible for data acquisition and statistical analysis. H-CH, Y-BL, and C-CC were responsible for article writing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.624343/full#supplementary-material

Supplementary Figure 1 | Lag-specific percentage change in odds ratio per 1°C decrease (increase) when daily HI <15°C (>30°C) for **(a)** all 172 patients, **(b)** 44 patients with ES, and **(c)** 128 non-ES patients.

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SYSTEMATIC REVIEW
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Advanced Life Support vs. Basic Life Support for Patients With Trauma in Prehospital Settings: A Systematic Review and Meta-Analysis

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Background: Advanced Life Support (ALS) is regarded to be associated with improved survival in pre-hospital trauma care when compared to Basic Life Support (BLS) irrespective of lack of evidence. The aim of this study is to ascertain ALS improves survival for trauma in prehospital settings when compared to BLS.

Methods: We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for published controlled trials (CTs), and observational studies that were published until Aug 2017. The population of interest were adults (>18 years old) trauma patients who were transported by ground transportation and required resuscitation in prehospital settings. We compared outcomes between the ALS and BLS groups. The primary outcome was in-hospital mortality and secondary outcomes were neurological outcome and time spent on scene.

Results: We identified 2,502 studies from various databases and 10 studies were included in the analysis (two CTs, and eight observational studies). The outcomes were not statistically significant between the ALS and BLS groups (pooled OR 1.14; 95% CI 0.95 to 1.36 for mortality, pooled OR 1.12; 95% CI 0.88 to 1.42 for good neurological outcomes, pooled mean difference −0.96; 95% CI−6.64 to 4.72 for on-scene time) in CTs. In observational studies, ALS prolonged on-scene time and increased mortality (pooled OR 1.56; 95% CI: 1.31 to 1.86 for mortality, and pooled mean difference, 1.26; 95% CI: 0.07 to 2.45 for on-scene time).

Conclusions: In prehospital settings, the present study showed no advantages of ALS on the outcomes in patients with trauma compared to BLS.

Keywords: first aid, emergency medical services, resuscitation, mortality, injury

INTRODUCTION

Advanced Life Support (ALS) is widely accepted as the standard of prehospital care in patients with cardiac arrest caused by internal diseases (1–3). ALS procedure includes invasive interventions, such as endotracheal intubation for airway management, and intravenous catheters for drug and fluid delivery. ALS is also used to resuscitate trauma patients in prehospital settings.

On the contrary, an observational study using two large registry data sets reported that prehospital ALS procedures in patients with trauma were not associated with increased survival rate (4). Furthermore, other studies reported that prehospital ALS increased the spending time on the scene and thus delayed definitive in-hospital care (5, 6). Rapid transportation to the hospital is required as in-hospital surgery is typically needed to improve the prognosis of trauma patients.

Some researchers argue that basic life support (BLS) is more beneficial for trauma because of rapid transportation (5). Prehospital BLS consists of non-invasive interventions that are easy to perform, require little added on-scene time, and can often be performed *en route* to a medical facility by minimally trained emergency medical staff. Thus, the benefits of prehospital ALS on trauma have not been clearly established yet (7–9).

The aim of the present study is to clarify if ALS improves survival in patients with trauma in prehospital settings when compared to BLS by conducting a systematic review and meta-analysis.

METHODS AND ANALYSIS

Ethics and Approval

This systematic review and meta-analysis protocol has been registered in PROSPERO, an International Prospective Register of Systematic Reviews at the National Institute for Health Research and Center for Reviews and Dissemination (CRD) at the University of York (http://www.crd.york.ac.uk/PROSPERO/; registration no. CRD42017054389) (10). The protocol also has already been published (11).

The systematic review and meta-analysis was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12, 13) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and does not require ethical approval (14).

Search Strategies

Database searches were conducted in MEDLINE (*via* PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) to retrieve relevant articles for the literature review. We searched for full-text controlled trials (CTs) [included controlled before-and-after studies (CBAs), randomized controlled trials (RCTs)], and observational studies in humans that were published until Aug 2017. We used a combination of key terms and established a full search strategy (**Supplementary Material 1**).

Abbreviations: ALS, advanced life support; BLS, basic life support; CRD, center for reviews and dissemination; CTs, controlled trials; CBAs, controlled before-and-after studies; RCTs, randomized controlled trials; OS, observational studies; OR, Odds ratios; CI, confidence intervals.

Study Selection and Inclusion Criteria

CTs, CBAs, RCTs, and observational studies were included. We defined CTs, CBAs, and RCTs, as the CTs design group and prospective or retrospective observational study as the observational study (OS) design group.

Our study population of interest was adults (>18 years old) trauma patients who were transported by ground and required resuscitation in prehospital settings. We did not restrict our analysis by country and included all severities and types of trauma. Conference abstracts, studies in animals, and those that only include trauma patients transported by helicopter were excluded. We only included studies which were written in English or Japanese.

The interventions of interest are ALS and BLS. The ALS group was defined as having undergone one or more of the following intervention components: (1) tracheal intubation, (2) needle tracheostomy, and administration of (3) intravenous (IV) fluids, (4) epinephrine, or (5) other IV drugs (e.g., amiodarone, lidocaine, or magnesium). The BLS group was defined as not having undergone any of the above ALS procedures, only BLS was instituted (chest compression, mouth-to-mouth breathing, bag valve mask ventilation, and automated external defibrillator).

We compared the outcomes between the ALS and BLS groups. Primary outcome was in-hospital mortality and secondary outcomes were neurological outcome and time spent on scene (minutes).

Assessment of Risk of Bias

To assess the quality of the included studies, we adapted the Cochrane risk of bias tool for CTs design (15). Each study was assessed for: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of related outcomes assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other bias. Studies were categorized as having a low, unclear, or high risk of bias in each domain. The risk of bias for each element was considered "high" when bias was present and likely to affect outcomes and "low" when bias was not present or present but unlikely to affect outcomes (16). For OS design, we applied the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) to assess the risk of bias of observational studies, which is compatible with the Cochrane risk-of-bias tool (17). Two independent reviewers (YK and HS) chosen by the authors performed the risk of bias assessment. Disagreements were resolved through discussion.

Data Extraction and Management

The following data were extracted: author(s), title, journal name, year of publication, website (URL), and abstract. After removal of duplicates, two independent reviewers (MK and SK) screened the abstracts and titles of the studies and subsequently reviewed the full-text articles for inclusion using an electronic screening form (Covidence web platform: http://

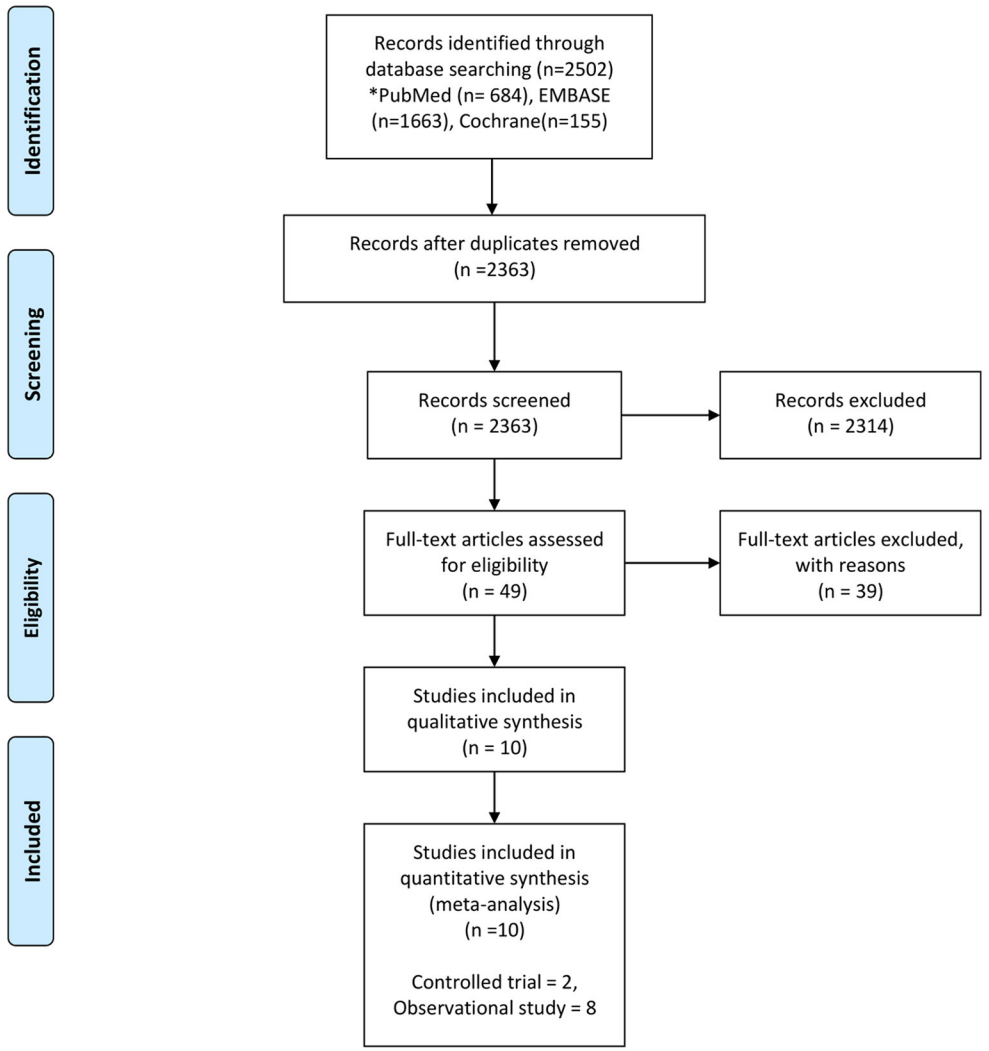

FIGURE 1 | Flow chart of the study selection process From Moher et al. (13).

www.COVIDENCE.org). Disagreements were reconsidered and discussed until a consensus was reached. The full-text of the articles included in the final selection was independently reviewed by other two reviewers (TF and UR). Disagreements were solved by a third reviewer (YK). The flow diagram of our study, has been adapted from the PRISMA statement (2009) (13), (**Figure 1**).

Rating the Quality of Evidence Using the GRADE Approach

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool to rate the quality of the evidence on the effect of ALS and BLS on important outcomes in trauma patients (18–21). The quality of evidence was assessed for each outcome and categorized as high, moderate, low, or very low using the GRADE pro Guideline Development Tool.

Statistical Analysis

We performed a meta-analysis because one or more data were available according to the "Cochrane Handbook for Systematic Reviews of Interventions" and the PRISMA guidelines. Results were summarized using a random effects model to facilitate pooling of estimates of the treatment effects. Odds ratios (OR) and 95% confidence intervals (CI) were used for dichotomous outcomes and mean differences and 95% CIs for continuous outcomes. Heterogeneity between trials for each outcome was evaluated using the I^2 statistic for quantifying inconsistency (22). We considered heterogeneity as being significant if the reason for heterogeneity could not be explained, and if I^2 was 50% or greater.

Regarding assessment of reporting bias, we investigated the potential for publication bias using a funnel plot. Estimates were pooled using a random effects model. The meta-analysis was

TABLE 1 | Baseline characteristics of eligible studies.

No.	References	Country	Design	Number of study participants	Type of trauma	Body region	ISS (mean or median)	Performed by		Procedures	
								BLS	ALS	BLS	ALS
1	Potter et al. (23)	Australia	Controlled Trial	1,061	Blunt and Penetrating	Head, Torso and Extremity	37	Physician and Paramedics	Physician and Paramedics	All BLS procedures	All ALS procedures
2	Murphy et al. (24)	US	Retrospective Cohort	2,394	Blunt and Penetrating	Head, Torso and Extremity with multiple injuries	17	Not described	Not described	All BLS procedures	All ALS procedures
3	Liberman et al. (25)	Canada	Prospective Cohort	9405	Blunt and Penetrating	Head, Torso and Extremity	26	Paramedics	Physician and Paramedics	All BLS procedures	All ALS procedures
4	Osterwalder (26)	Switzerland	Prospective Cohort	196	Blunt	Head, Torso and Extremity	24	Physician and Paramedics	Physician and Paramedics	All BLS procedures	All ALS procedures
5	Steil (27)	Canada	Before-after controlled trial	2,867	Blunt, Penetrating and Burn	Head, Torso and Extremity	24 for BLS, 22 for ALS	Paramedics	Paramedics	All BLS procedures	All ALS procedures
6	Seamon et al. (6)	US	Prospective Cohort	236	Penetrating	Head, Torso and Extremity	20.8	Paramedics	Paramedics	All BLS procedures	All ALS procedures
7	Meizono (28)	US	Retrospective Cohort	3,733 (122, after adjustment)	Blunt, Penetrating and Burn	Not described	5	Not described	Not described	No Procedures of ALS group	*ALS procedures
8	Sanghavi et al. (29)	US	Retrospective Cohort	79,687	Not described	Not described	New ISS was used.	Not described	Not described	All BLS procedures	All ALS procedures
9	Rappold et al. (5)	US	Retrospective Cohort	1,490	Penetrating	Not described	13 for ALS, 10 for BLS	Paramedics	Paramedics	All BLS procedures	All ALS procedures
10	Fukuda et al. (30)	Japan	Retrospective Cohort	4,382	Blunt and Penetrating	Head, Torso and Extremity	Unknown	Physician and Paramedics	Physician and Paramedics	All BLS procedures	All ALS procedures

ISS, injury severity score; BLS, basic life support; ALS, advanced life support; US, United States.
**Needle decompression, tourniquet use, cricothyroidotomy, or ACLS procedures other than intravenous fluid.*

performed based on all published data and data made available to us (16).

All analyses were performed by using the Review Manager software (RevMan 5.3, Copenhagen, Denmark: The Nordic Cochrane Centre, the Cochrane Collaboration 2014).

RESULTS

We identified 2,502 studies from the electronic databases. We eliminated 139 duplicates and excluded 2,314 studies because their design did not fit. Finally, we retained 16 studies for review of the full lengths reports and included 10 studies (5, 6, 23–30) in the final analysis (**Figure 1**).

Study Characteristics

The 10 studies (5, 6, 23–30) included 105,451 patients (two studies for the CTs design group, and eight studies for the OS design group) (**Table 1**). In the CTs design group, 1,966 were assigned to the ALS group and 1,962 to the BLS group. In the OS design group, 54,982 were assigned to the ALS group and 42,080 to the BLS group. Five studies (5, 6, 24, 28, 29) took place in United States, two in Canada (27, 31), and one each in Australia (23), Switzerland (26), and Japan (30). Four studies were conducted prospectively (one CBAs, one CTs, and two observational studies), and the others were retrospective. The risk of bias was evaluated for each study in the CTs design group and is shown in the risk of bias summary (**Figure 2**). Because only one CBAs and one CTs were included as the CTs group, random sequence generation could not be performed and was rated high risk selection bias in these two studies. The risk of bias assessment of the observational studies was done using RoBANS (**Figure 2B**).

Outcomes

The CTs design group with 3,928 patients (two studies) reported in-hospital mortality as a primary outcome with 1,966 patients in the ALS group and 1,962 patients in the BLS group (**Figure 3A**). Of these, 319 patients (16.2%) died in the ALS group and 273 patients (13.9%) died in the BLS group. The pooled OR of mortality was not statistically significant (OR 1.14; 95% CI 0.95 to 1.36) (**Figure 3A**). When comparing neurological outcomes and time spent on scene, there were no significant differences between the ALS and BLS groups. The pooled OR was 1.12 (95% CI: 0.88 to 1.42) for neurological outcomes, and −0.96 (95% CI: −6.64 to 4.72) for time spent on scene (**Figures 4**, **5A**).

The OS design group which had 97,062 patients (eight studies) reported in-hospital mortality as a primary outcome and of these, 54,982 patients belonged to the ALS group and 42,080 patients belonged to the BLS group (**Figure 3B**). Of these, 11,494 patients (20.9%) died in the ALS group and 6786 patients (16.1%) died in the BLS group. The pooled OR of mortality was statistically

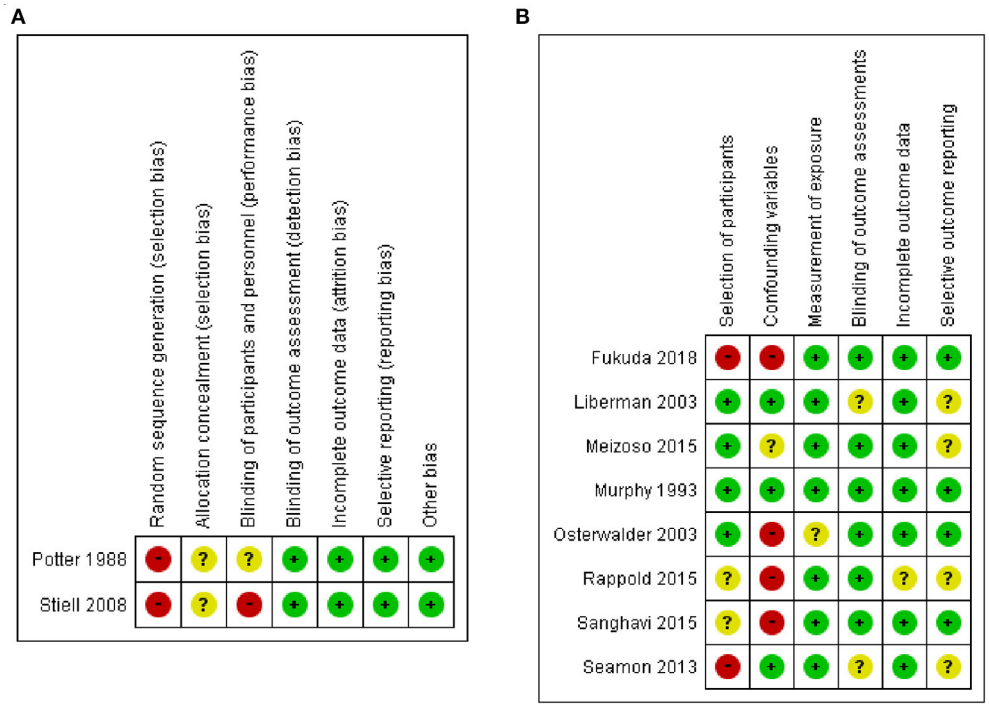

FIGURE 2 | Risk of bias summary in included studies: **(A)** based on the criteria recommended by the Cochrane Collaboration for RCTs, and **(B)** based on the Risk of Bias Assessment Tool for Nonrandomized Studies for observational studies.

significant in favor of BLS (pooled OR 1.56; 95% CI: 1.31 to 1.86) (**Figure 3B**). None of the studies included information regarding neurological outcomes. Time spent on scene was significantly prolonged in the ALS group (pooled mean difference, 1.26; 95% CI: 0.07 to 2.45) (**Figure 5B**).

Heterogeneity

No statistically significant heterogeneity in short-term mortality was observed between the ALS and the BLS groups in the CTs group ($I^2 = 0\%$; $\chi^2 = 1.00$; $p = 0.32$) whereas the OS design groups showed statistical heterogeneity ($I^2 = 74.0\%$; $\chi^2 = 26.65$; $p \leq 0.001$). No statistically significant heterogeneity in neurological outcomes was observed between the ALS and the BLS groups in the CTs design group ($I^2 = 0\%$; $\chi^2 = 0.00$; $p = 0.97$). A statistical heterogeneity was observed in time spent on scene (minutes) in the CTs design group ($I^2 = 95.0\%$; $\chi^2 = 18.95$; $p \leq 0.001$) and the OS group ($I^2 = 55.0\%$; $\chi^2 = 4.49$; $p = 0.11$).

Publication Biases, and Quality of Evidence

We tested for the presence of publication biases for the primary outcome. A visual inspection of the funnel plots suggested no existence of publication biases in the in-hospital mortality CTs design group whereas the OS design group showed publication biases (**Supplementary Material 2**).

The quality of evidence was rated as moderate due to the high risk of biases for the effect of ALS on the in-hospital mortality compared with BLS in the CTs design groups. The grade for in-hospital mortality in the OS design group was rated very low, due to an inconsistency, which the Cochrane chi-square test revealed to be a significant heterogeneity, and due to a publication bias. The quality of evidence was rated as moderate for the effect of ALS on neurological outcome, compared with BLS. The quality of evidence was rated as moderate due to high risk of biases for the effect of ALS on time spent on scene compared with BLS in the CTs design groups and the grade in the OS design group was rated low (**Table 2**).

DISCUSSION

In this systematic review, we have summarized the available evidence from CTs that compared to the BLS group, the ALS group showed no significant improvement on in-hospital mortality, neurological outcomes, and time spent on scene in patients with trauma in the CTs design group. Moreover, the OS design groups showed increased mortality and time spent on scene in the ALS group.

Our results of CTs are consistent with the results of a previous meta-analysis which was reported in 2011 and ALS care was not associated with increased survival in trauma patients (32). The authors retrieved data from 9 trials including 16,857 patients that met their inclusion criteria (23, 25–27, 33–37) and included helicopter transportation. In the present study, we excluded helicopter transportation because resource was very limited, and it could affect results; tracheal intubation or chest compressions are difficult to perform in a flying helicopter. In the studies that met our criteria, the patients were mostly transported by

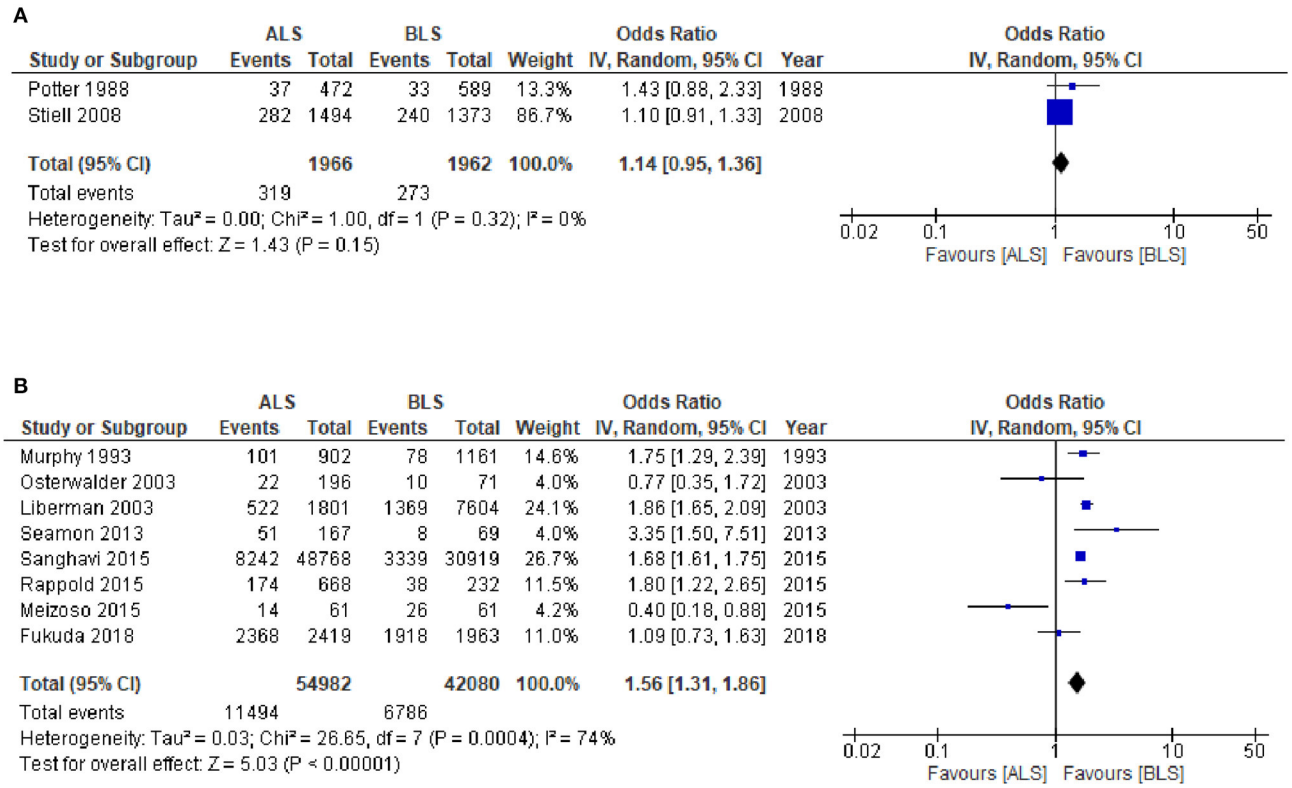

FIGURE 3 | Forest plot of the comparison: ALS vs. BLS for in-hospital mortality **(A)** Controlled trials; **(B)** Observational studies. ALS, advanced life support, BLS, basic life support, IV, inverse variance weighted method, CI, confidence interval.

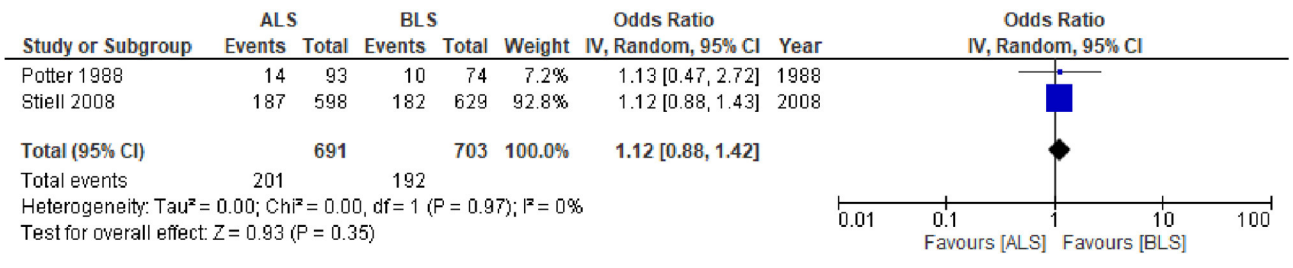

FIGURE 4 | Forest plot of the comparison: ALS vs. BLS for neurological outcomes. ALS, advanced life support; BLS, basic life support; IV, inverse variance weighted method; CI, confidence interval.

ambulance and there was no difference in outcomes between the ALS and BLS groups.

We performed meta-analysis using observational studies to confirm the robustness of results. Regarding the OS design group, ALS prolonged time spent on scene and increased in-hospital mortality compared to BLS, although certainty of evidence was very low. A previous study showed that ALS was associated with an increased mortality rate compared to BLS (31). In this previous study, the time spent on scene was higher for ALS than for BLS providers (18.5 min vs. 13.5 min, $p = 0.005$) (31); this can affect mortality. Another observational study reported that an increase in total prehospital time was associated with increasing in-hospital mortality in trauma patients (38). These results are correlated with our OS design group results.

Our findings showed no ALS advantages in both CTs and OS groups. Previous studies regarding ALS procedures reported that endotracheal intubation in prehospital settings has not been shown to reduce mortality and morbidity in severe trauma patients. Moreover, performing ALS procedures in a difficult task under trying conditions and could be harmful (27, 39–41). Endotracheal intubation by unskilled practitioners could result in adverse events and result in low quality of chest compressions with significant interruptions (39). The value of prehospital IV fluid resuscitation has also been questioned (42–44). IV infusions of crystalloid may promote hemorrhage by diluting coagulation factors and by lowering blood viscosity (42). Theoretically, these previous reports of ALS procedures in prehospital settings may support our

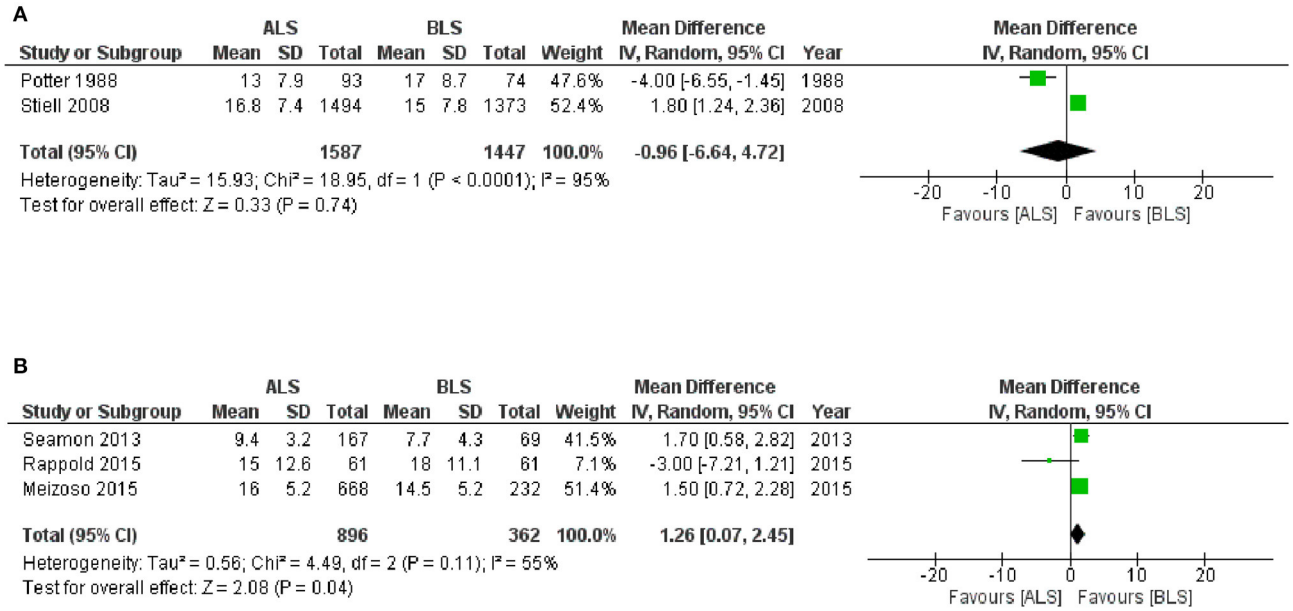

FIGURE 5 | Forest plot of the comparison: ALS vs. BLS for on-scene spending time **(A)** controlled trials; **(B)** observational studies. The unit of number in mean is minutes. ALS, advanced life support; BLS, basic life support, IV, Inverse variance weighted method; CI, confidence interval.

TABLE 2 | Summary of finding table.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with BLS	Risk with ALS			
Mortality (CTs)	139 per 1,000	156 per 1,000 (133 to 180)	OR 1.14 (0.95 to 1.36)	3,928 (2 studies)	⊕ ⊕ ⊕ ◯ Moderate
Mortality (OS)	161 per 1,000	231 per 1,000 (201 to 263)	OR 1.56 (1.31 to 1.86)	97,062 (8 studies)	⊕ ◯ ◯ ◯ Very low
Disability of CNS (CTs)	273 per 1,000	296 per 1,000 (248 to 348)	OR 1.12 (0.88 to 1.42)	1,394 (2 studies)	⊕ ⊕ ◯ ◯ LOW
On-scene time (CTs)	The mean total time on scene was 0	MD 0.96 lower (6.64 lower to 4.72 higher)	-	3,034 (2 studies)	⊕ ⊕ ⊕ ◯ Moderate
On-scene time (OS)	The mean on-scene time was 0	MD 1.26 higher (0.07 higher to 2.45 higher)	-	1,258 (3 studies)	⊕ ⊕ ◯ ◯ LOW

**The risk in the ALS group (and its 95% confidence interval) is based on the assumed risk in the BLS group and the relative effect of the ALS (and its 95% CI).*
CI, confidence interval; BLS, basic life support; ALS, advanced life support; GRADE, The Grading of Recommendations Assessment, Development and Evaluation, RCT, randomized control trial; OS, observational study; OR, odds ratio; CNS, central nerve system; MD, mean difference.

findings. However, caution is required to interpret our results. Recently, ALS equipment has improved; tracheal intubation using a video laryngoscope are being introduced. In the future, ALS may improve clinical outcomes due to advances in resuscitation equipment.

There are number of strengths in the present study. A major strength of this analysis is that the present study was evaluated by the quality of the evidence by the GRADE approach, which is widely accepted, and which offers an objective system for rating quality of evidence in systematic reviews and clinical practice guidelines. The other strength of this study is that could include both CTs and OS design. Our findings therefore become more robust.

The present study has several limitations. First, the meta-analyses were based on data from only two CTs and eight observational studies. Two CTs are not enough and observational studies have a limited ability to control for confounding variables, and the retrospective designs must be interpreted with particular attention. More severe patients might include in the ALS group than the BLS group in OS design. Thus, we judged the quality of the evidence provided by the observational studies as "very low." Second, procedures of ALS or eligible populations were varied

in the individual studies. Third, we could not perform subgroup analysis such as divide trauma into blunt and penetrating because of insufficient data from the included studies.

CONCLUSION

The present study showed no advantage of prehospital ALS intervention on in-hospital mortality, neurological outcomes, and spending time on scene in prehospital trauma patients. Immediate definitive treatment may be important for trauma and should avoid prolonged time spent on scene. Further studies are warranted to validate our results.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. The data and material used for this meta-analysis are contained in our list of references.

AUTHOR CONTRIBUTIONS

YK conceived the idea for this systematic review and drafted the manuscript. YK, TF, RU, MK, SK, and HS developed the methodology. TF, RU, MK, SK, HS, TH, and KH revised the manuscript. All authors critically reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.660367/full#supplementary-material

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ORIGINAL RESEARCH
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Microcirculatory Response to Changes in Venoarterial Extracorporeal Membrane Oxygenation Pump Flow: A Prospective Observational Study

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Background: Venoarterial extracorporeal membrane oxygenation (VA-ECMO) pump flow is crucial for maintaining organ perfusion in patients with cardiogenic shock, but VA-ECMO pump flow optimization remains as a clinical challenge. This study aimed to investigate the response of sublingual microcirculation to changes in VA-ECMO pump flow.

Methods: Sublingual microcirculation was measured before and after changing VA-ECMO pump flow according to the treatment plan of ECMO team within 24 h and at 24-48 h after VA-ECMO placement. In clinical events of increasing VA-ECMO pump flow, those events with increased perfused vessel density (PVD) were grouped into group A, and the others were grouped into group B. In clinical events of decreasing VA-ECMO pump flow, those events with increased PVD were grouped into group C, and the others were grouped into group D.

Results: Increased PVD was observed in 60% (95% CI, 38.5–81.5%) of the events with increasing VA-ECMO pump flow. The probability of increasing PVD after increasing VA-ECMO pump flow were higher in the events with a PVD < 15 mm/mm^2 at baseline than those with a PVD ≥ 15 mm/mm^2 [100% (95% CI, 54.1–100%) vs. 42.9% (95% CI, 17.7–71.1%), $P = 0.042$]. Other microcirculatory and hemodynamic parameters at baseline did not differ significantly between group A and B or between group C and D.

Conclusion: This study revealed contradictory and non-contradictory responses of sublingual microcirculation to changes in VA-ECMO pump flow. Tandem measurements of microcirculation before and after changing VA-ECMO pump flow may help to ensure a good microcirculation.

Keywords: microcirculation, extracorporeal membrane oxygenation, hemodynamics, cardiogenic shock, critical care

INTRODUCTION

Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO) has become a promising option for bridge support in patients with acute cardiopulmonary failure (1–3). An inadequate low VA-ECMO pump flow leads to abnormal tissue perfusion and poor prognosis, and flow optimization is essential to maintaining adequate tissue and brain perfusion (4). In addition, high pump flow–related complications such as kidney injury, cerebral stroke, and hemorrhage are associated with high morbidity and mortality (5, 6).

Poor microcirculatory flow or function may indicate tissue hypoperfusion or hypoxia (7, 8). Our previous study and that conducted by Kara et al. revealed that a microcirculatory unresponsiveness to VA-ECMO predicted adverse outcomes (9, 10), and we found that mortality was higher in VA-ECMO patients with a perfused vessel density (PVD) less than 15 mm/mm^2 (9). Akin et al. identified an association between microcirculation and successful weaning from VA-ECMO in late weaning process (11), but no study has reported the effects of changes in pump flow on microcirculation at early stage of VA-ECMO support. In current clinical practice, VA-ECMO pump flow is adjusted by achieving preset goals of macro-hemodynamic parameters like mean arterial pressure (MAP) and pulse pressure (12, 13). However, dissociation between sublingual microcirculation and macrocirculation has been observed in shock states (7, 14), and microcirculatory dysfunction can co-exist with normal macrocirculatory parameters (10). Investigating microcirculation after increasing or weaning VA-ECMO pump flow is crucial to ensure adequate tissue perfusion. This study aimed to investigate the responses of sublingual microcirculation to changes in VA-ECMO pump flow.

MATERIALS AND METHODS

Study Design and Patient Enrollment

This prospective observational study was approved by the Research Ethics Committee of National Taiwan University Hospital (approval number: 201703011RINA, approval date: April 28, 2017) and registered on the ClinicalTrials.gov protocol registration system (ID: NCT03210818). It was conducted at a university medical center between November 2017 and December 2018, consistent with STROBE guidelines (15). Participants were selected from patients receiving ECMO support on the basis of eligibility screening conducted within 12 h following ECMO placement. Patients who received VA-ECMO support and were above 20 years old were included. Patients were excluded if they declined to participate, had received re-implantation of ECMO, died within 12 h, or had circumstance that prevented sublingual microcirculation from being measured within 24 h after initiating VA-ECMO, such as those in which placement occurred in the evening or the research nurse was on leave. Written informed consent was obtained from patients' legally authorized representatives before study enrollment.

VA-ECMO Components and Treatment Goals

For all enrolled patients, placement and the principal components of the VA-ECMO were the same as described in our previous study (9). To avoid possible malperfusion of the distal limb, an antegrade distal perfusion catheter was used when the mean pressure of the superficial femoral artery was below 50 mm Hg (16). All patients received standard VA-ECMO management and routine intensive care unit (ICU) care. Heparin was continuously administered to maintain an activated clotting time of 160–180 s if no active bleeding or other complications were observed. The ECMO team adjusted the VA-ECMO pump flow according to their treatment goal to maintain a MAP >60 mm Hg, central venous oxygen saturation ($ScvO_2$) >70%, central venous pressure <15 mm Hg, and lactate level of <3 mmol/L; and to avoid a urine output of <0.5 ml/kg/h, pulse pressure >10 mm Hg, and ECMO-induced hemolysis; or to wean the patients off VA-ECMO support.

Record of Clinical Information

The following data were recorded: age, gender, height, body weight, sequential organ failure assessment (SOFA) score (17), indications for VA-ECMO, VA-ECMO pump flow, heart rate, MAP, $ScvO_2$, lactate level, activated clotting time, hemoglobin level, fluid balance, and inotropic score. The inotropic score was calculated as 100 × epinephrine dose (mcg/kg/min) + 100 × norepinephrine dose (mcg/kg/min) + dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) (18). The length of ICU and hospital stay, as well as survival status at 28 days were also recorded.

Analysis of Microcirculation Videos and Grouping of Microcirculatory Responses

Sublingual microcirculation videos were recorded using an incident dark-field video microscope (CytoCam, Braedius Medical, Huizen, Netherlands) (19). Analysis of sublingual microcirculation videos was performed according to the international consensus guidelines for performing sublingual microcirculation by a Task Force of the European Society for Intensive Care Medicine (20). At each time point, five video sequences (length: 6 s each) were recorded at different sublingual sites and were digitally stored with code numbers to ensure the anonymity of patient information. Subsequent offline analyses were performed by a single observer blinded to patient information. Two or three sequences with appropriate image quality were selected for analysis using the semi-automated analysis software package Automated Vascular Analysis 3.0 (21). In accordance with the afore mentioned consensus guidelines (20), the following parameters were investigated: (a) total vessel density (TVD; vessels <20 μm), (b) PVD, and (c) proportion of perfused vessels (PPV). The software was used to automatically calculate TVD. The calculation of PVD was semiautomated using the procedure described in our previous study (9, 22).

When the ECMO team decided to increase or decrease the VA-ECMO pump flow according to their treatment goal within

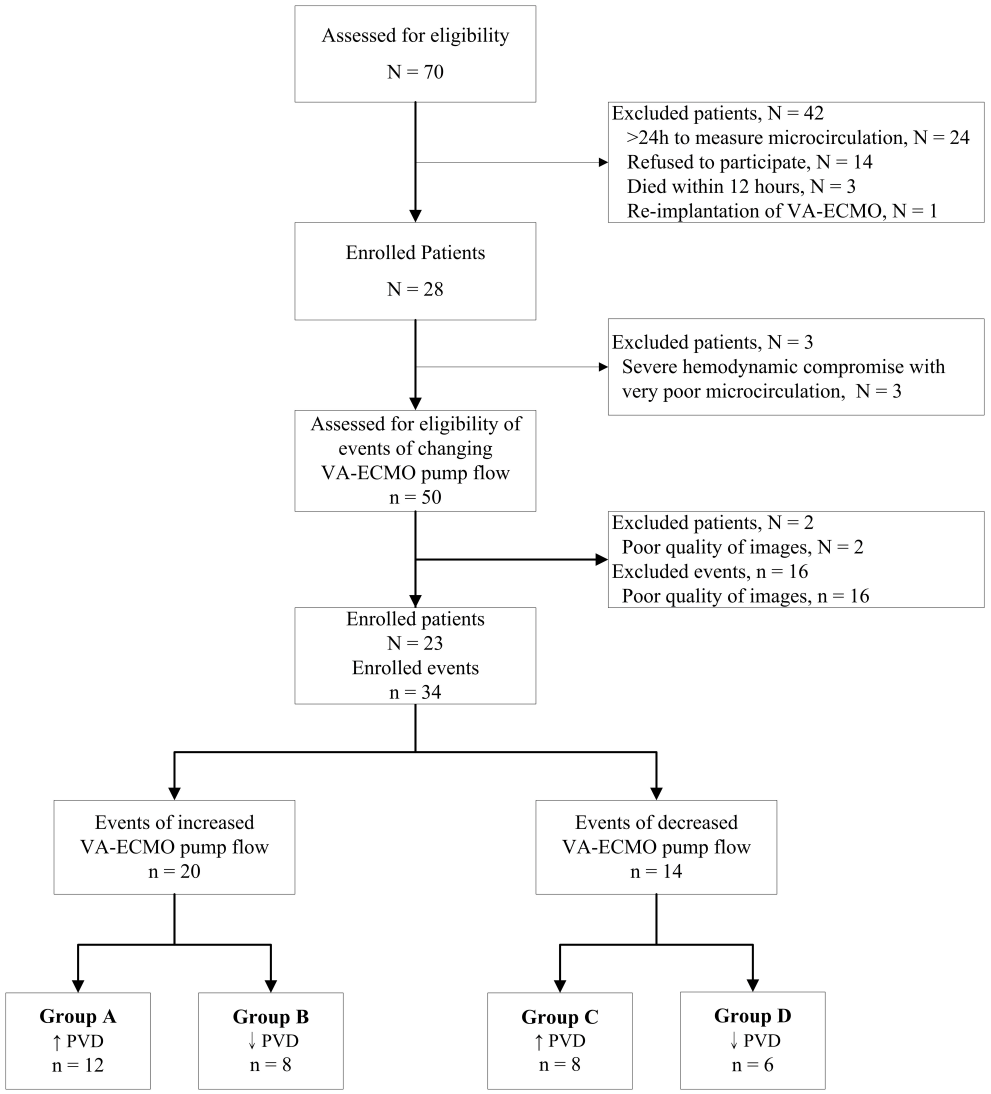


FIGURE 1 | Consort flow chart of analyzed events in patients receiving venoarterial extracorporeal membrane oxygenation. *N*, number of patients; *n*, number of events of changing VA-ECMO pump flow; PVD, perfused vessel density; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

24 h and at 24 to 48 h after VA-ECMO placement, the sublingual microcirculation videos were recorded before changing the VA-ECMO pump flow and 5 min after the changes. In clinical events of increasing VA-ECMO pump flow, those events with increased PVD were grouped into group A, and the others were grouped into group B. In clinical events of decreasing VA-ECMO pump flow, those events with increased PVD were grouped into group C, and the others were grouped into group D.

Statistical Analysis

All statistical analyses were performed using SPSS version 20 (IBM, Armonk, NY, USA). Categorical variables were described as number (percentage) and were compared using chi-square tests or Fisher's exact tests as appropriate. Continuous variables were expressed as medians (interquartile range) and compared using independent-samples Mann–Whitney test and the median test. The 95% confidence interval (CI) of the proportion was calculated with binomial exact calculations (23, 24). Association between two continuous variables was compared with Pearson's r correlation analysis. All the *P*-values were not adjusted in this observational pilot study. A *P*-value of < 0.05 indicated a significant difference.

RESULTS

Patient Distribution and Characteristics

A total of 70 patients receiving VA-ECMO were considered for inclusion in this trial. A total of 47 patients were excluded, and a total of 34 events with good quality of microcirculation images were analyzed (**Figure 1**). The patient characteristics

TABLE 1 | Patients characteristics.

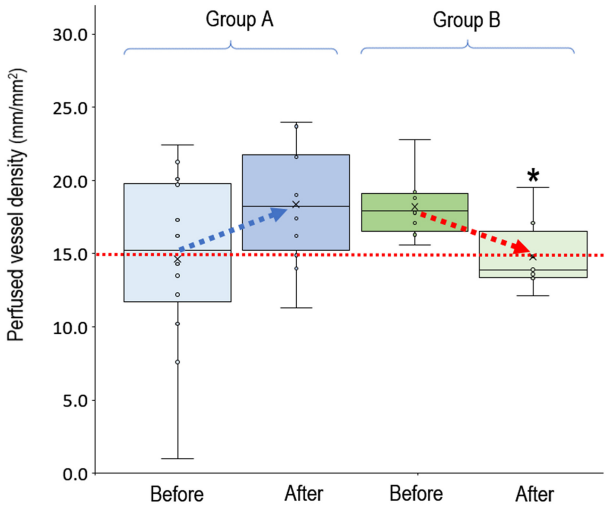
Group	Total	28-day survivors	28-day non-survivors	*P*-values
n	23	12	11	
Female/male	5/18	2/10	3/8	0.640
Age	64 (55–73)	64.5 (53–72.5)	64 (55–73)	1.000
Height	168 (160–175)	168 (160–175)	167 (160–175)	1.000
Weight	66.9 (57.9–74.7)	68 (58.3–84.7)	66.9 (56.2–74.7)	1.000
VA-ECMO flow (L/min)	2.6 (2.1–3.2)	2.3 (1.9–2.9)	2.9 (2.3–3.3)	0.220
Heart rate (bpm)	97 (79–110)	96 (78–108)	100 (90–121)	0.684
MAP (mm Hg)	76 (71–84)	75 (65–78)	79 (75–87)	0.220
Pulse pressure (mm Hg)	36 (21–55)	36 (23–62)	36 (19–45)	1.000
Hemoglobin level (g/dL)	11 (10–12)	12 (11–12)	11 (9–13)	0.214
Platelet (K/μL)	118 (68–201)	131 (89–237)	100 (32–131)	0.214
Lactate (mmol/L)	3.0 (2.0–8.0)	2.5 (2.0–8.5)	4 (3.0–8.0)	0.684
Inotropic score	14 (7–32)	9 (7–20)	20 (4–35)	0.220
SOFA score	13 (10–15)	11 (8–13)	14 (13–16)	0.027
Heart failure, n(%)	13 (57%)	7 (58%)	6 (55%)	1.000
E-CPR, n(%)	10 (43%)	5 (42%)	5 (45%)	1.000

Data are presented as number or median (interquartile range). P-values were calculated using Fisher's exact test and independent-samples median tests. E-CPR, extracorporeal cardiopulmonary resuscitation; MAP, mean arterial pressure; SOFA, sequential organ failure assessment; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

and indications of VA-ECMO of the 23 enrolled patients are presented in **Table 1**. The 28-day survival rate of the enrolled patients was 52%.

Microcirculatory Response to Increasing VA-ECMO Pump Flow

In the 20 clinical events of increasing VA-ECMO pump flow, we observed only 12 (60%, 95% CI, 38.5–81.5%) events with increased PVD (**Figure 2**). In *post-hoc* analysis, these events were divided into two groups according to their PVD before changing the VA-ECMO pump flow: PVD < 15 mm/mm^2 and PVD ≥ 15 mm/mm^2, respectively. The probability of increasing PVD after increasing VA-ECMO pump flow were higher in the events with PVD < 15 mm/mm^2 at baseline than those with PVD ≥ 15 mm/mm^2 at baseline [100% (95% CI, 54.1–100%) vs. 42.9% (95% CI, 17.7–71.1%), $P = 0.042$. The values of PVD before increasing VA-ECMO pump flow were negatively correlated to the changes of PVD after increasing VA-ECMO pump flow (Pearson correlation coefficient $= -0.706$, $P = 0.001$). TVD and PPV before and after increasing VA-ECMO pump flow are presented in **Figure 3**. The values of TVD before increasing VA-ECMO pump flow were negatively correlated to the changes of TVD after increasing VA-ECMO pump flow (Pearson correlation coefficient $= -0.641$, $P = 0.002$). The values of PPV before increasing VA-ECMO pump flow were negatively correlated to the changes of PPV after increasing VA-ECMO pump flow (Pearson correlation coefficient $= -0.872$, $P < 0.001$). **Figure 4** summarizes the VA-ECMO pump flow, MAP, lactate level, and inotropic score before increasing the VA-ECOM pump flow between group A and B. All the parameters did not differ significantly between group A and B. $ScvO_2$ before increasing the VA-ECOM pump flow did not differ significantly between group A and B [77 (69–82)% vs. 83 (77–93) %, $P = 0.065$).



PVD before↑ECMO flow	Group A	Group B	Total	Portion of ↑PVD after ↑ECMO flow
≥ 15 mm/mm²	6	8	14	6/14 (42.9%, 95 CI 17.7-71.1%)#
< 15 mm/mm²	6	0	6	6/6 (100%, 95% CI 54.1-100%)

FIGURE 2 | Perfused vessel density before and after increasing venoarterial extracorporeal membrane oxygenation pump flow. Group A ($n = 12$), PVD increased after increasing VA-ECMO pump flow; Group B ($n = 8$), PVD decreased after increasing VA-ECMO pump flow. PVD before increasing ECMO pump flow did not differ significantly between group A and B ($P = 0.238$). PVD was higher in the group A than in group B after increasing ECMO pump flow ($P = 0.025$). Patients with PVD < 15 mm/mm^2 had a higher probability to increase PVD after increasing VA-ECMO pump flow ($P = 0.042$). $^*P < 0.05$ comparison between group A and B using independent-samples median tests. $^{\#}P < 0.05$ comparison between PVD ≥ 15 mm/mm^2 vs. PVD < 15 mm/mm^2 using Fisher's exact test. CI, confidence interval; *n*, number of events; PVD, perfused vessel density; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Microcirculatory Response to Deceasing VA-ECMO Pump Flow

In the 14 clinical events of decreasing VA-ECMO pump flow, we observed 6 (42.9%, 95% CI, 17.7–71.1%) events with decreased PVD (**Figure 5**). TVD and PPV before and after decreasing VA-ECMO pump flow are presented in **Figure 6**. PVD, TVD, and PPV before decreasing VA-ECMO pump flow were not significantly correlated to their changes after decreasing VA-ECMO pump flow. In *post-hoc* analysis, PVD, VA-ECMO pump flow, MAP, lactate level, and inotropic score before decreasing the VA-ECOM pump flow did not differ significantly between group C and D.

DISCUSSION

This study revealed both contradictory and non-contradictory responses of microcirculation to changes in VA-ECMO pump

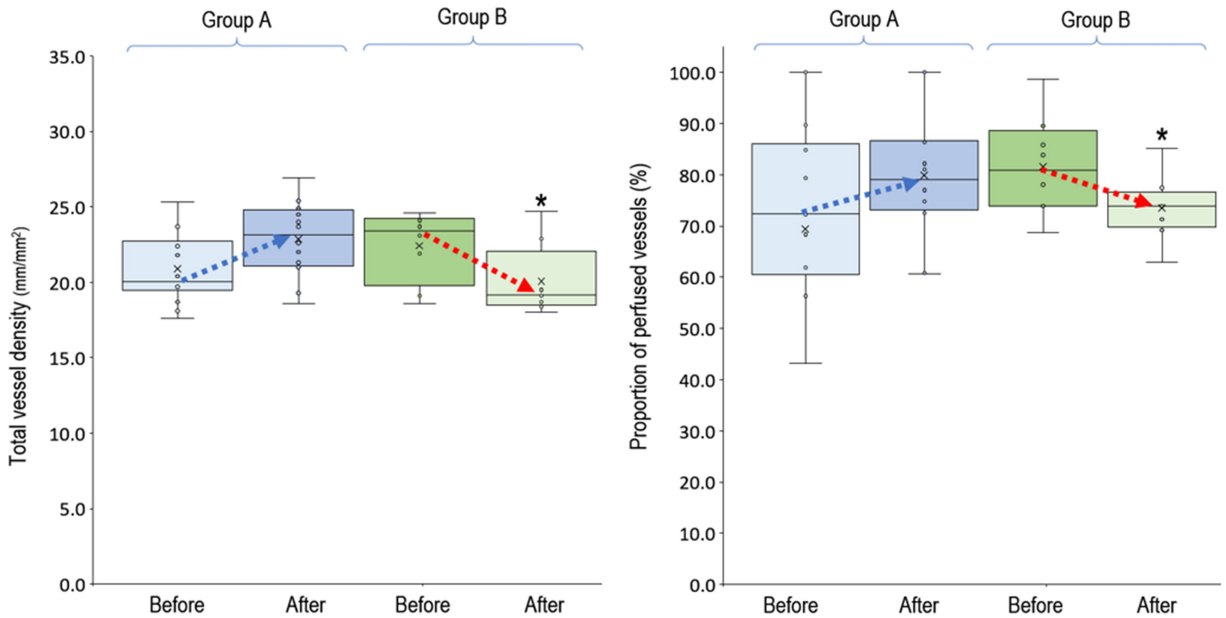


FIGURE 3 | Total vessel density and proportion of perfused vessels before and after increasing venoarterial extracorporeal membrane oxygen pump flow. Group A (n = 12), PVD increased after increasing VA-ECMO pump flow; group B (n = 8), PVD decreased after increasing VA-ECMO pump flow. $^{*}P < 0.05$ comparison between group A and B using independent-samples median tests. n, number of events; PVD, perfused vessel density; PPV, proportion of perfused vessels; TVD, total vessel density; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

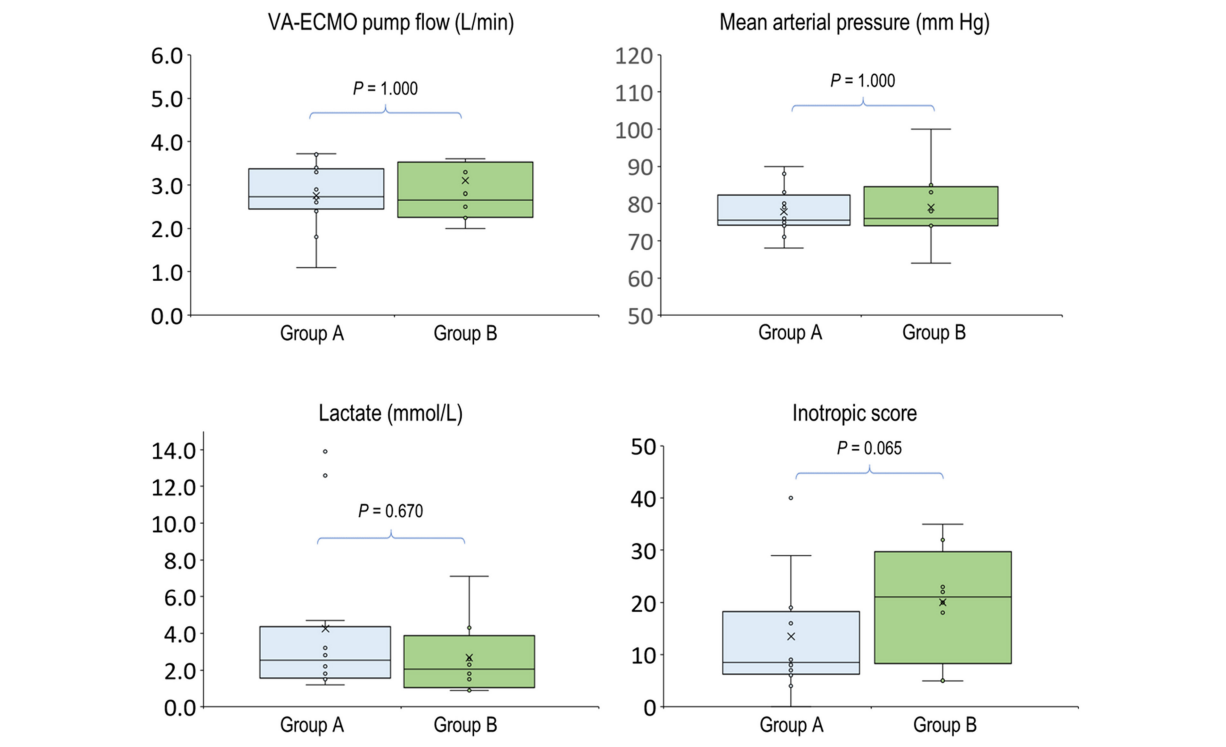
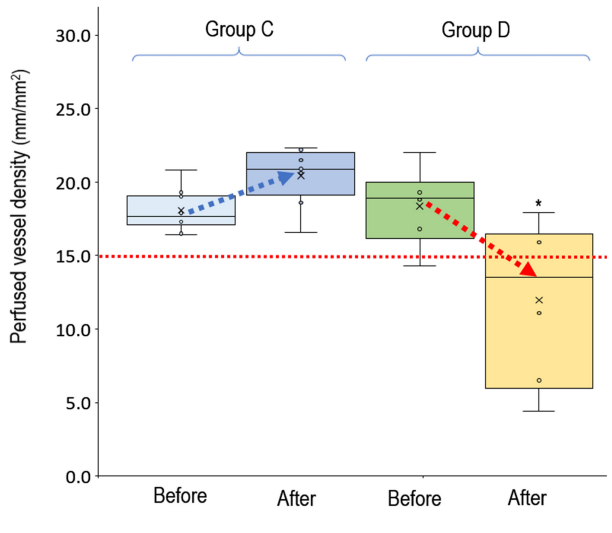


FIGURE 4 | Hemodynamic parameters before increasing venoarterial extracorporeal membrane oxygenation pump flow. Group A (n = 12), PVD increased after increasing VA-ECMO pump flow; group B (n = 8), PVD decreased after increasing VA-ECMO pump flow. P-values were calculated using independent-samples median tests. n, number of events; VA-ECMO, venoarterial extracorporeal membrane oxygenation.



PVD before↓ECMO flow	Group C	Group D	Total	Portion of ↑PVD after ↓ECMO flow
≥ 15 mm/mm²	8	5	13	8/13 (61.5%, 95 CI 31.6-86.1%)
< 15 mm/mm²	0	1	1	0/1 (0%, 95% CI 0-97.5%)

FIGURE 5 | Perfused small vessel before and after decreasing venoarterial extracorporeal membrane oxygenation pump flow. Group C ($n = 8$), PVD increased after decreasing VA-ECMO pump flow; group D ($n = 6$), PVD decreased after decreasing VA-ECMO pump flow. PVD before decreasing ECMO pump flow did not differ significantly between group C and D ($P = 0.698$). PVD was higher in the group C than in group D after decreasing ECMO pump flow ($P = 0.003$). $^{*}P < 0.05$ comparison between group C and D. CI, confidence interval; PVD, perfused vessel density; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

flow. This finding suggested that adjusting VA-ECMO pump flow according to current treatment goals might not ensure a good microcirculation. Moreover, we found that PVD < 15 mm/mm^2 before increasing VA-ECMO pump flow is associated with a higher probability to increase PVD after increasing VA-ECMO pump flow.

The finding that PVD < 15 mm/mm^2 at baseline had better response to increasing VA-ECMO pump flow is compatible with several previous studies of microcirculation resuscitation. First, red blood cell transfusion improves microcirculation in those patients with impaired microvascular flow at baseline (25–27). Second, fluid therapy improve microvascular flow in patients with abnormal microvascular flow at baseline, but not in patients with normal microvascular flow at baseline (28). Third, dobutamine only improved sublingual microcirculation in patients with severe alteration at baseline (29). These studies had a common finding that dissociation between microcirculation and systemic hemodynamics was frequently seen. It suggests that only direct measurement of the microcirculation before and after the treatments can see the real response of microcirculation (30).

The finding of contradictory decrease in PVD after increasing VA-EMCO pump flow is compatible with that of Busch et al. (31). They suggest that cerebral blood flow and oxygenation are not well-predicted by VA-ECMO pump flow or blood pressure. Moreover, increasing VA-ECMO pump flow may have two effects on patient's own cardiac output. First, increased venous drainage of VA-ECMO decrease venous return of blood flow to the right atrium. Second, increased VA-ECMO arterial blood flow increases cardiac afterload (32, 33). The decreased preload and increased afterload may reduce the patient's own cardiac output. In patients with VA-ECMO, head and brain perfusions are determined according to the balance between VA-ECMO pump flow and the patient's own cardiac output (34, 35). Further studies are required to investigate whether sublingual microcirculation is correlated with cerebral blood flow in patients with VA-ECMO.

Timely weaning of VA-ECMO can reduce its associated complications and shorten its duration. The finding of decrease in PVD after decreasing VA-ECMO pump flow is compatible with the study of Akin et al. (11). They suggest that sublingual microcirculation is a novel potential marker for identifying successful weaning from VA-ECMO. There are two differences between these two studies. First, we investigated the microcirculatory response to decreasing VA-ECMO pump flow within 48 h after placement of VA-ECMO, and Akin et al. investigated the microcirculatory response to weaning VA-ECMO pump flow at 48 h or up to 3 weeks after placement of VA-ECMO. Second, the decreases in VA-ECMO pump flow were 10 to 30% of the baseline value in our study, and the decreases in VA-ECMO pump flow were 50% of the baseline value in the study of Akin et al. (11). Therefore, our study further identified that sublingual microcirculation might be a potential marker for ensuring adequate tissue perfusion during early weaning VA-ECMO pump flow.

This study has several limitations. First, all patients received peripheral VA-ECMO, and the microcirculatory response to changes in VA-ECMO pump flow might be different in those patients with central VA-ECMO. Second, this observational pilot study was not powered to find out the predictors of microcirculation response after changing VA-ECMO pump flow. However, our preliminary results show that lower PVD before increasing VA-ECMO pump was associated with increased PVD after increasing VA-ECMO flow. Other parameters before increasing VA-ECMO pump flow, include $ScvO_2$ and inotropic score, are warranted for further investigation. Third, this study enrolled patients with different indications of VA-ECMO support. Further studies with specific indication of VA-ECMO support are warranted to investigate the predictors for contradictory responses of microcirculation after changing the VA-ECMO pump flow. Fourth, further studies with more enrolled patients and more time points of microcirculation examinations are warranted to investigate whether aiming to maintain an adequate microcirculation after changing VA-ECMO pump flow can ensure better clinical outcomes.

CONCLUSION

Our study revealed both contradictory and non-contradictory responses of sublingual microcirculation to changing VA-ECMO pump flow. At this stage, tandem measurements of microcirculation before and after changing VA-ECMO flow may help to ensure a good microcirculation.

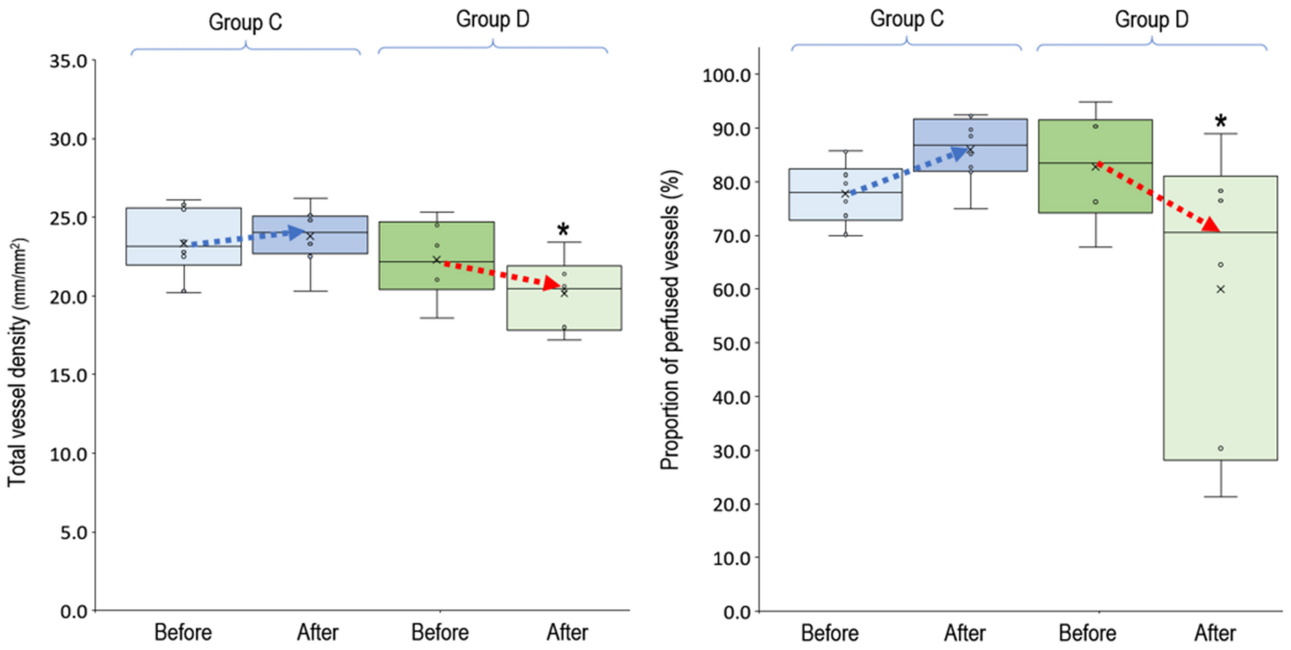


FIGURE 6 | Total vessel density and proportion of perfused vessels before and after decreasing venoarterial extracorporeal membrane oxygen pump flow. Group C ($n = 8$), PVD increased after decreasing VA-ECMO pump flow; group D ($n = 6$), PVD decreased after decreasing VA-ECMO pump flow. $^{*}P < 0.05$ comparison between group C and D using independent-samples median tests. *n*, number of events; PVD, perfused vessel density; PPV, proportion of perfused vessels; TVD, total vessel density; VA-ECMO, venoarterial extracorporeal membrane oxygenation.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of the regulation of the Research Ethics Committee of authors' hospital. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Requests to access the datasets should be directed to Yu-Chang Yeh, tonyyeh@ntuh.gov.tw.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of National Taiwan University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

T-JW, C-HW, W-SC, CI, T-YL, and Y-CY: concept and design. T-JW, C-HW, C-HH, C-HL, and Y-CY: patient enrollment and data collection. T-JW, W-SC, CI, T-YL, and Y-CY: interpretation of data. T-JW, W-SC, and Y-CY: drafting manuscript. C-HW, C-HH, M-JW, Y-SC, CI, T-YL, and Y-CY: critical revision of the manuscript. M-JW and Y-SC: study supervision. All authors: contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Methodological Issue of Mitochondrial Isolation in Acute-Injury Rat Model: Asphyxia Cardiac Arrest and Resuscitation

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Background: Identification of the mechanisms underlying mitochondrial dysfunction is key to understanding the pathophysiology of acute injuries such as cardiac arrest (CA); however, effective methods for measurement of mitochondrial function associated with mitochondrial isolation have been debated for a long time. This study aimed to evaluate the dysregulation of mitochondrial respiratory function after CA while testing the sampling bias that might be induced by the mitochondrial isolation method.

Materials and Methods: Adult rats were subjected to 10-min asphyxia-induced CA. 30 min after resuscitation, the brain and kidney mitochondria from animals in sham and CA groups were isolated ($n = 8$, each). The mitochondrial quantity, expressed as protein concentration (isolation yields), was determined, and the oxygen consumption rates were measured. ADP-dependent (state-3) and ADP-limited (state-4) respiration activities were compared between the groups. Mitochondrial quantity was evaluated based on citrate synthase (CS) activity and cytochrome c concentration, measured independent of the isolation yields.

Results: The state-3 respiration activity and isolation yield in the CA group were significantly lower than those in the sham group (brain, $p < 0.01$; kidney, $p < 0.001$). The CS activity was significantly lower in the CA group as compared to that in the sham group (brain, $p < 0.01$; kidney, $p < 0.01$). Cytochrome c levels in the CA group showed a similar trend (brain, $p = 0.08$; kidney, $p = 0.25$).

Conclusions: CA decreased mitochondrial respiration activity and the quantity of mitochondria isolated from the tissues. Owing to the nature of fragmented or damaged mitochondrial membranes caused by acute injury, there is a potential loss of disrupted mitochondria. Thus, it is plausible that the mitochondrial function in the acute-injury model may be underestimated as this loss is not considered.

Keywords: mitochondria, mitochondrial dysfunction, mitochondrial isolation, oxygen consumption, ischemic reperfusion injury

INTRODUCTION

Cardiac arrest (CA) is a major public health issue affecting approximately 600,000 patients each year in the United States (1). Various pathophysiological changes occur during and after CA, including mitochondrial dysfunction, multiple organ failure, and prolonged neurological dysfunction, that increase the mortality of patients with CA (2). Studies have suggested that therapies effective against mitochondrial dysfunction may improve mortality and neurological damage after CA in rodent models (3, 4). These results implicate the mitochondria as effectors or targets to improve the survival of patients with CA. Thus, studies focusing on mitochondrial pathophysiology are imperative to understanding the mechanisms underlying complex biological responses preceded by ischemia/reperfusion injury.

Mitochondrial research using experimental animal models plays an important role in the study of mitochondria, and mitochondrial isolation is the foremost method for studying the pathophysiology of mitochondrial dysfunction (5, 6). Therefore, the development of methods for mitochondrial purity assessment are currently in high demand, and different mitochondrial isolation methods have been reported by several investigators (7, 8).

Picard et al. (5) investigated the potential complications arising from isolation methods that involve structural and functional disruption of the mitochondria. They attributed the functional alterations induced by mitochondrial isolation to disruption of the mitochondrial morphology caused by mechanical homogenization as well as loss of soluble proteins and other molecules from the mitochondrial matrix. This is significant under experimental conditions given that animal models with acute injuries likely have mitochondrial disruption in nature. However, although Picard et al. discussed a potential risk of sampling bias as a result of the loss of disrupted mitochondria during the isolation process, no studies have shown such a bias in acute-injury animal models.

We previously reported responses to resuscitation of tissues, including the brain and kidneys, following prolonged CA by examining mitochondrial respiration using isolated mitochondria. The present study aimed to evaluate mitochondrial dysfunction in the brain and kidney tissues after CA while testing the sampling bias induced by our mitochondrial isolation method, which was performed by measuring multiple indicators of the purity of mitochondrial samples.

MATERIALS AND METHODS

The Institutional Animal Care and Use Committee of the Feinstein Institutes for Medical Research approved this study protocol. All methods were performed in accordance with the Guide for the Care and Use of Laboratory Animals, American Veterinary Medical Association Guidelines on Euthanasia and all other related regulations. This report is in compliance with the Animal Research Reporting of *In Vivo* Experiments guidelines.

Generation of Rat CA Model and Interventions

All instrumentation and surgical preparations in this non-randomized, prospective, and experimental controlled study were performed according to our previously described protocols (9). In brief, 16 adult male Sprague–Dawley rats (450–550 g, Charles River Laboratories, MA,USA) were anesthetized with 4% isoflurane (Isosthesia, Butler-Schein AHS, OH, USA) and intubated with a 14-gauge plastic catheter (Surflo, Terumo Medical Corporation, NJ, USA). We used male rats to avoid potential hormonal or genetic differences among animal subjects and ensure that the observed differences could be attributed to the experimental intervention (i.e., to minimize potential sources of variability). Inhaled anesthesia was induced to rats and they were mechanically ventilated (Ventilator Model 683, Harvard Apparatus, MA, USA), and anesthesia was maintained with 2% isoflurane and a fraction of inspired O_2 (FIO_2) equivalent to 0.3. Core temperature was maintained at 36.5 $\pm$ 1.0°C during the surgical procedure. Animals were assigned to two groups: CA and sham ($n = 8$ for each group). The CA group included rats successfully resuscitated with cardiopulmonary resuscitation (CPR) after a 10-min asphyxia. The sham group included rats that were not treated with asphyxia or CPR. After cannulation through the left femoral vein, neuromuscular blockade was achieved by slow intravenous administration of 2 mg/kg vecuronium bromide (Hospira, IL, USA) for the CA group rats, and asphyxia was induced by turning off the ventilator. After 10 min, the animals were resuscitated by restarting mechanical ventilation at an FIO_2 of 1.0 and performing manual chest compression CPR. Chest compressions were performed with two fingers over the sternum at a rate of 260–300 beats/min. Immediately after beginning CPR, a 20 μg/kg bolus of epinephrine was administered to the rats through the venous catheter. Following restoration of spontaneous circulation, defined as systolic blood pressure > 60 mmHg, CPR was discontinued. The same surgical procedures were performed for rats in the sham group, including vecuronium and epinephrine injections. Mechanical ventilation was discontinued 30 min post CPR; thereafter, the rats were euthanized, and tissues were collected for mitochondrial experiments.

All surgical procedures, including resuscitation, were performed by one investigator; therefore, blinding procedures were not performed. Allocation concealment is not possible when using an acute-injury model as opposed to healthy control animals. Therefore, we used sham-surgery animals as our control group to reduce the risk of exaggerated effects. The other investigator independently and unbiasedly performed the subsequent biochemical assays.

Isolation of the Brain and Kidney Mitochondria and Evaluation of Mitochondrial Respiratory Function

Mitochondrial samples from the brain and kidneys were isolated from the sham and CA groups according to a modified procedure described by Scholte et al. (10). All the procedures were performed at 4°C. Briefly, excised tissues

were immediately placed in mitochondrial isolation buffer composed of 210 mM mannitol, 70 mM sucrose, 10 mM HEPES (pH 7.3), and 0.2 mM EGTA with 0.2% w/v fatty acid-free bovine serum albumin (MESH-BSA). The spinal cord, extra ventricular tissue of the brain, and fats from both tissues were isolated in MESH-BSA buffer. Next, tissues were blot-dried on filter paper, weighed, and placed in MESH-BSA buffer. After mincing and washing, the tissues were diluted in MESH-BSA buffer, and subsequently homogenized using a Teflon motor-driven homogenizer (Model BDC2010, Caframo Lab Solutions, Ontario, Canada) at eight and three strokes for the brain and kidneys, respectively. Homogenates were centrifuged at 5,600*g* for 1 min, and supernatants were decanted into a polycarbonate tube and centrifuged again at 12,000*g* for 6 min. For brain samples, homogenization was performed twice, and the pooled supernatants were centrifuged. The brain tissue homogenization supernatants were gently decanted until the synaptosomes layer reached the top, and the remaining loose pellets were suspended with 20 mL of 12.5% Percoll (GE Healthcare, IL, USA) in MESH buffer without BSA and centrifuged at 12,000*g* for 6 min. Kidney homogenization did not require this process because of the lack of myelin synaptosome structures. For both the brain and kidney samples, supernatants were gently removed with pipettes without disturbing mitochondrial pellets (usually ∼200 μL buffer remained). Finally, the pellets were resuspended in 20 mL MESH buffer and centrifuged at 12,000*g* for 6 min. After mitochondrial pellets were collected and their volumes measured, mitochondrial concentrations were determined using BCA assay with BSA as a protein standard, and then, isolation yields (mg protein/g tissue) were calculated.

Subsequently, the oxygen consumption was measured using a Strathkelvin oxygen electrode (30°C). Isolated mitochondria samples were diluted in an oxygen electrode mix buffer containing 80 mM KCl, 50 mM MOPS, 1 mM EGTA, 5 mM KH_2PO_4, and 1 mg defatted BSA/mL at pH 7.4 (11). ADP-dependent (state-3), ADP-limited (state-4), and DNP-dependent (uncoupled) respiration were measured in 150 μL mitochondrial suspension (0.5 mg/mL) using glutamate and malate as substrates. The rates of substrate oxidation were expressed as nmol/min/mg protein. The respiratory control ratio (RCR) was calculated as the ratio of state-3 to state-4 respiration.

Citrate Synthase Activity Assay

The CS activity of each isolated mitochondrial sample was measured using a CS activity assay kit (MAK193, Sigma-Aldrich, MO, USA) according to the manufacturer's instructions. Briefly, after preparing the reagents, isolated mitochondrial samples were diluted with CS assay buffer. Diluted samples, reduced glutathione (GSH) standard solutions, and positive controls were added to 96-well plates, followed by reaction mixes containing CS developer and CS substrate mix. The specific absorbance at 412 nm was measured every 5 min for 30 min. Finally, CS activity was calculated according to the GSH amount, calculated using a standard curve, and the reaction time.

Cytochrome C ELISA

The cytochrome c concentration in each isolated mitochondrial sample was measured using a cytochrome c profiling ELISA kit (ab110172, Abcam, Cambridge, UK), according to the manufacturer's instructions. Briefly, after preparing the reagents, isolated mitochondria samples were diluted with a solution containing 0.1% sodium dodecyl sulfate (SDS) and centrifuged at 15,000*g* for 20 min. Supernatants of samples and standards were added to the supplied 96-well microplates and incubated for 3 h. After the antigen–antibody reaction using a detector antibody against cytochrome c and HRP labels, HRP development solution was added. Absorbance was measured at 600 nm using a plate reader (Spark®, TECAN, Männedorf, Switzerland). Finally, the cytochrome c concentration in each sample was calculated according to a standard curve.

Statistical Analysis

Data are shown as mean ± standard deviation (SD) for continuous variables. An unpaired two-tailed Student's *t*-test was used to compare two independent groups. Two-tailed ***p***-values were calculated, and statistical significance was set at $p < 0.05$. SPSS 25.0 (IBM, Armonk, NY, USA) was used to perform all statistical analyses.

RESULTS

Cardiac Arrest Decreases Mitochondrial Respiratory Function

Tables 1, **2** show the basal characteristics and oxygen consumption rates, respectively, of isolated mitochondria from the brain and kidneys. Brain tissue weight of rats in the CA group was greater than that of rats in the sham group (2.03 ± 0.05 and 1.91 ± 0.06 g, respectively; $p < 0.01$), but kidney tissue weight did not differ between the two groups (1.63 ± 0.09 and 1.62 ± 0.09 g, respectively; $p = 0.78$). The isolated mitochondrial volume of the CA group was significantly lower than that of the sham group in the brain and kidney tissues (brain: 146 ± 42 and 196 ± 44 μL, $p < 0.05$; kidney: 554 ± 68 and 692 ± 113 μL, $p < 0.05$, respectively). Similarly, isolation yield of the CA group was significantly lower than that of the sham group in both tissues (brain: 2.71 ± 0.49 and 4.29 ± 0.82 mg protein/g tissue, $p < 0.001$; kidney: 18.4 ± 1.7 and 22.6 ± 1.3 mg protein/g tissue, $p < 0.001$, respectively).

The state-3 respiration activities in the brain and kidney mitochondria of the CA group declined significantly compared to those in the sham group (brain: 209 ± 26 and 286 ± 50 nmol/min/mg protein, $p < 0.01$; kidney: 148 ± 37 and 269 ± 55 nmol/min/mg protein, $p < 0.001$, respectively). In contrast, we did not observe significant differences in state-4 respiration activities in either tissue. Thus, the RCR showed a decreasing trend after CA in both tissues.

Cardiac Arrest Decreases Tissue Citrate Synthase Activity

Figure 1 shows the results of CS activity assay of isolated mitochondria from the brain and the kidney. The CS activity of the brain and kidney mitochondria in the CA group declined

TABLE 1 | Basal characteristics and oxygen consumption rates of the isolated mitochondria from the brain.

Brain			
Measurement	**Sham ($n = 8$)**	**CA ($n = 8$)**	***p*-value**
Rat weight (g ± SD)	509 ± 26	513 ± 18	0.7247
Tissue weight (g ± SD)	1.91 ± 0.06	2.03 ± 0.05	0.0010**
Mitochondria volume (μL ± SD)	196 ± 44	146 ± 42	0.0369*
Isolation yield (mg protein/g tissue ± SD)	4.29 ± 0.82	2.71 ± 0.49	0.0004***
State-3 activity (nmol/min/mg protein ± SD)	286 ± 50	209 ± 26	0.0016**
State-4 activity (nmol/min/mg protein ± SD)	45.4 ± 12.6	43.9 ± 14.7	0.8296
RCR ± SD	6.57 ± 1.42	5.17 ± 1.63	0.0881

CA, cardiac arrest; SD, standard deviation; RCR, respiratory control ratio.
**p < 0.05 in all variables.*
***p < 0.01 in all variables.*
****p < 0.001 in all variables.*

TABLE 2 | Basal characteristics and oxygen consumption rates of the isolated mitochondria from the kidney.

Kidney			
Measurement	**Sham ($n = 8$)**	**CA ($n = 8$)**	***p*-value**
Rat weight (g ± SD)	509 ± 26	513 ± 18	0.7247
Tissue weight (g ± SD)	1.62 ± 0.09	1.63 ± 0.09	0.7780
Mitochondria volume (μL ± SD)	692 ± 113	554 ± 68	0.0105*
Isolation yield (mg protein/g tissue ± SD)	22.6 ± 1.3	18.4 ± 1.7	< 0.0001***
State-3 activity (nmol/min/mg protein ± SD)	269 ± 55	148 ± 37	0.0001***
State-4 activity (nmol/min/mg protein ± SD)	42.8 ± 19.9	27.6 ± 6.5	0.0602
RCR ± SD	6.94 ± 1.96	5.75 ± 2.58	0.3166

CA, cardiac arrest; SD, standard deviation; RCR, respiratory control ratio.
**p < 0.05 in all variables.*
****p < 0.001 in all variables.*

significantly compared to that in the sham group (brain: 2.40 ± 1.01 and 4.19 ± 0.89 μmol/min/g tissue, $p < 0.01$; kidney: 5.07 ± 1.92 and 7.73 ± 1.07 μmol/min/g tissue, $p < 0.01$, respectively).

Tissue Cytochrome C Levels Were Low After Cardiac Arrest

Figure 2 shows the results of cytochrome c profiling ELISA for isolated mitochondria from the brain and kidneys. Although there was no statistical difference, cytochrome c levels in the brain and kidney mitochondria of the CA group decreased compared to levels in the sham group (brain: 10.8 ± 4.2 and 17.0 ± 8.4 μg/g tissue, $p = 0.08$; kidney: 146 ± 26 and 162 ± 27 μg/g tissue, $p = 0.25$).

DISCUSSION

Our data indicate that 10-min asphyxia CA followed by resuscitation for 30 min decreases mitochondrial respiratory function in the brain and kidneys. These results are in line with our previous findings (12) and other reports on mitochondrial dysfunction in ischemia/reperfusion injury models (13). Although the underlying mechanism for the decreased isolation yield in tissues remains unclear, alterations in cell viability and mitochondrial physiological activity after injury may affect the isolated mitochondrial volume (5). This is supported by our findings that decreased mitochondrial quantity, measured by three independent assays, in the acute-injury rodent model. Considering the potential bias generated by mitochondrial isolation methods and the lack of reliable information on the same, our findings are important for mitochondrial research using acute-injury models.

In addition to being an indicator of mitochondrial quantity in the isolated samples, the protein amount (yield) may represent differences in the mitochondrial content between sham (non-injured) and CA (injured) rats. In other words, the mitochondrial purification method used could affect the sample volume after injury. However, the protein assay was non-specific; therefore, in order to evaluate the decrease in mitochondria-specific quantity in injured tissues, we performed a CS activity assay and cytochrome c ELISA, independent of the number of mitochondrial yields.

CS plays a central role in the mitochondrial oxidative capacity during the first step of the citric acid cycle and is commonly used as a quantitative enzyme marker for the presence of intact mitochondria. Cytochrome c, a key protein involved in cellular respiration, contains an iron porphyrin cofactor. Cytochrome c is primarily involved in the electron transport chain of the mitochondrial inner membrane and is widely believed to be localized solely in the mitochondrial inner membrane space under normal physiological conditions. Because these assays are independent and mitochondria-specific, we used these as independent indicators of mitochondrial quantity in our mitochondria samples.

Collectively, our findings suggest that CA might cause decreased mitochondrial respiration activity and reduced mitochondrial purification in the brain and kidneys. Despite the decrease in mitochondrial quantity in the injured tissues, mitochondrial respiration activity was standardized and adjusted based on the number of yields. The use of standardized values to compare rats with different injury levels is the most widely accepted method worldwide.

Cytochrome c is also known to be extruded into the soluble cytoplasm through pores in the outer mitochondrial membrane during the early phase of apoptosis. In clinical settings, Donnino et al. reported that non-surviving CA patients had higher

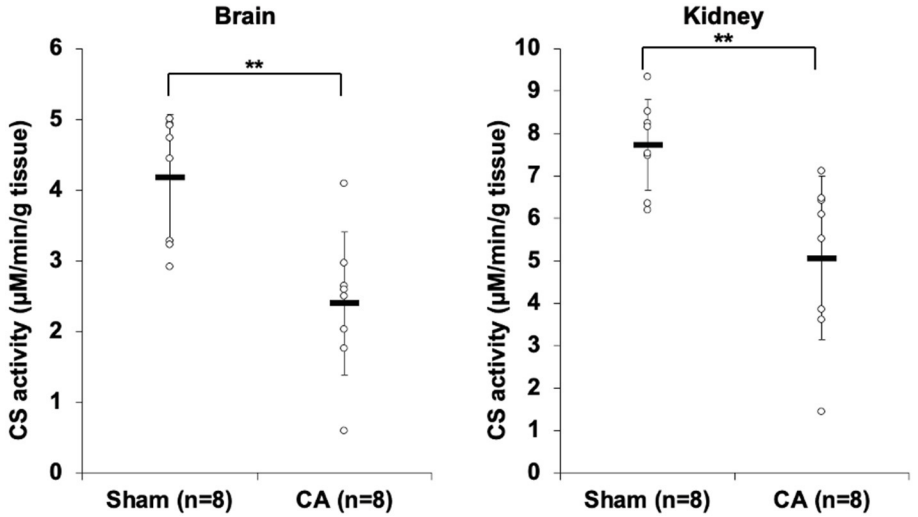

FIGURE 1 | Results of citrate synthase activity assay comparing isolated mitochondria of cardiac arrest rats with that of sham rats. The CS activity of the brain and kidney mitochondria in the CA group declined significantly compared to that in the sham group (brain, 2.40 ± 1.01 and 4.19 ± 0.89 μmol/min/g tissue, $p < 0.01$; kidney, 5.07 ± 1.92 and 7.73 ± 1.07 μmol/min/g tissue, $p < 0.01$, respectively). $^{**}p < 0.01$.

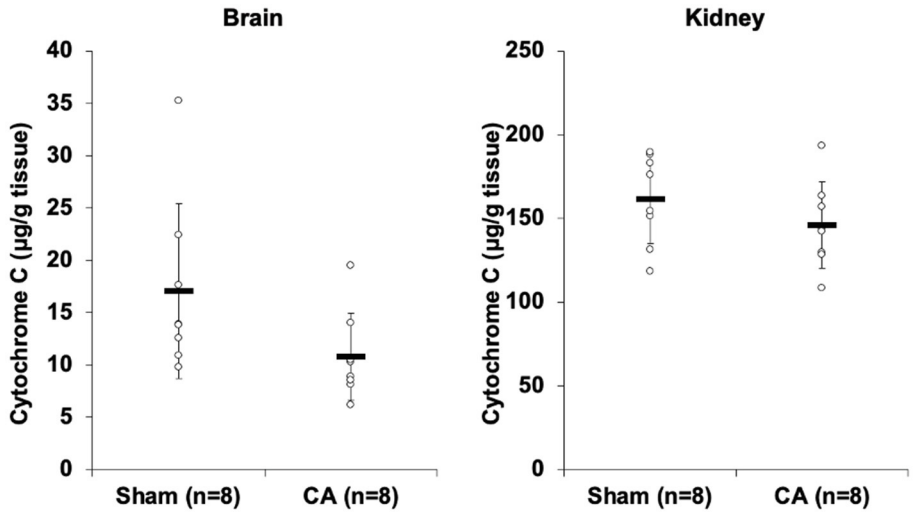

FIGURE 2 | Results of cytochrome C profiling ELISA comparing isolated mitochondria of cardiac arrest rats with that of sham rats. Cytochrome c concentration (μg/g tissue) of isolated mitochondria in the brain and the kidneys. Although there was no statistical difference, cytochrome c levels in the brain and kidney mitochondria of the CA group decreased compared to levels in the sham group (brain, 10.8 ± 4.2 and 17.0 ± 8.4 μg/g tissue, $p = 0.08$; kidney, 146 ± 26 and 162 ± 27 μg/g tissue, $p = 0.25$).

cytochrome c levels in plasma samples than survivors (14). Accordingly, if we consider that the isolated mitochondria in CA rats could release cytochrome c and mitochondrial fragments into the cytosol and bloodstream, then detection of lower cytochrome c levels might represent a potential selection bias of the samples. This may result in loss of information from damaged mitochondria because of the isolation procedure. Thus, if we could obtain information from damaged/fragmented mitochondria in our mitochondrial functional analysis, the results could be even worse than that observed in the present study, especially as mitochondria require intact inner and outer membranes to complete oxidative phosphorylation.

This study had several limitations. First, our isolation procedure can either increase or decrease the amount of loss in damaged mitochondria from injured tissues. Multiple isolation procedures are still being reported, particularly focusing on the centrifugation speed. The initial centrifugation is key to separating mitochondria from other cytosolic organelles and requires a centrifugation speed ranging from 400*g* to 30,700*g* (15, 16) and 600*g* to 1,000*g* (17, 18) for the brain and kidney samples,

respectively. The isolation conditions vary depending on the target tissues, and this probably depends on the investigator's goal. It is difficult to compare our method to those reported previously, as the information regarding their sample quality, which is measured by the yield, CS activity, or cytochrome c level, is not generally reported by the investigators. We selected a balance between low and high centrifugation speeds and used 5,600*g* in our experiment. It is possible that other centrifugation speeds can alter the dignity of sampling bias as compared to those we have shown in this study. However, because centrifugation uses gravity to separate the cytosol organelles, it is plausible that any centrifugation may generate a certain level of bias in the mitochondrial isolation sample. Second, we did not perform mitochondrial DNA measurement, which might have strengthened the results of isolated mitochondrial quantitation, nor did we perform mitochondrial immunostaining of the harvested tissues, which might help understand the morphological and quantitative alterations in the mitochondria after CA. Fan et al. performed histological evaluation of mitochondrial morphology after CA using transmission electron microscopy and found that mitochondria appeared smaller, lost their typical round or tubular morphology, and exhibited an irregular shape after CA (19). Therefore, further histological assessment is of great importance in evaluating the potential sampling bias of mitochondrial isolation methods.

In conclusion, CA decreased mitochondrial respiration activity and the quantity of the mitochondria isolated using our method from the brain and kidneys of rats. Thus, for mitochondrial research, it is important to evaluate the mitochondrial quantity and accordingly adjust the value of mitochondrial function in order to standardize and compare the results obtained under different experimental conditions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by The Institutional Animal Care and Use Committees of Feinstein Institutes for Medical Research approved this study protocol.

AUTHOR CONTRIBUTIONS

KS has full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and supervised the project. KS and LB designed the conception of the study. KS, TA, and YO performed acquisition of data. TA and YO analyzed data. TA drafted and KS critically edited the manuscript. All authors made interpretations of data and added intellectual content of revisions to the paper and gave full approval of the version to be published.

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Conflict of Interest: KS and LB have a patent right of metabolic measurements in critically ill patients. KS has a grant/research support from Nihon Kohden Corp. LB has a grant/research support from Philips Healthcare, the NIH, Nihon Kohden Corp., Zoll Medical Corp, PCORI, BrainCool, and United Therapeutics and owes patents including 7 issued patents and several pending patents involving the use of medical slurries as human coolant devices to create slurries, reperfusion cocktails, and measurement of respiratory quotient.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Do Digital Handover Checklists Influence the Clinical Outcome Parameters of Intensive Care Unit Patients? A Randomized Controlled Pilot Study

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Background: Clinical handovers have been identified as high-risk situations for medical treatment errors. It has been shown that handover checklists lead to a reduced rate of medical errors and mortality. However, the influence of handover checklists on essential patient outcomes such as prevalence of sepsis, mortality, and length of hospitalization has not yet been investigated in a randomized controlled trial (RCT).

Objectives: The aim of the present pilot study was to estimate the effect of two different handover checklists on the 48 h sepsis-related organ failure assessment (SOFA) score and the feasibility of a respective clinical RCT.

Methods: Outcome parameters and feasibility were investigated implementing and comparing an intervention with a control checklist.

Design: Single center two-armed cluster randomized prospective crossover pilot study.

Setting: The study took place over three 1-month periods in an intensive care unit (ICU) setting at the University Hospital Aachen.

Patients/Participants: Data from 1,882 patients on seven ICU wards were assessed, of which 1,038 were included in the analysis.

Intervention: A digital standardized handover checklist ($ISBAR_3$) was compared to a control checklist (VICUR).

Main Outcome Measures: Primary outcome was the 2nd 24 h time window sepsis-related organ failure assessment (SOFA) score. Secondary outcomes were SOFA scores on the 3rd and 5th 24 h time window, mortality, reuptake, and length of stay; handover duration, degree of satisfaction, and compliance as feasibility-related outcomes.

Results: Different sepsis scores were observed only for the 1st 24 h time window after admission to the ICU, with higher values for $ISBAR_3$. With respect to the patient-centered

outcomes, both checklists achieved similar results. Average handover duration was shorter for VICUR, whereas satisfaction and compliance were higher for $ISBAR_3$. However, overall compliance was low (25.4% for $ISBAR_3$ and 15.8% for VICUR).

Conclusions: Based on the results, a stratified randomization procedure is recommended for following RCTs, in which medical treatment errors should also be investigated as an additional variable. The use of control checklists is discouraged due to lower acceptance and compliance among healthcare practitioners. Measures should be undertaken to increase compliance with the use of checklists. Clinical outcome parameters should be carefully selected.

Trial Registration: ClinicalTrials.gov, Identifier [NCT03117088]. Registered April 14, 2017.

Keywords: standardized handover, checklists, $ISBAR_3$, ICU, patient safety, study design, pilot study, feasibility

INTRODUCTION

Improving safety for patients in health care is a crucial, yet challenging endeavor. The World Health Organization (WHO) defines patient safety as "the absence of preventable harm to a patient during the process of health care and reduction of risk of unnecessary harm associated with health care to an acceptable minimum" (1). High prevalence rates of procedural errors in health care, often leading to patient harm, emphasize the relevance of the patient safety concept. As an example, the WHO points out that medical errors and health care related events occur in 8–12% of hospitalized patients in Europe (2). Fifty to seventy percent of these medical errors could be avoided by comprehensive systematic strategies (2), such as evidence-based interventions (3, 4). Accordingly, patient safety has increasingly gained public (4, 5) and scientific interest (6) and a growing awareness of the importance of patient safety in clinical practice.

In the course of continuous medical and technological development and the increasing complexity of health care, error possibilities rise. During treatment, patients are cared for in an interdisciplinary and interprofessional setting. Moreover, the treatment often takes place in different locations and the treatment team varies frequently due to shift changes. This complexity creates interface situations such as clinical handovers, which have been identified as high-risk situations for medical treatment errors (7–10).

Being a long-identified risk factor in other safety-related domains such as aviation (11), inadequate communication is a threat to patient safety as well (10, 12). A largescale European Commission project considers deficient handover communication as the cause of 25–40% of all adverse events (13). Similarly, according to McSweeney et al. (14) communication failures during handover lead to negative effects on patient care, such as subsequent medication errors, inaccurate patient plans or delayed hospital discharges. Additionally, Starmer et al. (15) substantiated the relationship between poor handovers, errors, and preventable adverse events.

The identification of handovers as risk situations (16) has made them a main target of patient safety initiatives (17, 18). Handovers regarding intensive care patients may be especially critical as these patients are often unable to verbalize their own health care problems and needs. Accordingly, the Agency for Healthcare Research and Quality (AHRQ) and the Accreditation Council for Graduate Medical Education (ACGME) have declared the improvement of handovers as a top priority of the US-wide efforts to improve patient safety (15). To increase patient safety in handover situations, the use of checklists has been recommended (19, 20). Checklists support memory and attention and standardize the communication in handover situations. Thus, they can help to prevent misunderstandings and the loss of valuable information. It has been shown that the implementation of checklists leads to a reduced rate of medical errors (15). However, research has only recently begun to address the impact of handover checklists on clinical patient outcomes (21). So far, no clinical trials have investigated the influence of handover checklists on essential parameters such as patient mortality, prevalence of sepsis, and length of hospitalization in a randomized controlled trial.

The aim of the present pilot study was to estimate the effect size of a checklist intervention on the emergence of sepsis after 48 h for a future randomized controlled trial (RCT). Moreover, a second aim was to evaluate feasibility aspects of the respective RCT.

For this purpose, the present pilot study evaluated the following aspects:

1) The potential effect of a structured clinical handover checklist ($ISBAR_3$: Identification, Situation, Background, Assessment, Recommendation, Read-back, Risk) (see **Figure 1**) on patient-related objective outcome parameters (sepsis-related organ failure assessment (SOFA) scores after 48 h (primary

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; DGAI, German Society of Anaesthesiology and Intensive Care Medicine; ICAA-System, IntelliSpace Critical Care and Anesthesia-System; ICU, Intensive care unit; IHI, Institute for Healthcare Improvement; $ISBAR_3$, Identity, Situation, Background, Assessment, Recommendation, Read-back, Risk; LOS, Length of stay; OIM, ICU Ward for Operative Intensive Care Medicine; RCT, Randomized controlled trial; SOFA, Sepsis-related organ failure assessment; UKA, University Hospital Aachen; VICUR, Vaccination status, Insurance status, Contact person, Utilization, Rehabilitation; WEA, Weaning station; WHO, World Health Organization.

FIGURE 1 | The ISBAR$_3$ checklist.

FIGURE 2 | The VICUR checklist.

outcome) and on mortality, reuptake, and length of stay (secondary outcomes) in an ICU setting. To exclude a potential bias of unspecific observer effects (22), a control condition was employed, i.e., an unspecific handover checklist (VICUR: vaccination status, insurance status, contact person, utilization, rehabilitation) (see **Figure 2**).

2) As feasibility-related outcome parameters, we evaluated handover duration, degree of satisfaction, and compliance among the ICU staff. The aim of the feasibility aspect was to evaluate a large-scale dummy run of the trial procedures and to determine recruitment and compliance rates; moreover, our aims were to estimate the effect size for our primary outcome parameter and to evaluate the suitability of the primary and secondary outcome parameters for a future large-scale RCT (23).

MATERIALS AND METHODS

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Faculty of Medicine of RWTH Aachen University (Chairperson Prof. Dr. med. G. Schmalzing) (EK 075/17) on May 24th, 2017.

Study Setting

The single center pilot study was conducted during 6 months (May–October 2017) simultaneously on seven ICU wards at the University Hospital RWTH Aachen, Germany (Department of Intensive Care Medicine and Intermediate Care), providing 105 operative intensive care beds and focusing in part on a specific patient clientele. The main focal points are neurosurgery, cardiac surgery, visceral surgery, burn surgery, and weaning. Surgical ICU patients outside of this scope can be admitted to any of the ICU wards.

Participants, Inclusion, and Exclusion Criteria

All physicians working on ICU wards during data acquisition received the study information and signed the written consent. They were informed that their participation was voluntary and could be discontinued at any time without explanation or any disadvantages. The medical personnel was informed how to use the tablet PC, but there was no special training on how to use the checklist to minimize the risk of performance bias. Those meeting the following criteria were excluded: chief of the department, colleagues involved in study group or expert group.

All patients treated on the ICU wards during the study were included in the analysis except for patients with less

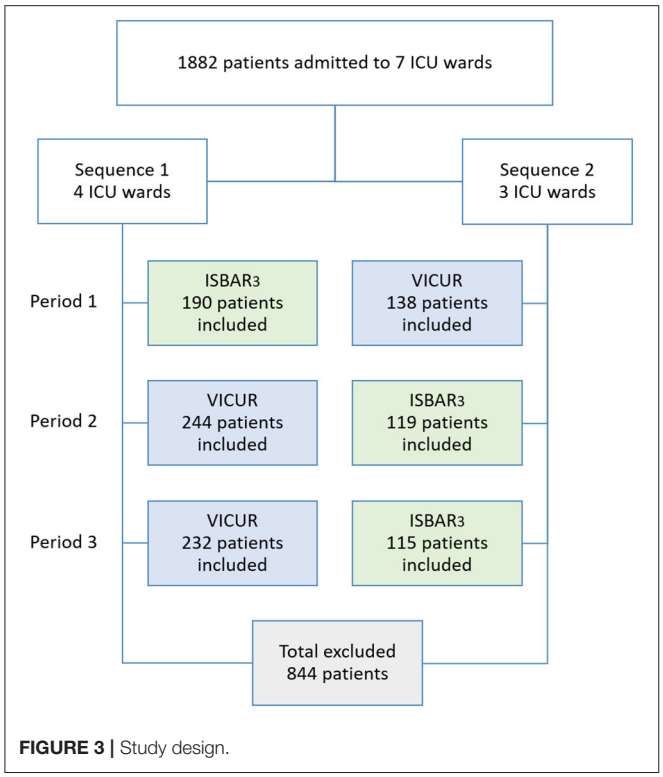

FIGURE 3 | Study design.

than two documented handovers with the checklist. Moreover, all patients under the age of 18 years and pregnant women were excluded due to different standard values for the patient-related outcomes.

Study Design

We conducted a two-armed cluster-randomized crossover prospective single center pilot study, using a three-period two-conditions layout, in which $ISBAR_3$ (A) and VICUR (B) served as two conditions. Specifically, we used a balanced model with the two sequences ABB and BAA. The participating ICU wards were assigned to two sequences by a random allocation rule with a ratio of 3:4 (**Figure 3**). Randomization lists were created with randomizeR (24) and conducted by our statistician.

Three times a data collection period of one month was followed by a one-month wash-out period (30 days each). During the data collection periods, two different checklists were used (see Intervention section for details) and online satisfaction questionnaires were delivered afterwards. Blinding was reached by concealing the purpose of both checklists from the study participants, i.e., the physicians were not told what the idea behind the $ISBAR_3$ and VICUR checklists was. Respectively participants were instructed to carry out the bedside handover as usual—performing it at the physicians' shift changes every 12 h—while using the checklists and ticking off all items. The participants did not know in advance which checklist would be used.

Intervention

An *online based application* (app), to which the physicians had access via tablets (iPad Mini®), was created in collaboration with the Department for Medical Statistics. The use of the app had the following benefits: Recording the demographic data (e.g., age, function, or experience) of the performing physicians, providing the checklists, and checking off of items that have already been completed, recording of time and assignment of the recorded data to the patient. Brief instructions for the usage of the tablets and the study-procedure were performed before data collection.

Physicians were instructed to use the checklists as mnemonic and structuring aid during shift-to-shift handovers that took place twice a day. The two *checklists* used were $ISBAR_3$ and VICUR.

Checklist $ISBAR_3$ (**Figure 1**): The concept SBAR (Situation, Background, Assessment, Recommendation), initially established in the US Navy (16), is a communication tool that creates the conditions for an effective, succinct, timely, and consistent transfer of communication (16) in complex situations (25). It is standardized, simple, structured, flexibly applicable to a wide variety of settings (26) and has also been adapted to healthcare (27, 28). The use of SBAR allows the reduction or avoidance of errors caused by misunderstandings, loss of information, or misinterpretation (26). It has been recommended by the WHO (29), the Joint Commission (30), and the German Society of Anaesthesiology and Intensive Care Medicine (DGAI) (31) for use during handover as well as by the Institute for Healthcare Improvement (IHI) (32) and the Agency for Healthcare Research and Quality (AHRQ) (33) for use in critical situations.

$ISBAR_3$ (Identification, Situation, Background, Assessment, Recommendation, Read-back, Risk) is an adaptation of SBAR. The addition of the letter "I" is intended to ensure knowledge of the identity of the conversation partners and the patient they are talking about (7) and to guarantee mutual attention. Adding two "Rs" allows the sender to check if the conversation partner has received the transmitted information (7, 34) and enables possible further inquiries (10). Potential risks for the subsequent patient treatment are pointed out.

Checklist VICUR (**Figure 2**): VICUR (Vaccination status, Insurance status, Contact person, Utilization, Rehabilitation) is a checklist developed by a group of experts inspired by the "Project White List" ("Projekt Weisse Liste") (35) which is a guidepost in the German health care system offering patients and their relatives support in their search for suitable doctors, hospitals, and nursing facilities. VICUR is an alternative checklist with healthcare background which does not include communication and patient safety aspects and was therefore introduced as a control condition to minimize Hawthorne effects.

A *satisfaction questionnaire* was designed on the basis of expert opinions to assess the potential influence of using checklists on the completeness, structure and duration of physician handovers. Also, the perceived influence on the patient outcome and the willingness to continue using the checklist were captured. Finally, the overall checklist was evaluated on the basis of grades (scale from 1 to 6, 1 being "excellent", 6 being "very poor") and free text evaluation.

Outcome Measurements

For descriptive purposes, we assessed demographic data, specialization, professional experience in years, and professional status of the physicians. Next to physicians' data and handover duration, the patient outcome parameters SOFA score (for Days 1–5 after submission, with 2 days (48 h) being our primary outcome), mortality, length of stay (LOS), and reuptake on ICU were recorded during intervention using the IntelliSpace Critical Care and Anesthesia-system® (ICCA-system®), which is used by default in the ICUs of the University Hospital Aachen (UKA) to document patient data such as patient diagnoses, vital signs, medication and progress documentation, both by nursing staff and physicians. Communication with clinical IT systems and devices enabled precise information transfer (36). SOFA scores were recorded routinely each morning at ∼06:00 A.M. These parameters had been considered important by a group of experts, who were interviewed using the Delphi method. As a quality indicator, handover duration was recorded automatically and invisibly for the physicians. Moreover, we evaluated compliance (i.e., the percentage of handovers for which the checklists were used) and satisfaction (grades from 1 to 6, 1 being "excellent," 6 being "very poor"), via an online-based questionnaire.

Sample Size

In concordance with the extensions of the CONSORT 2010 statement (37) for randomized pilot and feasibility trials, a formal sample size calculation is not required for pilot studies. Nevertheless, a sample size justification was conducted on the basis of the number of handovers being carried out regularly within a time period of 6 months. We estimated that about 1,700 patients would receive treatments on the seven ICU wards at the University Hospital Aachen during a 6-month period.

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics (Version 25; IBM Corp., Armonk, NJ, USA) and on the basis of the intention-to-treat principle. Analyses for patient-related endpoints were performed on cluster level. Mortality was defined as the ratio of deaths and the total number of patients (in %) during the respective period; reuptake was determined as the ratio of reuptakes and the total number of patients (in %) during the respective period. Unbiased estimates for treatment differences between these endpoints were calculated after Reed (38). First, mean SOFA scores were calculated for each of the seven wards for each period in both sequences. Second, for each ward, a *treatment contrast* C was calculated based on these mean values. For Arm 1, the calculation was based on the formula C1 = (2*A – B1 – B2); for Arm 2, the calculation was based on the formula C2 = (2*B – A1 – A2), respectively. The *treatment difference* was then calculated as the difference between treatment effects, i.e., C1 – C2. Significance testing was subsequently performed based on these ward-wise treatment differences. Handover durations were calculated on handover level and compared with independent samples t-tests between checklists and, for explorative purposes, with respect to weekday (working day, i.e., Monday–Friday vs. weekend, i.e., Saturday and Sunday) and daytime (morning shift change vs. evening shift change). Moreover, assessments of the checklists by the users were analyzed. Ratings of the checklists by the employees were aggregated over periods and compared between checklists by independent samples *t*-tests. Compliance was defined as the ratio of handovers using the checklists and the number of total possible handovers. Besides comparisons between checklists, we again investigated weekday and daytime effects on the frequency of checklist use. Differences in frequency distributions between checklists were assessed with χ^2 tests. Significance for all statistical tests was assessed in a two-tailed fashion (if applicable). Significance levels were defined as $p < 0.05$ for all tests. All reported mean differences reflect the treatment difference ($ISBAR_3$ – VICUR).

RESULTS

Descriptive Statistics: Patient Data

From 1,882 patients on the wards in the respective time frame, 1038 met the inclusion criteria. 63.1% of the patients were male; mean patient age was 64.6 years. Patients were assigned from 15 different clinical departments, most frequently from the thoracic surgery, general surgery, and neurosurgery. Most of the admission diagnoses ($n = 376$) were diseases of the circulatory system. Thus, the total patient number exceeds our a-priori estimate (1,700 patients), and the final sample size of 1,038 patients meets the recommendations from the scientific literature (39–41).

Descriptive Statistics: Physician's Data

Sixty-one physicians signed the written consent and participated. 60.7% of the physicians ($n = 37$) were residents, 18% were board certified specialists ($n = 11$), 19.7% ($n = 12$) were attending physicians and 1 function (1.6%) was not reported. The most frequently reported discipline was anesthesia with 48 (78.7%) physicians. 13.1% were surgeons and only four physicians (6.6%) belonged to internal disciplines.

Clinical Outcome Parameters

SOFA Score

The results reported in **Table 1** show a significant difference for the 1st 24 h time window after ICU admission, with higher SOFA scores for $ISBAR_3$ compared to VICUR ($p = 0.02$) while the other time points yielded no significant differences. The primary outcome parameter was the SOFA score at the 2nd 24 h time window (48 h).

Mortality, LOS, and Reuptake on ICU

Within 30 days after admission, the mortality rate of patients was 8.1%. No significant difference between the checklists emerged (mean difference 1.59, $t = 0.30$, and $p = 0.77$).

The mean LOS within 30 days after admission was 6.8 ± 8.8 days. No significant difference between the checklists emerged (mean difference 5.26, $t = 1.47$, and $p = 0.20$).

The reuptake rate of patients within 30 days after admission was 7.5%. No significant difference between the checklists emerged (mean difference −7.03, $t = -1.43$, and $p = 0.21$).

TABLE 1 | Treatment difference ($ISBAR_3$ – VICUR) in SOFA scores after ICU admission.

SOFA score	Treatment difference ($ISBAR_3$ – VICUR)	*t*	*p*
First 24-h time window	2.19	3.35	**0.02***
Second 24-h time window	1.78	1.48	0.20
Third 24-h time window	0.38	0.30	0.78
Fourth 24-h time window	1.16	0.64	0.60
Fifth 24-h time window	2.22	1.33	0.25

*SOFA, sepsis-related organ failure assessment; ICU, intensive care unit; *significant at $p < 0.05$.*

Handover Duration

Average handover duration was 66.32 ± 87.10 seconds for $ISBAR_3$ and 43.91 ± 73.37 seconds for VICUR. Durations differed significantly between checklists, indicating a shorter duration for VICUR ($t = 8.02$, $p > 0.001$). No differences with respect to duration emerged between working days (Monday–Friday) and weekends (Saturday–Sunday) for both $ISBAR_3$ ($t = 0.20$, $p = 0.84$) and VICUR ($t = 1.02$, $p = 0.31$). Remarkably, for VICUR, morning handovers were significantly shorter than evening handovers ($t = 4.50$, $p < 0.001$), whereas no such effect was observed for $ISBAR_3$ ($t = 0.75$, $p = 0.45$).

Satisfaction and Compliance

Concerning satisfaction $ISBAR_3$ achieved significantly better grades than VICUR (mean difference 0.87, $t = 3.43$, $p < 0.001$). Overall, compliance was 25.4% for $ISBAR_3$ and 15.8% for VICUR. Thus, compliance was significantly higher for $ISBAR_3$ ($\chi^2 = 216.55$, $p < 0.001$). 85.1% of all $ISBAR_3$ handovers were on working days (i.e., 14.9% were on weekends), whereas the proportion was 77.2% on working days for VICUR handovers (i.e., 22.8% were on weekends). Assuming an equal distribution over all weekdays, we would expect 71.43% of handovers for working days and 28.57 of handovers for weekends. Thus, there was a culmination of checklist handovers on working days, which was more pronounced for the $ISBAR_3$ condition. This difference in distributions between checklists was statistically significant ($X^2 = 33.54$, $p < 0.001$). 58.2% of all $ISBAR_3$ handovers took place in the morning shift change; 29.7% took place in the evening shift change. In other words, $ISBAR_3$ was used almost twice as often in the morning as in the evening. For VICUR, 52.9% of handovers took place in the morning and 36.0% in the evening shift change (numbers missing to 100% were shift changes on other daytimes). Again, the difference in distributions between the two checklists was significant, confirming a relatively higher proportion for the morning shift change for $ISBAR_3$ ($X^2 = 13.65$, $p < 0.001$).

The satisfaction questionnaire was filled out by physicians 35 times (57.4%) in the first period, 31 times (50.8%) in the second period, and 27 times (44.3%) in the third period. The evaluation of the free text comments reflects the preference of $ISBAR_3$. Overall, regardless of the checklist used, the criticism ranged from occurrence of technical problems over request for detailed description of the checklist items to request for extensive training. The contents of the VICUR checklist, in contrast to $ISBAR_3$, were not considered to be relevant. Moreover, an increased expenditure of time as compared to the regular handover procedure was criticized for VICUR.

DISCUSSION

The aim of the present pilot study was to estimate effect sizes of a structured clinical handover checklist on patient-related objective outcome parameters and to investigate feasibility aspects with regard to an RCT on patient safety. Specifically, the study was the first RCT to define patient safety based on clinical outcome parameters. Results show the potential of an RCT to include large samples of patient handovers, but they also highlight a number of points to be considered. The randomized and controlled crossover design is a clear methodical strength of the study (42).

When comparing the checklists, results did not reveal a superiority concerning outcomes. In specific, no effect of the checklist was observed on our primary outcome parameter (SOFA score for the second 24 h time window/after 48 h). On the contrary, $ISBAR_3$ even yielded higher average SOFA scores on a descriptive level. The treatment difference ($ISBAR_3$ – VICUR) for this time point was 1.78, indicating a higher mean SOFA score for $ISBAR_3$, although only on a descriptive and not on a statistically significant level. However, there is evidence that the latter does not argue against the use of $ISBAR_3$ but may instead be attributed to different baseline levels in SOFA scores at the time of admission. In fact, the analysis of the SOFA scores yielded a difference between the checklists only for the first time point (first 24 h time window), which indicates differences already shortly after admission to the ICU. It appears likely that these differences were present already at the time of admission. In summary, the present data does not allow the estimation of an effect size for our primary outcome in favor of $ISBAR_3$,, and we have no reason to assume that any effect in favor of VICUR (significant or not) can be attributed to the checklist; instead, a systematic difference in baseline levels is the likely explanation. Nonetheless, from the study findings there is no reason for us to believe that SOFA scores per se are not suited as outcome parameters for a future RCT on the effects of handover checklists.

The baseline difference in SOFA scores is remarkable, given the randomization and the crossover design. Although the scores were recorded during the regular daily visits and not at the time point of admission, it seems justifiable to assume that this difference was unrelated to the checklist in use and affected SOFA scores at all following time points. A possible explanation may be a random fluctuation of SOFA scores within as well as between the ICUs over time. **Table 2** shows a considerable variation for the average day 1 SOFA scores over the three periods. Remarkably, this was most pronounced for the ICU Ward for Operative Intensive Care Medicine (OIM2) with the largest sample size,whereas the small weaning station (WEA) had relatively stable average values. This may result from different specializations and patient groups of the units. Patients on the WEA are generally already long-term treated and recovering, whereas post-abdominal-surgery patients on the OIM2 are

TABLE 2 | SOFA scores by ICU and sequence.

ICU	Sequence*	Average SOFA score for first 24 h time window (number of patients in parentheses)		
		Period 1	Period 2	Period 3
OIM1	1	8.41 (36)	7.57 (64)	7.70 (60)
OIM2	2	8.00 (92)	9.21 (83)	7.66 (78)
OIM3	1	9.26 (60)	8.66 (65)	8.85 (61)
OIM4	2	7.58 (26)	8.92 (21)	8.92 (20)
OIM5	1	7.73 (48)	7.89 (65)	7.64 (58)
OIM6	1	6.76 (46)	6.54 (50)	6.86 (53)
WEA	2	6.89 (20)	7.27 (15)	7.58 (17)

SOFA, sepsis-related organ failure assessment; ICU, intensive care unit; OIM, operative intensive care medicine; WEA, weaning ward 1 = $ISBAR_3$ – VICUR – VICUR; 2 = VICUR – $ISBAR_3$ – $ISBAR_3$; green = $ISBAR_3$, blue = VICUR.*

usually in an acute condition. The latter may foster fluctuations in average illness severity, which is captured by SOFA scores. In addition, it should be considered that patients treated on the WEA have already been to an ICU and are in a clinically improved condition ready to be weaned from ventilation. This pre-selection may have caused the lower fluctuation on WEA.

Furthermore, as seen in our study, even randomized studies may be confronted with different baseline levels of clinical outcome parameters. In an ABB/BAA design, one sequence may be more affected by within-cluster fluctuations than the other if these fluctuations vary systematically between ICU types. Both effects are likely to be more pronounced in monocentric studies with a rather small number of clusters. However, for future studies we consider it essential to avoid such baseline confounds in patient outcomes, especially since sepsis scores also have a potential influence on other patient outcomes, such as mortality, reuptake, or duration of stay. To circumvent these methodical problems, we recommend the use of a stratified randomization according to specialization for future multicentre studies. To provide an adequate randomization in a single center design, we recommend a randomization on handover level instead of cluster level.

Besides the above-mentioned baseline differences, the missing effect of checklists on mortality rates may indicate that mortality per se is a too insensitive outcome parameter. Specifically, it may be necessary to consider that the death of a patient is rather frequent in an ICU (8.1% of all patients in our sample), whereas death due to a faulty handover is a rather rare event. In the vast majority of all cases, a faulty handover will have no negative consequences at all. Only those cases are critical where handover errors lead to treatment errors. A theory on how such treatment errors can occur and lead to death is explained in Reason's Swiss Cheese Model of System Accidents (43). According to Reason, accidents do not occur due to individual failures, but require a chain of failures caused by defects in various safety barriers. In addition, particular external circumstances must arise so that these defects emerge in a certain constellation entailing that the accident actually occurs. Thus, it can be assumed for handover processes that the potential failure during handover can only be detected if certain failures result in a certain constellation of treatment errors, occurring coincidently to external relevant circumstances (e.g., the increasing health condition of a patient caused by a hospital acquired infection making him or her more vulnerable) and end up in a fatal event. For further studies it thus seems reasonable to focus on deaths as a consequence of medical treatment errors. Additionally, larger sample sizes are required to detect differences in patient safety outcome parameters like mortality. This elaborate study has some limitations which are summarized in the following topics. An important point of discussion is that the study is conducted in a single-center design and further investigations are necessary to confirm a strong transferability. Furthermore, it is a challenge to define a good standard comparison group within the two options given. Comparing either the investigated intervention using digital handovers checklist with the current most representable situation in clinical departments, where handovers are done without a checklist is methodically very imprecise, or with content that does not concern patient safety issues difficult in terms of acceptance of the users thus challenging.

The randomized and controlled crossover design is a clear methodical strength of the study (42). However, looking at the satisfaction ratings our findings indicate that the two study arms (checklists) differed in their acceptance among the medical staff, suggesting that the perceived uselessness of VICUR was the major cause for the low compliance. VICUR was easily recognized as a control checklist by the physicians, which is also a likely explanation for the shorter duration of VICUR handovers. In a way, this corresponds to a kind of unvoluntary "self-unblinding" of the experimental condition. VICUR can thus be considered critical as a control condition. With regard to future multicentre studies, the use of control checklists such as VICUR should therefore be scrutinized. Instead, it appears more valid to compare a checklist to conventional handovers without a checklist. Here, potential Hawthorne effects could be avoided by informing the participants in both conditions that their performance is part of a study.

Furthermore, overall compliance was very low, with $ISBAR_3$ being used in 25.4% and VICUR in only 15.8% of handovers. Under these circumstances clinical outcomes in both conditions are mainly based on handovers without any checklist and these low compliance rates drastically reduce statistical power. In order to increase the physicians' long-term motivation in future studies, incentives could be provided through an incentive system which analyses the physicians' needs and improvement suggestions such as simplifications of the daily workflow by integrating the checklist into the computer system and accessing it via tablet.

A remarkable finding was that, compared to VICUR, $ISBAR_3$ was used preferably on working days and in the morning shift change. This is a very interesting aspect that, in our view, is a valuable puzzle piece for understanding the compliance with checklist use. A plausible explanation for this pattern of use is the presence of a senior physician during the handover/shift change in the morning on working days. In particular, we assume that senior physicians foster compliance by encouraging the use of a handover checklist since, based on their knowledge and experience, they consider it useful. Remarkably, this effect

is mainly limited to $ISBAR_3$, which is again in line with the perceived uselessness of VICUR.

There are two tentative conclusions that can be drawn from these findings. First, compliance with checklist use may benefit from an education on background and purpose of checklists. Second, control checklists such as VICUR are seemingly inadequate control conditions. Based on the present findings, it should even be taken into consideration that their use in studies may be harmful. If they are perceived as useless and if their use is not encouraged by senior physicians, it appears conceivable that they evoke the general impression of checklists being a waste of time. Especially for young residents, this would be a highly undesired effect.

In addition, compliance and the overall outcome could be increased by training in handover practices (15), to improve and fasten handover during stressful situations (31). Indeed, findings on the WHO Surgical Safety Checklist suggest that the effect of a checklist on patient safety aspects may be substantially larger when combined with team training on its correct application (44).

As these are complex strains, more experience has to be gathered and analyzed in further investigations. The authors are convinced that the present study provides an important scientific contribution to this topic and serves as guidance for further research.

CONCLUSION

Medical handovers are a burning issue in medicine concerning patient safety. Their continuous application and improvement are important goals. The present pilot study illustrates the complexity of this topic and shows both the potential and the pitfalls concerning outcome parameters and feasibility that should be considered in a future multicentre study. Further research is needed to measure the direct impact of structured handovers on patient outcomes with unambiguous parameters.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was reviewed and approved by the Ethics Committee of the Faculty of Medicine of RWTH Aachen University (EK 075/17) on 24 May 2017. The study protocol was designed and performed in line with the Declaration of Helsinki. Written informed consent was obtained from all physicians working on ICU wards during data acquisition. They were informed that their participation was voluntary and could be discontinued at any time without explanation or any disadvantages.

AUTHOR CONTRIBUTIONS

NV contributed substantially to the acquisition, analysis, and interpretation of the data and has written the manuscript. SS, SB, MS, and GM contributed substantially to the interpretation of the data and have critically revised the manuscript for important intellectual content. SS, MK, and LV contributed substantially to the designing of this study, the statistical analysis, and interpretation of the data. SS made substantial contributions to the planning and designing the study protocol, analysis, and interpretation of the data, assisted to the writing of the manuscript as well he revised it critically for important intellectual content. SS supervised the study and supported NV as senior investigator. All authors reviewed and revised the manuscript. All authors have made contributions to the manuscript.

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Delta Shock Index During Emergency Department Stay Is Associated With in Hospital Mortality in Critically Ill Patients

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Background: Delta shock index (SI; i.e., change in SI over time) has been shown to predict mortality and need for surgical intervention among trauma patients at the emergency department (ED). However, the usefulness of delta SI for prognosis assessment in non-traumatic critically ill patients at the ED remains unknown. The aim of this study was to analyze the association between delta SI during ED management and in-hospital outcomes in patients admitted to the intensive care unit (ICU).

Method: This was a retrospective study conducted in two tertiary medical centers in Taiwan from January 1, 2016, to December 31, 2017. All adult non-traumatic patients who visited the ED and who were subsequently admitted to the ICU were included. We calculated delta SI by subtracting SI at ICU admission from SI at ED triage, and we analyzed its association with in-hospital outcomes. SI was defined as the ratio of heart rate to systolic blood pressure (SBP). The primary outcome was in-hospital mortality, and the secondary outcomes were hospital length of stay (HLOS) and early mortality. Early mortality was defined as mortality within 48 h of ICU admission.

Result: During the study period, 11,268 patients met the criteria and were included. Their mean age was 64.5 ± 15.9 years old. Overall, 5,830 (51.6%) patients had positive delta SI. Factors associated with a positive delta SI were multiple comorbidities (51.2% vs. 46.3%, $p < 0.001$) and high Simplified Acute Physiology Score [39 (29–51) vs. 37 (28–47), $p < 0.001$). Patients with positive delta SI were more likely to have tachycardia, hypotension, and higher SI at ICU admission. In the regression analysis, high delta SI was associated with in-hospital mortality [aOR (95% CI): 1.21 (1.03–1.42)] and early mortality [aOR (95% CI): 1.26 (1.07–1.48)], but not for HLOS [difference (95% CI): 0.34 (−0.48 to 1.17)]. In the subgroup analysis, high delta SI had higher odds ratios for both mortality and early mortality in elderly [aOR (95% CI): 1.59 (1.11–2.29)] and septic patients [aOR (95% CI): 1.54 (1.13–2.11)]. It also showed a higher odds ratio for early mortality in patients with triage SBP < 100 mmHg [aOR (95% CI): 2.14 (1.21–3.77)] and patients with triage SI ≥ 0.9 [aOR (95% CI): 1.62 (1.01–2.60)].

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Conclusion: High delta SI during ED stay is correlated with in-hospital mortality and early mortality in patients admitted to the ICU via ED. Prompt resuscitation should be performed, especially for those with old age, sepsis, triage SBP < 100 mmHg, or triage SI ≥ 0.9.

Keywords: delta shock index, emergency department, mortality, critical ill, intensive care unit

INTRODUCTION

In the emergency department (ED), the survival rate of patients is mainly determined by the severity of acute illness on admission (1, 2) and the quality of care throughout the treatment process (3). Numerous scoring systems based on physiological parameters recorded in the ED have been developed for initial patient assessment and the identification of patients at risk (4–7). Nevertheless, patient deterioration and unexpected death are often preceded by abnormalities in vital signs in the ED (8, 9). It is important to document vital sign changes in the ED for physicians to provide adequate management.

Shock index (SI), calculated from the two most commonly used physiological measures [heart rate (HR) divided by systolic blood pressure (SBP)], is a simple bedside assessment originally developed to evaluate the degree of shock in hemorrhagic and septic patients (10). In recent studies, it has been used for the prediction of outcomes in other critically ill patients, including those with severe sepsis (11, 12), hemorrhagic shock (13), pulmonary embolism (14), and acute myocardial infarction (15). An SI <0.9 is considered to be associated with increased mortality risk (16). This cutoff value of the SI may help with early mobilization of resources in the ED.

Recently, it has been noted that delta SI (i.e., change of SI over time) predicts mortality in apparently hemodynamically stable trauma patients with normal traditional vital signs in the ED (17, 18). A similar result has been observed for postpartum hemorrhage in the ED; delta SI was superior in identifying the need for emergent intervention than other traditional vital signs (19).

However, research on the prognosis value of delta SI in critically ill patients in the ED is scarce. The aim of this study was to analyze the association between delta SI in the ED and in-hospital outcomes of critically ill patients who required intensive care unit (ICU) admission. Having a simple index that reliably correlates pre-ICU admission physiological parameters to mortality would be ideal to assess the quality of care in critically ill patients.

METHOD

This was a retrospective database study conducted in two tertiary medical centers in Taiwan from January 1, 2016, to December 31, 2017. One hospital was located in northern Taiwan and the other in southern Taiwan, and they were both the largest medical centers in their metropolitan areas. The study protocol was approved by the institutional review board of both hospitals (IRB number 202002043B0; date of approval, December 1, 2020). All patients' and physicians' records and information were anonymized and de-identified before analysis.

All adult non-traumatic patients visiting the ED and subsequently admitted to the ICU were included. Patients with uncertain outcomes (discharged against medical advice and transferred to another hospital), transferred from other hospitals, presented with out-of-hospital cardiac arrest, or deceased at the ED were excluded (**Figure 1**). Patients' demographic data (age and sex), underlying comorbidities, vital signs at triage and at ICU admission, laboratory tests, and diagnosis at ICU admission were extracted from the electronic medical records of the studied hospitals for analysis. The Simplified Acute Physiology Score (SAPS) was computed based on the collected parameters for severity evaluation (20).

We calculated SI, defined as the ratio of HR to SBP, from vital signs at ED triage and at ICU admission. Delta SI was calculated by subtracting SI at ICU admission from SI at ED triage. Patients were then divided into two groups (patients with a positive delta SI and patients with zero or negative delta SI), and their demographics and clinical characteristics were compared. The primary outcome was in-hospital mortality, and the secondary outcomes were hospital length of stay (HLOS) and early mortality. Early mortality was defined as mortality within 48 h of ICU admission. We also performed subgroup analysis based on patient's age, comorbidity, vital signs, and diagnostic categories to clarify the association of delta SI to patient's outcome in different clinical conditions. Age older than 65 years was considered as elderly.

Data are presented as the mean (standard deviation) for continuous variables, proportions for nominal variables, and median (interquartile range) for ordinal variables. We performed Student's *t*-test and chi square analysis to determine the parameters that correlated with positive delta SI and with zero or negative SI. Logistic regressions assessing the association of clinical outcomes with delta SI were performed after adjusting for confounding factors. A two-sided $p < 0.05$ was considered statistically significant. Stratified regression analyses assessing the relationship between delta SI and clinical outcomes in different ages, comorbidities, vital signs, and diagnosis categories were also performed. All statistical analyses were conducted using IBM SPSS Statistics for Mac (Version 26).

RESULT

During the study period, 11,268 patients who met the criteria were included. Their mean age was 64.5 ± 15.9 years, and 64.3% were male. The average SAPS was 38 (29–49). Of all patients,

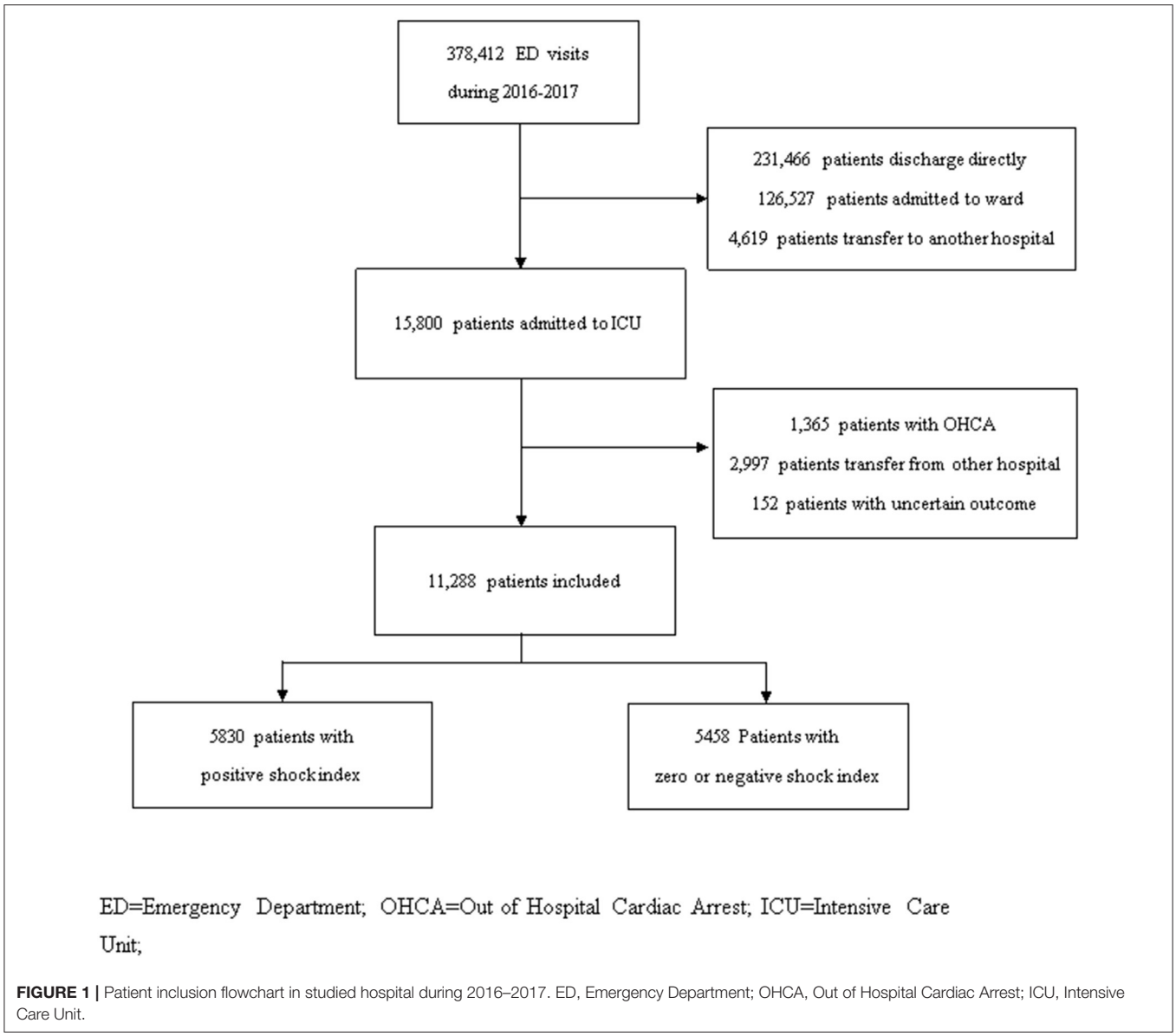

FIGURE 1 | Patient inclusion flowchart in studied hospital during 2016–2017. ED, Emergency Department; OHCA, Out of Hospital Cardiac Arrest; ICU, Intensive Care Unit.

5,830 (51.6%) had a positive delta SI. The parameters significantly associated with positive delta SI were multiple comorbidities (51.2% vs. 46.3%, $p < 0.001$) and high SAPS [39 (29–51) vs. 37 (28–47), $p < 0.001$]. In addition, compared with patients with zero or negative delta SI, patients with positive delta SI were less likely to have tachycardia, hypotension, and high SI at ED triage. Conversely, they were more likely to present with tachycardia, hypotension, and high SI at ICU admission (**Table 1**). Regarding prognosis at the ICU (**Table 2**), positive delta SI was significantly associated with higher mortality (20.3 vs. 18.9%, $p = 0.032$) and early mortality (6.5 vs. 5.2%, $p = 0.005$) than was zero or negative delta SI, while no significant relationship was observed with HLOS (13 vs. 13 days, $p = 0.277$).

On binary logistic regression analysis, highly positive delta SI was an independent risk factor for in-hospital mortality [adjusted odds ratio (95% CI): 1.21 (1.03–1.42)] and early mortality [adjusted odds ratio (95% CI): 1.26 (1.07–1.48)]. On the other hand, the linear regression analysis on the association of delta SI with HLOS showed no significant difference [difference (95% CI): 0.34 (−0.48 to 1.17); **Table 3**].

In the subgroup analysis, high delta SI had higher odds ratios for mortality in elderly patients [adjusted odds ratio (95% CI): 1.59 (1.11–2.29)] and in patients with a diagnosis of sepsis [adjusted odds ratio (95% CI): 1.54 (1.13–2.11)], with respect to other age ranges and diagnoses, respectively. The analysis also showed higher odds ratios for early mortality in elderly patients [adjusted odds ratio (95% CI): 1.66 (1.06–2.38)], in patients with triage SBP < 100 [adjusted odds ratio (95% CI): 2.14 (1.21–3.77)], in patients with triage SI ≥ 0.9 [adjusted odds ratio (95% CI): 1.62 (1.01–2.60)], and in patients with a diagnosis of sepsis [adjusted odds ratio (95% CI): 1.46 (1.03–1.94)], compared with the other possibilities of each category. There were no statistical

TABLE 1 | Demographic and clinical characteristics in comparison of positive delta SI with zero or negative delta SI.

Variables	Positive delta SI (n = 5,830)	Zero or negative delta SI (n = 5,458)	p-value
Age, year, median (IQR)	65 (54–76)	66 (54–77)	0.984
Male sex, %	64.0	64.6	0.467
Comorbidity≥2, %	51.2	46.3	<0.001
ED LOS, hours, median (IQR)	12.1 (6.3-18.1)	11.9 (6.1-17.7)	0.639
at ED Triage, mean (SD)			
Heart rate	90 (24.1)	104 (25.8)	<0.001
SBP	158 (37.0)	124 (33.5)	<0.001
DBP	90 (22.5)	75 (22.8)	<0.001
SI	0.60 (0.35)	0.91 (0.31)	<0.001
at ICU admission, mean (SD)			
Heart rate	94 (21.5)	89 (21.5)	<0.001
SBP	128 (26.6)	134 (26.9)	<0.001
DBP	74 (17.6)	76 (17.1)	<0.001
SI	0.78 (0.24)	0.69 (0.25)	<0.001
Severity score, median (IQR)			
SAPS	39 (29-51)	37 (28-47)	<0.001
In-hospital outcome			
Mortality, %	20.3	18.9	0.032
Mortality in 48 h, %	6.5	5.2	0.005
HLOS, d, median (IQR)	13 (7-23)	13 (7-23)	0.277
Comorbidity, %			
Hypertension	42.1	33.7	<0.001
Diabetes mellitus	23.0	22.4	0.449
Heart failure	13.5	14.5	0.128
Liver cirrhosis	6.9	9.8	<0.001
End stage renal disease	8.2	8.0	0.629
Malignancy	11.4	14.6	<0.001
Old stroke	30.7	22.8	<0.001

SI, Shock Index; IQR, Interquartile Range; SD, Standard Deviation; ED LOS, Emergency Department Length Of Stay; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SAPS, Simplified Acute Physiology Score; HLOS, Hospital Length Of Stay.

differences in the regression analyses regarding patients with a diagnosis of respiratory failure and heart failure in either of the two in-hospital outcomes with previous significant relationships.

TABLE 2 | Logistic Regression analysis of delta Shock Index to in-hospital outcome.

	aOR (95% CI)	p-value
Mortality	1.21 (1.03–1.42)	0.021
Early mortality	1.49 (1.13–1.96)	0.005
HLOS, d	0.34 (−0.48–1.17)	0.417

**logistic regression analysis performed by adjusting confounding factors include age, sex, comorbidities and SAPS.*
SI, Shock Index; HLOS, Hospital Length Of Stay; aOR, adjusted Odds Ratio.

DISCUSSION

The aim of this study was to determine the relationship between delta SI during ED management and in-hospital outcomes in patients admitted to the ICU via ED. In this study, we found that positive delta SI is more likely to occur in patients with multiple comorbidities and in patients who present at the ED with high SAPS, as shown in **Table 1**. There is no doubt that comorbidity is an important factor in estimating a patient's outcome; and in some cases, the patient's comorbid condition presents a greater risk than the index disease (21). Therefore, the association between delta SI and comorbidity was foreseeable: patients presenting to the ED with more comorbidities are at greater risk of deterioration. A similar conclusion can be drawn for patients with scores that indicate severe conditions, which were often admitted to the ICU. SAPS (20), which includes items such as age, physiological parameters, type of admission, and chronic diseases, is a reliable indicator of the risk of death upon ICU admission. Patients with high SAPS, which theoretically indicates poor outcome for patients admitted to the ICU, tended to have positive delta SI.

Moreover, the positive delta SI group had better initial vital signs than the zero or negative delta SI group. For this

TABLE 3 | Subgroup regression analysis of delta SI to in-hospital mortality and early mortality.

	Mortality		Early mortality	
	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Age				
≥65	1.59 (1.11–2.29)	0.012	1.66 (1.06–2.38)	0.013
18-64	1.02 (0.71–1.34)	0.875	1.65 (0.91–2.98)	0.098
Comorbidity≥2	1.09 (0.76–1.56)	0.657	1.45 (0.76–2.79)	0.260
Vital sign				
Triage SBP≥100	1.05 (0.74–1.49)	0.802	1.19 (0.65–2.17)	0.572
Triage SBP < 100	1.03 (0.65–1.61)	0.908	2.14 (1.21–3.77)	0.009
Triage SI ≥ 0.9	0.95 (0.64–1.39)	0.773	1.62 (1.01–2.60)	0.038
Triage SI < 0.9	1.07 (0.82–1.39)	0.641	1.13 (0.73–1.74)	0.594
Diagnosis				
Sepsis	1.54 (1.13–2.11)	0.007	1.46 (1.03–1.94)	0.033
Respiratory failure	0.97 (0.85–1.11)	0.645	1.06 (0.86–1.29)	0.596
Heart failure	1.22 (0.86–1.73)	0.260	1.64 (0.90–3.00)	0.108

**logistic regression analysis performed by adjusting confounding factors include age, sex, comorbidities and SAPS.*
SI, Shock Index; SBP, Systolic Blood Pressure; aOR, adjusted Odds Ratio.

paradoxical phenomenon, ED clinicians usually spend more time and effort managing patients with worse vital signs. And this condition may lead to delayed assessment and treatment or to relatively conservative treatment in this group of patients with initially better vital signs at ED assessment (22, 23). In addition, patients in the negative delta SI group presented with higher SI (mean: 0.91) at ED triage, so they required aggressive and fast management due to their initially unstable conditions. Thus, more effort (continuous bedside evaluation, resuscitation, and re-evaluation) was devoted to them (24–26). Intubation, ventilation, volume support, and even vasoactive therapy were initiated earlier in the group of patients with worse vital signs, leading to negative delta SI in this group of patients.

Regarding the association between delta SI and in-hospital outcomes, there was a statistically significant difference between positive delta SI (worsened SI) and zero or negative delta SI (improved SI) in mortality and early mortality. Previous studies have demonstrated that positive delta SI during ED management is a strong predictor of mortality and of need for blood product transfusion in trauma patients (27). Regarding the connection between delta SI and HLOS, there was no statistically significant difference between the positive and negative delta SI groups based on our data (**Table 2**). Similar results were obtained after adjusting for confounding factors: high delta SI was an independent risk factor for both mortality and early mortality. Delta SI appeared to be an effective and efficient index of great relevance in rapid deterioration after ED admission. Conversely, high delta SI was not related to long HLOS in the regression analysis.

In this study, we further separated participants into subgroups for stratified analysis. High delta SI had higher odds ratios for mortality and early mortality in the elderly. Since progressive decline in various physiological functions has been noted in the elderly (28, 29), physiological stresses that were not serious at young ages can be life-threatening in old age (30). Fluctuations in HR and SBP are key factors for mortality among critically ill elderly individuals. Therefore, closely monitoring vital signs and of changes in delta SI is more important in elderly patients in situations of illness deterioration.

The subgroup analysis of vital signs highlights the importance of altered SBP and SI at triage; in patients with these parameters, high delta SI has higher odds ratio for early mortality. Patients with SBP > 100 mmHg at triage and with high delta SI present higher incidence of early mortality after ICU admission. This is consistent with previous studies that revealed that SI may be a predictor of mortality (31, 32) in critically ill patients. Since mortality in patients with shock with hypoperfusion remains high, as reported previously (19), we offer a more robust dynamic index to ensure that early intervention and management are available to these critically ill patients. While a high SI at ED triage was a predictor of mortality in previous studies (31, 33), aggressive resuscitation and close monitoring before ICU admission should be performed to avoid adverse outcomes.

Concerning the stratified analysis per diagnoses, we found that high delta SI in patients with sepsis is correlated with high mortality and early mortality. This corroborates the results of previous studies on the association between high SI and outcome in septic patients (12, 32). Similar results were not found for patients with diagnoses of respiratory failure or heart failure. Respiratory distress and respiratory failure could be unrelated to hypotension and HR alterations (34). In addition, patients with respiratory failure may need advanced airway ventilation or even mechanical ventilation, and the hemodynamic effects of mechanical breathing are quite complex (35). These factors might affect delta SI during ED management. Moreover, heart failure is caused by structural and functional defects in the myocardium, which result in impairment of ventricular filling or ejection of blood. Early stages of heart failure often lack specific signs, such as tachycardia or other classic presentations (36–38). Therefore, less association of delta SI with clinical outcomes can be presumed in heart failure patients who were admitted to the ICU.

Our study has several limitations. First, retrospective studies rely mostly on administrative data, which is limited by the information documented on medical records. Second, the study was conducted in two tertiary care EDs with similar systems; thus, the generalizability of these findings may be limited to comparable institutions. However, we believe that the number of patients analyzed in our article is enough to support our conclusions, and both studied hospitals nearly meet the highest medical standards in Taiwan. Further prospective studies should be conducted for a more precise analysis of our results; nevertheless, we believe that our research has laid good foundations for this research field. In conclusion, our results indicate that high delta SI may be greatly related to poor prognosis among critically ill patients, especially to early mortality. Elderly critically ill patients with poor vital signs at ED triage and a diagnosis of sepsis should be carefully monitored and assisted with prompt resuscitation and intensive treatment before admission to the ICU. We

believe that it is crucial to monitor delta SI while managing patients and that delta SI could play an important role in clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study protocol was approved by the institutional review board of both hospitals. All patients' and physicians' records and information were anonymized and de-identified before analysis.

AUTHOR CONTRIBUTIONS

Chi-FL: conceptualization and supervision. Y-SH, Chu-FL, I-MC, and Chi-FL: data curation and methodology. M-TT and Y-SH: formal analysis. M-TT, Y-SH, and Chi-FL: investigation. I-MC and Chi-FL: validation, writing—review, and editing. Y-SH and Chi-FL: visualization. Y-SH, I-MC, and Chi-FL: writing—original draft. All authors contributed to the article and approved the submitted version.

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Coagulopathy Induced by Veno-Arterial Extracorporeal Membrane Oxygenation Is Associated With a Poor Outcome in Patients With Out-of-Hospital Cardiac Arrest

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Background: In recent years, the use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in patients with cardiopulmonary arrest who do not respond to conventional resuscitation, has increased. However, despite the development of VA-ECMO, the outcomes of resuscitated patients remain poor. The poor prognosis may be attributed to deterioration owing to the post-cardiac arrest syndrome (PCAS); this includes the systemic inflammatory response and coagulation activation caused by the extracorporeal circulation (VA-ECMO circuit) itself. This study aimed to evaluate the coagulofibrinolytic changes caused by VA-ECMO and to identify predictive factors of poor prognosis.

Methods: We analyzed 151 cases of PCAS with witnessed cardiac arrest. As biomarkers, platelet counts, prothrombin time ratio, fibrin/fibrinogen degradation products, fibrinogen, antithrombin, and lactate were recorded from blood samples from the time of delivery to the third day of hospitalization. The maximum (max) and minimum (min) values of each factor during the study period were calculated. To evaluate the impact of VA-ECMO on patients with PCAS, we performed propensity score matching between the patients who received and did not receive VA-ECMO. Sub-analysis was performed for the group with VA-ECMO.

Results: There were significant differences in all baseline characteristics and demographics except the time from detection to hospital arrival, percentage of cardiopulmonary resuscitations (CPR) by witnesses, and the initial rhythm between the groups. Propensity score matching adjusted for prehospital factors demonstrated that the patients who received VA-ECMO developed significantly severe coagulation disorders. In a sub-analysis, significant differences were noted in the prothrombin time ratio min, fibrinogen max, antithrombin max, and lactate min between survivors and non-survivors. In particular, the prothrombin time ratio min and antithrombin max were strongly correlated with poor outcome.

Conclusion: In the present study, significant coagulopathy was observed in patients who received VA-ECMO for CPR. In particular, in patients receiving VA-ECMO, the minimum prothrombin time ratio and maximum antithrombin by day 3 of hospitalization were strongly correlated with poor outcomes. These results suggest that VA-ECMO-induced coagulopathy can be a promising therapeutic target for patients resuscitated by VA-ECMO.

Keywords: veno-arterial extracorporeal membrane oxygenation, out-of-hospital cardiac arrest, post-cardiac arrest syndrome, disseminated intravascular coagulation, antithrombin

INTRODUCTION

Patients resuscitated after out-of-hospital cardiac arrest (OHCA) often develop a post-cardiac arrest syndrome (PCAS), a complex combination of the pathophysiological processes of post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion responses, and persistent precipitating pathology (1). The main pathophysiology of the systemic ischemia-reperfusion response is the systemic inflammatory response syndrome (SIRS) and hypercoagulation, that lead to disseminated intravascular coagulation (DIC) (2, 3). DIC is characterized by the widespread activation of tissue-factor-dependent coagulation, inadequate control of coagulation by physiological anticoagulation pathways due to endothelial activation and damage, fibrin formation within the vessels, and eventually thrombotic occlusion of the vessels and associated deterioration of oxygen supply to cells and tissues (4). These changes cause damage to the microvasculature and organ dysfunction (4, 5). In particular, DIC-induced thrombotic obstruction of the brain, called the "no-reflow phenomenon," is characterized by impaired reperfusion after cerebral ischemia, despite stable systemic circulatory status (6). These findings suggest that PCAS-related coagulopathy is closely associated with the pathophysiology of post-cardiac arrest brain injury, which is the leading cause of death in patients with PCAS (2).

In recent years, guidelines suggest the use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in patients with cardiopulmonary arrest (CPA) who are unresponsive to conventional resuscitation (7, 8); in addition, substantial experience and research data have been accumulated on VA-ECMO as a resuscitative strategy. Although the recommendation for VA-ECMO in the guideline is of level of 2b (level of evidence C-LD [limited data]) (8), the survival rate and neurological outcomes of PCAS remain poor.

A recent study showed that extracorporeal circulation itself induces systemic inflammation and coagulation activation due to the exposure of the patient's blood to non-endothelialized surfaces of the ECMO circuit (9). These results suggest that the induction of VA-ECMO exacerbates PCAS-related SIRS and DIC, leading to poor outcomes in those who receive VA-ECMO. Nonetheless, the prognostic effect of VA-ECMO-induced coagulopathy remains unclear.

The purpose of this study was to evaluate the coagulofibrinolytic changes caused by ECMO and to identify factors that may be associated with poor outcomes.

MATERIALS AND METHODS

Patients

We identified 246 patients aged 18 years or older, who were resuscitated after OHCA due to cardiac causes from January 2010 to December 2017, and were subsequently admitted to the intensive care unit of the Hokkaido University Hospital. The exclusion criteria were as follows: (1) patients under 18 years of age, (2) those who were not resuscitated after cardiac arrest, (3) those who had cardiac arrest due to trauma, acute aortic dissection, or rupture of aortic aneurysms, (4) those on anticoagulant therapy, and (5) those with an underlying coagulofibrinolytic disorder. After excluding cases with unknown times of cardiac arrest and cases with missing data, we analyzed data from those with witnessed cardiac arrest. We retrospectively conducted a systematic review of the computer-based medical records of these patients to obtain baseline data and DIC-related parameters. Coagulofibrinolytic markers, including platelet counts, prothrombin time (PT) ratios, fibrin/fibrinogen degradation products (FDP), fibrinogen values, antithrombin values (AT), and lactate values from the blood samples, were recorded from the time of arrival to the third day of hospitalization. Each parameter was measured at the following four time points: time of arrival in the ED, ED arrival to 24 h after hospitalization, 24–48 h after hospitalization, and 48–72 h after hospitalization. To evaluate the changes in each factor on the prognosis, the maximum (max) and minimum (min) values of each factor at these four points were also calculated. All the patients were divided into two groups: the VA-ECMO+ group, consisting of patients who received VA-ECMO and the VA-ECMO- group, consisting of patients who did not receive VA-ECMO. VA-ECMO was introduced in accordance with the criteria of the SAVE-J study (**Table 1**) (10). Unfractionated heparin was used for anticoagulation during VA-ECMO. The dose of unfractionated heparin was adjusted to maintain an activated clotting time (ACT) of 180–220 seconds or an activated partial thromboplastin time (APTT) of 1.5–2.5 times the baseline value.

Definition

DIC was diagnosed based on the Japanese Association for Acute Medicine (JAAM) DIC score (11) and the International Society on Thrombosis and Haemostasis (ISTH) DIC score (5). Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) score (12). In addition, during the study period, we calculated the maximum and minimum values for

TABLE 1 | Criteria for implementing veno-arterial extracorporeal membrane oxygenation.

Inclusion criteria
VF/VT on the initial ECG
No ROSC at least during the 15 min after hospital arrival (or after contact with a doctor) even though conventional CPR was performed
Within 45 min from reception of the emergency call or the onset of cardiac arrest to the hospital arrival
Exclusion criteria
Under the age of 20 years or those aged 75 years or older
Poor level of activities of daily livings before the onset of cardiac arrest
No informed consent from the individuals representing patients

VF, ventricular fibrillation; VT, ventricular tachycardia; ECG, electrocardiogram; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation.

each score as well as those for the coagulofibrinolytic markers. Disease severity was assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) II score (13). The outcomes were assessed using the hospital mortality and cerebral performance category (CPC) scale (14) at 28-hospital days. We defined CPC 1 and 2 as favorable neurological outcomes and CPC 3 to 5 as unfavorable neurological outcomes.

Statistical Analysis

Data for continuous variables have been presented as medians and interquartile ranges (25th–75th percentiles). Categorical data have been presented as frequencies and percentages. Patient characteristics and outcomes were compared between the two groups using the Mann–Whitney U test (for numerical variables) and the Fisher's exact test (for categorical variables). Propensity score matching was performed between the VA-ECMO+ group and the VA-ECMO- group using three factors: age, sex, and time from detection to hospital arrival. A sub-analysis evaluated the impact of each coagulofibrinolytic marker on the prognosis using logistic regression analysis (backward elimination [likelihood ratio]) and area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The optimal cutoff value of the ROC curve was calculated using the Youden index. Variables found to be statistically significant at the 10% level on univariate analysis were included in the multivariate model. All analyses were performed using IBM SPSS software (version 25; IBM Japan, Tokyo, Japan). All reported p values were two-tailed, and differences were considered statistically significant at p values of < 0.05.

Ethics

The study protocol was approved by our Institutional Review Board (approval number: 180831), and the requirement for informed consent was waived due to the retrospective design of the study.

RESULTS

Clinical Characteristics of the Patients

We analyzed 151 cases from 246 OHCA patients with ROSC, excluding those with no witnesses and those with missing data (**Figure 1**). **Table 2** shows the background of the OHCA patients ($n = 151$) who were included in this study. Sixty-one patients received VA-ECMO (VA-ECMO+) and 90 did not (VA-ECMO-). There was a significantly higher proportion of males in

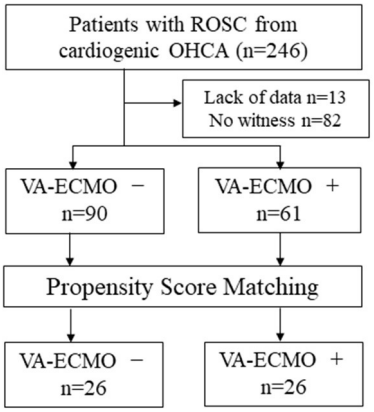


FIGURE 1 | Flow chart of study population. ROSC, return of spontaneous circulation; OHCA, out-of-hospital cardiac arrest; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

TABLE 2 | Baseline characteristics of witnessed out-of-hospital cardiac arrest.

	VA-ECMO − ($n = 90$)	VA-ECMO + ($n = 61$)	p-Value
Age, yr	73.5 (61.0–80.0)	63.0 (52.0–68.0)	<0.001
Gender; male (%)	54 (60.0)	53 (88.3)	<0.001
Time interval (min)			
1	33.0 (27.0–38.0)	31.0 (27.0–44.0)	0.780
2	25.0 (16.3–37.0)	51.0 (42.0–64.0)	<0.001
CPR by witness, n (%)	54 (60.0)	37 (60.7)	0.536
Shockable rhythm, n (%)	43 (47.8)	40 (65.6)	0.072
Adrenalin dosage (mg)	0.0 (0.0–1.0)	2.0 (1.0–3.0)	<0.001
APACHE II score	33.0 (28.0–36.0)	37.0 (34.0–41.0)	<0.001
JAAM DIC score max	3.0 (2.0–5.0)	7.0 (6.0–8.0)	<0.001
JAAM DIC score min	1.0 (0.0–1.8)	5.0 (3.0–6.0)	<0.001
ISTH DIC score max	3.0 (2.0–4.0)	6.0 (5.0–6.0)	<0.001
ISTH DIC score min	0.0 (0.0–2.0)	3.0 (1.0–4.0)	<0.001
SOFA score max	7.0 (6.0–10.0)	13.0 (12.0–15.0)	<0.001
SOFA score min	3.0 (1.3–5.0)	10.0 (7.0–12.0)	<0.001
Hospital stay	13.5 (5.0–21.8)	12.0 (5.0–24.0)	0.824
Unfavorable neurological outcome (n, %)	61 (67.8)	54 (88.5)	0.003
Hospital mortality (n, %)	18 (20.0)	30 (49.2)	<0.001

Data presented as median (25th−75th percentile), percentage or numbers.
1, interval between the receipt of the emergency call and the hospital arrival; 2, interval between the receipt of the emergency call and ROSC or ECMO start; ROSC, return of spontaneous circulation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; APACHE II, Acute Physiology and Chronic Health Evaluation II; JAAM, Japanese Association for Acute Medicine; ISTH, International Society on Thrombosis and Haemostasis; SOFA, Sequential Organ Failure Assessment; maximum, max; minimum, min.
The unfavorable neurological outcome is defined by the cerebral performance category (CPC) scale as 3 to 5 at 28-hospital day.

TABLE 3 | Baseline characteristics of witnessed out-of-hospital cardiac arrest after propensity score matching.

	VA-ECMO − (*n* = 26)	VA-ECMO + (*n* = 26)	*p*-Value
Age, yr	62.5 (55.3–76.0)	66.5 (58.5–72.8)	0.905
Gender; male, n (%)	21 (80.1)	22 (84.6)	0.500
Time interval (min)			
1	34.5 (27.3–39.3)	30.0 (27.0–38.3)	0.436
2	34.0 (21.0–44.0)	42.0 (29.0–53.0)	0.245
CPR by witness, n (%)	15 (57.7)	16 (61.5)	0.500
Shockable rhythm, n (%)	21 (80.8)	19 (73.1)	0.372
Adrenalin dosage (mg)	0.0 (0.0–1.6)	2.0 (1.3–3.8)	<0.001
APACHE II score	34 (29.5–36.0)	37 (33.0–39.8)	0.060
JAAM DIC score max	3.5 (2.0–5.0)	7.0 (6.0–8.0)	<0.001
JAAM DIC score min	1.0 (1.0–1.0)	5.0 (3.3–6.0)	<0.001
ISTH DIC score max	3.0 (2.0–4.0)	5.5 (5.0–6.0)	<0.001
ISTH DIC score min	0.0 (0.0–1.8)	3.5 (1.3–4.0)	<0.001
SOFA score max	7.0 (5.3–8.0)	13.0 (11.3–14.8)	<0.001
SOFA score min	3.0 (2.0–4.8)	10.0 (6.0–12.0)	<0.001
Hospital stay	16.5 (8.5–28.8)	11.0 (4.3–24.8)	0.216
Unfavorable neurological outcome (n, %)	18 (69.2)	22 (84.6)	0.066
Hospital mortality (n, %)	5 (19.2)	11 (42.3)	0.143

Data presented as median (25th−75th percentile), percentage or numbers.
1, interval between the receipt of the emergency call and the hospital arrival; 2, interval between the receipt of the emergency call and ROSC or ECMO start; ROSC, return of spontaneous circulation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; APACHE II, Acute Physiology and Chronic Health Evaluation II; JAAM, Japanese Association for Acute Medicine; ISTH, International Society on Thrombosis and Haemostasis; SOFA, Sequential Organ Failure Assessment; maximum, max; minimum, min.
The unfavorable neurological outcome is defined by the cerebral performance category (CPC) scale as 3 to 5 at 28-hospital day.

TABLE 4 | Results of coagulation and fibrinolysis markers and lactate levels in propensity score matched patients.

	VA-ECMO – (*n* = 26)	VA-ECMO + (*n* = 26)	*p*-Value
Platelet counts on day 0 (10^9/L)	169 (132–216)	75 (57–103)	<0.001
Platelet counts max (10^9/L)	169 (132–216)	88 (71–106)	<0.001
Platelet counts min (10^9/L)	12.5 (9.4–14.8)	5.5 (4.7–7.7)	<0.001
PT ratio on day 0	1.1 (1.0–1.3)	1.7 (1.4–2.2)	<0.001
PT ratio max	1.2 (1.1–1.4)	1.8 (1.4–2.3)	<0.001
PT ratio min	1.0 (1.0–1.1)	1.1 (1.0–1.3)	0.056
FDP on day 0 (mg/L)	23.4 (11.2–48.4)	205.0 (82.1–412.0)	<0.001
FDP max (mg/L)	24.5 (11.7–48.4)	205.0 (86.3–412.0)	<0.001
FDP min (mg/L)	5.9 (3.8–9.1)	16.8 (8.7–47.6)	<0.001
Fibrinogen on day 0 (g/L)	2.58 (2.12–3.01)	2.13 (1.50–2.47)	<0.001
Fibrinogen max (g/L)	4.87 (4.11–5.64)	3.97 (3.01–4.49)	0.001
Fibrinogen min (g/L)	2.45 (2.12–3.01)	2.08 (1.48–2.40)	0.004
AT on day 0 (%)	70.5 (61.0–85.3)	49.0 (42.0–63.8)	<0.001
AT max (%)	82.0 (69.0–90.5)	64.0 (53.0–70.8)	0.001
AT min (%)	68.0 (56.8–79.0)	44.0 (40.0–53.0)	<0.001
Lactate on day 0 (mmol/L)	10.0 (7.2–12.8)	15.0 (12.9–17.8)	<0.001
Lactate max (mmol/L)	10.0 (7.2–12.8)	15.0 (12.9–17.8)	<0.001
Lactate min (mmol/L)	1.0 (0.8–1.6)	1.7 (1.2–3.2)	0.001

Data presented as median (25th−75th percentile).
VA-ECMO, veno-arterial extracorporeal membrane oxygenation; PT, prothrombin time; FDP, fibrin/fibrinogen degradation products; AT, antithrombin.

the VA-ECMO+ group. In addition, the VA-ECMO+ group was younger than the VA-ECMO- group. Prehospital factors, including the interval between the receipt of the emergency call and hospital arrival, cardiopulmonary resuscitation (CPR) by witness and shockable rhythm did not differ significantly between VA-ECMO+ and VA-ECMO- groups. However, the time interval between the receipt of the emergency call and the commencement of the ROSC or VA-ECMO in the VA-ECMO+ group was much longer than that in the VA-ECMO- group. In addition, the APACHE II, DIC, and SOFA scores in the VA-ECMO+ group were significantly higher than those in the VA-ECMO- group, and both the neurological outcomes and hospital mortality were significantly worse in the VA-ECMO+ group than in the VA-ECMO- group.

Propensity Score Matching Adjusted for Prehospital Factors

In the comparison of the VA-ECMO+ group with the VA-ECMO- group, propensity score matching was performed between the two groups for the three factors: age, sex, and time from detection to hospital arrival; this was performed to reduce any bias due to individual patient variations and the level of severity before arrival at the hospital. The propensity score model had a c-statistic of 0.885, which indicated good discrimination between the two groups. Using the propensity score matching process, 26 patients were ultimately selected from each group. **Table 3** shows the characteristics of the matched patients. There were no significant differences in the time factors before arrival at the hospital between the two groups, and there was no difference in the time from cardiac arrest to ROSC. The APACHE II scores tended to be higher in the VA-ECMO+ group, but were not significantly different; the two groups generally had balanced characteristics. The VA-ECMO+ group had worse scores for each item that comprehensively assessed the severity of organ failure and DIC. Furthermore, significant severe coagulopathies were found in the VA-ECMO+ group (**Table 4**). The VA-ECMO+ group showed a significant increase in fibrinolytic markers and a decrease in platelets, fibrinogen, and AT. There was no significant difference in hospital mortality between the two groups, but there was a trend toward poorer outcomes in the VA-ECMO+ group. Even after adjusting for prehospital factors by propensity score matching, the VA-ECMO+ group had higher SOFA, ISTH DIC, and JAAM DIC scores, and more severe coagulopathy than the VA-ECMO- group.

Subgroup Analyses of the VA-ECMO Patients

Sub-analyses were performed on the data of 61 patients who received VA-ECMO. The patients were divided into two groups

TABLE 5 | Background characteristics and illness severities in patients who received VA-ECMO.

	Survivors ($n = 31$)	Non-survivors ($n = 30$)	*p*-Value	Favorable ($n = 7$)	Poor ($n = 54$)	*p*-Value
Age, yr	63.0 (48.0–68.0)	62.5 (53.0–69.8)	0.644	66.0 (47.0–67.5)	62.5 (52.3–68.8)	0.851
Gender; male, n (%)	27 (87.1)	26 (86.7)	0.628	6 (85.7)	47 (87.0)	0.647
Time interval (min)						
1	30.0 (27.0–42.0)	32.5 (27.3–43.3)	0.634	28.0 (25.5–34.0)	32.0 (27.0–44.0)	0.279
2	52.0 (44.0–66.5)	48.0 (38.0–61.8)	0.462	51.0 (48.5–56.5)	50.5 (39.8–64.0)	0.956
CPR by witness, n (%)	19 (61.3)	18 (60.0)	0.563	6 (85.7)	31 (57.4)	0.151
Shockable rhythm, n (%)	22 (71.0)	18 (60.0)	0.206	6 (85.7)	34 (63.0)	0.247
Adrenalin dosage (mg)	2.0 (0.0–3.0)	2.0 (1.3–3.0)	0.475	2.0 (1.5–2.5)	2.0 (1.0–3.0)	0.903
APACHE II score	37.0 (33.5–38.5)	38.0 (35.0–42.0)	0.107	36.0 (33.5–37.5)	38.0 (34.0–41.0)	0.428
JAAM DIC score max	8.0 (6.5–8.0)	7.0 (6.0–8.0)	0.160	7.0 (7.0–8.0)	7.5 (6.0–8.0)	0.682
JAAM DIC score min	4.0 (3.0–5.0)	5.0 (3.3–6.0)	0.725	4.0 (4.0–4.5)	5.0 (3.0–6.0)	0.634
ISTH DIC score max	6.0 (5.0–6.5)	6.0 (5.0–6.0)	0.638	6.0 (5.0–6.0)	6.0 (5.0–6.0)	0.974
ISTH DIC score min	3.0 (1.0–4.0)	4.0 (2.0–5.0)	0.098	2.0 (1.0–3.0)	4.0 (1.3–4.0)	0.161
SOFA score max	13.0 (12.0–14.0)	14.5 (12.0–17.0)	0.036	12.0 (10.5–12.5)	13.0 (12.0–15.0)	0.030
SOFA score min	9.0 (5.5–11.0)	11.0 (9.0–12.0)	0.015	8.0 (5.0–10.5)	10.0 (7.3–12.0)	0.250

Data presented as median (25th−75th percentile), percentage or numbers.
1, interval between the receipt of the emergency call and the hospital arrival; 2, interval between the receipt of the emergency call and ROSC or ECMO start; ROSC, return of spontaneous circulation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; APACHE II, Acute Physiology and Chronic Health Evaluation II; JAAM, Japanese Association for Acute Medicine; ISTH, International Society on Thrombosis and Haemostasis; SOFA, Sequential Organ Failure Assessment; maximum, max; minimum, min.
Patient survival and death were evaluated during hospitalization.
The unfavorable neurological outcome is defined by the cerebral performance category (CPC) scale 3 to 5 at 28-hospital day.

TABLE 6 | Results of coagulation and fibrinolysis markers and lactate levels in patients receiving VA-ECMO.

	Survivor ($n = 31$)	Non-survivor ($n = 30$)	*p*-Value	Favorable ($n = 7$)	Poor ($n = 54$)	*p*-Value
Platelet counts max (10^9/L)	89 (73–115)	90 (65–112)	0.702	89 (82–102)	87 (67–114)	0.765
Platelet counts min (10^9/L)	52 (40–62)	46 (32–93)	0.614	54 (44–59)	50 (35–65)	0.765
PT ratio max ×10	1.8 (1.4–2.3)	1.8 (1.5–2.7)	0.480	1.8 (1.3–2.0)	1.8 (1.5–2.5)	0.310
PT ratio min ×10	1.1 (1.0–1.1)	1.4 (1.1–1.8)	<0.001	1.0 (1.0–1.1)	1.1 (1.0–1.5)	0.025
FDP max (mg/L)	258.0 (163.0–448.0)	135.3 (73.9–363.0)	0.091	310.0 (218.8–396.5)	200.0 (83.7–436.0)	0.232
FDP min (mg/L)	13.6 (8.1–24.5)	24.1 (13.6–53.9)	0.020	9.7 (7.7–18.8)	17.3 (12.0–48.2)	0.088
Fibrinogen max (g/L)	4.19 (3.71–4.72)	3.26 (2.48–4.77)	0.016	4.36 (3.96–4.48)	3.91 (2.96–4.79)	0.269
Fibrinogen min (g/L)	2.02 (1.51–2.32)	1.78 (1.46–2.37)	0.634	1.85 (1.37–1.98)	1.92 (1.49–2.35)	0.417
AT max (%)	70.0 (63.0–81.5)	57.5 (50.3–64.0)	0.001	98.0 (69.0–104.0)	64.0 (52.0–72.8)	0.002
AT min (%)	48.0 (38.0–57.5)	45.0 (38.0–55.5)	0.415	48.0 (40.0–58.0)	46.0 (38.0–56.0)	0.666
Lactate max (mmol/L)	15.0 (13.0–17.0)	16.5 (13.5–19.0)	0.193	15.0 (14.7–16.5)	15.5 (12.8–18.0)	0.715
Lactate min (mmol/L)	1.6 (1.3–2.3)	3.9 (2.0–14.4)	<0.001	1.5 (1.4–1.9)	2.3 (1.5–6.2)	0.088

Data presented as median (25th−75th percentile).
VA-ECMO, veno-arterial extracorporeal membrane oxygenation; PT, prothrombin time; FDP, fibrin/fibrinogen degradation products; AT, antithrombin; maximum, max; minimum, min.
Patient survival and death were evaluated during hospitalization.
The unfavorable neurological outcome is defined by the cerebral performance category (CPC) scale 3 to 5 at 28-hospital day.

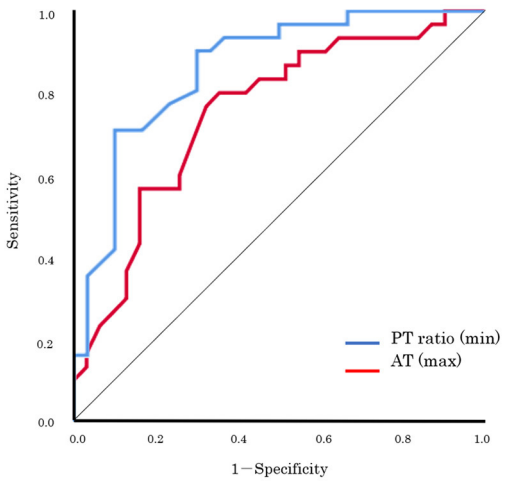
according to survival during hospitalization and neurological outcomes at day 28 after hospital admission (**Tables 5**, **6**). There were no significant differences in pre-hospitalization factors between the two groups, even after grouping by outcome; however, there were significant differences in the SOFA scores (max), PT ratios (min), and AT values (max) in both analyses. Furthermore, there were significant differences in the SOFA scores (min), FDP values (max), fibrinogen values (max), and lactate values (min) between the survivors and non-survivors. Logistic regression analysis was also performed to evaluate the impact of each factor on mortality in patients receiving VA-ECMO (**Table 7**). Univariate analysis showed significant differences in the PT ratios (min), fibrinogen values (max), AT values (max), and lactate values (min). Multiple logistic regression analysis showed that the PT ratio (min) was an independent predictor of mortality during hospitalization ($p =$

TABLE 7 | The results of the univariate and multivariate logistic regression analysis for prediction of hospital mortality in patients receiving VA-ECMO.

Variables	Univariate			Multivariate		
	Odds ratio	95% CI	*p*-Value	Odds ratio	95% CI	*p*-Value
Age	1.009	0.971–1.049	0.644			
Gender	1.038	0.235–4.593	0.960			
Platelet counts max	0.988	0.864–1.131	0.865			
Platelet counts min	1.098	0.926–1.303	0.282			
PT ratio max	1.025	0.975–1.076	0.333			
PT ratio min	1.892	1.267–2.826	0.002	1.714	1.147–2.562	0.009
FDP max	0.998	0.996–1.001	0.168			
FDP min	1.013	0.997–1.030	0.121			
Fibrinogen max	0.996	0.992–0.999	0.025			
Fibrinogen min	0.996	0.998–1.005	0.393			
AT max	0.940	0.902–0.979	0.003	0.961	0.916–1.007	0.094
AT min	0.265	0.945–1.016	0.265			
Lactate max	1.111	0.966–1.278	0.139			
Lactate min	2.072	1.132–3.793	0.018			

Data presented as median (25th−75th percentile).
VA-ECMO, veno-arterial extracorporeal membrane oxygenation; PT, prothrombin time; FDP, fibrin/fibrinogen degradation products; AT, antithrombin; maximum, max; minimum, min.

0.009), and that AT (max) may be a predictor of mortality during hospitalization ($p = 0.094$). **Figure 2** shows the results of the analysis for predicting hospital mortality using ROC curves for both factors. Both, the PT ratio (min) and the AT (max) were found to be good predictors of hospital mortality (AUCs of 0.861 and 0.751, respectively). The optimal cutoff value was 67 % (sensitivity: 80.0, specificity: 64.5) for AT (max) and 1.2 (sensitivity: 90.3, specificity: 70.0) for the PT ratio (min). Moreover, logistic regression analysis using ISTH DIC score components (PT ratio, platelet, FDP and fibrinogen) as independent variables showed that the PT ratio (min) was an independent predictor for hospital mortality ($p = 0.001$).



	AUC	SE	95% CI	*p*-Value	Optimal Cutoff	Sensitivity	Specificity
PT ratio min	0.861	0.048	0.767-0.954	0.000	1.2	0.903	0.700
AT max	0.751	0.063	0.627-0.875	0.001	67	0.800	0.645

FIGURE 2 | Receiver operating characteristic (ROC) curve analysis for hospital mortality. PT, prothrombin time; AT, antithrombin; maximum, max; minimum, min.; AUC, area under the curve; SE, standard error; CI, confidence interval.

DISCUSSION

In the present study, more severe coagulopathy was observed in patients who received VA-ECMO for CPR than in those who did not receive VA-ECMO. This finding indicated that VA-ECMO may evoke coagulopathy itself. In the analysis of patients receiving VA-ECMO, there was a correlation between poor outcomes and PT ratios (min), fibrinogen values (max), AT values (max), and lactate values (min), with a particularly strong correlation between the PT ratio (min) and AT (max); this showed significant predictive ability for hospital mortality. These factors were also correlated with neurological outcomes. To the best of our knowledge, this was the first study to investigate coagulofibrinolytic responses associated with VA-ECMO.

Patients who received VA-ECMO experienced significantly more severe coagulopathy than those who did not receive VA-ECMO. However, the interval between the receipt of the emergency call and the commencement of ROSC or VA-ECMO in the VA-ECMO+ group was much longer than that in the VA-ECMO- group (**Table 2**). A previous study indicated that the degree of hypoxia, defined as the time from the onset of cardiac arrest to first CPR, and the duration of CPR were significant determinants of the severity of coagulopathy associated with PCAS (3, 15, 16). The current study showed that the patients who received VA-ECMO had significantly more severe coagulopathy than those who did not receive VA-ECMO, even after adjusting for the cardiac arrest time. These results indicate that VA-ECMO may itself cause the deterioration of coagulopathy associated

with PCAS; this suggests that coagulofibrinolytic impairment induced by VA-ECMO may result in poor outcomes in patients with PCAS.

Logistic regression analysis showed that PT ratios (min) and AT values (max) were strongly correlated with poor outcomes in patients in the VA-ECMO+ group (**Table 6** and **Figure 2**). The AT, which forms a complex with thrombin and inhibits thrombin and activated coagulation factor X, is an important anticoagulant factor. The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock recommend AT replacement therapy in patients with sepsis-associated DIC, whose AT activity has decreased to <70% (17). This is similar to the optimal cutoff value of 67 obtained in this study. Previous studies have confirmed reduced AT levels in patients with PCAS (18, 19), especially in those with DIC (20). In addition, it has been suggested that AT protects against myocardial ischemia and reperfusion injury (21). Although no prospective studies have shown the beneficial effects of AT therapy in cardiac arrest patients receiving VA-ECMO (22), these findings suggest that patients receiving VA-ECMO should be administered AT with a target of ∼70% AT activity.

The main pathophysiology of DIC involves massive thrombin generation caused by tissue factor-factor VII pathway activation; this was formerly known as the extrinsic coagulation pathway, and its activity was generally assessed by PT. The current study showed coagulopathy with predominant prolongation of PT in the ECMO+ group. All patients who received VA-ECMO were administered unfractionated heparin for anticoagulation during the procedure. The dose of heparin, which was strictly adjusted in accordance to ACT or APTT, does not generally affect the value of PT. Patients with a PT ratio >1.2 have been shown to have a significantly higher incidence of mortality and multiple organ failure (23), and the JAAM DIC criteria awards 1 point with a PT ratio >1.2 (11); this is similar to the results obtained in the present study, that showed that the optimal cutoff value of the PT ratio for predicting hospital mortality in PCAS patients with VA-ECMO was 1.2.

Conversely, there were no significant relationships between DIC scores and outcomes (**Table 5**). The discrepancy of PT and DIC scores can be explained by the results of the logistic regression analysis, which showed that among the ISTH DIC score components, only the PT ratio was an independent predictor of hospital mortality. This finding suggests that in the ISTH DIC score, items other than PT do not sensitively reflect the outcome of PCAS patients, as these items may be affected by various factors that are not closely related to outcome.

PCAS is often compared to "sepsis-like syndrome," which is commonly associated with high levels of circulating cytokines and coagulofibrinolytic abnormalities, namely DIC (24). The development of DIC has been recognized as one of the most critical conditions in sepsis due to its frequency and high severity. Previous studies have demonstrated that the mortality rate of sepsis patients with DIC was significantly higher than the overall mortality rate of sepsis patients (25, 26). In addition, a recent study showed that active screening and diagnosis of DIC in sepsis was associated with the improvement in patients' outcomes (27). This evidence may support our present findings, which suggest that the induction of VA-ECMO may itself cause the deterioration of DIC associated with PCAS. The evaluation of coagulation-related biomarkers, especially PT and AT, may predict poor outcomes in patients with PCAS who were resuscitated using VA-ECMO. In addition, VA-ECMO-induced coagulopathy can be a promising therapeutic target in these patients, and target values of AT and the PT ratio may be 70% and 1.2, respectively.

Study Limitations

In the present study, 13 patients who received VA-ECMO and 29 patients who did not receive VA-ECMO died by day 3, resulting in a survival bias. This study was conducted retrospectively in a single institution, and the number of enrolled patients was relatively small. In addition, there may have been the potential for a selection bias and confounding due to unknown or unmeasured variables. Patients in this study did not receive platelet concentrates, AT, and fibrinogen products during the data collection period; however, the use of heparin, fresh frozen plasma, and other drugs that affect coagulation and fibrinolysis were not assessed.

CONCLUSIONS

In the present study, significantly severe coagulopathy was observed in patients who received VA-ECMO for CPR. In particular, in patients receiving VA-ECMO, the minimum PT ratio and maximum antithrombin by day 3 of hospitalization had a strong correlation with poor outcomes. VA-ECMO-induced coagulopathy can be a promising therapeutic target for patients resuscitated using VA-ECMO.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hokkaido University Hospital Division of Clinical Research Administration. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TT and TW contributed to study conception, analysis, and manuscript preparation. SG contributed to manuscript preparation and revision for intellectual content. All authors read and approved the final version of the manuscript prior to submission.

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BRIEF RESEARCH REPORT
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Near-Infrared Spectroscopy Assessment of Tissue Oxygenation During Selective Cerebral Perfusion for Neonatal Aortic Arch Reconstruction

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Objective: Optimal selective cerebral perfusion (SCP) management for neonatal aortic arch surgery has not been extensively studied. We induced mild hypothermia during SCP and used the tissue oxygenation monitor to ensure adequate perfusion during the cardiopulmonary bypass (CPB).

Methods: Eight cases were recruited from September 2018 to April 2020. SCP was maintained at 30°C, and CPB was adjusted to achieve a mean right radial artery pressure of 30 mmHg. The near-infrared tissue saturation (NIRS) monitor was applied to assess the right and left brain, flank, and lower extremity during the surgery.

Results: During surgery, the mean age was 4.75 days, the mean body weight was 2.92 kg, the CPB duration was 86.5 ±18.7 min, the aortic cross-clamp time was 46.1 ± 12.7 min, and the SCP duration was 14.6±3.4 min. The brain NIRS before, during, and after SCP was 64.2, 67.2, and 71.5 on the left side and 67.9, 66.2, and 70.1 on the right side (p = NS), respectively. However, renal and lower extremity tissue oxygenation, respectively decreased from 61.6 and 62.4 before SCP to 37.7 and 39.9 after SCP ($p < 0.05$) and then increased to 70.1 and 90.4 after full body flow resumed. No stroke was reported postoperatively.

Conclusion: SCP under mild hypothermia can aid in efficient maintenance of brain perfusion during neonatal arch reconstruction. The clinical outcome of this strategy was favorable for up to 20 min, but the safety duration of lower body ischemia warrants further analysis.

Keywords: selective cerebral perfusion, cardiopulmonary bypass, hypothermia, near-infrared tissue saturation, aortic arch surgery

INTRODUCTION

The optimal perfusion strategy for infant aortic arch reconstruction surgery is debatable. Deep hypothermia can reduce the metabolic demand and prolong the ischemic tolerance, and circulatory arrest can provide a bloodless surgical field during aortic reconstruction; therefore, deep hypothermic circulatory arrest (DHCA) has been used in mainstream cardiopulmonary

bypass (CPB) management for aortic arch reconstruction. However, many lines of evidence have indicated its deleterious effect on the brain (1). The safe threshold for DHCA duration remains uncertain. Selective cerebral perfusion (SCP) has been adopted as an adjunct or alternative method for arch repair surgery (2). Antegrade cerebral perfusion through the innominate artery can enable symmetric blood flow in neonates with a normal circle of Willis (3). Comparable perioperative and short-term neurological outcomes have been achieved using both SCP and DHCA in complex neonatal arch reconstruction surgical procedures (4). However, visceral organ perfusion is not achieved in SCP; thus, the impact of the distal ischemia remains controversial (5, 6). The Society of Thoracic Surgeons Congenital Heart Surgery Database indicated that SCP is selected in 59% of the surgical procedures as either the main perfusion strategy or a strategy in combination with DHCA. DHCA is still used in a substantial percentage of patients (7).

Studies on aortic arch surgery and SCP in neonates differ in terms of patient groups and surgical management (4, 8, 9). In adult elective aortic arch surgery, moderate hypothermic circulatory arrest with selective antegrade cerebral perfusion can be a safe procedure in terms of visceral organ complications, neurocognitive morbidity, and mortality, but the relevant evidence in neonates is limited (5). Many centers perform neonatal complex aortic arch surgical procedure by employing SCP under deep hypothermia at 18–22°C (10–12). In recent years, mild hypothermia has become an increasingly popular choice for neonatal cardiac surgery instead of deep hypothermia. However, whether SCP provides the most favorable postoperative outcomes in short procedure under mild hypothermia was unknown (6). Because the optimal temperature for SCP has not been determined, we conducted a prospective observational study on neonate aortic arch reconstruction with mild hypothermia and SCP.

MATERIALS AND METHODS

Study Design

After obtaining approval from the institutional ethics committee, we conducted this single-institutional (tertiary university-affiliated medical center) cohort study to analyze outcomes of neonates undergoing aortic arch surgery from September 2018 to April 2020. Patients who were in profound shock and with abnormalities other than cardiac defects were excluded. Data such as age, sex, gestational age, body weight, body height, diagnosis, and preoperative inotropic support were recorded. The vasoactive-inotropic score was measured as follows: dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min) (13). The following intraoperative variables were obtained: duration of CPB, duration of hypothermic circulatory arrest, minimum hematocrit during CPB, lowest rectal temperature attained during CPB, duration of peritoneal dialysis, ventilator use, urine output, and hospital stay. The follow-up continued until October 2020.

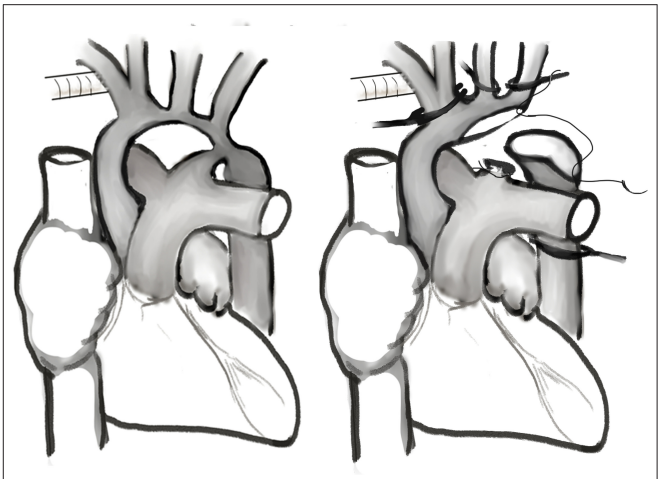

FIGURE 1 | Neonatal aortic arch repair with selective cerebral perfusion.

Surgical Technique

As shown in **Figure 1**, an arterial cannula was inserted into a 3.5-mm expanded polytetrafluoroethylene tube (Gore-Tex; W.L.Gore & Associates, Flagstaff, AZ, USA) that was anastomosed to the innominate artery. Another arterial cannula was inserted into the descending aorta through the ductus arteriosus for lower body perfusion during the cooling phase. After insertion of a venous cannula into the right atrium, cardiopulmonary bypass was conducted at a flow rate of 150–180 mL/kg/min. During the cooling phase, the ductus arteriosus was ligated and divided from the pulmonary artery (proximal to the cannulation site). The descending thoracic aorta was extensively mobilized through blunt dissection as far distally as possible for further reconstruction surgery (14). After the target temperature was achieved, the cannula through the descending aorta was removed, the innominate artery was clamped, and SCP was started. Arch reconstruction is typically performed through resection of the coarctation tissue and extended end-to-end anastomosis. A peritoneal dialysis catheter was inserted during the operation to augment fluid removal in selective patients (15).

Perfusion Methods

Blood gas management was performed using the alpha stat technique. Regional cerebral perfusion rates were maintained between 35 and 40 mL/kg/min with a rectal temperature of 30°C and the right radial artery pressure between 30 and 40 mmHg.

Near-Infrared Spectroscopy Measurements

During the perioperative period, regional saturations of the bilateral frontal forehead, left flank, and left thigh were estimated using near-infrared spectroscopy (NIRS) with neonatal cerebral and somatic sensors (INVOS 5100C; COVIDIEN, Mansfield, MA, USA). The left kidney position was confirmed using ultrasound before flank somatic sensor placement.

Statistical Analysis

Descriptive data for continuous variables are shown as means and their standard deviations (SDs). Differences in continuous variables before and during SCP were compared using the Student *t*-test. GraphPad Prism (version 6.0; GraphPad Software, La Jolla, CA, USA) was used for statistical analysis and generation of graphics.

RESULTS

Among the eight patients who participated in the study, five had coarctation of the aorta (CoA) with ventricular septal defect (VSD), and three had interrupted aortic arch type A with VSD and atrial septal defect. One patient with CoA with VSD underwent DHCA during arch repair surgery because during the right innominate artery cannulation, clamping of the innominate artery caused simultaneous blood pressure drop in the lower extremity. The other seven patients underwent surgery with SCP for arch repair. The mean body weight of the patients was 2.93 kg. Their preoperative data are shown in the **Supplementary Table 1**. The mean cardiopulmonary bypass duration was 86.5 ± 18.7 min, the aortic cross-clamp time was 46.1 ± 12.7 min, and the SCP duration was 14.6 ± 3.4 min. The cardiopulmonary bypass setting and duration are shown in **Table 1**.

TABLE 1 | Cardiopulmonary bypass setting for included patients.

	Operation duration (min)	Aortic cross-clamp duration (min)	Total CPB duration (min)	SCP duration (min)	SCP Temperature (°C)	SCP MBP (mmHg)
1	129	45	75	13	33.1	25.7
2	139	39	83	14	29.1	32
3	152	58	93	20	29.6	28
4	153	56	91	14	31	27
5	167	50	82	18	29.6	27
6	137	22	55	9	32	31.5
7	157	39	92	13	32.8	26.7
8	160	60	121	16	20.8	6.7

CPB, cardiopulmonary bypass; SCP, selective cerebral perfusion; MBP, mean blood pressure.

The regional saturation in the bilateral frontal area did not differ between the SCP period and the full-flow period (right side full flow vs. SCP: 67.9 ± 4.7% vs. 66.2 ± 4.6%; $p = 0.81$; left side full flow vs. SCP: 64.2 ± 3.0% vs. 67.2 ± 1.8%; $p = 0.42$). The regional saturation in the left flank area was significantly lower during SCP (61.6 ± 3.7% vs. 37.7 ± 6.2%; $p = 0.01$). The regional saturation in the left thigh area was significantly lower during SCP (62.4 ± 7.56% vs. 39.9 ± 4.71%; $p = 0.02$; **Figure 2**). In patients who underwent DHCA, the cerebral regional saturation decreased by 21 and 44%, respectively, in the left and right brain during total circulatory arrest status. The saturation levels in the flank and lower extremity were high at low temperature with full flow and decreased during SCP and lower body circulatory arrest. We compared the absolute regional saturation data in SCP patients at 30°C and DHCA patients at 20°C and found that the regional saturation for the DHCA patients was 15% higher in the flank and 30% higher in the lower extremity compared with the SCP patients.

No death, stroke, or seizure events were reported in our patients. As shown in **Table 2**, two patients who had SCP had inadequate urine output in the postoperative day 1, but their urine output increased to more than 0.5 mL/kg/h in postoperative day 2. A peritoneal dialysis catheter was inserted perioperatively and removed uneventfully for 7 and 5 days in

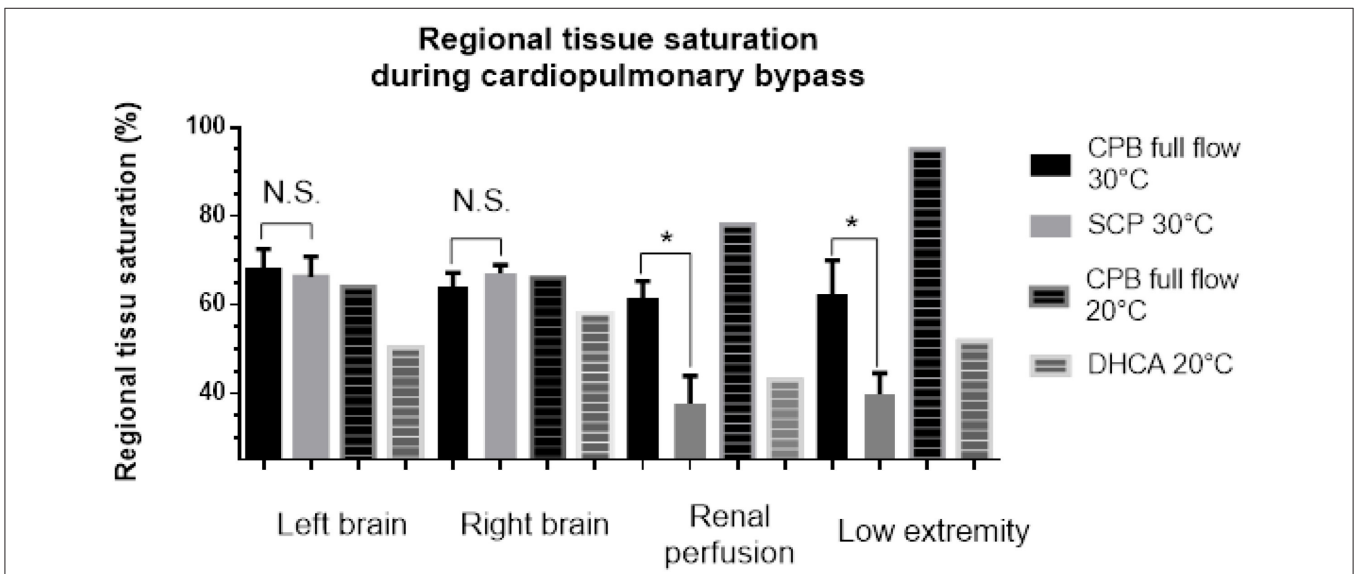

FIGURE 2 | Tissue saturation in different organs in selective cerebral perfusion patients under mild hypothermia and deep hypothermic cardiac arrest patients.

TABLE 2 | Clinical outcomes for included patients.

	Post-operation ECMO	ICU stay (day)	Peritoneal dialysis (day)	Urine output by mL/kg/h in post-operative day 1 (mL)	Lactate immediately after CPB (mmole/L)	Post-operation day 1 lactate (mmole/L)	VIS before ICU admission
1	0	2	0	5.46	3.4	2.49	6.3
2	0	2	0	5.17	4.01	3.65	5
3	0	3	0	0.37	3.89	3.03	9
4	0	3	0	0.65	7.05	5.08	8.6
5	0	9	7	0.51	5.46	4.16	16
6	0	3	0	5.40	4.69	3.37	11
7	0	5	5	0.23	4.44	5.94	10
8.	0	12	0	4.90	2.12	2.37	10.8

ECMO, extracorporeal membrane oxygenator; ICU, intensive care unit; CPB, cardiopulmonary bypass; VIS, vasoactive-inotropic score.

postoperative care. The patients who underwent DHCA needed the longest ventilator support in the intensive care unit. All the patients recovered favorably and were followed up regularly at the outpatient clinic.

DISCUSSION

Our study demonstrated that mild hypothermia with SCP was feasible for aortic arch repair surgery in neonates. During isolated cerebral perfusion, the cerebral oximeter readings were similar during full flow and SCP status. No stroke, seizure, or neurological complications were reported during follow-up. However, renal perfusion was significantly lower in the isolated cerebral perfusion status in mild hypothermia. ∼30% of our patients had low urine output for 2 days. All patients recovered favorably. Nevertheless, the safety of a longer SCP for arch repair with mild hypothermia during complex cardiac surgery was questionable.

The optimal perfusion pressure, optimal flow rate, hematocrit, and temperature for SCP in neonate surgery are controversial. Both underperfusion and overperfusion have deleterious effects on neurocognitive function. Overperfusion, either excess pressure or flow, could lead to increased intracranial pressure, cerebral edema, and slow neurocognitive recovery. Underperfusion leads to brain ischemia (16, 17). Mean arterial pressure, either radial artery pressure or femoral artery pressure, had a poor correlation with the bypass flow rate during SCP (18), and real-time measurement of cerebral blood flow, oxygen delivery, oxygen extraction rate, and neuronal stress during cardiac surgery and adjustment of perfusion pressure and flow accordingly are difficult; therefore, non-invasive cerebral oximetry monitoring through NIRS is commonly adopted as an alternative. In adult arch surgery with SCP, the decrease in regional cerebral tissue oxygen saturation between 76 and 86% from baseline had a sensitivity of up to 83% and a specificity of up to 94% in identifying individuals with stroke. In deep hypothermic status, a sustained drop in cerebral rSO2 below 55% correlated with transient neurologic events (19). NIRS is limited to the detection of overperfusion, embolic events, or hypoperfusion in the basilar region. Further measurement of reactive oxygen species, neuronal stress markers, or neuroimaging data is needed to provide more information on cerebral metabolism under SCP.

Randomized controlled trials for neonatal arch surgery have shown that under deep hypothermia, total arrest and selective antegrade cerebral perfusion had similar neurological outcomes (11). However, few studies have compared neurological outcomes of SCP between mild hypothermia and deep hypothermia. Algra et al. (20) demonstrated a correlation of prolonged postoperative recovery with increasing DHCA duration during neonatal arch reconstruction. Cerebral ischemia for 30 min in neonates induces an immediate innate immune response despite cooling the temperature to deep hypothermia (21). Mild hypothermia attenuates the left shift of the hemoglobin dissociation curve, resulting in a better oxygen release in tissue, which might be physiologically better. In a piglet study, cerebral oxygenation and microdialysis findings showed a depletion of the cerebral energy store during circulatory arrest in the DHCA group (22). Although both DHCA and SCP patients in our study recovered favorably with no neurological deficits, SCP patients with mild hypothermia exhibited less cerebral saturation disturbance.

Visceral organ ischemia is not uncommon after neonatal arch surgery and is associated with delayed postoperative recovery. Distal organ ischemia during arch repair is inevitable, and systemic inflammatory responses after ischemia–reperfusion injuries may cause kidney, liver, and intestinal dysfunction (23). During hemorrhagic shock in normothermia, renal blood flow pressure autoregulation is impaired in advance of cerebral blood flow autoregulation (24). A comparison of renal dysfunction incidence by cardiopulmonary bypass core temperature showed that the renal dysfunction incidence was significantly higher in the SCP patients with moderate hypothermia than in those with deep hypothermia (25). Low renal oximetry values during cardiac surgery correlate with the development of acute kidney injury in neonates (26). In our study, the visceral ischemia time for all patients was under 20 min. Nevertheless, two patients had short-term decreased urine output postoperatively. Deep hypothermia in the DHCA patient may have protected the kidney in the absence of any perfusion, as shown by the higher renal rSO2 levels. For complex procedures and longer ischemic duration, a lower core temperature might be more favorable for visceral organ protection.

Our study has some limitations. First, it was an observational study without a randomization design; thus, we could not conclude that mild hypothermia was better for shorter durations in neonatal aortic arch surgery. However, from our experience, mild hypothermia with SCP provided constantly stable intraoperative cerebral oxygenation, with a low inotropic requirement immediately after cardiopulmonary bypass. Moreover, no neurological deficit was noted during hospitalization and follow-up. Second, we included only a few cases, which may have affected the statistical power of analysis. In our institution, we use SCP but in lower core temperature to protect against visceral ischemia in complex aortic arch surgery. Thus, the patient number for SCP with mild hypothermia was limited. However, we hope that the homogeneity in our patients could eliminate unnecessary confounding factors and offer evidence for the feasibility of SCP in neonate arch surgery. Third, we only followed up the patients for neurological outcomes for 6 months and did not undertake brain imaging. Long-term follow-up should be conducted in the future to validate the safety and efficacy of SCP in mild hypothermia for short durations.

CONCLUSION

Neonatal arch repair surgery could be performed under mild hypothermia with SCP with low neurological complication risk. However, whether visceral organ ischemia risk is higher with the use of this method warrants further prospective randomized trial study. The SCP parameters need to be individualized and adjusted according to regional saturations.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Naional Taiwan University Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

C-HH: conceptualization, review, and editing manuscript. Y-CW: original draft preparation. H-WC: project administration. S-CH: funding acquisition and supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.637257/full#supplementary-material

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Treatment With Vasopressor Agents for Cardiovascular Shock Patients With Poor Renal Function; Results From the Japanese Circulation Society Cardiovascular Shock Registry

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According to the guidelines for cardiogenic shock, norepinephrine is associated with fewer arrhythmias than dopamine and may be the better first-line vasopressor agent. This study aimed to evaluate the utility of norepinephrine vs. dopamine as first-line vasopressor agent for cardiovascular shock depending on the presence and severity of renal dysfunction at hospitalization. This was a secondary analysis of the prospective, multicenter Japanese Circulation Society Cardiovascular Shock Registry (JCS Shock Registry) conducted between 2012 and 2014, which included patients with shock complicating emergency cardiovascular disease at hospital arrival. The analysis included 240 adult patients treated with norepinephrine alone ($n = 98$) or dopamine alone ($n = 142$) as the first-line vasopressor agent. Primary endpoint was mortality at 30 days after hospital arrival. The two groups had similar baseline characteristics, including estimated glomerular filtration rate (eGFR), and similar 30-day mortality rates. The analysis of the relationship between 30-day mortality rate after hospital arrival and vasopressor agent used in patients categorized according to the eGFR-based chronic kidney disease classification revealed that norepinephrine as the first-line vasopressor agent might be associated with better prognosis of cardiovascular shock in patients

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with mildly compromised renal function at admission (0.0 vs. 22.6%; $P = 0.010$) and that dopamine as the first-line vasopressor agent might be beneficial for cardiovascular shock in patients with severely compromised renal function [odds ratio; 0.22 (95% confidence interval 0.05–0.88; $P = 0.032$)]. Choice of first-line vasopressor agent should be based on renal function at hospital arrival for patients in cardiovascular shock.

Clinical Trial Registration: http://www.umin.ac.jp/ctr/, Unique identifier: 000008441.

Keywords: cardiogenic shock, cardiovascular disease, vasopressor agents, norepinephrine, dopamine

INTRODUCTION

The number of patients with chronic kidney disease (CKD) has been markedly increasing worldwide (1). CKD is an important risk factor for cardiovascular events and accounts for all-cause mortality in patients with cardiovascular disease (CVD) (2–5). Moreover, cardiogenic shock is a serious cardiovascular event associated with a high mortality rate (6–8). In patients with cardiogenic shock, vasopressor agents are indicated in patients with severe or persistent hypotension despite fluid administration, and various vasopressor agents have been used for the treatment of cardiogenic shock. According to the clinical statements and guidelines for the management of cardiogenic shock, norepinephrine is associated with fewer arrhythmias and is therefore the vasopressor agent of choice in many patients with cardiogenic shock; however, the optimal first-line vasopressor agent for cardiogenic shock patients remains unclear (9, 10). To our knowledge, no clinical studies to date have investigated the effects of first-line vasopressor agents for cardiogenic shock in patients with poor renal function.

We previously reported that estimated glomerular filtration rate (eGFR) was a strong predictor of 30-day mortality in patients in cardiovascular shock (11); consistent with this finding, other studies also reported that a history of CKD, presence of renal dysfunction at hospitalization, and acute renal dysfunction were strong predictors of 30-day mortality in patients in cardiogenic shock (12–15). In addition, some vasopressor agents are known to impact renal blood flow. Specifically, the administration of norepinephrine usually results in reduced blood flow to organs, particularly to kidneys (16), and the administration of low-dose dopamine, which selectively activates dopamine-specific receptors in renal and visceral blood vessels, results in increased blood flow to kidneys (17).

Therefore, we aimed to evaluate the utility of norepinephrine vs. dopamine for patients in cardiovascular shock and to elucidate the efficacy of vasopressors based on the presence and extent of renal dysfunction at the time of hospitalization in these patients.

METHODS

Study Design

This was a secondary analysis of the Japanese Circulation Society Cardiovascular Shock Registry (JCS Shock Registry) (11). We have previously conducted a prospective, observational, multicenter cohort study based on the JCS Shock Registry (11, 18, 19). Patients diagnosed with cardiovascular shock complicating emergency CVD were registered from 82 centers in Japan between May 2012 and June 2014 (11). Maintenance of the registry was approved by the ethics committee of each participant hospital, and the present study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000008441; http://www.umin.ac.jp/ctr/index/htm/). We prepared the manuscript according to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.

The design and data collection methods for the JCS Shock Registry have been reported previously (11). Briefly, patients eligible for inclusion in the JCS Shock Registry had out-of-hospital onset of cardiovascular shock and met one major criterion and one or more minor criteria described below. The major criteria were systolic blood pressure $\leq$ 100 mmHg, including decline of systolic blood pressure by >30 mmHg from the usual value, and heart rate $<$ 60 beats/min or $>$ 100 beats/min. The minor criteria were the presence of cold sweating, skin pallor, cyanosis, capillary refill time $>$ 2 s, and altered consciousness. Patients who had out-of-hospital cardiac arrest without return of spontaneous circulation on arrival at hospital and those younger than 16 years of age were excluded. The causes of cardiovascular shock included acute coronary syndrome, non-ischemic arrhythmia, aortic disease, myocarditis, cardiomyopathy, pulmonary thromboembolism, valvular heart disease, infective endocarditis, cardiac tamponade, and others.

Study Patients

Patients from the JCS Shock Registry who were administered intravenous norepinephrine alone or dopamine alone as the first vasopressor agent within 24 h of arrival at the emergency department (ED) were included in the present study. Patients who received both agents were excluded because it was difficult to determine which of the two drugs was used initially or whether both were used simultaneously. In addition, patients who received intra-aortic balloon pump (IABP) support and/or veno-arterial extracorporeal membrane oxygenation (VA ECMO) were excluded for the same reason.

To analyze the relationship between mortality rate at 30 days after hospital arrival and vasopressor agent use, the patients were categorized into four groups according to the eGFR-based CKD classification: CKD stage G0/1/2, eGFR $>$ 60 mL/min/1.73 m^2 (Group G0/1/2); CKD stage G3a, eGFR 45–59 mL/min/1.73 m^2 (Group G3a); CKD stage G3b, eGFR 30–44 mL/min/1.73 m^2 (Group G3b); and CKD stage G4/5, eGFR $<$ 30 mL/min/1.73 m^2

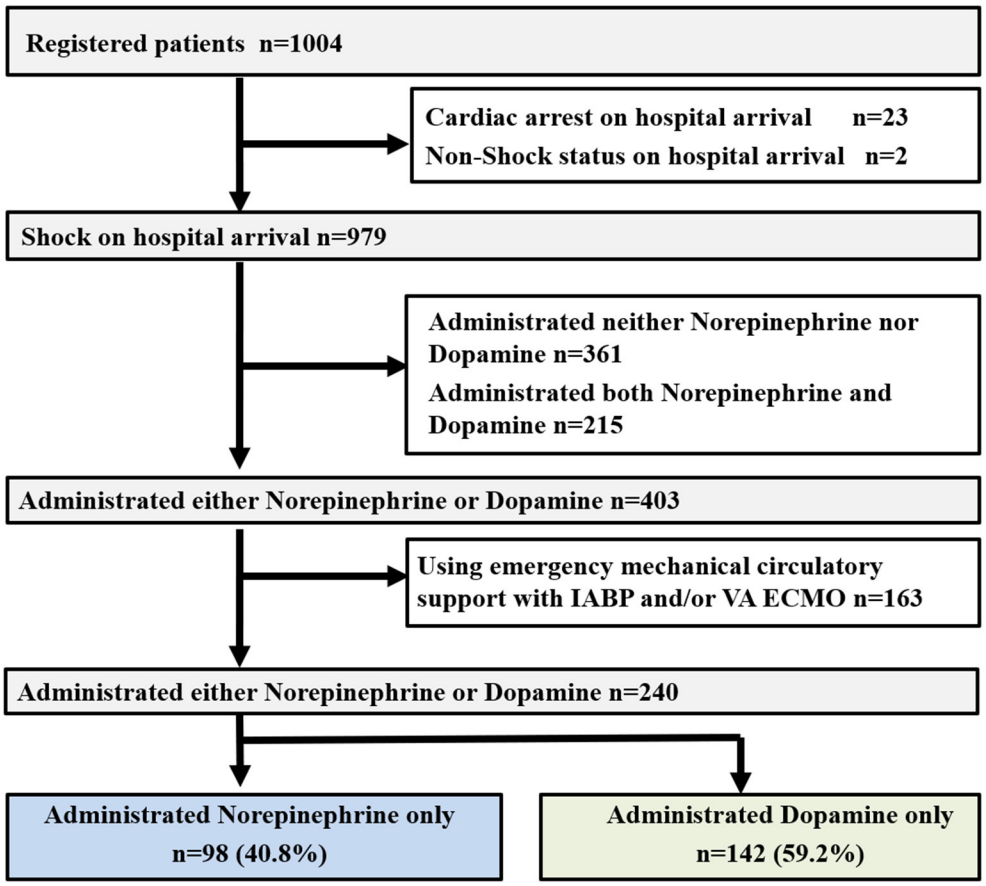

FIGURE 1 | Study profile. OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; IABP, intra-aortic balloon pumping; VA ECMO, veno-arterial extracorporeal membrane oxygenation.

(Group G4/5). The following three-variable Japanese equation for GFR estimation based on serum creatinine (SCr) level and age, which is recommended in both clinical settings and epidemiological studies, was used: eGFR $= 194 \times \mathrm{SCr}^{-1.094} \times \mathrm{age}^{-0.287} \times 0.739$ (if female) (20).

Endpoints

The primary endpoint was mortality rate at 30 days after hospital arrival in the entire study population. The secondary endpoint was the 30-day mortality rate after hospital arrival in each group.

Statistical Methods

Data were expressed as medians with interquartile range for continuous variables and as percentages for discrete variables. Baseline characteristics of the subjects enrolled in the present study were compared using the chi-square test for categorical variables and the Mann-Whitney *U* test for continuous variables, as appropriate. The primary endpoint was compared using the chi-square test, and a $P \leq 0.05$ were considered to indicate statistical significance.

Trends were examined using univariate regression models. Multivariable logistic regression analysis was used to assess the contribution of the administered vasopressor agent to 30-day mortality after hospital arrival, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Potential confounding factors based on biological plausibility and previous studies were included in the multivariable logistic regression analysis. These variables included age, sex (male, female), systolic blood pressure at ED arrival, heart rate at ED arrival, respiratory rate at ED arrival, pathophysiology of shock (pump, non-pump, including volume, and rate), CKD stage based on eGFR, and administration of vasopressor agents (norepinephrine or dopamine) (6, 11, 21).

RESULTS

Patient Population

Of a total of 1,004 patients entered in the JCS Shock Registry, 979 eligible patients were included in the present study (**Figure 1**) (11). Among these, 361 patients did not receive norepinephrine or dopamine and 215 patients received both norepinephrine and dopamine. Among the remaining 403 patients who received norepinephrine or dopamine alone, 163 patients who received IABP and/or VA ECMO support were excluded. Therefore,

the final study population included the remaining 240 patients (**Figure 1**).

Baseline Characteristics

In the study population of 240 patients, 98 (40.8%) and 142 (59.2%) patients received norepinephrine alone and dopamine alone, respectively, and the number of patients administered dopamine alone was significantly higher than that of patients administered norepinephrine alone ($P = 0.005$). The characteristics of the patients are presented in **Table 1**. There were no significant differences in the baseline characteristics between the norepinephrine and dopamine groups. According to the eGFR-based CKD classification, the study population included 46, 57, 72, and 62 patients in Group G0/1/2, G3a, G3b, and G4/5, respectively.

Primary Outcome

Table 2 shows the outcomes in the entire study population. The mortality rate at 30-day after hospital arrival was 26.5% in the norepinephrine group and 25.4% in the dopamine group ($P = 0.838$). In the multivariate logistic regression analysis including the entire study population, the adjusted OR for 30-day mortality in the dopamine group compared to the norepinephrine group was 1.00 (95%CI 0.48–2.09; $P = 0.994$) (**Table 2**). In addition, the 30-day mortality rate was lower in the subgroups with better renal function (Group G0/1/2 vs. G3a, G3b, and G4/5 13.0 vs. 12.3, 33.3, and 38.7%; $P = 0.001$). In the multivariate logistic regression analysis of the entire study population, the adjusted ORs for 30-day mortality in the patients with Group G3a, G3b, and G4/5 were 0.97 (95%CI 0.25–3.66; $P = 0.959$), 3.33 (95%CI 1.24–8.95; $P = 0.135$), and 4.21 (95%CI 1.55–12.2; $P = 0.029$), respectively, compared to the patients with Group G0/1/2 (**Table 2**). Similar results were observed based on the analysis of the norepinephrine group alone (**Supplementary Table 1**). Conversely, in the dopamine group (**Supplementary Table 2**), no significant differences in 30-day mortality rate were noted among the four groups.

Secondary Outcome

We examined the relationship between the 30-day mortality rate and vasopressor use in each group according to the CKD stage (**Table 3**). The characteristics of the patients in each group are presented in **Supplementary Tables 3–6**. Among the patients with stage Group G3a, the 30-day mortality rate was significantly lower in the norepinephrine group than in the dopamine group (0.0 vs. 22.6%; $P = 0.010$). However, among the patients with Group G4/5, the mortality rate tended to be higher in the norepinephrine group than in the dopamine group (51.9 vs. 28.6%; $P = 0.062$). Furthermore, there was no significant difference in the 30-day mortality rate between the norepinephrine vs. dopamine groups among patients with Group G0/1/2 (norepinephrine vs. dopamine, 13.3 vs. 12.9%; $P = 0.968$) and among those with Group G3b (norepinephrine vs. dopamine, 34.5 vs. 32.6%; $P = 0.865$). In the multivariate logistic regression analysis, the adjusted ORs for 30-day mortality in the dopamine group compared to the norepinephrine group were 15.1 (95%CI 0.08–2,928, $P = 0.312$), 0.60 (95%CI 0.15–2.47; $P = 0.474$), and 0.22 (95%CI 0.05–0.88; $P = 0.032$) in patients with Group G0/1/2, G3b, and G4/5, respectively.

TABLE 1 | Patient characteristics.

Characters	Norepinephrine group ($n = 98$)	Dopamine group ($n = 142$)	*P*-value
Age-yr median (IQR)	75 (67–82)	76 (67–83)	0.977
Male sex—no. (%)	60 (61.2)	83 (58.5)	0.668
The pathophysiology of shock—no. (%)			0.387
Pump	57 (58.2)	70 (49.3)	
Volume	20 (20.4)	37 (26.1)	
Rate	21 (21.4)	35 (24.6)	
Cardiogenic source—no. (%)			0.261
ACS	45 (45.9)	46 (32.4)	
Arrhythmia	10 (10.2)	28 (19.7)	
Aortic disease	15 (15.3)	44 (31.0)	
The others	28 (28.6)	24 (16.9)	
SBP on ED arrival-mmHg median (IQR)	72 (50–85)	78 (60–87)	0.100
HR on ED arrival—beats/min median (IQR)	67 (39–98)	72 (42–102)	0.430
RR on ED arrival—per min median (IQR)	20 (15–25)	20 (12–26)	0.971
BT on ED—degree centigrade median (IQR)	36.0 (35.0–36.0)	36.0 (35.0–36.0)	0.586
Arterial pH on ED arrival* median (IQR)	7.32 (7.14–7.39)	7.30 (7.18–7.38)	0.904
Arterial Lactate on ED arrival—mmol/l** median (IQR)	2.90 (1.00–7.50)	4.90 (2.80–7.80)	0.379
eGFR at ED arrival§ median (IQR)	43.7 (27.1–55.4)	43.1 (30.1–59.6)	0.255
LVEF on ED arrival median (IQR)	49.0 (35.5–60.0)	50.0 (39.0–65.5)	0.191
Heart failure,—no. (%)	57 (58.8)	78 (55.7)	0.641
Out-of–hospital cardiac arrest before hospital arrival,—no. (%)	24 (24.5)	38 (26.8)	0.693
Mechanical ventilation—no. (%)	38 (38.8)	63 (44.4)	0.389
Continuous hemodiafiltration—no. (%)	2 (2.0)	4 (2.8)	0.698
Patients treated anti-arrhythmic agents within 12 h of arrival at ED—no. (%)	7 (7.1)	12 (8.5)	0.083
The volume of infusion within 30 min of arrival at ED—no. (%)#			0.141
≤ 500 ml	8/20 (40.0)	8/37 (21.6)	
> 500 ml	12/20 (60.0)	29/37 (78.4)	

the arterial ph was recorded for 72 patients in the norepinephrine group and for 115 patients in the dopamine group.

**the arterial lactate was recorded for 55 patients in the norepinephrine group and for 83 patients the dopamine group.*

§*the estimated glomerular filtration rate (eGFR) was recorded for 97 patients in the norepinephrine group and for 140 patients in the dopamine group.*

#*the number of patients who treated the volume of infusion within 30 min of arrival at emergency department was divided by the number of patients who the pathophysiology of shock was "volume".*

ACS, acute coronary syndrome; SBP, systolic blood pressure; ED, emergency department; IQR, interquartile range; HR, heart rate; RR, respiratory rate; BT, body temperature; LVEF, left ventricular ejection fraction.

TABLE 2 | In entire study population, factors associating with 30-day mortality after hospital arrival.

Variable	Mortality (%)	Crude OR (95%CI)	Adjusted OR (95%CI)	*P*-value
Age—yr		1.029 (1.002–1.057)	1.037 (0.998–1.078)	0.065
Sex Female	25/97 (25.8)	(Reference)	(Reference)	
Male	37/143 (25.9)	1.005 (0.558–1.812)	1.341 (0.617–2.916)	0.459
SBP on ED arrival		0.990 (0.980–0.999)	0.990 (0.977–1.004)	0.164
HR on ED arrival		1.001 (0.994–1.009)	1.003 (0.993–1.013)	0.570
RR on ED arrival		0.968 (0.937–0.999)	0.979 (0.940–1.020)	0.318
The pathophysiology of shock* Non—pump	22/113 (19.5)	(Reference)	(Reference)	
Pump	40/127 (31.5)	1.902 (1.046–3.457)	2.278 (1.062–4.888)	0.035
eGFR G0/1/2	6/46 (13.0)	(Reference)	(Reference)	
G3a	7/57 (12.3)	0.933 (0.291–2.998)	0.966 (0.255–3.657)	0.959
G3b	24/72 (33.3)	3.333 (1.241–8.954)	2.463 (0.756–8.032)	0.135
G4/5	24/62 (38.7)	4.211 (1.551–11.43)	3.748 (1.148–12.24)	0.029
Administration of vasopressor agents Norepinephrine	26/98 (26.5)	(Reference)	(Reference)	
Dopamine	36/142 (25.4)	0.940 (0.523–1.691)	1.003 (0.480–2.094)	0.994

**the pathophysiology of shock consisted of pump and non-pump including volume and rate. OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; ED, emergency department; HR, heart rate; eGFR, estimated glomerular filtration rate.*

TABLE 3 | Relation between administration of vasopressor agents and 30-day Mortality After Hospital Arrival in each group.

eGFR (mL/min/1.73 m^2)	Variable	Mortality (%)	Crude OR (95%CI)	Adjusted OR (95%CI)	*P*-value
> 60 (G0/1/2)	Norepinephrine	2/15 (13.3)	(Reference)	(Reference)	
	Dopamine	4/31 (12.9)	0.963 (0.156–5.954)	15.12 (0.078–2,928)	0.312
45–59 (G3a)	Norepinephrine	0/26 (0.0)	(Reference)	(Reference)	
	Dopamine	7/31 (22.6)	–	–	–
30–44 (G3b)	Norepinephrine	10/29 (34.5)	(Reference)	(Reference)	
	Dopamine	14/43 (32.6)	0.917 (0.339–2.485)	0.598 (0.145–2.466)	0.477
< 30 (G4/5)	Norepinephrine	14/27 (51.9)	(Reference)	(Reference)	
	Dopamine	10/35 (28.6)	0.371 (0.130–1.064)	0.217 (0.054–0.877)	0.032

eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval.

DISCUSSION

In the present study based on the largest nationwide registry of patients with cardiovascular shock caused by various causes of CVD, we assessed the actual use and utility of vasopressor agents for cardiovascular shock within 24 h of arrival at ED in patients with poor renal function. We showed the first-line vasopressor agent, such as norepinephrine and dopamine, should be chosen based on renal function at hospital arrival for patients in cardiovascular shock. As the patients in the present study reflect the real-world situation, our findings have important implications for clinical practice, especially in cases where determining the origin of cardiovascular shock is difficult at hospital arrival.

The present study indicated that the 30-day mortality rate was significantly lower in patients with eGFR 45–59 ml/min/1.73 m^2 treated with norepinephrine compared to those treated with dopamine. Conversely, among patients with eGFR < 30 ml/min/1.73 m^2, the 30-day mortality rate was significantly higher in those treated with norepinephrine than in those treated with dopamine. In a randomized multicenter study (6), the 28-day mortality rate for patients in shock did not differ significantly between those administered dopamine and those administered norepinephrine as the vasopressor agent of first choice, although the incidence of arrhythmias was higher in patients treated with dopamine than in those treated with norepinephrine as the initial vasopressor agent. In addition, the same study reported that the dopamine treatment was more closely associated with increased 28-day mortality rate than the norepinephrine treatment for patients in cardiogenic shock whereas a similar association was not found for patients in septic or hypovolemic shock (6). Some studies have also recommended norepinephrine as the vasopressor agent of first choice as it primarily stimulates alpha adrenergic receptors, causing an elevation in systemic vascular resistance in a volume-dependent manner, and modestly stimulates cardiac beta adrenergic receptors, thereby aiding in the maintenance of cardiac output (10, 22). Thus, norepinephrine may be superior to dopamine, considering the lower risk of adverse reactions including tachycardia and other arrhythmias, which is the presumed cause for its recommendation for patients in shock (10, 22). However, they did not comment on the utility of norepinephrine or dopamine in patients with poor renal function.

The present study revealed that the 30-day mortality rate was significantly higher in patients with an eGFR < 45 mL/min/1.73 m^2 than in those with an eGFR > 45 mL/min/1.73 m^2 among those treated with norepinephrine. However, the 30-day mortality rate in patients treated with dopamine as the initial vasopressor agent was similar regardless of the level of renal function at admission. Numerous epidemiological studies have demonstrated that the progression of nephropathy is directly associated with an increase in the frequency of cardiovascular events (3, 23–25). An observational study involving 1.12 million adults in the United States has revealed that the mortality rate and CVD incidence increased significantly with decreasing eGFR (3). The rate of increase in CVD-associated mortality rate is higher than the rate of decline in renal function, indicating

the importance of suppressing the risk of death from CVD in addition to suppressing CKD progression as a major treatment goal in patients with CKD (26, 27). A major reason for this proposal was the finding that an increase in CKD stage from G3a (eGFR 45–59 mL/min/1.73 m^2) to G3b (eGFR 30–44 mL/min/1.73 m^2) was associated with a marked increase in the risk for CVD and the onset of terminal renal failure (28).

The present study has several limitations. First, this was not a randomized controlled trial. Second, details of the treatment, such as administration of norepinephrine and/or dopamine and administration of the other agents, were left to the physician's discretion at each hospital. The exact norepinephrine and dopamine doses and durations used in the study patients were not always known. Dopamine is an endogenous catecholamine and serves as a neurotransmitter and norepinephrine precursor. Dopamine activates diverse receptors in a dose-dependent manner. Specifically, low-dose dopamine selectively activates dopamine receptors of the renal and visceral blood vessels, leading to increased blood flow (17). Low-dose dopamine also acts directly on tubular epithelial cells, causing an increase in the excretion of sodium into urine, which is not dependent on the increase of renal blood flow (29). Conversely, norepinephrine stimulates alpha adrenergic receptors, causing a blood volume-dependent increase in systemic vascular resistance. This vasoconstrictive activity usually leads to reduced organ blood flow, in particular renal blood flow (16). Therefore, the optimal doses and durations of these vasopressor agents should be elucidated in future studies. Third, the present study excluded patients who received IABP or VA ECMO support; the analyses including these patients did not reveal a significant difference in the 30-day mortality rate after hospital arrival between those treated with dopamine and those treated with norepinephrine as the initial vasopressor agent. Furthermore, in both patients with and without compromised renal function at admission, the multivariate logistic regression analysis revealed a minimal difference in the 30-day mortality between patients treated with norepinephrine and dopamine as the initial vasopressor agent. Fourth, details of the treatment, including to decide vasopressor agents, were left to the physician's discretion at each hospital. Finally, SCr and not urine output was recorded at admission in the study population, and it was often difficult to confirm whether the patients had acute kidney injury or CKD. Among 979 patients in the JCS Shock Registry, the median time from onset to hospital arrival was 72 min (interquartile range, 40–284 min) (11). Therefore, we considered that the eGFR values calculated at the time of ED arrival reflected the chronic renal function status. However, for severe shock patients, it might be important to decide vasopressor agents by eGFR at admission in ED despite acute kidney injury or CKD. In future studies, it is necessary to record eGFR and urine output overtime to clarify this issue.

In conclusion, the first-line vasopressor agent should be chosen based on renal function at hospital arrival for patients in cardiovascular shock. Furthermore, in patients with mildly compromised renal function at admission (eGFR 45–59 mL/min/1.73 m^2), norepinephrine as the vasopressor agent of first choice might be associated with better prognosis. Conversely, in patients with severely compromised renal function (eGFR < 30 mL/min/1.73 m^2), dopamine might be more beneficial as the first-line vasopressor agent. Future studies are warranted to elucidate optimal therapeutic strategies for patients with compromised renal function presenting with cardiovascular shock.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University Hospital Medical Information Network Clinical Trials Registry (UMIN000008441; http://www.umin.ac.jp/ctr/index/htm/). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TY, KN, ET, and NY analyzed data. TY, KN, KS, YU, HI, TM, HT, and HH interpreted data. TY, KN, ET, NC, and ST wrote the paper. TY, KN, ET, NM, and YO reviewed and edited the paper. TY, KN, ET, NY, KS, YU, HI, TM, HT, and HH designed the overall study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.648824/full#supplementary-material

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ORIGINAL RESEARCH
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Vasopressin Loading for Refractory Septic Shock: A Preliminary Analysis of a Case Series

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Background: Vasopressin is one of the strong vasopressor agents associated with ischemic events. Responses to the administration of vasopressin differ among patients with septic shock. Although the administration of a high dose of vasopressin needs to be avoided, the effects of bolus loading have not yet been examined. Since the half-life of vasopressin is longer than that of catecholamines, we hypothesized that vasopressin loading may be effective for predicting responses to its continuous administration.

Methods: We retrospectively analyzed consecutive cases of septic shock for which vasopressin was introduced with loading under noradrenaline at >0.2 μg/kg/min during the study period. Vasopressin was administered in a 1 U bolus followed by its continuous administration at 1 U/h. The proportion of patients with a negative catecholamine index (CAI) change 6 h after the introduction of vasopressin was set as the primary outcome. We defined non-responders for exploration as those with a mean arterial pressure change <18 mmHg 1 min after vasopressin loading, among whom none had a change in CAI <0.

Results: Twenty-one consecutive cases were examined in the present study, and included 14 responders and 7 non-responders. The primary outcome accounted for 71.4% of responders and 0% of non-responders, with a significant difference ($p = 0.0039$). Median CAI changes 2, 4, and 6 h after the administration of vasopressin were 0, −5, and −10 in responders and +20, +10, and +10 in non-responders, respectively. CAI was not reduced in any non-responder. Outcomes including mortality were not significantly different between responders and non-responders. Digital ischemia (1/21) and mesenteric ischemia (1/21) were observed.

Conclusions: Vasopressin loading may predict responses to its continuous administration in septic shock patients. Further investigations involving a safety analysis are needed.

Keywords: critical care, septic shock, sepsis, vasopressin, loading

INTRODUCTION

Vasopressin is one of the strongest vasopressor agents used to treat septic shock (1). Its effects have been demonstrated in several randomized control trials (2–4). Surviving Sepsis Campaign guidelines recommend the use of vasopressin as a second- or third-line vasopressor after noradrenaline for septic shock (5). As the adverse effects of vasopressin, ischemia events, such as digital ischemia (6, 7), mesenteric ischemia (8, 9), myocardial ischemia, and alterations in circulation dynamics (10) may be induced by strong vasoconstriction. However, recent clinical studies suggested that these adverse events are less frequent than previously reported, except for digital ischemia, when the appropriate dosage is administered (11, 12).

Regarding the dosage and administration of vasopressin, recent guidelines recommend continuous infusion up to 0.03 U/min (1.8 U/h) (5) because adverse events were occasionally reported with the administration of a high dose of vasopressin (13). However, since the half-life of vasopressin is 10–35 min (14) and a minimum blood concentration is needed for vasoconstriction (15), more time is needed to reach a steady state and achieve an adequate increase in blood pressure than that by catecholamines when continuously administered. Therefore, vasopressin loading with a bolus administration is occasionally performed in emergency medicine when immediate increases in blood pressure are needed to maintain the circulation. In our facility, we administer a 1 U bolus of vasopressin followed by continuous administration to patients with septic shock in whom blood pressure is not maintained at the target with adequate noradrenaline.

The beneficial effects of vasopressin loading may not only be rapid increases in blood pressure. Since responses to the administration of vasopressin may differ among patients, some may show marked improvements (1), whereas others do not (16). By identifying responders and non-responders to vasopressin loading, it may be possible to predict responses to its continuous administration, i.e., continuous administration may be effective for responders, while other strategies may be needed for non-responders.

Therefore, we herein retrospectively analyzed 21 consecutive cases of septic shock for which >0.2 μg/kg/min of noradrenaline was needed and vasopressin was introduced with loading. We hypothesized that vasopressin loading may be effective for predicting responses to its continuous administration. Outcomes and adverse events with immediate responses in blood pressure after vasopressin loading were assessed to investigate its significance and safety.

MATERIALS AND METHODS

This was a single-center retrospective study of patients with septic shock to whom vasopressin was administered with bolus loading. Consecutive cases of septic shock (sepsis-3) in the Hitachi General Hospital Emergency and Critical Care Center between August and October 2020, for which >0.2 μg/kg/min noradrenaline was administered and vasopressin was introduced with bolus loading, were analyzed. Patients administered vasopressin without bolus loading were excluded. In our facility, the introduction of vasopressin was only considered for cases of septic shock for which minimum noradrenaline >0.2 μg/kg/min was administered and additional doses were expected to be needed. In our clinical practice, vasopressin was administered as a 1 U bolus for loading, followed by its continuous administration at 1 U/h.

We classified patients into responders and non-responders based on hemodynamic changes with vasopressin loading. We extracted data on blood pressure (systolic, diastolic, and mean on arterial line monitoring) and heart rate just before and 1 min after 1 U vasopressin loading. Blood pressure was monitored and recorded using a radial or femoral arterial line continuously in all cases. Furthermore, the catecholamine index (CAI) [dopamine + dobutamine + (noradrenaline + adrenaline) × 100 μg/kg/min] (17) at pre-loading and 2, 4, and 6 h after the introduction of vasopressin, urine output every 2 h after the introduction of vasopressin, mortality, and the lengths of intensive care unit (ICU) and hospital stays were analyzed for outcomes. The proportion of patients with ΔCAI <0 6 h after the initiation of vasopressin, i.e., catecholamine doses were reduced due to the administration of vasopressin, was the primary outcome. We set a mean arterial pressure (MAP) increase of 18 mmHg 1 min after vasopressin loading as the cut-off of responders/non-responders for exploration, such that there was no case with changes in ΔCAI <0 at 2, 4, or 6 h in any non-responders. Responders were defined as those with a MAP change ≥18 mmHg 1 min after vasopressin loading, and non-responders as those with MAP <18 mmHg after loading. Digital ischemia, mesenteric ischemia, and myocardial ischemia were observed systematically by ICU nurses in this study period. Digital ischemia was visually checked every 4 h when patients stayed in the ICU. Mesenteric ischemia, defined as obvious ischemia, was confirmed by examinations including computed tomography. Myocardial ischemia, defined as acute ST-segment elevations, was confirmed by a 12-lead electrocardiogram or elevated cardiac enzymes. After discharge from the ICU, patients were evaluated from a review of medical records during the entire admission period. Outcome data were compared between responders and non-responders.

Regarding patient baseline information, age, sex, height, weight, the infection focus, and the presence/absence of cardiac failure, coronary artery disease (CAD), peripheral artery occlusion disease (PAOD), and immune disease were extracted. The sequential organ failure assessment (SOFA) score (18), Acute Physiology and Chronic Health Disease Classification System (APACHEII) score (19), modified shock index (heart rate/MAP)(20), body temperature, lactate, C-reactive protein (CRP), white blood cell (WBC) counts, albumin, platelet counts, the prothrombin time international normalized ratio (PT-INR), sodium, potassium, chloride, and blood glucose on the day of vasopressin use were evaluated. Steroid use equivalent to >40 mg/day of prednisolone, mechanical ventilation, renal replacement therapy (RRT), and extracorporeal membrane oxygenation (ECMO) were assessed as adjunctive therapies. These baseline information were also compared between responders and non-responders.

Since this was exploratory research, the sample size was not calculated and clinical practice was performed as usual. The present study was approved by our hospital ethics board (2017–19). Patients were included for analysis using an opt-out form.

The significance of differences was evaluated using the Student's *t*-test and Fisher's exact test for parametric data. The Mann–Whitney U test was performed for non-parametric data. The normality of the distribution of each parameter was assessed using the Shapiro–Wilk test. A *post-hoc* power analysis was conducted for the primary outcome, ischemia events, and severity scores. All statistical analyses were conducted using software (JMP 14; SAS Institute Inc., Cary, NC, USA). Results were expressed as a mean ± standard deviation or median (interquartile range). *P*-values < 0.05 were considered to be significant and indicated with *.

RESULTS

The patient extraction outline is shown in **Figure 1**. In the study period, 39 patients with septic shock defined as sepsis-3 were admitted to our Emergency and Critical Care Center. Twenty-six patients required noradrenaline >0.2 μg/kg/min, and 21 of these patients administered vasopressin were included in the present study. In this period, no patient was administered vasopressin without bolus loading. The noradrenaline dose before vasopressin administration was 0.35 ± 0.12 μg/kg/min. Bolus loading of 1 U following by the continuous administration of 1 U/h was performed for all patients administered vasopressin. The baseline characteristics of the 21 patients are shown in **Supplementary Table 1**. Hemodynamic changes before/after vasopressin loading and outcomes were shown in **Supplementary Table 2**. No obvious circulatory alteration was observed in any cases with 1 U vasopressin loading; however, MAP increased to higher than 120 mmHg after loading in two cases (**Supplementary Table 2**), and subsequently decreased to <100 mmHg within the next few minutes.

Based on the definition of a responder to vasopressin loading of a MAP change ≥18 mmHg from before to 1 min after loading, 14 responders (66.7%) and 7 non-responders (33.3%) were identified. Differences in baseline characteristics between responders and non-responders are shown in **Table 1**. No significant difference was observed in age. A male predominance, larger body size, severity and pneumonia as the infection focus were observed in non-responders. Power $(1 - \beta)$ for SOFA and APACHEII were 0.257 and 0.055, respectively. No significant differences were noted in the noradrenaline dose on vasopressin administration, cardiac failure, CAD, PAOD, or immunodeficiency. However, the time between vasopressin administration and shock onset was significantly longer in responders.

Table 2 shows the outcomes of vasopressin loading and continuous administration. The vasopressin dose (1 U) normalized by body weight was similar in responders and non-responders. The duration of the vasopressin infusion did not significantly differ between responders and non-responders, and vasopressin was administered to all patients for 6 h. The primary outcome of the proportion of patients with ΔCAI <0 6 h after the initiation of vasopressin accounted for 71.4% of responders and 0% of non-responders, with a significant difference ($p = 0.0039$). In the *post-hoc* analysis, power $(1 - \beta)$ for the primary outcome was 0.999. The proportion of patients with ΔCAI <0 at 2 and 4 h accounted 42.9 and 50.0% of responders, respectively, and 0% of non-responders at both time points. ΔCAI are shown in **Figure 2**. Median ΔCAI changes 2, 4, and 6 h after the administration of vasopressin were 0, −5, and −10 in responders and +20, +10, and +10 in non-responders, respectively, with significant differences (**Figure 2**). Responses to vasopressin loading correlated with ΔCAI after the initiation of its administration.

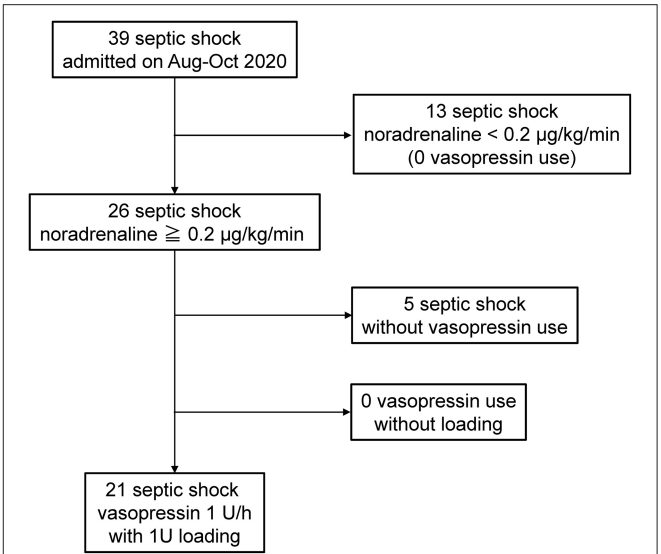

FIGURE 1 | Study outline. Twenty-one consecutive patients with septic shock administered vasopressin with loading under noradrenaline >0.2 μg/kg/min. Bolus loading with 1 U following by continuous administration with 1 U/h was performed for all patients.

No significant differences were observed in other outcomes, including mortality (**Table 2**). Digital ischemia, mesenteric ischemia, and myocardial ischemia as adverse events did not significantly differ between responders and non-responders. Power $(1 - \beta)$ for all ischemia events was 0.246. In all patients in the present study for whom vasopressin loading was performed, few adverse events were observed. Mesenteric ischemia was noted in patients with PAOD (**Supplementary Tables 1**, **2**). Causality was unclear in all cases. Significant differences were also observed in blood glucose and PT-INR.

DISCUSSION

Based on the bolus loading of 1 U vasopressin in patients with septic shock for whom the administration of vasopressin was needed under noradrenaline >0.2 μg/kg/min, two-thirds

TABLE 1 | Differences in baseline characteristics between vasopressin loading responders and non-responders.

n	Responder 14	Non-Responder 7	*p*-value
age	78.7 ± 7.6	78.1 ± 9.8	0.88
male	5 (35.7%)	5 (71.4%)	0.18
height (cm)	156.2 ± 10.9	160.5 ± 11.2	0.4
weight (kg)	52.5 (46.9, 57)	58 (41.1, 78.8)	0.85
SOFA	7 (5.8, 8.5)	11 (4, 14)	0.22
APACHEII	17.5 (13.5, 24)	21 (14, 28)	0.41
modified shock index	1.45 (1.11, 1.72)	1.58 (1.34, 2.49)	0.28
noradrenaline dose on vasopressin administration (μg/kg/min)	0.34 ± 0.15	0.37 ± 0.08	0.63
time of vasopressin administration from shock onset (hours)	6.5 (3, 10)	2 (2, 2.5)	0.017*
immunodeficiency	3 (21.4%)	1 (14.3%)	1
Infection focus			0.5
pneumonia	4 (28.6%)	5 (71.4%)	
urinary tract infection	3 (21.4%)	1 (14.3%)	
CRBSI	1 (7.1%)	0 (0%)	
cholangitis	1 (7.1%)	1 (14.3%)	
peritonitis	1 (7.1%)	0 (0%)	
meningitis	1 (7.1%)	0 (0%)	
unknown	3 (21.4%)	0 (0%)	
cardiac failure	4 (28.6%)	2 (28.6%)	1
CAD	1 (7.1%)	1 (14.3%)	1
PAOD	0 (0%)	1 (7.1%)	1
mechanical ventilation	10 (71.4%)	5 (71.4%)	1
RRT	3 (21.4%)	2 (28.6%)	1
ECMO	0 (0%)	1 (14.3%)	0.33
body temperature (°C)	37.8 ± 1.1	38.5 ± 1.7	0.26
lactate (mmol/l)	3.0 (1.6, 4.2)	3.9 (2.3, 10.4)	0.29
glucose (mg/dl)	136 (98, 175)	221 (190, 258)	0.0032*
PT-INR	1.4 ± 0.4	2.0 ± 0.8	0.040*

SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; CRBSI, catheter-related bloodstream infection; CAD, coronary artery disease; PAOD, peripheral arterial obstructive disease; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; PT-INR, prothrombin time international normalized ratio.
**p < 0.05.*

TABLE 2 | Outcome differences between vasopressin loading responders and non-responders.

n	Responder 14	Non-Responder 7	*p*-value
Primary outcome			
post 6 h CAI—pre CAI <0	10 (71.4%)	0 (0%)	0.0039*
pre SBP (mmHg)	85.6 ± 17.3	84.8 ± 18.1	0.93
pre DBP (mmHg)	45.4 ± 11.7	44.1 ± 6.5	0.79
pre MAP (mmHg)	59.9 ± 13.1	56.7 ± 9.2	0.58
pre HR (beats/min)	87.7 ± 19.3	101.7 ± 20.3	0.14
CVP (mmHg)	8.5 (4, 13.5)	11 (3.5, 15.3)	0.67
pre CAI	34.6 ± 15.2	37.1 ± 7.6	0.32
post 2 h CAI—pre CAI <0	6 (42.9%)	0 (0%)	0.061
post 4 h CAI—pre CAI <0	7 (50%)	0 (0%)	0.047*
vasopressin (U/kg)	0.019 ± 0.004	0.019 ± 0.006	0.99
vasopressin (hours)	44 (27.3, 84)	38 (26, 56)	0.65
mortality	6 (42.9%)	3 (42.9%)	1
(DNAR after treatment)	6 (42.9%)	2 (28.6%)	0.66
ICU stay (days)	8 (5.8, 11.8)	7 (4, 7)	0.29
hospital stay (days)	23 (13.3, 37.8)	11 (4, 15)	0.13
digital ischemia	0 (0%)	1 (14.3%)	0.33
mesenteric ischemia	1 (7.1%)	0 (0%)	1
myocardial ischemia	0 (0%)	0 (0%)	1
urine output pre-2 h	85 (16, 143)	50 (20, 100)	0.88
urine output 2–4 h	73 (7.5, 158)	50 (5, 250)	0.94

CAI, catecholamine index; SBP, systolic blood pressure, DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; DNAR, Do Not Attempt Resuscitation; ICU, intensive care unit.
**p < 0.05.*

of patients were identified as responders and one-third as non-responders, and bolus loading correlated with the need for another catecholamine dose after the administration of vasopressin. The primary outcome of the proportion of patients with ΔCAI <0 6 h after the initiation of vasopressin was significantly higher in responders. Ischemia events may not be excessive with vasopressin loading.

Rapid increases in blood pressure may be achieved with vasopressin loading. As shown in the change in blood pressure for 1 min after loading, blood pressure increased more rapidly with loading than with continuous administration without loading. An increase in blood pressure after continuous administration without loading may only be observed when a steady state is achieved with priming and the appropriate preparation of the infusion.

Vasoconstriction and blood pressure increases by vasopressin may only be achieved in humans when plasma vasopressin concentrations are higher than 50 pg/ml (15). Noradrenaline and other catecholamines may induce vasoconstriction linearly from the lowest concentration (21). These differences in the concentration-vasoconstriction relationship are caused by vasopressin and catecholamines receptors, namely, V1 and α1 (22). Therefore, the time needed for vasopressin to increase blood pressure before an adequate blood concentration is attained may be longer than that by noradrenaline. Moreover, the half-life of catecholamines, including noradrenaline, is 2 min (23), while that of vasopressin is 10–35 min (14); therefore, loading appears to be appropriate for the early achievement of the blood pressure target. The bolus administration of vasopressin has not yet been examined in detail. Terlipressin, an analogue of vasopressin (24) with a longer half-life of 50 min (25), has been administered with bolus loading in clinical trials (26) and animal studies (27). Although the risk of ischemia increases at high doses of terlipressin (28), it may be safe when administered at an appropriate dose. The bolus administration of vasopressors has been recommended in emergency and critical care cases (29).

However, vasopressin loading is not discussed in the Surviving Sepsis Campaign guidelines (5) due to the adverse effects

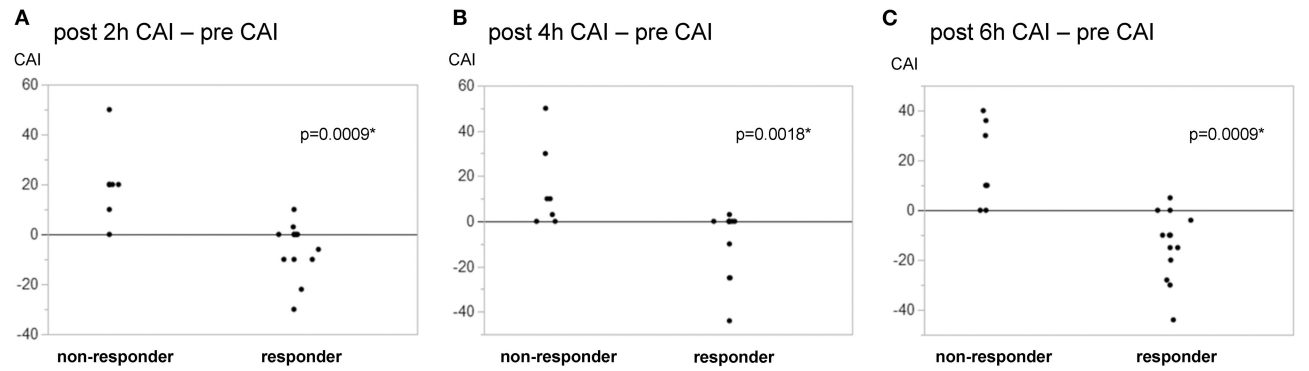

FIGURE 2 | Changes in the catecholamine index in responders/non-responders to vasopressin loading. Responders to vasopressin loading were defined by a MAP change ≥18 mmHg from before to 1 min after loading. Fourteen responders (66.7%) and 7 non-responders were identified. A change was observed in the catecholamine index (CAI) [dopamine + dobutamine + (noradrenaline + adrenaline)×100 μg/kg/min] from pre-loading to 2, 4, and 6 h after the initiation of vasopressin. **(A)** post 2-h−pre. **(B)** post 4-h−pre. **(C)** post–pre. Changes in CAI significantly differed between responders and non-responders at 2, 4, and 6 h. *$p < 0.05$.

associated with its administration at a high dose. High-dose vasopressin may induce digital (6, 7), mesenteric (8, 9), and myocardial ischemia (10). Previous case series and clinical trials suggested that the administration of more than 0.05 U/min increased the risk of these adverse effects (11), and, thus, <0.03 U/min is recommended (5). However, few studies have investigated the effects of a vasopressin bolus. To the best of our knowledge, there has only been one study on 7 cases for which a bolus of 50 mU/kg vasopressin was administered (30); 4 out of 7 cases died due to mesenteric ischemia. In contrast, the mortality rate in the present study was 40% with a lower bolus dose of 1 U because patients required noradrenaline >0.2 μg/kg/min and another vasopressor. The rates of digital and mesenteric ischemia were similar to that reported by VASST (3). However, since this was a preliminary analysis of a limited case series, the safety of vasopressin loading needs to be investigated in a larger number of patients. Furthermore, in two out of 21 cases in the present study, MAP increased to higher than 120 mmHg after loading. A transient increase in noradrenaline may be associated with a delayed blood pressure increase and vasopressin may cause excessive vasoconstriction. This condition may decrease cardiac output and oxygen delivery; therefore, it needs to be considered prior to vasopressin loading.

In the present study, two-thirds of patients with septic shock for whom noradrenaline >0.2 μg/kg/min and another vasopressor were required responded to vasopressin loading. In all responders, another catecholamine was not needed after the administration of vasopressin. On the other hand, it was not possible to reduce the dose of catecholamines in the remaining one-third of non-responders, the majority of whom still required additional catecholamine doses even after the administration of vasopressin. Differences in responses to the administration of vasopressin have been attributed to the depletion of vasopressin and a cortisol insufficiency (16). Prognostic differences in the use of vasopressin for septic shock were previously attributed to hormonal differences in clinical trials (3, 4). We did not assess blood antidiuretic hormone (ADH) or cortisol levels or perform an adrenocorticotropic hormone (ACTH) loading test because this was a retrospective study. However, the time between vasopressin administration and shock onset was significantly longer in responders in the present study. One reason for this may be the depletion of vasopressin after the onset of septic shock. Furthermore, irrespective of hormonal changes, it may be necessary to monitor continuous vasopressin administration in responders and immediately introduce another procedure to increase blood pressure (such as adrenaline or a circulatory assist device) in non-responders, suggesting the usefulness of vasopressin loading to predict responses to vasopressin. Since another potential advantage of vasopressin is the prevention of tachyarrhythmia by reducing the requirement for noradrenaline (12), vasopressin responder predictions may contribute to decreases in the administration of unnecessary noradrenaline and tachycardia.

There are several limitations that need to be addressed. This was a retrospective analysis of a case series in a limited time period. The sample size was small and underpowered. Therefore, a prospective study that examines the safety of vasopressin loading and its effects on patient prognosis is needed, and we are now preparing the VAsopressin LOading for Refractory septic shock VALOR trial. It will be important to assess blood ADH and cortisol levels and perform an ACTH loading test before vasopressin loading and compare the data obtained between responders and non-responders. Furthermore, vasopressin was administered at a dose of 1 U for loading and 1 U/h for continuous infusion. Since Japanese ICU patients are often smaller and older than those in Western countries, a dose of 0.03 U/min (1.8 U/h) may be too high; therefore, we adopted the described protocol. The effects of vasopressin may markedly change depending on the dosage administered (31, 32), and, hence, vasopressin loading at other dosages needs to be investigated. In addition, several factors, including norepinephrine and vasopressin doses, may influence responses to vasopressin and other outcomes (33).

CONCLUSIONS

Vasopressin loading may predict responses to its continuous administration in septic shock patients. Further investigations involving a safety analysis are needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hitachi General Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KN: conception of the study, interpretation, and drafting of the manuscript. HNak, HNar, MM, YT, TS, and HH: performance of clinical practices. TA, MH, and KY: data analysis and supervision of the study. All authors: have read and approved the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.644195/full#supplementary-material

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ORIGINAL RESEARCH
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Measuring Core Body Temperature Using a Non-invasive, Disposable Double-Sensor During Targeted Temperature Management in Post-cardiac Arrest Patients

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Background: Precisely measuring the core body temperature during targeted temperature management after return of spontaneous circulation is mandatory, as deviations from the recommended temperature might result in side effects such as electrolyte imbalances or infections. However, previous methods are invasive and lack easy handling. A disposable, non-invasive temperature sensor using the heat flux approach (Double Sensor), was tested against the standard method: an esophagus thermometer.

Methods: The sensor was placed on the forehead of adult patients ($n = 25$, M/F, median age 61 years) with return of spontaneous circulation after cardiac arrest undergoing targeted temperature management. The recorded temperatures were compared to the established measurement method of an esophageal thermometer. A paired t-test was performed to examine differences between methods. A Bland-Altman-Plot and the intraclass correlation coefficient were used to assess agreement and reliability. To rule out possible influence on measurements, the patients' medication was recorded as well.

Results: Over the span of 1 year and 3 months, data from 25 patients were recorded. The t-test showed no significant difference between the two measuring methods ($t = 1.47$, $p = 0.14$, $n = 1{,}319$). Bland-Altman results showed a mean bias of 0.02°C (95% confidence interval 0.00–0.04) and 95% limits of agreement of −1.023°C and 1.066°C. The intraclass correlation coefficient was 0.94. No skin irritation or allergic reaction was observed where the sensor was placed. In six patients the bias differed noticeably from the rest of the participants, but no sex-based or ethnicity-based differences could be identified. Influences on the measurements of the Double Sensor by drugs administered could also be ruled out.

Conclusions: This study could demonstrate that measuring the core body temperature with the non-invasive, disposable sensor shows excellent reliability during targeted

temperature management after survived cardiac arrest. Nonetheless, clinical research concerning the implementation of the sensor in other fields of application should be supported, as well as verifying our results by a larger patient cohort to possibly improve the limits of agreement.

Keywords: core body temperature, return of spontaneous circulation, targeted temperature management, cardiac arrest, hypothermia, intraclass correlation coefficient, heat-flux sensor

INTRODUCTION

The post-resuscitation phase is critical for patients with return of spontaneous circulation (ROSC), specifically considering both the overall outcome and the quality of neurological recovery (1, 2). One of the recommended treatments after ROSC is targeted temperature management (TTM) (3) as it improves neurological outcome and survival (4–6), although there is still disagreement over the duration of the treatment (7) and the ideal temperature (3). The European Resuscitation Council Guidelines recommend limits between 32 and 36°C (3).

With decreasing core body temperature (CBT) the risk of side effects such as hypokalemia or infections might increase (8, 9) even though the quality of evidence is still moderate to low (5). Temperatures below 30°C can even increase the risk of arrhythmias (9) which makes it clear that a precise monitoring of the CBT is mandatory.

Since the hypothetical gold standard of measuring the temperature of the blood perfusing the hypothalamus is not suitable for routine CBT assessment, alternative methods have been implemented. Potential measurement sites include the pulmonary artery, the esophagus and the bladder (10).

However, a significant disadvantage of the aforementioned methods is that they are all invasive. A promising substitute are non-invasive zero-heat flux and heat flux sensors. Having first been described in the 1970s (11), these sensors use a mathematical model to calculate the CBT from temperatures measured on a perfectly insulated small skin area. The clinical value of zero-heat flux sensors has already been verified but reports cite long calibration time and a bulky sensor as inconvenient factors (12–15). Without the need for a heating element, heat flux sensors provide a quicker response time and increased wearing comfort, while delivering comparable results (16–18).

With this study a new disposable, non-invasive, heat-flux double-sensor (DS) was tested and compared it to the established method for monitoring CBT with an esophageal thermometer (OeT) during induction and maintenance of TTM as well as during rewarming in patients with ROSC after cardiac arrest.

MATERIALS AND METHODS

A prospective observational trial of a convenience sample of patients treated at the intensive care unit (ICU) at the Department of Nephrology and Medical Intensive Care of the Charité Universitätsmedizin Berlin was conducted. The sample size needed to prove excellent reliability of the DS using the Intraclass correlation coefficient (ICC) was calculated to be 16 patients (power 90%, alpha 0.05). For this, R (R Core Team, Version 4.0.3) (19) with ICC.Sample.Size (20, 21) was used with references from a similar study (22). Considering potential dropouts, 29 patients were included in the study.

Patients were recruited between November 2015 and January 2017. The in- and exclusion criteria for this study are listed in **Table 1**. Protocols were approved by the local ethics committee (EA4/032/16). Taking into account the underlying condition of the subjects this included waiving of informed consent. This concurs with the recommendations by the European Resuscitation Council (23). The study was conducted following the guidelines of the Declaration of Helsinki from 2013 (24). All data sets were pseudonymized and the raw data was only accessible by the author of this study. Patients or their relatives could request that the patient's data will not be included in the study.

Study Protocol

Following the standard operation procedures of the ICU, the TTM was initiated immediately after admitting the patient to the ward. A target temperature of 33°C was achieved with the Arctic Sun® 5000 temperature management system (BD, Heidelberg, Germany). Vital signs (including esophageal temperature), medication, procedures etc. were recorded and stored by the patient data management system Copra (Copra Systems GmbH, Berlin, Germany) every 30 min. The DS was attached to the patients' forehead before TTM was initiated.

Gloves and socks were used as countermeasures to prevent shivering during hypothermia. Pancuronium for muscle relaxation was only administered if the aforementioned arrangements were not sufficient. The target temperature was maintained for 24 h followed by a rewarming phase at a rate of 0.25°C/h. Subsequently the target temperature was held at 37°C for another 24 h to intercept any rebound fever that might occur.

The temperatures of the OeT and the DS were simultaneously recorded until 48 h after the start of TTM. **Figure 1** shows a flowchart of the study protocol.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Age <18 years
Any patient after cardiac arrest with return of spontaneous circulation	
Undergoing targeted temperature management	

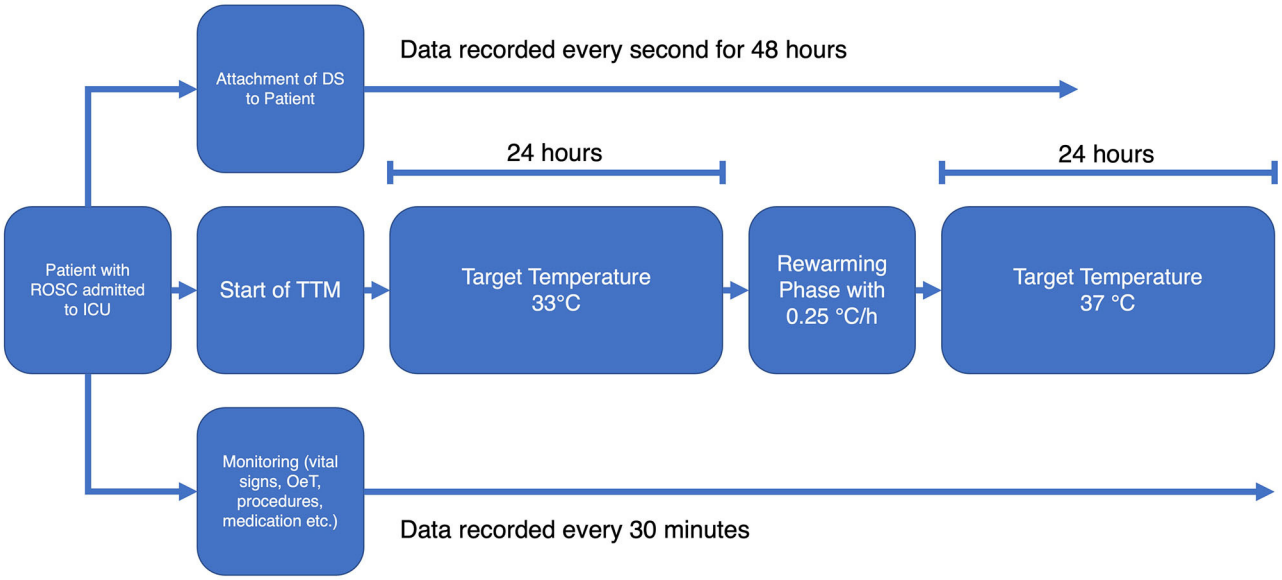

FIGURE 1 | Flowchart of the study protocol.

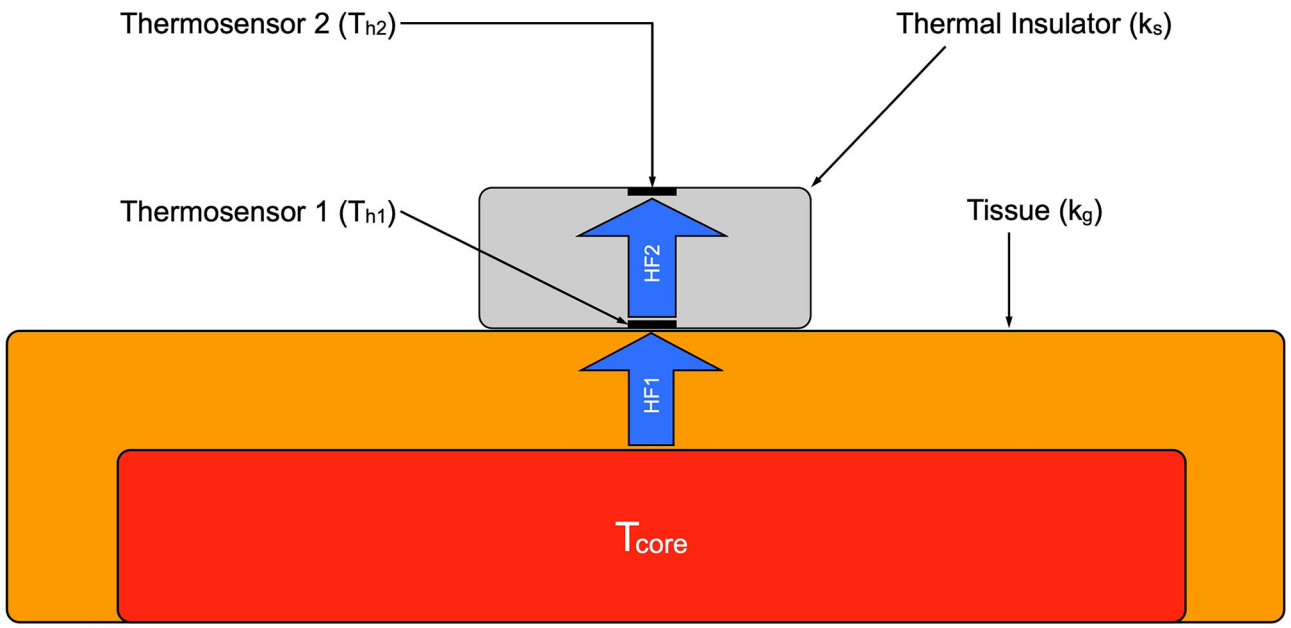

FIGURE 2 | Schematic of the double sensor. Tcore, core body temperature; HF 1, heat flux from body core to the sensor; HF 2, heat flux through the sensor.

Arctic Sun™ 5000 Temperature Management System

This non-invasive temperature management system monitors and controls the patient's temperature. It uses temperature-controlled water circulating through reusable pads that are wrapped around the chest and thighs of the patient. This leads to a heat exchange between the patient and the water. The patient's temperature feedback is provided by the OeT via a special connector to the control module.

Double-Sensor and Esophageal Thermometer

For this study the double-sensor system developed by Dräger (Draegerwerk AG & Co. KGaA, Lübeck, Germany) was used. **Figure 2** shows a schematic structure. It consists of two independent temperature sensors which are separated by an insulating layer. The unit is enclosed in an isolated casing. While one sensor (T_{h1}) measures the temperature of the skin, the other one (T_{h2}) measures the heat flux through the sensor to the

environment. The heat transfer coefficient of the insulation (K_s) and of the human tissue (K_g) are given. The heat flux through the insulation (HF_2) is assumed to be equivalent to the heat flux through the skin (HF_1). With these values it is possible to calculate the core temperature (T_{core}) with the formula developed by Gunga et al. (25):

$$T_{core} = T_{h1} + K_s/K_g * (T_{h1} - T_{h2})$$

Once the sensor is attached to the skin continuous measurements can be conducted within a few minutes. The usage of the above-mentioned heat-flux method allows for the sensor to be considered indifferent to the ambient temperature.

Using the self-adhesive surface, the sensor was placed on the patients' forehead above the left eyebrow and afterwards connected to the data logger system (Health Lab System, Koralewski Elektronik, Hambühren, Germany). This also gives the advantage of measuring in the proximity to the organ of interest (i.e., the brain).

Temperatures for both units of the DS were recorded with a frequency of 1/s and stored with a timestamp to the data logger. To ensure the internal validity of the recording and to rule out any influence on the measurement, environmental data were recorded, such as air pressure, ambient temperature and humidity. Data from the data logger were exported using SpaceBit Heally HLCC (Koralewski Elektronik, Hambuhren, Germany).

The esophagus thermometer in use was the Mon-a-Therm™ (Mallinckrodt Inc., St Louis, MO, USA) and was placed in the distal third of the esophagus at approximately 30 cm lip level. Given the proximity to the left atrium a good estimate of the CBT can be obtained from there (26). The preset recording frequency for the OeT was every 30 min, which unfortunately could not be changed beforehand without intensive reprogramming of the patient data management system.

Sedation, Analgesia and Other Vasoactive Agents

Analgosedation was achieved using Midazolam, Ketamine or Propofol in combination with Sufentanil. Isoflurane in the Anesthetic Conserving Device (AnaConDa, Sedana Medical AB, Sweden) combined with Remifentanil was preferably used whenever feasible mainly because of the short half-life with low risk of accumulation and rapid reawakening. To account for the effect which most inhalative and intravenous agents for sedation have on vasomotion (27) and consequently on the DS measurements, dosages and flow rate of drugs administered were recorded.

Data Analysis

The data sets were analyzed using MS Excel (Version 16.16.20) as well as IBM SPSS (Version 26.0.0). DS derived core temperature was calculated from temperatures Th_1 and Th_2 with the formula mentioned above. A two-sided p-value of < 0.05 was considered statistically significant. Continuous data are reported as means and standard deviation (SD). Artifacts were defined as difference > 2 SD. After proving the normal distribution of the data sets, a t-test for paired samples was used to examine the difference between methods. Furthermore, mean differences and standard deviation were calculated and used for a Bland-Altman Plot (28). The acceptable limits of agreement (LoA) were defined *a priori* as $\pm$ 0.5°C. These limits have been used in previous studies (12, 13, 16–18) and correspond to the usual magnitude of the human circadian temperature variation (29, 30). The intraclass correlation coefficient (ICC) (31, 32) was additionally used to evaluate the agreement and correlation between the OeT and the DS on the CBT. ICC estimates and their 95% confident intervals (CI) were calculated based on a single-rating ($k = 2$), consistency-agreement and a 2-way mixed effects model.

For the classification of the ICC Cicchetti's (33) definition is commonly used with an ICC < 0.4 indicating a poor, between 0.4 and 0.59 a moderate, between 0.6 and 0.74 a good and > 0.75 an excellent level of reliability.

RESULTS

Twenty nine patients were initially included in the study. In the process of data analysis four patients were excluded because of data storage errors due to a malfunction of the data logger's battery. This was resolved by switching to lithium-ion batteries.

TABLE 2 | Epidemiologic data.

N	25	
Sex, *n* (%)	Female	5 (20%)
	Male	20 (80%)
Age in years, mean (SD)	60 (12)	
BMI in kg/m^2, mean (SD)	27 (3.6)	
Length of stay in days, mean (SD)	11.49 (8.85)	
Initial rhythm, *n* (%)	VF	12 (48%)
	Asystole	6 (24%)
	PEA	7 (28%)
Adrenaline administered during CPR in mg, mean (SD)	4 (5)	
Time to ROSC in minutes, mean (SD)	22 (18)	
Out-of-hospital cardiac arrest, *n* (%)	21 (84%)	
Collapse witnessed, *n* (%)	22 (88%)	
Bystander CPR, *n* (%)	18 (72%)	
Admission diagnosis, *n* (%)	Acute myocardial infarction	12 (48%)
	Cardiac arrhythmia	1 (4%)
	Hyperkalemia	2 (8%)
	Respiratory insufficiency	7 (28%)
	Cardiogenic shock	1 (4%)
	Electrical accident	1 (4%)
	Other	1 (4%)
SAPSII at admission, mean (SD)	62 (17)	
Discharged from hospital, *n* (%)	10 (40%)	

BMI, body mass index; VF, ventricular fibrillation; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; SAPSII, simplified acute physiology score II.

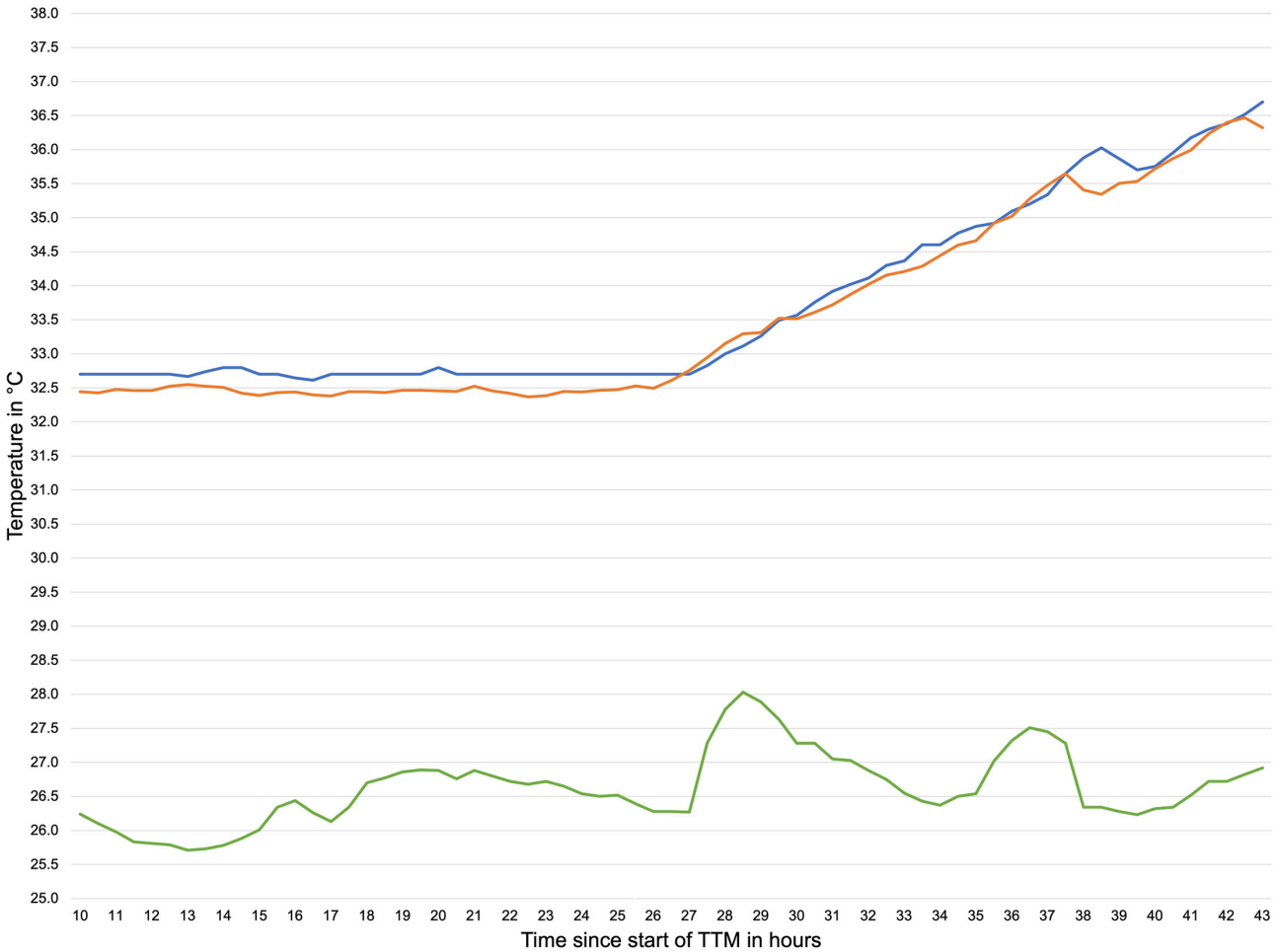

FIGURE 3 | Exemplary temperature profile during TTM. orange line: temperature measured by double sensor, blue line: temperature measured by esophageal thermometer, green line: ambient temperature.

Epidemiologic data for the remaining patients are listed in **Table 2**.

In total 2,695,806 temperature data samples were recorded with the DS and 15,084 with the OeT. After adjusting to the different sample rates of the DS and the OeT and the removal of artifacts (95 temperature pairs; 6.7%) this led to 1,319 time-paired temperature samples. The mean temperature for the DS was 34.11°C (SD 1.63°C) ranging from 29.3 to 38.03°C and 34.13°C (SD 1.42°C) ranging from 28.76 to 37.26°C for the OeT. Seventy one percent of the data recorded with the DS were in between ± 0.5°C of the temperatures recorded with the OeT. Mean ambient temperature was 25.22°C (SD 1.48°C). **Figure 3** shows an exemplary temperature profile of one patient.

The calculated data are shown in **Table 3**. The paired sample *t*-test showed no difference between the means of the two sensors ($t = 1.47$, $p = 0.14$, $n = 1{,}319$). The Bland-Altman plot is shown in **Figure 4**.

In one case the bias suddenly increased from −0.03 to −1.01°C within 17 h and in a second case from −0.23 to −1.43°C within 14 h. In both cases the DS reported an increase in temperature ∼3 to 4 h before the OeT. Four more cases with a noticeable baseline bias were identified and are shown with the other two cases in **Table 4**.

TABLE 3 | Agreements between double-sensor and esophageal temperature.

Double sensor vs. esophageal temperatures		95% CI	*P*-value
Mean bias in °C	0.02	0.0–0.04	0.14
SD in °C	0.53		
95% LoA in °C (Bias ± 1.96*SD)	−1.023; +1.066	Lower LoA: −1.025– −1.022 Upper LoA: 1.065–1.068	
ICC (95% CI)	0.94	0.93–0.95	<0.001

CI, confidence interval; SD, standard deviation; ICC, intraclass correlation coefficient; LoA, limits of agreement.

The temperatures for obese patients with a Body Mass Index (BMI) ≥ 30 kg/m^2 ($n = 3$) were similar to the whole group except for one case. No sex-based or ethnicity-based differences were detected.

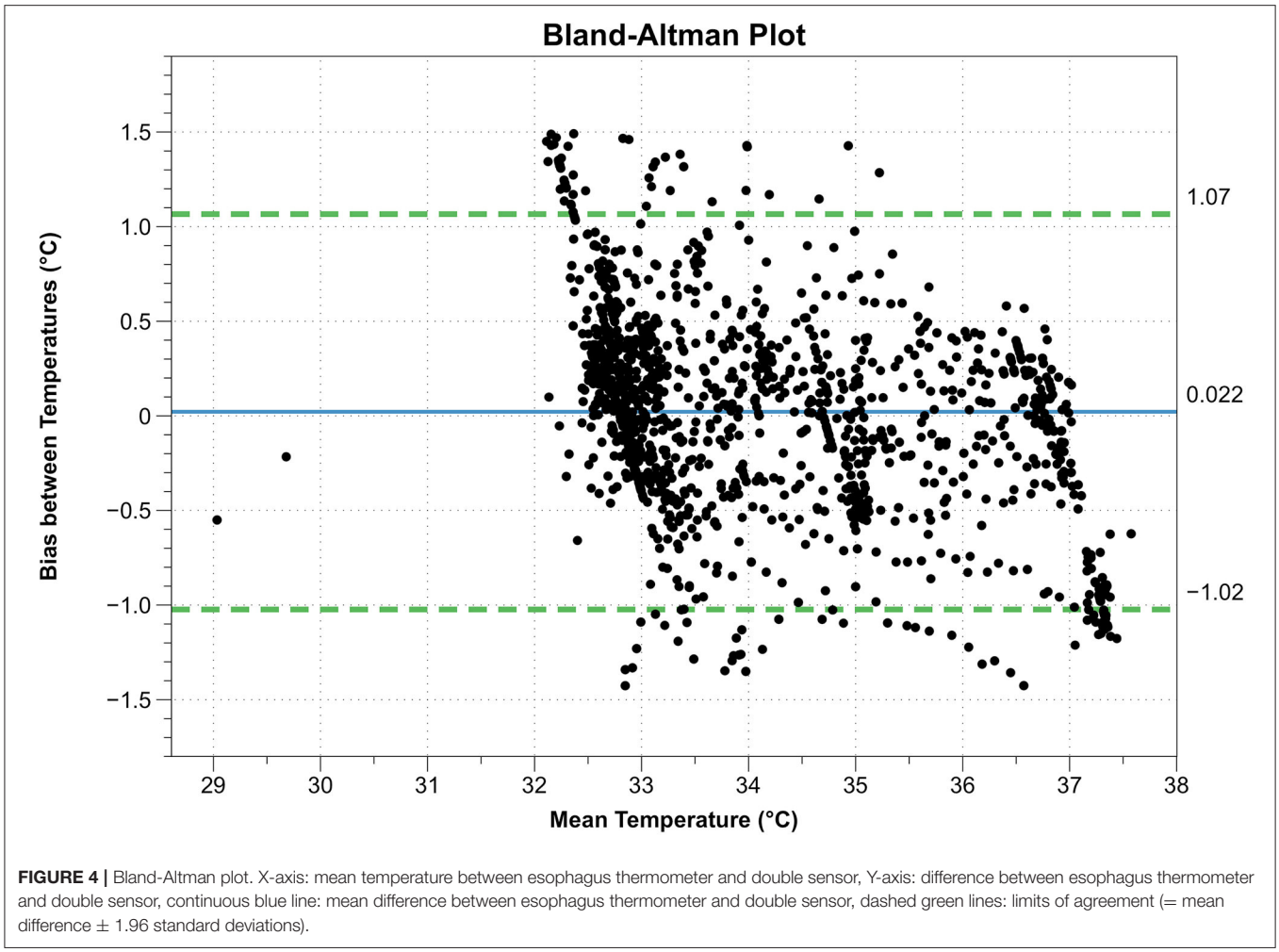

FIGURE 4 | Bland-Altman plot. X-axis: mean temperature between esophagus thermometer and double sensor, Y-axis: difference between esophagus thermometer and double sensor, continuous blue line: mean difference between esophagus thermometer and double sensor, dashed green lines: limits of agreement (= mean difference ± 1.96 standard deviations).

TABLE 4 | Patients with a noticeable difference in the bias between temperatures measured between esophageal temperatures and the double sensor.

Patient ID	Sex	Mean bias (SD) in °C	Minimum bias in °C	Maximum bias in °C	BMI in kg/m²
7	m	0.88 (0.47)	0.21	1.49	21.4
10	f	−0.53 (0.88)	−0.09	1.42	27.5
14	m	−0.4 (0.34)	0.00	−1.01	29.1
18	m	−0.8 (0.37)	0.02	−1.43	26.1
23	m	0.68 (0.5)	0.02	1.47	35.1
25	m	0.87 (0.12)	0.66	1.19	29.2

m, male; f, female; SD, standard deviation; BMI, body mass index.

DISCUSSION

For this clinical study the capabilities of a new disposable heat flux sensor were tested on patients undergoing TTM after cardiac arrest and compared to the established method of an OeT. This setting requires the ability to measure temperatures both precisely and over a relatively wide range of temperatures (∼6°C).

To date, the gold standard for measuring CBT is the temperature in the pulmonary artery (34, 35). However, Stone et al. (10) observed that during cardiac arrest or deep hypothermia the pulmonary artery's temperature does not always correlate with the brain's temperature. The esophageal temperature, however, corresponded closely and combines accuracy, response time and invasiveness appropriately. Nonetheless, the OeT is not the ideal tool: the correct placement of the probe in the distal esophagus is necessary to acquire precise data and to prevent inspired gases from distorting the measurements (36). It is also not suitable for use during esophageal interventions and some head and neck surgical procedures. Furthermore, this method causes discomfort in awake patients, so the thermometer is usually removed once the patients regain consciousness and is replaced by less precise (e.g., bladder temperature, rectal temperature) (10, 34) or even discontinuous methods (e.g., spot checking with an infrared thermometer, axillary thermometer). In contrast, the DS provides easy handling and is much more tolerable for the patient. Previously described skin irritations (12, 16, 17) were not observed in this study. Neither did this study show the often cited (17, 37) extensive calibration time. Two patients' data sets

were identified, which allowed for a direct comparison of the two thermometers' initial parallel recording performance: after 2 min (patient 1, bias of 0.25°C) and after 3 min (patient 2, bias of 0.36°C) the first data pairs were recorded. A higher frequency of esophageal temperature measurements is necessary to generate more comparable data pairs. But from these two examples it can be concluded that the calibration time amounts to <3 min.

The statistical analysis of a comparison between two sensors requires the consideration of two decisive details:

- First, not only correlation, but also agreement must be examined. Most studies use Pearson's r to measure correlation omitting their agreement. In order to assess the reproducibility between the different methods the ICC was used which also quantifies the agreement. In contrast to other correlation coefficients, it also takes the systematic error into account, which makes it a great alternative for showing agreement between two methods (38). According to the classifications described earlier the calculated ICC of 0.94 indicates excellent reliability for determining the CBT for the DS in this study.
- Second, precision and accuracy must be ensured. The OeT is widely considered to be of equivalent quality to the existing gold standard (10) which attests both precision and accuracy. This study showed a high level of agreement between the esophagus sensor and the DS, extending these attributes to the DS as well. Taking these analytical details into account the DS can be considered a reliable alternative.

A limitation to this study was the relatively small paired-sample size in comparison to the overall number of collected samples for each method. One of the reasons for this discrepancy was the low data collection frequency of the OeT which could not be changed beforehand. Another limiting factor were interruptions of the data collection through the Copra system for patients who underwent percutaneous coronary intervention as part of the post-arrest treatment (3) after their admission to the ICU. The DS however was still attached to the patients' forehead and continued recording. Lastly the above-mentioned technical problems of the data logger disrupted measurements in a few cases before the end of the 48-h period. These disruptions occurred even after the batteries had been replaced and after a software bug had been ruled out, thus making accidental manipulation of the data logger through nursing or physician staff (e.g., while positioning or examining the patient) the most likely cause.

Another limitation is the discrepancy between a low bias and wide limits of agreement. Our percentage of values diverging 0.5°C from the mean bias is comparable to results by Eshraghi et al. (13) (71 vs. 78%), suggesting homogeneity for most of the recordings. Six patients were identified with a larger bias than the rest seen in **Table 4**. One patient had a BMI > 35 kg/m^2. Since the sensor works best on skin with low subcutaneous fat tissue (39) and few large veins (40), the patients' obesity might account for the high bias in this case. Two other patients' data sets showed a gradually increasing offset between the two sensors' measurements after 12 (Patient ID 7) or 24 h (Patient ID 18) from the start of the recording. The DS registered higher temperatures approximately 4 h before the esophagus sensor measured the same increased values. Dosages and flow rates in agents influencing vasomotion were constant for both patients during this time. The remaining three patients showed a constant larger bias while following the temperature trend of the OeT. Possible explanations for all patients that were ruled out were prone positioning of the patient, unintentional covering or removal of the DS as well as changes in the ambient temperature. Additionally, Mazgaoker et al. (41) demonstrated that the DS measurements were not affected by changes in the environmental temperature. Another explanation is given by Opatz et al. (42), who found a non-linear relationship between sensor sites to measure the CBT. The more remote the sensor position from the organ of interest, the greater the effect of non-linearity. This means that the increase in temperature as measured by the DS is not linear to the temperature in the esophagus as it is further away from the brain (the organ of interest). The authors state that the time lag between sensor positions is not constant but individual for each patient. Further study is needed to evaluate contributory factors since this phenomenon only occurred in two of our patients and after a certain amount of time.

Another possible factor influencing our results is the medication regimen of patients in the ICU. General anesthetics and opioids (e.g., Propofol, Dexmedetomidine, Isoflurane, Clonidine, Fentanyl) decrease the cold-response threshold and thereby the vasoconstriction threshold (27, 43), which could interfere with the measurements. However, Ikeda et al. (44) showed that anesthesia had almost no effect on the core-to-skin temperature gradient.

To our knowledge this is the only study testing the Draeger DS in such a setting to date. Zeiner et al. (12) had a comparable setting but used a prototype zero-heat flux sensor. The results were similar with a bias of −0.12°C but with smaller limits of agreement. Other studies were mostly set in an operational setting (15, 17, 18, 40, 42) or compared the heat flux principle to nasopharyngeal (14), pulmonary arterial (13, 14), or vesical (42) temperature. Even though most of the studies report the use of a zero-heat flux sensor with a heating element or a sensor from a different manufacturer the results are similar. A recently published review by Conway et al. (45) on the use of the 3M^{TM} heat flow sensor supports this statement.

Building on the findings of our study we recommend three further steps:

1. Verifying our results by a larger patient cohort to possibly improve the limits of agreement.
2. Modification of the recording system of the OeT in order to generate more data pairs per patient and time unit.
3. Additionally, further possible applications for this type of sensor need to be explored. The lack of an omnipotent temperature sensor and a large variety of application settings call for the use of the DS as a non-invasive alternative to the established methods.

So far, however, the DS technology has not yet been established in clinical practice. The possible reasons for this are diverse, as Wartzek et al. (46) show in their review. As a way of

implementing this method into clinical standards, the use as a complementary secondary monitoring site to evaluate other temperature measurements is suggested. It could also be incorporated into other monitoring devices such as electroencephalography, electrocardiogram, SpO_2 etc. In conclusion this study showed that the DS is a reliable and non-invasive tool to measure the CBT in patients during TTM after cardiac arrest and ROSC. Further clinical research concerning the implementation of the sensor in other fields of application should be supported.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by Ethics committee Charité Universitätsmedizin Berlin (EA4/032/16). Considering the underlying condition of patients, waiving of informed consent, when necessary, was accepted. This concurs with the recommendations by the European Resuscitation Council (23).

AUTHOR CONTRIBUTIONS

OO: conceptualization and project administration. OO, CS, and MM: methodology. CS: software, investigation, and resources. DJ and CS: validation. DJ: formal analysis, visualization, and writing—original draft. OO, NK, H-CG, MM, and CK: writing—review and editing. OO and CS: supervision. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Successful Treatment of a Critically Ill COVID-19 Patient Using Continuous Renal Replacement Therapy With Enhanced Cytokine Removal and Tocilizumab: A Case Report

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The COVID-19 pandemic has caused multiple deaths worldwide. Since no specific therapies are currently available, treatment for critically ill patients with COVID-19 is supportive. The most severe patients need sustained life support for recovery. We herein describe the course of a critically ill COVID-19 patient with multi-organ failure, including acute respiratory failure, acute kidney injury, and fulminant cytokine release syndrome (CRS), who required mechanical ventilation and extracorporeal membrane oxygenation support. This patient with a predicted high mortality risk was successfully managed with a careful strategy of oxygenation, uremic toxin removal, hemodynamic support, and most importantly, cytokine-targeted intervention for CRS, including cytokine/endotoxin removal, anti-cytokine therapy, and immune modulation. Comprehensive cytokine data, CRS parameters, and biochemical data of extracorporeal removal were provided to strengthen the rationale of this strategy. In this report, we demonstrate that timely combined hemoperfusion with cytokine adsorptive capacity and anti-cytokine therapy can successfully treat COVID-19 patients with fulminant CRS. It also highlights the importance of implementing cytokine-targeted therapy for severe COVID-19 guided by the precise measurement of disease activity.

Keywords: COVID-19, cytokine release syndrome, extracorporeal membrane oxygenation, continuous renal replacement therapy, tocilizumab

INTRODUCTION

The emerging and rapid transmission of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with its associated syndrome, coronavirus disease (COVID-19), has spread worldwide after its outbreak in Wuhan, China in late 2019 (1). Although most patients may be asymptomatic, patients with advanced ages or multiple comorbidities can develop

fatal illnesses and rapidly succumb to them. It is estimated that 2–10% of the patients may develop critical illness and may need intensive care and advanced life support (1–5). The associated pathophysiology is diverse and might range from transient organ dysfunction to deadly multi-organ failure. The organs involved include the cardiovascular system, kidneys, lungs, hematologic system, and immune system. Severely ill patients may have cytokine release syndrome (CRS) (6), presenting with refractory hypotension, hemophagocytic lymphohistiocytosis (7), anti-phospholipid activity (8), and kidney damage (9). Since effective antiviral therapy is not available at this time; life-supportive measures and effective complication management are pivotal measures for patient survival. We report herein a successful treatment strategy using cytokine-targeted therapy, including CRS management and extracorporeal cytokine removal, in a critically ill COVID-19 patient with a devastating clinical course.

CASE DESCRIPTION

A 53-year-old man with a history of colon cancer and bladder cancer with disease-free status for more than 5 years developed watery diarrhea 3 d after close contact with a confirmed COVID-19 patient. Fever (body temperature, 37.7°C), general malaise, myalgia, and poor appetite prompted him to seek medical advice on the 11th day, and he was admitted to a regional hospital. The hemogram was normal (white blood cell count: 4,900/μL, hemoglobin concentration: 16.6 g/dL, and platelet count: 203 k/μL). The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 44 and 45 U/L, respectively. There was an elevation in the C-reactive protein (CRP) level (12.5 mg/dL), although the procalcitonin level was within normal limits (0.15 ng/mL). Polymerase chain reaction (PCR) from a nasal swab for SARS-CoV-2 was positive. Moxifloxacin (400 mg daily) and hydroxychloroquine were administered.

On day 16, he developed respiratory distress with an escalation of his oxygen needs from nasal prongs to a non-rebreathing mask. A chest radiograph revealed rapid progression of pulmonary infiltrates (**Figure 2A**). He underwent tracheal intubation for severe hypoxemia with an arterial oxygen partial pressure to fractional inspired oxygen ratio of 109 mmHg. In addition, he had lactic acidosis (lactic acid level 2.3 mg/dL), rhabdomyolysis (creatinine kinase level 261 U/L), high CRP level (14.6 mg/dL), and hyperferritinemia (ferritin level 2,957 ng/mL). His urine volume was ∼840 mL in 24 h, and the renal reserve was adequate with a serum creatinine level of 1.1 mg/dL. With this presentation, he was transferred to our intensive care unit (ICU) for advanced life support (**Figure 1**).

Abbreviations: ALT, alanine aminotransferase; AKI, acute kidney injury; APACHE II, Physiologic Assessment and Chronic Health Evaluation II; AST, aspartate aminotransferase; RBC, red blood cell; RTC, renal tubular cells; CBA, cytometric bead array; COVID-19, coronavirus disease; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CRS, cytokine release syndrome; GFR, glomerular filtration rate; ICU, intensive care unit; IL, interleukin; RCA, regional citrate anticoagulation; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, sequential organ failure assessment; VIE, Vasoactive-Inotropic Equivalent; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

DISEASE ASSESSMENT

Clinical Parameters and SARS-CoV-2 Detection

Acute disease severity was assessed using Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores collected on ICU admission and the next day of ICU stay (10). Sequential organ failure assessment (SOFA) scores were collected daily (11). Vasoactive-Inotropic Equivalent (VIE) scores were calculated from the infusion rates of vasopressors and inotropes and automatically summed up in the computerized database (12). Acute kidney injury was defined using the Kidney Disease: Improving Global Outcomes 2012 criteria (13). We also calculated the kinetic glomerular filtration rate (GFR), which forecasts future renal dysfunction derived from two consecutive days' serum creatinine data (14). Collection and detection of SARS-CoV-2 from biological samples were compliant with the World Health Organization guidance (15). Sputum, nasopharyngeal swabs, and oropharyngeal swabs were obtained for real-time PCR (RT-PCR). We determined the SARS-CoV-2 viral loads in each biological sample.

Continuous Renal Replacement Therapy

The indication for continuous renal replacement therapy (CRRT) was oliguria for more than 12 h, with clinical evidence of fluid overload and hemodynamic compromise. We used a standard CRRT machine (Plasmaflex®, Baxter®, France) with either a standard AN69 based hemofilter (M150, Baxter®, France) or a specialized hemofilter composed of AN69 and polyethyleneimine (AN69ST/PEI, oXiris®, Baxter® France) used for increased clearance of cytokines and endotoxins in patients with sepsis (16). The CRRT prescription was compatible with the current standard (13). We used continuous veno-venous hemodiafiltration (CVVHDF) with a dialysate flow of 10–15 mL/kg/h along with a filtration flow of 15–20 mL/kg/h via a 14 Fr-uncuffed tunneled catheter. To decrease filtration fraction and prolong circuit lives, we chose CVVHDF as the main treatment modality. The filtration fraction was set to below 20% to avoid pre-mature dysfunction of the circuit. The AN69ST/PEI hemofilter with increased adsorptive capacity for cytokines and endotoxins has been emergently approved by the United States in response to the COVID-19 pandemic under EUA200164 and has been granted permission for use in Taiwan in recent years. We set up CRRT with an AN69ST/PEI along with heparin or regional citrate anticoagulation (RCA) (17). We targeted the activated prothrombin time around 50–70 s while using heparin and targeted a post-filter ionized calcium around 0.3–0.45 mmol/L while using RCA (18).

Veno-Venous Extracorporeal Membrane Oxygenation Life Support

The indication for veno-venous extracorporeal membrane oxygenation (VV-ECMO) support was refractory hypoxemia. We cannulated the patient via the right internal jugular and femoral vein using the cut-down method. The VV-ECMO comprised a circuit with heparin-bound surfaces, an oxygenator (Affinity NT, Medtronic), a centrifugal pump (BPX-80 Bio-Pump Plus,

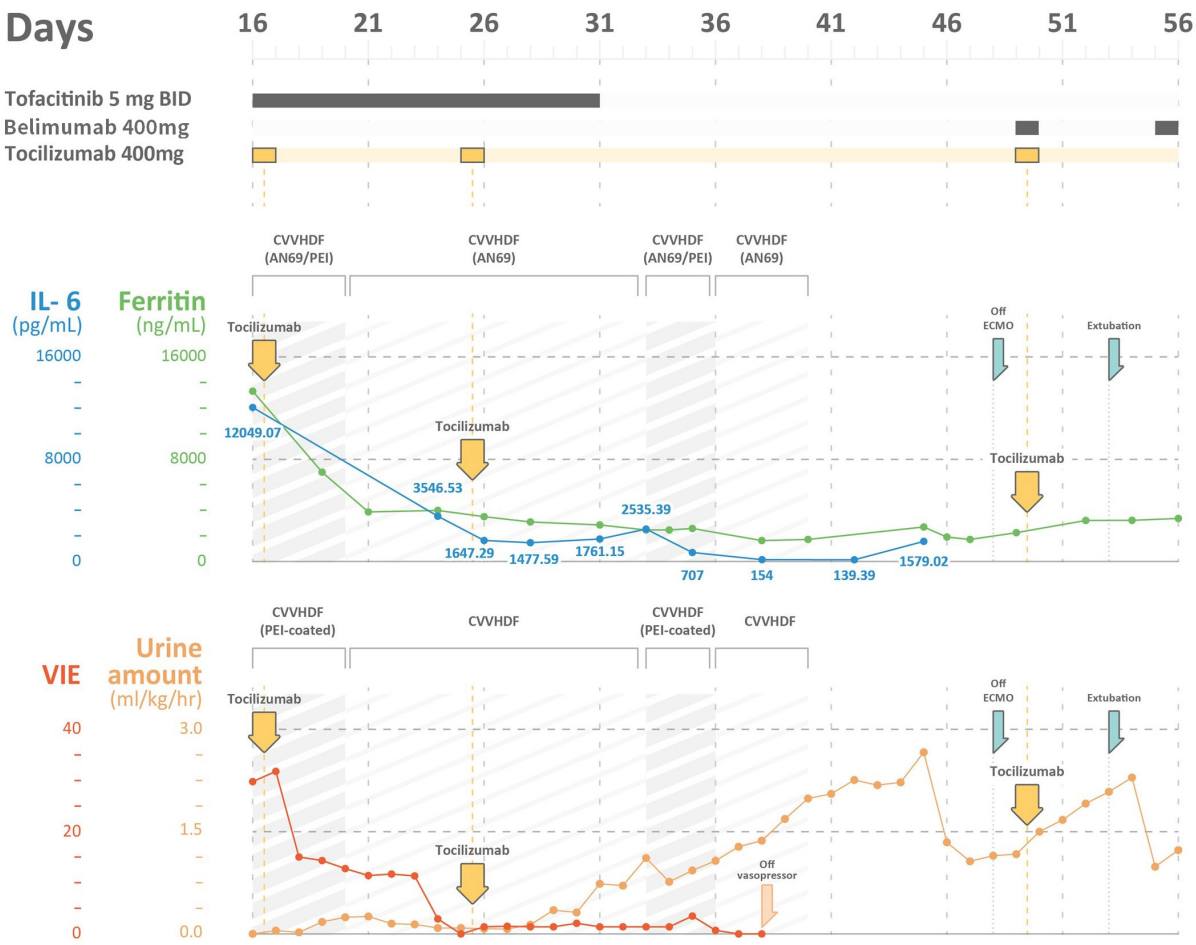

FIGURE 1 | The time course of ferritin levels, IL-6 levels, vasoactive-inotropic equivalent (VIE) scores, and urine amount in a severe COVID-19 patient with multi-organ failures. IL-6, interleukin 6; VIE, vasoactive-inotropic equivalent; CVVHDF, continuous venovenous hemodiafiltration; AN69ST/PEI: hemofilter with AN69 and polyethyleneimine.

Medtronic, Anaheim, CA, USA), and an oxygen-air blender (Model 3500 CP-G gas mixer, Sechrist, Anaheim, CA, USA) (19).

Cytokine Measurement

We used the cytometric bead array (CBA) method to determine cytokine levels (20). Approximately 5 mL peripheral blood samples were obtained from patients at each time point. Plasma was isolated after centrifugation at 1,500 rpm for 10 min. The concentrations of cytokines (interleukin [IL]-2, IL-4, IL-6, IL-10, IL-17, interferon-γ, and tumor necrosis factor in plasma were determined using cytometric bead array (CBA; BD Biosciences), according to the manufacturer's protocol. Briefly, 350 μL samples were subjected to analysis in duplicate using the CBA kit on BD caliber cytometry. The concentrations of cytokines in culture supernatants were quantified using FCAP Array software v3.0 (20). We determined cytokine levels in samples collected from plasma and CRRT effluent. Plasma cytokine levels were checked at three-time points (before CRRT, hour 12, and 24) to determine the number of total cytokines removed using the area under the curve method. Because it was impossible to check the adsorptive capacity of AN69ST/PEI hemofilter, we checked cytokine levels from the CRRT effluent collected in the first 24 h on CRRT with the AN69ST/PEI hemofilter. The differences between these two values could approximate the number of cytokines absorbed by the hemofilter.

Medications for Immune Modulation

The patient was prescribed tocilizumab, tofacitinib, hydroxychloroquine, and belimumab during his hospital course. Tocilizumab acts as an IL-6 receptor blockade and has been approved for rheumatoid arthritis, giant cell arteritis, and chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (21). Tofacitinib is an inhibitor of Janus kinase (JAKs) 1 and 3. It also has partial selectivity to JAK 2. Tofacitinib may suppress pro-inflammatory signaling including IL-6. It has not been tested in COVID-19 patients for cytokine blockade (22). Hydroxychloroquine is an anti-malarial drug and *in vitro* study confirmed its ability to

inhibit SARS-CoV-2 (23). Antiphospholipid activities may be detected in COVID-19 patients. The mechanism of belimumab is to inhibit the binding of soluble circulating B lymphocyte stimulator to surface ligands of B cells, which may downregulate the anti-phospholipid activities (24).

RESULTS

Upon arrival to the ICU, the patient experienced rapid deterioration of oxygenation and hemodynamics. The body temperature was high (38.3°C), arterial blood pressure was low (79/51 mmHg), and he had tachycardia (heart rate, 136 bpm). He needed vasopressors with a VIE of 29.80: norepinephrine at 0.26 mcg/kg/min, and dopamine at 3.7 μg/kg/min were administered to maintain adequate mean artery pressure. The APACHE II score was 40 (corresponding to an estimated mortality rate of 85%), and the SOFA score was 17. There was a severe acute kidney injury (AKI) with an absence of urine output for more than 12 h and an increase in creatinine level to 3.1 mg/dL. The kinetic GFR was calculated to be 0 mL/min (14). Urinalysis showed dysmorphic red blood cells (RBCs) and renal tubular cells (RTCs), which indicated glomerulonephritis and acute tubular necrosis. A VV-ECMO circuit was promptly set for refractory hypoxemia (2). His laboratory values indicated a relative lymphopenia (lymphocyte percentage: 6.1%, with an absolute count of 722/μL). The ferritin level increased to 13,317 ng/mL, and the triglyceride level was 446 mg/dL. The AST level was 121 U/L, along with an ALT level of 47 U/L. The cytokine profiles displayed an extremely high IL-6 level (12,049.07 pg/mL). A rapidly evolving CRS was likely. In addition, with rapidly elevating procalcitonin levels (from 0.15 to >100 pg/mL), ceftazidime and levofloxacin were prescribed empirically for concern of a superimposed bacterial infection, although the bacterial cultures did not yield until discharge. CRRT with an AN69ST/PEI hemofilter was delivered using a separate uncuffed tunneled catheter. Intravenous immunoglobulin (1 g/kg/day) was administered for two consecutive days for hypogammaglobulinemia (immunoglobulin G: 629 mg/dL).

The poor renal reserve precluded the patient from remdesivir therapy. Hydroxychloroquine with 400 mg twice daily was continued, and tocilizumab with a total dose of 400 mg (5.2 mg/kg) was prescribed 2 h after the initiation of CRRT. Tofacitinib (5 mg twice daily) was also prescribed for suspected antiphospholipid activity. We changed the AN69ST/PEA hemofilter circuit every 24 h for better clearance of cytokine/endotoxin. After 26-h treatment, the patient's hemodynamics improved. On day 20, we changed the CRRT hemofilter to an AN69 based hemofilter, after 3 days of cytokine adsorptive treatment. The viral load from the sputum was 2,762 copies/mL. Dopamine and norepinephrine were tapered off on day 22 (after 6-day cytokine-targeted therapy). The ferritin level declined from 13,317 ng/mL on day 16 to 3,875 ng/mL on day 21. The total bilirubin level was 2.28 mg/dL, and the triglyceride level decreased to 320 mg/dL. Another dose of tocilizumab with the same dosage of 400 mg was administered on day 25. The viral load at that time from sputum was 1.35 million copies/mL (**Table 1**).

On day 33, he was found to have an elevation of ferritin level and persistent tachycardia. Low dose norepinephrine (0.02 mcg/kg/min) was added. Ferritin levels increased from 1,761.15 to 2,535.39 ng/mL, and IL-6 levels increased from 1,477.59 to 2,535.39 pg/mL. There was persistent viral shedding from sputum with a viral load of 99.65 copies/mL. For suspected recurrence of CRS, another session of CRRT with an AN69ST/PEA hemofilter was performed on day 34, and the IL-6 level decreased to 707 pg/mL on day 35 and 154 pg/mL on day 38. We collected the CRRT effluent to estimate the removal of IL-6 from either CRRT or hemadsorption. The pre-AN69ST/PEI IL-6 level was 715.85 pg/mL, and the level 24 h later was 541.59 pg/mL. A total of 2,369,936 pg of IL-6 was removed, with 483,600 pg (20.4%) removed through the CRRT effluent and 1,886,336 pg (79.6%) removed by hemadsorptions. With adequate urine output and decreased oxygen demand, CRRT was discontinued on day 40.

He developed another recurrence of CRS on day 45 with an elevation of IL-6 (1,579 pg/mL) and ferritin (2,690 ng/mL) levels. An additional dose of tocilizumab 400 mg and belimumab (B-cell activating factor inhibitor) was administered. ECMO was terminated on day 49, and he was successfully extubated on day 52 (**Figures 2B,C**). The urine output was 2,000–2,500 mL/day after extubation. The urinalysis findings of dysmorphic RBC, glycosuria, leukocyturia, and RTC resolved. The follow-up diluted Russell viper venom test for lupus anticoagulant level was negative. The sputum RT-PCR revealed persistently positive results for SARS-CoV-2 until day 52. The patient was discharged without oxygen support on day 70 (**Figure 1**).

DISCUSSION

Critically ill COVID-19 patients, especially those with multi-organ failure, such as cardiovascular collapse, AKI, CRS, or thromboembolic events, challenge clinicians with a substantial risk of patient mortality (25–27) Thus, treatment for these patients should target multiple derangements induced by COVID-19, including ventilator support and ECMO for refractory hypoxemia, CRRT for AKI and extracorporeal cytokine removal, and biologic agents for cytokine blockade. We used a lung-protective strategy in mechanical ventilation and a CRRT with an AN69ST/PEA hemofilter for uremic toxin removal, volume management, cytokine, and endotoxin removal. VV-ECMO was initiated for oxygenation support. In addition, immunomodulating agents were prescribed to control CRS. We successfully treated a critically ill COVID-19 patient with predicted high mortality. This report also demonstrates a successful experience for managing severe COVID-19 without effective antiviral agents. We also recommend timely implementation of the cytokine-targeted strategy combining CRRT with an AN69ST/PEI hemofilter and tocilizumab for severe COVID-19 with CRS and multi-organ failure.

CRS in COVID-19 originates from a dysregulated immune response to SARS-CoV-2, which is not new to coronary virus infection (6, 28). Treatment for CRS includes removal of the

TABLE 1 | Baseline characteristics, treatment courses, and relevant data of the reported patient.

Date (day of symptom onset)	1 April (11th)	5 April (16th)	13 April (24th)	22 April (33rd)	27 April (38th)	4 May (45th)	11 May (52nd)
Clinical status							
BP (mmHg)	153/75	79/51	131/72	130/69	165/84	154/75	136/85
Pulse rates (bpm)		136	113	106	60	123	73
Urine output (mL/kg/h)	0	0.09	0.09	1.11	1.37	2.26	1.91
Viral loads (copies/mL)							
Sputum	Positive	2,762	1,354,580 (Day 26)	99.65	83.26	51.78	932.27
Throat swab	Positive	267	232,822				
Nasal swab			595,075 (Day 28)	72.46	1,128.65	6.59	65.67 (Day50)
Vasopressors							
Norepinephrine (mcg/kg/min)	–	0.26	0.02	0.01	–	–	–
Dopamine (mcg/kg/min)	–	3.70	1.45	0.00	–	–	–
VIS	0	29.80	2.95	1.40	0	0	0
Hemogram							
Hemoglobin (g/dL)	16.6	15.4	10.2	8.8	9.9	9.5	8.7
White blood cell (/μL)	4,900	12,430	19,430	11,480	6,610	13,180	11,660
Lymphocyte (/μL)		723	1,263	787	568	667 (D42)	1,118 (D51)
Lymphocyte (%)		6.1	6.5	7.4	8.6	8.5 (D42)	8.7 (D51)
Platelet (K/μL)	203	255	221	165	198	174	379
Biochemistry							
ALT (U/L)	44	47	27	18	25	89	107
AST(U/L)	45	121	83	47	40	57	58
BUN (mg/dL)	10	26.5	40	58.3	44.8	29.1	32.9
Creatinine (mg/dL)	1.12	3.1	2.7	4.1	1.6	1.9	1.1
Sodium (mmol/L)	–	144	133	137	137	142	138
Total Bilirubin (mg/dL)	1.1	2.18	1.39	1.76	2.43	4.76	2.77
CK (U/L)	261	820	1,672	288	128	107	219 (D49)
CK-MB (U/L)	–	8.53	7.35 (D23)	4.18	3.38 (D35)	3.14 (D42)	–
Ferritin (ng/mL)	–	13,317.09	3,993.02	2,461.61	1,636.28	2,690.1	3,200.13
Fibrinogen (mg/dL)	–	527.6 (D17)	363	240.5	227	233.1	178.2 (D53)
Lactic Acid (mmol/L)	–	5.83	1.44	2.54	0.9	0.94	0.77 (D51)
LDH (U/L)	–	813	663	412	358	427	302
TG (mg/dL)	–	446	320	116 (D34)	–	–	–
D-dimer (mg/L)	–	21.9	>35	>35	12.95	>35	6.81
Inflammatory markers							
Procalcitonin (ng/mL)	0.15	>100.0	4.03	2.15	0.587	0.645	0.128
CRP (mg/dL)	12.5	20.1	12.24	1.06	0.27	2.94	1.12
Cytokines (pg/mL)							
IL-6	–	12,049.1	3,546.5	2,535.4	154.0	1,579.02	
IL-4	–	0.46	0	0.66	0.07	0.1	
IL-10	–	2.45	2.22	5.24	3.71	4.77	
IL-17	–	0	0	0	0.55	0.88	
TNF	–	0	0	0	0	0	
IFN-gamma	–	0	0	0.03	0	2.01	
Ventilator settings							
Modes	Ambient Air	Pressure control	Pressure control	Pressure control			**Off on D52**
PaO_2 (mmHg)		159	127	99	128	116	
FiO_2		40%	40%	40%	40%	40%	
CRRT settings							
BFR (mL/min)		200	200	200	200	**Off on D40**	

(Continued)

TABLE 1 | Continued

Date (day of symptom onset)	1 April (11th)	5 April (16th)	13 April (24th)	22 April (33rd)	27 April (38th)	4 May (45th)	11 May (52nd)
Total wastes (mL/h)		2,000	2,000	2,000	1,700		
Anticoagulant		RCA	Heparin	Heparin	Heparin		
VV-ECMO Settings							
BFR (L/min)		3.7	3.75	3.3	3.91	2.58	**Off on D49**
ECMO FiO_2		100%	50%	100%	40%	21%	
Medications							
Methylprednisolone (mg/kg/day)		–	–	0.4	0.4	0.3	0.4
Tocilizumab 400 mg			✓ (D25)			✓ (D49)	
Tofacitinib 5 mg BID		✓	✓				
Belimumab 400 mg						✓ (D49)	
AN69ST/PEI		✓		✓			

COVID-19, coronavirus disease; ICU, intensive care unit; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; AN69ST/PEI, hemofilter with AN69 and polyethyleneimine; BP, arterial blood pressure; VIS, vasoactive inotropic score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; CK, creatinine kinase; CK-MB, creatinine kinase muscle and brain form; CRP; TG, triglyceride; C-reactive protein; IL, interleukin; TNF, tumor necrotizing factor; IFN, interferon; FiO_2, fraction of inhaled oxygen; VV-ECMO, veno-venous extracorporeal membrane oxygenation; BPF, blood flow rates.

✓: usage of this device or medications.

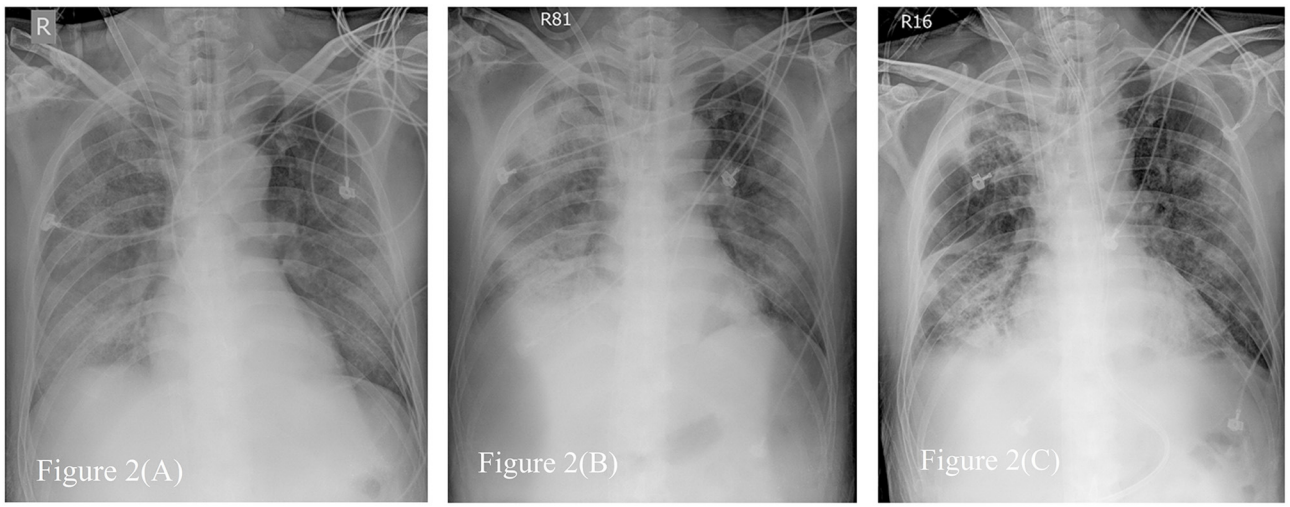

FIGURE 2 | Serial Chest radiographs of the patient. **(A)** The film showing diffuse alveolar process over bilateral lung field, especially right lower lung field just after extracorporeal membrane oxygenator (ECMO setup). **(B)** The film revealing consolidation over both lungs when first time we tried to wean from ECMO. **(C)** The film on the day before removing ECMO, demonstrating fibrotic change as lung filed in **(B)**.

offending pathogen and limiting the propagation of cytokines, in order to limit organ damage. Effective anti-SARS-CoV-2 therapies are not available at this time (29). Mechanical removal of the offending cytokines was reasonable. Methods for cytokine removal include direct hemoperfusion, conventional CRRT, high-dose CRRT, or CRRT with hemofilters with higher cut-off membranes (5). In patients with severe sepsis, CRRT with an AN69ST/PEA hemofilter might be associated with better outcomes. However, the only randomized control trial failed to balance its intervention group and placebo group and showed no benefit (16). However, CRRT with an AN69ST/PEA hemofilter has been shown to have better cytokine removal properties than conventional CRRT (16). This was also evident in our observation.

In addition to cytokine removal, we also used tocilizumab to neutralize the deleterious effects of IL-6. Recent publications have suggested that tocilizumab might mitigate CRS, although the studies were limited by non-controlled designs or case reports (30, 31) In their reports, the IL-6 level before tocilizumab treatment was 41 ng/L (interquartile range [IQR]: 10–102 ng/L), and elevated to 1,812 ng/L (IQR: 375–2,600 ng/L). Our case had a much higher pre-treatment level (12,049.07 ng/L); further, concurrent CRRT with an AN69ST/PEA hemofilter, the level rapidly reduced to 3,546.53 ng/L, and the second course of CRRT with an AN69ST/PEA hemofilter further reduced the IL-6 level from 2,535.39 ng/L to 139.39 ng/L. A retrospective study, based on data from 85 patients, demonstrated lower mortality rates. However, no IL-6 data were available in this

study (32). We propose that there are synergistic benefits from combined CRRT with AN69ST/PEA hemofilter therapy and tocilizumab therapy.

Another concern about immunomodulation therapy in the absence of effective antiviral therapy is the potential for prolonged viral infection. In our patient, the viral shedding persisted for over 60 days. There is an urgent, but unmet, need for effective antiviral therapy in patients with severe COVID-19 and renal dysfunction. Remdesivir was not be considered universally to be an effective anti-viral agent for SARS-CoV-2; there were negative clinical trials, although the analytic methods may have led to negative trials (33). Of note, remdesivir is not indicated for patients with renal dysfunction (<30 mL/1.73 m^2) (4).

VV-ECMO is a reasonable option for refractory ARDS caused by viral pneumonia. Based on the recent meta-analysis, the 90-day mortality rates decreased in the VV-ECMO arm (relative risk [RR] = 0.73 [95% CI 0.58–0.92]; $p = 0.008$) (34). But bleeding risk was one major complication for ECMO. The current guideline still use VV-ECMO as salvage therapy for severe ARDS with refractory hypoxemia. Advanced age, morbid obesity, and immunocompromised status are relative contra-indications as stated by ESLO guideline. It is not clear whether ECMO would be beneficial in patients with severe ARDS. But good organ support and meticulous prevention and management are keys to success in our patient (35). AKI is a common complication in patients with severe COVID-19 and is associated with worse outcomes (26). Interestingly, renal complications are not limited to AKI; hematuria, proteinuria, or glycosuria also develop with COVID-19 (9). Evidence has shown that hematuria, proteinuria, and glycosuria develop during the critical illness and subside after renal recovery, similar to that observed in our patient (36). We had limited renal biopsy data to explore the underlying pathogenesis of SARS-CoV-2 infections (37), although data from SARS-CoV may give us hints that renal damage from COVID-19 is diverse (38). The increased hematuria and proteinuria are also associated with adverse outcomes (36).

The plain radiograph is less sensitive than chest CT, but chest radiography is typically the first-line imaging modality ordered for patients with suspected COVID-19. Compared to typical bacteremic pneumonia, the correlation of chest radiography to oxygen demand is poor. In our patient, more consolidation was detected on chest radiography when less O_2 demand, shown in **Figure 2**. The follow-up chest radiograph revealed sequelae of pulmonary fibrosis. It is not useful to predict severity by image evaluation once before diagnosis or during treatment for COVID-19 (39).

There were some limitations to this case report. As a report of a single case, it is not possible to generalize the experience to the whole patient group with severe COVID-19. However, we are confident that this report would inspire future clinical trials involving the cytokine-targeted therapy, proposed in this study. Second, the patient was treated in an area where there were few critical cases and thus, cannot be generalized to a medical system overwhelmed by the COVID-19 pandemic (2). However, if further clinical trials prove its efficacy, timely cytokine-targeted therapy for critically ill patients with COVID-19 is likely to improve patient outcomes. Third, we did not use antiviral therapy for this patient. Poor renal reserve precluded the patient from remdesivir therapy (4, 29).

In summary, we demonstrated in this report that timely combined hemoperfusion with cytokine adsorptive capacity and anti-cytokine therapy may successfully treat COVID-19 patients with devastating CRS. For the rapid progression of severe COVID-19 ARDS, cytokine releasing syndrome, acute kidney injury, and multiple organ failure. We would suggest timely initiation of life support and use of multimodality treatment for blockade of cytokine effects (by tocilizumab) and rapid removal of pro-inflammatory cytokines to limit organ damage. This further highlights the importance of implementing cytokine-targeted therapy in severe COVID-19 guided by precise measurement of disease activity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TH, Y-CC, C-HW, S-YC, B-LC, and S-CH performed the data collection. TH, Y-CC, C-HW, Y-CY, S-CK, and AT wrote the manuscript. J-TW, C-JY, and S-CC carried out the project administration. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.649583/full#supplementary-material

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ORIGINAL RESEARCH
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Change of Hemoglobin Levels in the Early Post-cardiac Arrest Phase Is Associated With Outcome

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Background: The post-cardiac arrest (CA) phase is characterized by high fluid requirements, endothelial activation and increased vascular permeability. Erythrocytes are large cells and may not leave circulation despite massive capillary leak. We hypothesized that dynamic changes in hemoglobin concentrations may reflect the degree of vascular permeability and may be associated with neurologic function after CA.

Methods: We included patients ≥18 years, who suffered a non-traumatic CA between 2013 and 2018 from the prospective Vienna Clinical Cardiac Arrest Registry. Patients without return of spontaneous circulation (ROSC), with extracorporeal life support, with any form of bleeding, undergoing surgery, receiving transfusions, without targeted temperature management or with incomplete datasets for multivariable analysis were excluded. The primary outcome was neurologic function at day 30 assessed by the Cerebral Performance Category scale. Differences of hemoglobin concentrations at admission and 12 h after ROSC were calculated and associations with neurologic function were investigated by uni- and multivariable logistic regression.

Results: Two hundred and seventy-five patients were eligible for analysis of which 143 (52%) had poor neurologic function. For every g/dl increase in hemoglobin from admission to 12 h the odds of poor neurologic function increased by 26% (crude OR 1.26, 1.07–1.49, $p = 0.006$). The effect remained unchanged after adjustment for fluid balance and traditional prognostication markers (adjusted OR 1.27, 1.05–1.54, $p = 0.014$).

Conclusion: Increasing hemoglobin levels in spite of a positive fluid balance may serve as a surrogate parameter of vascular permeability and are associated with poor neurologic function in the early post-cardiac arrest period.

Keywords: critical care, cardiac arrest, post-cardiac arrest syndrome, hemoglobin, resuscitation, mortality, neurologic outcome, vascular permeability

INTRODUCTION

Low hemoglobin (Hb) levels have been associated with poor clinical outcome in cardiac arrest patients. Anemia is common in the post-resuscitation period and, conceivably, the oxygen-transport capacity of Hb may be especially important during and after global hypoxia. Previous studies therefore focused on mean Hb levels either on admission or in the first days after cardiac arrest and its associations with clinical outcomes, but the kinetics of Hb after successful resuscitation and their clinical significance remain unknown (1–5).

During the last decades the post-cardiac arrest syndrome (PCAS) has been increasingly understood as a sepsis-like condition. Comparable to sepsis, patients after cardiac arrest may display dysregulated inflammation, myocardial and adrenal dysfunction, coagulopathy and a disrupted endothelial barrier function indicating similar pathomechanisms (6, 7). However, especially the latter demands further investigation. Capillary leak is characterized by increased endothelial permeability leading to a consecutive loss of proteins and fluid from the intravascular to the interstitial space (8–12). Biomarkers such as angiopoietin-2, vascular endothelial growth factor and soluble fms-like tyrosine kinase 1, have been suggested as indicative for endothelial permeability and were likewise associated with mortality in septic patients (13), but may lack specificity and are mostly not available during routine care.

Still, extravascular fluid loss due to lacking endothelial barrier function challenges treating physicians as optimal fluid resuscitation and vasopressor support are required to provide adequate cardiac output and consecutive organ perfusion (14). However, the extent of extravascular fluid loss remains difficult to determine *in vivo*. With regards to PCAS, oedema formation, especially in the brain, is a crucial factor for neurologic outcome (15, 16).

Similar to PCAS, vascular hyperpermeability has also been described in other critical conditions such as severe burn injury (17, 18). In a burn injury animal model, hematocrit increased continuously in the first hours after the injury indicating the loss of fluid to the extracellular space and a relative increase of red blood cells (19).

In this context, we hypothesized that Hb kinetics may reflect extravascular fluid losses. Due to their large size, erythrocytes, and therefore Hb, remain in the circulation. As a consequence of the increased vascular permeability, Hb concentrations increase, similar to capillary leak syndrome, in which values >20 g/dL may occur, even in spite of intravenous fluid administration (9, 10).

In this study we investigated dynamic changes in Hb concentrations as an indicator of vascular permeability in the early post-cardiac arrest phase and its association with neurologic outcome.

METHODS

Study Design

We analyzed prospectively collected data from the Vienna Clinical Cardiac Arrest Registry of the Department of Emergency Medicine at the Medical University of Vienna, a tertiary care facility. The registry includes all adult cardiac arrest patients, admitted to, and treated at the Department of Emergency Medicine.

Data acquisition and documentation was conducted in accordance with the Utstein style recommendations for cardiac arrest related documentation (20) and has recently been described in detail for our registry (21).

Blood samples were drawn immediately after admission and analyzed by the ISO-certified central laboratory of the Vienna General Hospital. The first blood sample always includes hemoglobin (g/dL) as a standard hematological parameter. Further blood samples including hematological variables were routinely drawn every 6 h after ROSC for the first day. Total intravenous fluid, fluid balance, total urine volume and catecholamine doses were documented after 12 and 24 h in health care records as a routine documentation. This study complies with the declaration of Helsinki and was approved by the local Ethics Committee of the Medical University of Vienna (EK No. 1219/2018).

Study Population

All adults ≥18 years of age with a non-traumatic cardiac arrest (out-of hospital and in-hospital cardiac arrest) between January 2013 and December 2018 were included. Patients (i) without return of spontaneous circulation, (ii) with extracorporeal cardiopulmonary resuscitation (eCPR) therapy, (iii) immediately regaining consciousness, (iv) who died within 24 h after ROSC, (v) undergoing surgery within 24 h after ROSC, (vi) requiring blood transfusions within 24 h after ROSC, (vii) with bleeding (any form of bleeding within 24 h documented in the patient charts or transfer reports), and (viii) without targeted temperature management (TTM) were excluded. Furthermore, only patients with full datasets for multivariable analysis were eligible.

Patient treatment was based on current guidelines, including post-resuscitation management (14). TTM (32–34°C) was conducted as soon as possible (via surface or intravascular cooling) for all comatose patients according to an institutional protocol based on the current guidelines within 60 min after admission. TTM was maintained for 24 h until the start of rewarming. Rewarming was performed with 0.25°C/h with a maximum rate of 0.5°C/h. As all patients in our cohort were treated according to the institutional protocol, all analyses and blood sampling were performed within the TTM phase.

During the observation period 1,591 cardiac arrest patients were enrolled in our registry. Of those patients, 275 fulfilled the inclusion criteria and were finally analyzed (**Figure 1**).

Endpoints

The primary endpoint was neurologic function at day 30, defined according to the Cerebral Performance Category (CPC) scale: good neurologic outcome was defined as a CPC 1 (good cerebral performance) or 2 (moderate disability); poor neurologic outcome was defined as CPC 3–5 (severe disability, vegetative state, or death) or persistent unresponsiveness due to analgosedation during the study period or before death. The

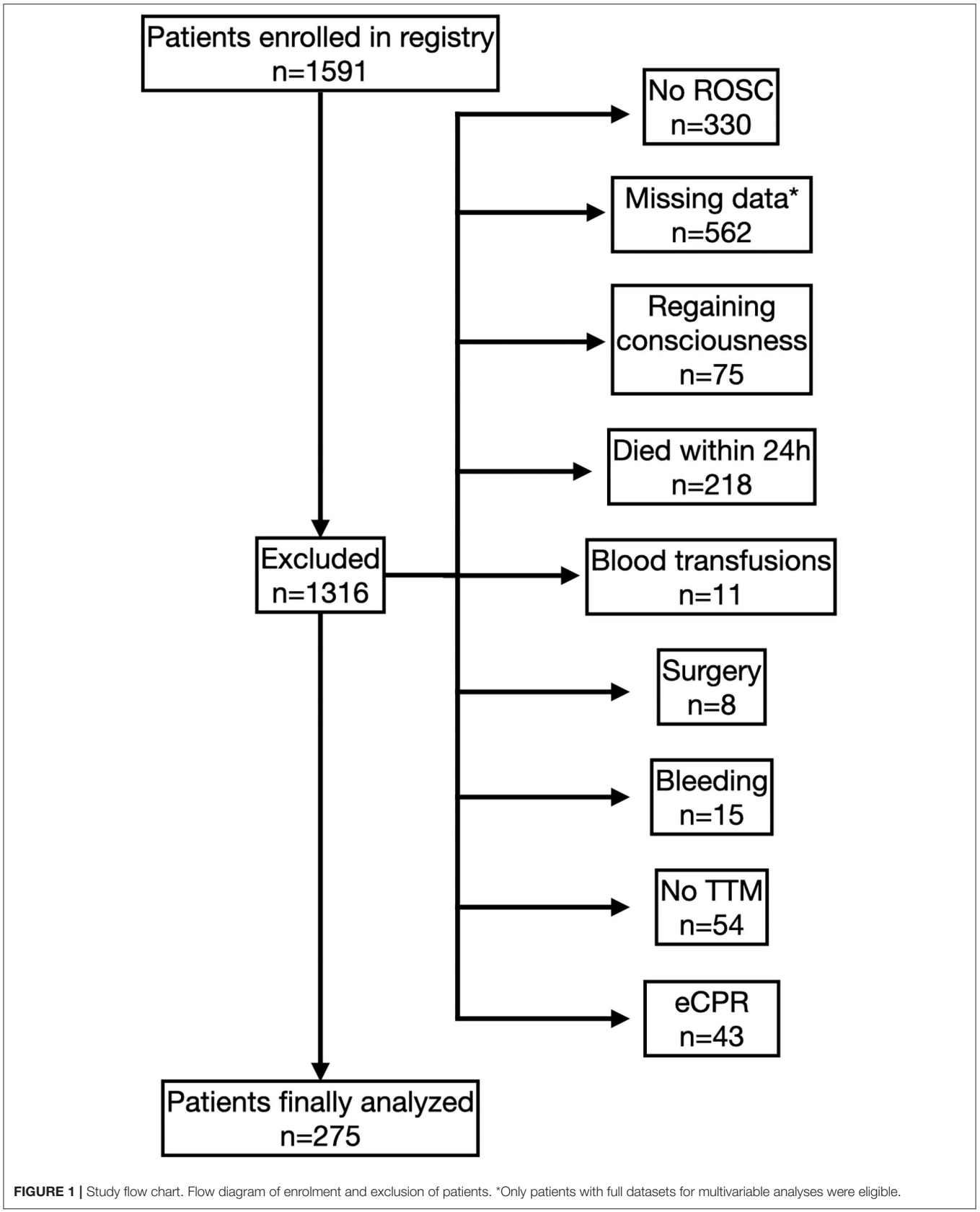

FIGURE 1 | Study flow chart. Flow diagram of enrolment and exclusion of patients. *Only patients with full datasets for multivariable analyses were eligible.

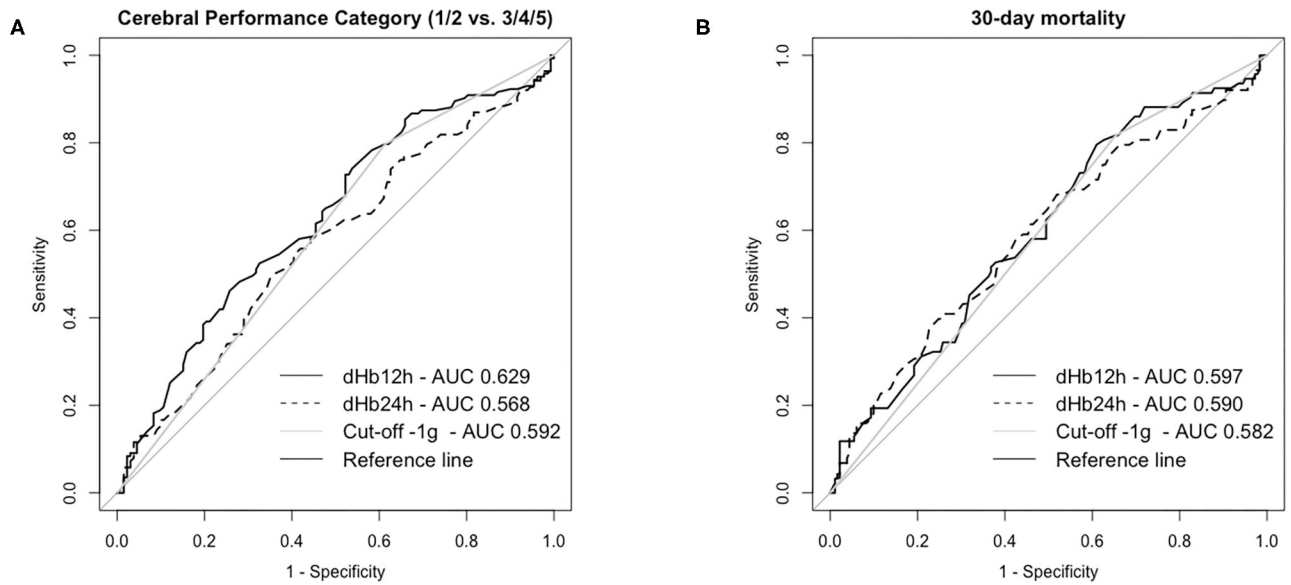

FIGURE 2 | Receiver Operating Characteristic Curves for neurologic outcome **(A)** and mortality **(B)** at day 30 in patients successfully resuscitated from cardiac arrest. dHb12h = Hemoglobin (Hb) levels 12 h after return of spontaneous circulation (ROSC)—Hb levels on admission; dHb24h = Hb levels 24 h after ROSC—Hb levels on admission; Cut-off−1g: categorized data for patients with </≥-1 g difference for Hb levels after 12 h—Hb levels on admission.

choice of this composite endpoint is in accordance with the Utstein recommendations (20).

Secondary endpoints included 30-day mortality and exploratory correlations between Hb kinetics, time intervals of resuscitation, fluid balance, noradrenaline (norepinephrine) dose and pH value.

Statistical Analysis

We present categorized data as counts (and relative frequency) and scale data as medians with 25–75% interquartile range (IQR). We calculated differences of Hb (dHb; Hb at 12 h–Hb at admission = dHb12h; Hb at 24 h–Hb at admission = dHb24h). For exploratory analysis of selected baseline variables and for the comparison of Hb differences between patients with good and poor neurologic function at day 30 the Mann-Whitney *U*-test or the Chi^2-test were applied, as applicable. We performed receiver operating characteristic (ROC) curve analysis to determine (i) the optimal timepoint for this analysis (12 or 24 h after ROSC) and (ii) the optimal cut-off of Hb differences between the chosen time-points. Results are given as area under the curve (AUC) with 95 % confidence intervals (95% CI) and *p*-value. According to this cut-off we dichotomized the patients into two groups. Selected baseline data were also compared between the two derived groups in an exploratory fashion, as explained above. Furthermore, we subdivided the sample into dHb quartiles. Percentages of patients with poor and good neurologic outcome at day 30 according to dHb12h quartiles are presented as table and plot.

We used a binary logistic regression analysis (backward stepwise elimination approach according to Wald test-statistics step-by-step) to estimate the effect of the respective dHb (as continuous variable and as categories) on the primary endpoint. The effect was quantified as odds ratio (OR) with 95 % confidence intervals (95% CI).

We used a Cox regression analysis (backward stepwise elimination approach according to Wald test-statistics step-by-step) to estimate the effect of dHb on the secondary endpoint taking the time-to-event into account. The effect was quantified as hazard ratio (HR) with 95 % confidence intervals (95% CI).

We selected covariables for the multivariable models based on previous studies (22–27). These variables included age (years), sex, initial heart rhythm at the scene (shockable vs. non-shockable), basic life support (BLS), witness status, number of shocks applied, cumulative adrenaline (epinephrine) dose (mg) during resuscitation and pH on admission. Furthermore we included noradrenaline (norepinephrine) dose and fluid balance of the first 12 h after ROSC in the analysis, because both therapies are used to ensure hemodynamic stability and fluid therapy might impact on the main parameter of interest: the Hb kinetics. The final results of the multivariable analyses are presented in tables. Those variables eliminated by the testing procedure were omitted. All steps of the logistic regression analysis (backward stepwise elimination approach according to Wald test-statistics step-by-step) for the primary endpoint are presented in the **Supplementary Tables 9, 10**.

We performed sensitivity analyses for the primary outcome including only patients with out-of-hospital cardiac arrest, with patients receiving BLS and with patients not receiving BLS. Furthermore we included C-reactive protein concentrations and white blood cell counts into an auxiliary multivariable analysis (**Supplementary Tables 7, 8**). Additionally, we modeled the expected decrease in hemoglobin based on estimated plasma volume and overall fluid balance. The difference between expected and real hemoglobin was calculated and included in

the analysis as an additional sensitivity analysis (refer to the **Supplementary Material** for further details).

Kaplan-Meier plots of the estimated 30-day mortality were conducted for each Hb category and compared using the log-rank test. Exploratory correlations were calculated by applying the non-parametric Spearman procedure.

For data management and analyses we used IBM SPSS Statistics (Version 26, IBM Corporation) and R (R Foundation for Statistical Computing, Version 3.6.2). A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

In ROC analysis, the AUC of dHb12h was 0.62 (95% CI 0.56–0.69, $p < 0.001$ compared to the reference line) and for dHb24h 0.57 (95% CI 0.50–0.64, $p = 0.054$) for neurologic outcome (**Figure 2**). We therefore decided to use dHb12h for our analysis.

There was no obvious cut-off identifiable in ROC analysis for neurologic outcome (**Figure 2** and **Supplementary Material**). Subsequently, we performed ROC analysis for 30-day mortality (AUC of dHb12h 0.60, 95% CI, 0.53–0.67, $p = 0.007$). Based on the results of both analyses, we decided to use a difference of −1 g/dL Hb (AUC 0.59, 95% CI 0.52–0.66, $p = 0.008$ for neurologic outcome and AUC 0.58, 95% CI 0.51–0.65, $p = 0.021$ for 30-day mortality) as a cut-off since this cut-off is (i) practicable for clinicians and (ii) shows acceptable sensitivity of ∼80% and a specificity of ∼40% for neurologic outcome and 30-day mortality. We dichotomized patients according to their dHb12h into two groups: dHb12h > -1 g/dL = "Group A" (equals a decrease in Hb concentrations of >1 g/dL in 12 h) and dHb12h ≤ -1 g/dL = "Group B" (equals any increase in Hb or a decrease of <1 g/dL in 12 h).

Baseline Characteristics

Table 1 shows the baseline characteristics of the study population, including distribution of cardiac arrest related parameters, according to 30-day neurologic outcome. Patients with poor neurologic outcome were older (median 63 vs. 55 years, $p < 0.001$) and presented less often with an initial shockable rhythm (41 vs. 80%, $p < 0.001$) or a cardiac cause of cardiac arrest (62 vs. 79%, $p < 0.001$). In addition, they had higher blood lactate levels (7.8 vs. 5.5 mmol/L, $p < 0.001$), lower pH values (7.12 vs. 7.22, $p < 0.001$), a greater, positive fluid balance (2.15 vs. 1.60 L, $p = 0.002$) and lower Hb levels at admission (13.3 vs. 14.1 g/dL, $p < 0.001$).

Baseline data and demographics of patients subdivided according to dHb12h also differed slightly (**Table 2**). Patients in group A were younger (58 vs. 62 years, $p = 0.044$) and had a higher percentage of cardiac cause of cardiac arrest (80 vs. 63% $p = 0.005$). The number of patients with an initial shockable rhythm (70 vs. 55%), lactate levels (6.8 vs. 6.7 mmol/L), pH levels (7.16 vs. 7.16), and fluid balance (1.95 vs. 1.88 L) did not differ significantly between groups.

Outcome Analysis

DHb12h differed significantly between patients with good or poor neurologic outcome [−0.5 (IQR: −1.4–0.4) vs. 0.2 (IQR: −0.8–1) g/dL, $p < 0.001$, **Table 1**] and 30-day mortality [−0.3 (IQR: −1.3–0.7) vs. 0.2 (IQR −0.7–0.9) g/dL, $p = 0.009$].

30-Day Neurologic Function

In univariate analysis, the crude OR for dHb12h was 1.26 (95% CI 1.07–1.49, $p = 0.006$) to have poor neurologic outcome. After multivariable adjustment for age, sex, initial rhythm, BLS, witness status, number of shocks, cumulative adrenaline dose, pH on admission, fluid balance and noradrenaline dose the adjusted OR of dHb12h was 1.27 (95% CI 1.05–1.54, $p = 0.014$) to have a poor neurologic outcome (**Table 3**). These results correspond to an approximate 26%, respectively 27%, increased risk of poor outcome for every g/dL increase in Hb concentrations within the first 12 h after ROSC.

In univariate analysis, the crude OR for group B was 2.48 (95% CI 1.45–4.24, $p < 0.001$) to have a poor neurologic outcome. After multivariable adjustment for the above-mentioned covariates the adjusted OR was 2.69 (95% CI 1.42–5.10, $p = 0.002$) to have a poor neurologic outcome (**Table 3**). Patients in group B have an ∼2.5-fold, respectively, 2.7-fold, increased risk to have poor neurologic outcome after cardiac arrest.

We performed sensitivity analyses in patients who received BLS (n =175) or not (n = 100) and in patients with out-of-hospital cardiac arrest only (n = 255), which are presented in detail in the **Supplementary Material**. In short, we obtained similar results in the population of patients with out-of-hospital cardiac arrest.

In the population of patients who received BLS, uni- and multivariable analyses of the continuous variable were non-significant, while the dichotomized variable was found to be significantly associated with neurologic outcome with an odds ratio of 2.38 (95% CI, 1.24–4.56, $p = 0.009$) in univariate analysis and 2.41 (95% CI, 1.11–5.25, $p = 0.027$) in multivariable analyses. In contrast to that, in patients who did not receive BLS ($n = 100$), effect sizes were larger [e.g., univariate analysis of dHb12h 1.50 (1.12–2.0, $p = 0.006$) and multivariable analysis 1.5 (1.09–2.07, $p = 0.013$)] and results were statistically significant despite the smaller sample size.

Furthermore, in another sensitivity analysis, we investigated whether the inclusion of inflammatory biomarkers C-reactive protein and white blood cell counts affected the model (**Supplementary Tables 7, 8**). In short, admission C-reactive protein concentrations and admission blood cell counts were eliminated from the model and effect sizes remained stable with an adjusted OR of dHb12h of 1.28 (95%CI, 1.05–1.56, $p = 0.014$). However, when we included C-reactive protein concentrations and white blood cell counts at 48 h both parameters remained in the model. The effect size of dHb12h was not relevantly altered with an adjusted OR of dHb12h of 1.22 (95%CI, 1.01–1.47, $p = 0.044$).

30-Day Mortality

In univariate analysis, the crude HR of dHb12h for 30-day mortality was 1.19 (95% CI 1.04–1.36, $p = 0.011$). After multivariable adjustment for the above-mentioned covariates, the estimates of dHb12h on 30-day mortality in the adjusted model showed a HR of 1.16 (95% CI 1.02–1.31, $p = 0.025$) (**Table 4**).

TABLE 1 | Baseline characteristics by neurologic outcome.

	All ***n* = 275**	**Good neurologic outcome** ***n* = 132**	**Poor neurologic outcome** ***n* = 143**
Age, median (IQR)	60 (50–71)	55 (47–67)	63 (53–74)
Female, *n* (%)	75 (27)	32 (24)	43 (30)
Height (cm), median (IQR)	175 (170–180)	180 (170–185)	175 (168–180)
Weight (kg), median (IQR)	85 (75–95)	85 (75–100)	80 (70–95)
Chronic health conditions, *n* (%)			
Diabetes	55 (20)	24 (18)	31 (22)
Hypertension	114 (41)	40 (32)	74 (52)
Current smoker	77 (28)	39 (29)	38 (19)
Chronic heart failure	24 (9)	7 (6)	17 (12)
Myocardial infarction	37 (13)	14 (11)	23 (16)
Cerebral vascular insufficiency	13 (5)	4 (5)	9 (6)
Coronary artery disease	55 (20)	22 (18)	33 (23)
Chronic obstructive pulmonary disease	37 (13)	9 (7)	28 (20)
Pre-arrest CPC 1/2, *n* (%)	275 (100)	132 (100)	143 (100)
Out of hospital cardiac arrest, *n* (%)	255 (93)	124 (94)	131 (92)
Witnessed, *n* (%)	232 (84)	117 (89)	115 (80)
BLS, *n* (%)	175 (64)	90 (68)	85 (59)
Initial shockable rhythm, *n* (%)	164 (60)	105 (80)	59 (41)
No flow (min), median (IQR)[a]	0 (0–1)	0 (0–1)	0 (0–1)
Low flow (min), median (IQR)[a]	22 (14–35)	17 (12–27)	26 (19–38)
Origin, *n* (%)			
Pulmonary	37 (13)	9 (67	28 (20)
Cardiac	186 (68)	104 (79)	82 (62)
Metabolic	5 (2)	1 (1)	4 (3)
Intoxication	8 (3)	2 (2)	6 (4)
Drowning	4 (1)	1 (1)	3 (2)
Sepsis	1 (0.4)	0 (0)	1 (1)
Cerebral	6 (2)	1 (1)	5 (3)
Other	6 (2)	4 (3)	2 (1)
Unknown	22 (8)	10 (8)	12 (8)
Total dose of adrenaline in mg, median (IQR)	2 (0–3)	1 (0–2)	3 (1–4)
Number of shocks applied, median (IQR)[b]	2 (0–4)	2 (1–4)	1 (0–4)
pH, median (IQR)	7.16 (7.05–7.27)	7.22 (7.12–7.28)	7.12 (7.0–7.22)
Lactate (mmol/l), median (IQR)	6.7 (4.3–9.7)	5.5 (3.4–8.4)	7.8 (5.7–10.6)
Hb at admission (g/dL), median (IQR)	13.7 (12.4–14.7)	14.1 (13.0–15.0)	13.3 (11.9–14.3)
Volume (ml/12 h), median (IQR)	2,950 (2,170–3,850)	2,900 (2,150–3,650)	3,030 (2,200–4,000)
Diuresis (ml/12 h), median (IQR)	900 (500–1,530)	1,130 (603–1,700)	750 (370–1,300)
Fluid balance (ml/12 h), median (IQR)	1,900 (1,000–2,700)	1,600 (860–2,350)	2,150 (1,200–3,000)
Noradrenaline dose (μg/kg/min), median (IQR)	0.1 (0.05–0.23)	0.08 (0.04–0.17)	0.15 (0.07–0.33)
Hb change 12 h (g/dl), median (IQR)	−0.1 (−1.1 to 0.8)	−0.5 (−1.4 to 0.4)	0.2 (−0.8 to 1)
CPC 1/2, *n* (%)	132 (48)	132 (100)	0 (0)
Mortality day 30, *n* (%)	93 (34)	0 (0)	93 (65)

Good neurologic outcome was defined as Cerebral Performance Category 1 to 2, poor neurologic outcome as Cerebral Performance Category 3–5.

No flow = time from collapse to the start of resuscitation efforts; Low flow = time is the interval between the start of resuscitation efforts and ROSC; Volume = total volume of intravenous fluids administered within 12 h; Diuresis = urine output from admission to 12 h; Fluid balance = difference between the total volume of intravenous fluids administered and the urine output at 12 h.

BLS, basic life support; CPC, Cerebral Performance Category; Hb, hemoglobin.

[a] *Data only for witnessed available.*

[b] *Data only from patients receiving at least one shock.*

TABLE 2 | Baseline characteristics according to dHb12h group.

	All ***n* = 275**	**Group A** ***n* = 80**	**Group B** ***n* = 195**
Age, median (IQR)	60 (50–71)	58 (47–66.5)	62 (50–72)
Female, *n* (%)	75 (27)	20 (25)	55 (28)
Height (cm), median (IQR)	175 (170–180)	176.5 (170–181)	175 (170–180)
Weight (kg), median (IQR)	85 (75–95)	85 (75–91)	85 (75–100)
Chronic health conditions, *n* (%)			
Diabetes	55 (20)	16 (20)	39 (20)
Hypertension	114 (41)	26 (33)	88 (45)
Current smoker	77 (28)	23 (29)	54 (28)
Chronic heart failure	24 (9)	7 (9)	17 (9)
Myocardial infarction	37 (13)	11 (14)	26 (13)
Cerebral vascular insufficiency	13 (5)	4 (5)	9 (5)
Coronary artery disease	55 (20)	15 (19)	40 (21)
Chronic obstructive pulmonary disease	37 (13)	7 (9)	30 (15)
Pre-arrest CPC 1/2, *n* (%)	275 (100)	80 (100)	195 (100)
Out of hospital cardiac arrest, *n* (%)	255 (93)	78 (98)	177 (91)
Witnessed, *n* (%)	232 (84)	68 (85)	164 (84)
BLS, *n* (%)	175 (64)	58 (73)	117 (60)
Initial shockable rhythm, *n* (%)	164 (60)	56 (70)	108 (55)
No flow (min), median (IQR)[a]	0 (0–1)	0 (0–0)	0 (0–1)
Low flow (min), median (IQR)[a]	22 (14–35)	21.5 (14–36)	23 (14–34)
Origin, *n* (%)			
Pulmonary	37 (13)	7 (9)	30 (15)
Cardiac	186 (68)	64 (80)	122 (63)
Metabolic	5 (2)	2 (3)	3 (2)
Intoxication	8 (3)	1 (1)	7 (4)
Drowning	4 (1)	2 (2)	2 (1)
Sepsis	1 (0.4)	0 (0)	1 (1)
Cerebral	6 (2)	2 (3)	4 (2)
Other	6 (2)	0 (0)	6 (3)
Unknown	22 (8)	2 (3)	20 (10)
Total dose of adrenaline in mg, median (IQR)	2 (0–3)	2 (0–3.5)	2 (0.5–3)
Number of shocks applied, median (IQR)[b]	2 (0–4)	2 (1–4)	1 (0–4)
pH, median (IQR)	7.16 (7.05–7.27)	7.16 (7.05–7.26)	7.16 (7.06–7.27)
Lactate (mmol/l), median (IQR)	6.7 (4.3-9.7)	6.8 (4.5-9.3)	6.7 (4.2-9.7)
Hb at admission (g/dL), median (IQR)	13.7 (12.4–14.7)	14.2 (13.3–15.2)	13.4 (12.2–14.6)
Volume (ml/12 hrs), median (IQR)	2,950 (2,170–3,850)	3,015 (2,200–4,000)	2,900 (2,150–3,750)
Diuresis (ml/12 h), median (IQR)	900 (500–1,530)	1,075 (565–1,600)	800 (450–1,500)
Fluid balance (ml/12 h), median (IQR)	1,900 (1,000–2,700)	1,949 (1,000–2,800)	1,875 (1,010–2,650)
Noradrenaline dose (μg/kg/min), median (IQR)	0.1 (0.05–0.23)	0.09 (0.05–0.18)	0.12 (0.06–0-29)
Hb change 12 h (g/dl), median (IQR)	−0.1 (−1.1 to 0.8)	−1.6 (−2.2 to 1.3)	0.4 (−0.2 to 1)
CPC 1/2, *n* (%)	132 (48)	51 (64)	81 (42)
Mortality day 30, *n* (%)	93 (34)	17 (21)	76 (39)

Group A = a decrease in hemoglobin (Hb) >1 g/dL within 12 h after return of spontaneous circulation (ROSC); group B = increase in Hb levels or a decrease of ≤ 1 g/dL Hb within 12 h after ROSC.

No flow = time from collapse to the start of resuscitation efforts; Low flow = time is the interval between the start of resuscitation efforts and ROSC; Volume = total volume of intravenous fluids administered within 12 h; Diuresis = urine output from admission to 12; Fluid balance = difference between the total volume of intravenous fluids administered and the urine output at 12 h.

BLS, basic life support; CPC, Cerebral Performance Category; Hb, hemoglobin.

[a] *Data only for witnessed available.*

[b] *Data only from patients receiving at least one shock.*

TABLE 3 | Multivariable analysis of the primary endpoint.

	Poor outcome (Cerebral Performance Category 3–5)			
Variables	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
dHb12h (g/dl)	1.27 (1.05–1.54)	0.014	-	
dHb12h group	-		2.69 (1.42–5.10)	0.002
Age (years)	1.04 (1.02–1.06)	<0.001	1.04 (1.02–1.06)	<0.001
Number of shocks applied	0.82 (0.74–0.91)	<0.001	0.83 (0.75–0.92)	<0.001
Total dose of adrenaline (mg)	1.55 (1.28–1.87)	<0.001	1.54 (1.28–1.85)	<0.001
pH value	0.11 (0.01–0.93)	0.042	0.09 (0.01–0.76)	0.027
Fluid balance 12 h (L)	1.23 (0.99–1.53)	0.067	1.23 (0.99–1.54)	0.062

Poor outcome was analyzed by binary logistic regression using a backward stepwise elimination approach according to Wald test statistic step-by-step. The presented variables are the ones remaining in the final step of the model.
dHb12h (g/dl) = Hemoglobin (Hb) levels 12 h after return of spontaneous circulation (ROSC)—Hb levels on admission. dHb12h group = group A (equals a decrease in Hb concentrations of >1 g/dL in 12 h after ROSC) vs. group B (equals any increase in Hb or a decrease of ≤1 g/dL in 12 h after ROSC).
CI, confidence interval; Hb, hemoglobin; OR, odds ratio.

TABLE 4 | Multivariable analysis of the secondary endpoint.

	30-day mortality			
Variables	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
dHb12h (g/dl)	1.16 (1.02–1.31)	0.025	-	
dHb12h group	-		1.97 (1.16–3.34)	0.011
Age (years)	1.03 (1.01–1.04)	0.001	1.03 (1.01–1.04)	0.001
Number of shocks applied	1.01 (0.99–1.02)	0.091	1.01 (1.00–1.02)	0.043
Initial shockable rhythm	0.90 (0.83–0.97)	0.005	0.90 (0.84–0.97)	0.007
Total dose of adrenaline (mg)	1.23 (1.12–1.35)	<0.001	1.22 (1.11–1.34)	<0.001
pH value	-	-	0.19 (0.06–0.68)	0.011

30-day mortality was assessed by the Cox regression model using a backward stepwise elimination approach according to Wald test statistic step-by-step. The presented variables are the ones remaining in the final step of the model.
dHb12h (g/dl) = Hemoglobin (Hb) levels 12 h after return of spontaneous circulation (ROSC)—Hb levels on admission. dHb12h group = group A (equals a decrease in Hb concentrations of > 1g/dL in 12 h after ROSC) vs. group B (equals any increase in Hb or a decrease of ≤1 g/dL in 12 h after ROSC).
CI, confidence interval; Hb, hemoglobin; HR, hazard ratio.

These results correspond to an approximate 19%, respectively 16%, increased risk for 30-day mortality for every g/dL increase in Hb concentrations within the first 12 h after ROSC.

In univariate analysis, the crude HR of the Hb increase group for 30-day mortality was 2.06 (95% CI 1.22–3.48, $p = 0.007$). After multivariable adjustment for the above-mentioned covariates, the estimates for the Hb increase category on 30-day mortality showed a HR of 1.97 (95% CI 1.16–3.34, $p = 0.011$) (**Table 4**). Patients in group B have an ∼2-fold increased risk to die within 30-day after cardiopulmonary resuscitation (CPR).

TABLE 5 | Neurologic function at day 30 according to dHb12h quartiles.

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 3**
Good neurologic outcome, *n* (%)	45 (66)	32 (46)	34 (48)	21 (31)
Poor neurologic outcome, *n* (%)	23 (34)	37 (54)	37 (52)	46 (69)

The Kaplan-Meier survival plot of the estimated 30-day mortality according to both groups is presented in **Figure 3**. The between-group difference continues throughout the observation time and is still observed on day 30 (log-rank test $p = 0.006$).

Exploratory Analyses

Although there was a significant difference between patients with good or poor neurologic outcome in dHb12h [−0.5 g/dL (IQR: −1.4–0.5) vs. 0.2 g/dL (IQR: −0.8–1), $p < 0.001$], overall fluid balance [1.60 L (IQR: 0.86–2.35) vs. 2.15 L (IQR: 1.20–3.00), $p = 0.001$], noradrenaline dose [0.08 mcg/kg/min (IQR: 0.04–0.17) vs. 0.15 mcg/kg/min (IQR: 0.07–0.33), $p = <0.001$] and total urine output in the first 12 h [1.13 L (IQR: 0.60–0.17) vs. 0.75 L (IQR: 0.37–0.13), $p < 0.001$], there was no difference in the total amount of infused fluids [2.90 L (IQR: 2.15–3.65) vs. 3.03 L (IQR: 2.20–4.00, $p = 0.32$)].

DHb12h correlated poorly with noradrenaline dose ($r = 0.19$, $p = 0.001$), but not with fluid balance, urine volume, total infused volume or CPR-related variables.

Table 5 shows neurologic outcome at day 30 according to dHb12h quartiles. The proportion of patients with poor neurologic function at day 30 increases from 34% in quartile 1–69% in quartile 4. The percentage of poor neurologic function at day 30 according to dHb12h quartiles is presented in **Figure 4**.

DISCUSSION

The main finding of this study is that patients with increasing Hb concentrations in spite of positive fluid balance in the first 12 h after ROSC are more likely to have a poor neurologic outcome and to die within 30 days.

To our knowledge this is the first analysis of Hb kinetics in cardiac arrest survivors not focusing on Hb thresholds but on changes of Hb concentrations over time. Previous studies analyzing Hb concentrations after cardiac arrest mostly focused on the oxygen-transport capacity of Hb and associated venous oxygen saturation aiming to define a minimum Hb concentration to optimize clinical outcomes (1–5, 28–30). While Hb levels after ROSC may be associated with brain oxygenation, our study investigated Hb concentrations from a different perspective. We utilized the large size of erythrocytes, which cannot extravasate in spite of massively increased vascular permeability, and used dynamic changes in Hb concentrations over a 24 h period after resuscitation as a surrogate parameter for the degree of vascular permeability, as suggested by data from capillary leak syndrome or burn injury (8–12, 17, 18). Increased permeability may reflect the extent of post-cardiac

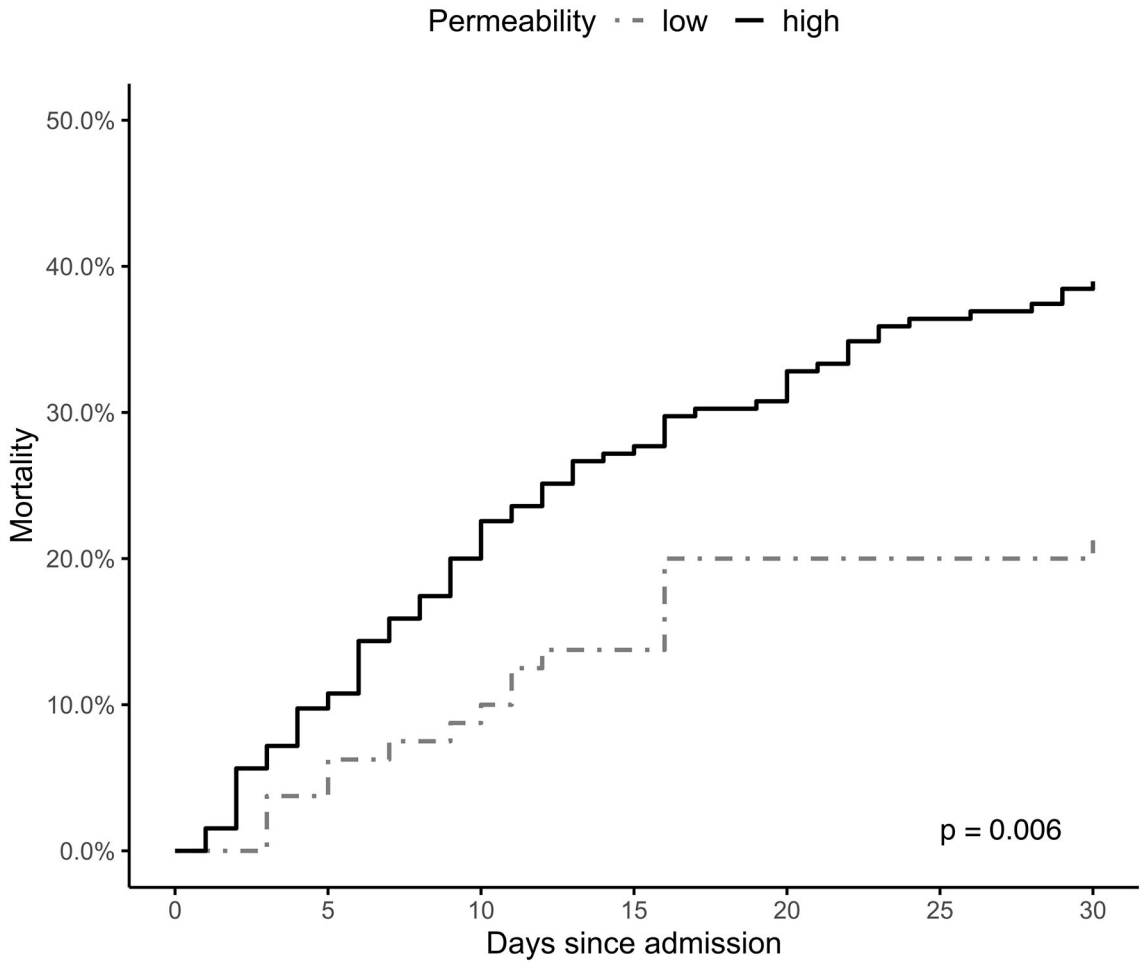

FIGURE 3 | Hb-stratified Kaplan-Meier estimates of the probability of 30-day mortality among patients successfully resuscitated from cardiac arrest. Group A = a decrease in hemoglobin (Hb) levels >1 g/dL within 12 h after return of spontaneous circulation (ROSC); Group B = increase in Hb levels or a decrease of <1 g/dL Hb within 12 h after ROSC.

arrest inflammation and may be associated with cerebral edema and dysfunction. In this context, results of our study showed that group B had an adjusted OR of 2.7 to have poor neurologic outcome.

Owing to the retrospective nature of this analysis, we were not able to quantify biomarkers of vascular permeability to further support our hypothesis. However, several factors may contribute to increased vascular permeability after successful cardiopulmonary resuscitation and could be of interest for further clinical studies. The endothelial glycocalyx covers the luminal surface of endothelial cells and, among other functions, is a critical regulator of fluid homeostasis (31). In the interplay of reactive oxygen species, inflammatory cytokines and activated leukocytes, the endothelial glycocalyx is degraded during ischemia-reperfusion injury by specific enzymes, so-called "sheddases," as demonstrated in various disease models and indicated by increased shedding of glycocalyx constituents after cardiac arrest (32, 33). Levels of syndecan-1 and hyaluronan measured immediately after ROSC predicted multiple organ failure and poor clinical outcome (33). In sepsis, angiopoietin-2 is considered a key protein in the regulation of vascular permeability and endothelial activation, which is underlined by clinical data that suggest associations of angiopoietin-2 levels and sepsis-associated mortality, associations of angiopoietin-2 levels with fluid overload in septic shock patients, and by animal models showing benefits of angiopoietin-2 blockade (13, 34, 35). In addition, the impact of angiopoietin-2 on vascular permeability seems to be mediated by glycocalyx degradation (36, 37). This is likewise underlined by angiopoietin-2 data from cardiac arrest patients, where imbalances in angiopoietin ratios (angiopoetin-1/angiopoetin-2) were associated with organ dysfunction and poor outcome (38). In agreement, Bro-Jeppesen et al. reported that the level of inflammation and endothelial injury, including biomarkers of degraded endothelial glycocalyx, in post-cardiac arrest patients correlated with the requirement of vasopressor support and partly also with hemodynamic variables (39). Finally, severe brain damage itself may compromise the vascular tone and thus increase vascular permeability (40).

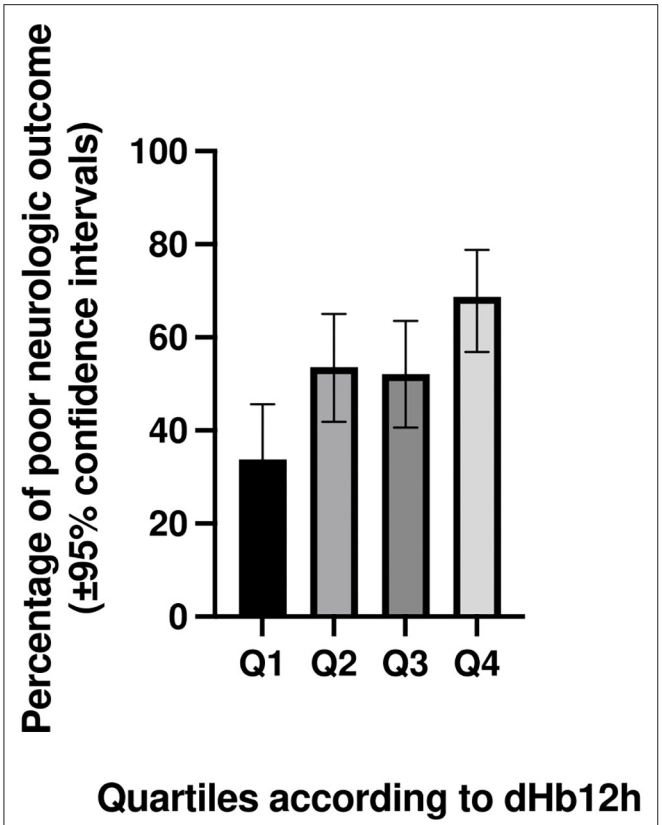

FIGURE 4 | Percentage (with 95% confidence intervals) of poor neurologic function at day 30 according to dHb12h quartiles in patients successfully resuscitated from cardiac arrest. dHb12h = Hemoglobin (Hb) levels 12 h after return of spontaneous circulation—Hb levels on admission.

A major advantage of using Hb kinetics as indicator for extravascular fluid loss is its prompt availability from blood gas analysis within seconds or from automatic blood cell counters within minutes. However, Hb kinetics' obvious limitation is limited specificity, as Hb concentrations are largely affected by other diseases and complications of critical illness per se. To maximize the validity of Hb kinetics in the presented study, we analyzed a homogenous patient collective. Therefore, (i) patients with signs of bleeding, receiving transfusions or requiring surgery were excluded, as these conditions may impact on Hb levels for other reasons than endothelial dysfunction; (ii) Only patients uniformly treated with TTM were included, as hypothermia per se may impact on vascular permeability (15, 16).

Due to the retrospective nature of the presented study, we can only speculate, whether increasing Hb concentrations should be counteracted by increasing fluid administration. However, increasing data suggest that especially hypervolemia is associated with poor outcome in critical illness (41). In agreement, patients with poor neurologic outcome had a greater positive fluid balance (and vasopressor requirement) in our study. Therefore, therapies targeting vascular permeability or the deterioration of endothelial function may be better suited to optimize patient outcome. The close association between endothelial dysfunction and volume resuscitation as well as their impact on organ dysfunction thereby requires optimal fluid resuscitation, guided by additional assessment, most likely echocardiography or continuous measurement of cardiac output. It needs to be determined, whether Hb kinetics may complement the evaluation of the patient's fluid status or should rather be seen as a prognostic marker.

In contrast to septic patients, where large clinical trials are available, prospective trials on fluid resuscitation (and endothelial dysfunction) in cardiac arrest are limited. In a small randomized trial ($n = 24$) Heradstveit et al. showed that infusion of hypertonic saline and hydroxyethyl starch significantly reduced the total fluid volume, improved fluid balance and increased serum osmolality compared to a standard crystalloid fluid regimen, but failed to show an impact on magnetic resonance imaging diagnosed brain oedema formation, which was, however, largely absent in their population (42). More recently, in a randomized placebo-controlled trial, iloprost, a prostacyclin analog aiming to improve endothelial function and reduce ischemia-reperfusion injury, failed to show beneficial effects in post-cardiac arrest patients (43). In a small randomized trial, urinastatin, an inhibitor of neutrophil elastase, was ineffective with regards to clinical endpoints (44). In a small randomized trial, Geri et al. attempted to remove inflammatory mediators from circulation of cardiac arrest survivors by means of high cut-off continuous veno-venous hemofiltration, but could not show effects on proinflammatory cytokines or clinical outcomes (45).

In addition, prospective studies have addressed vasopressor-complementary strategies. Two trials investigated the effects of adding vasopressin and corticosteroids to adrenaline during resuscitation itself and adding hydrocortisone to the treatment regimen in patients with post-resuscitation shock and found improved survival of these mostly in-hospital patients (46, 47). In contrast to other trials, patients received 40 mg methylprednisolone early during resuscitation, which may have had a more pronounced impact on ischemia-reperfusion injury. Furthermore, steroids provide a potent anti-inflammatory effect, which may be superior to other above-mentioned treatment strategies. Interestingly, dexamethasone increases angiopoietin-1, with antagonistic properties to angiopoietin-2, and decreases vascular endothelial growth factor, which disrupts endothelial cell junctions and increases permeability, thereby also providing an inflammation independent mechanism of improving vascular permeability (48). Moreover, a bolus infusion of steroids is practicable, inexpensive and widely available. Comparable data in out-of-hospital cardiac arrest patients, however, are lacking.

Limitations

The main limitation of this study is its retrospective, observational single center design. Markers of endothelial damage, constituents of the endothelial glycocalyx or biomarkers of leucocyte activation have not been measured to support our findings. Our hypothesis was driven by observations and data from other diseases and other clinical scenarios, e.g., capillary leak syndrome and burn injury, and on general theoretical considerations including the size of erythrocytes and the likelihood of erythrocyte extravasation, but we acknowledge that

have no experimental data to support it. Although we aimed to exclude any form of systematic bias by the application of in- and exclusion criteria and pathophysiological considerations, there is a remaining risk of systemic bias by not including further factors interfering with acute changes in hemoglobin levels after CPR. Furthermore, it needs to be noted that we analyzed a selected patient cohort, which limits the generalizability of our study results. Likewise, selection bias arising from missing data cannot be fully excluded. Thus, appropriate caution should be applied when interpreting our findings.

Conclusions

In conclusion, extravascular fluid loss as indicated by increasing Hb levels in cardiac arrest survivors appear to be crucial for both, neurologic function and survival. The clinical value of Hb kinetics to guide fluid resuscitation needs to be determined. However, Hb kinetics could display a surrogate marker for endothelial dysfunction and vascular permeability, which could be useful for addressing the effectiveness of endothelium-targeting therapeutic interventions in patients successfully resuscitated from cardiac arrest.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Vienna. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CScho, CSchr, BJ, NB, and MS conceived the study. CSchr, MP, CC, MM, FE, IM, MB, MH, and FS participated in data acquisition and including quality control. CScho, CSchr, JG, and MS provided statistical advice on study design and analyzed the data. CSchr drafted the macuscript. CScho takes responsibility for the paper as a whole. All authors contributed substantially to its revision, read, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.639803/full#supplementary-material

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Prediction of Left Double-Lumen Tube Size by Measurement of Cricoid Cartilage Transverse Diameter by Ultrasound and CT Multi-Planar Reconstruction

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Background: Currently, there is no uniform standard for selecting the left double lumen tubes (LDLT). Advantages, such as safety and convenience of the ultrasonic technology, and measurement accuracy, make it more widely applied in the clinical anesthesia, and computed tomography (CT) multi-planar reconstruction (MPR) technology will certainly provide a more accurate measurement. For better application for thoracic surgery choice LDLT, relieving the injury to patients, and reducing the complications, this study will compare the two approaches.

Methods: The first part, 120 cases of patients were selected according to the height and gender; recording the patient's optimum LDLT and measurement the transverse diameter of the cricoid cartilage (TD-C) by ultrasound and CT MPR, and then obtained the TD-C range measurement by ultrasound and CT MPR corresponding to different types of LDLT. The second part, total of 102 patients were divided into the ultrasound group and the CT MPR group. In the ultrasound group, TD-C was measured by ultrasound, the corresponding size for intubation was selected based on the conclusions derived from the first part. In the CT MPR group, TD-C was measured by CT MPR, the corresponding size of LDLT based on the conclusions derived from the first part.

Results: In the first part, 120 patients were no significant difference in the basic characteristics ($P > 0.05$). The accuracy of selecting the LDLT by conventional experience, namely height and gender was 58.3%. Ultrasonic measurement TD-C range was as follows: 32 Fr < 15.88, 35 Fr: 15.88–16.80, 37 Fr: 16.75–17.81, and 39 Fr > 17.80. CT MPR measurement TD-C range was as follows: 32 Fr < 15.74, 35 Fr: 15.74–16.65, 37 Fr: 16.56–17.68, and 39 Fr > 17.65. In the second part, there was no significant difference in the basic characteristics between the two groups ($P > 0.05$). The accuracy of intubation in the ultrasound group was 90.2% and the corresponding in the CT MPR group was 94.1% ($P > 0.05$).

Conclusions: The accuracy of selecting the LDLT based on TD-C is significantly higher than conventional experience; it can significantly reduce the post-operative complications and there was no statistical significance in the accuracy of LDLT selected for TD-C measurement by ultrasound vs. CT, and both of them could be safely used for the evaluation before intubation under anesthesia in thoracic surgery.

Keywords: ultrasound, CT multi-planar reconstruction, cricoid cartilage transverse diameter, left double lumen tube, one lung ventilation

INTRODUCTION

Double-lumen endotracheal intubation and one-lung ventilation are often used to perform effective lung isolation in patients undergoing thoracic, mediastinal, cardiac, and vascular surgery (1). Left double lumen tubes (LDLT) are often used clinically as a pulmonary isolation device, with high safety and strong practicability (1, 2), which can be successfully applied to the right and left surgeries of most patients (3). The most commonly chosen sizes are 32 Fr, 35 Fr, 37 Fr, 39 Fr, and 41 Fr (4). However, for the choice of LDLT, there is still no uniform standard, and it is usually based on the experience of anesthetist, depending on the patient's gender and height (5), but the accuracy is poor, often leading to selection of a too large or too small LDLT (6). If the LDLT is too small, the LDLT's tip may be too deep and it may block the upper bronchial opening, and there may be greater airflow resistance to the trachea, or there may be tracheal compression injury caused by very small LDLT but excessive inflation of the cuff, or part of the trachea may not reach the carina, affected the visual field of the operation which can even leading to pulmonary isolation or separation failure. If the LDLT is too large, the thicker and harder tube may lead to bronchial or airway damage (4). Therefore, selection of an appropriate LDLT is effective and it significantly avoids the complications associated with an oversized or undersized LDLT.

Computed tomography (CT) has been proved to measure the diameter of the trachea and bronchus (7). A spiral CT scan of the chest with multi-planar reconstruction (MPR) yields cross-sectional, coronal, and sagittal images of the chest, and the angles of inclination can be adjusted to obtain a strict orthogonal section of the cricoid cartilage and left main bronchus (LMB), so that the inner and outer diameters and the anterior and posterior diameters of the trachea and left main bronchus are measured accurately (8, 9). All patients undergoing chest surgery are required to have a CT scan before surgery, so it could be included in clinical protocols of pre-operative radiological evaluation. The correlation between the diameters of the trachea and LMB based on CT scan, was determined a 0.75 coefficient for males and a 0.77 coefficient for females. And then one formula about the bronchial diameter and the tracheal diameter is: ID LBM (mm) = (0.45*ID trachea) + 3.3(mm) (10). With the popularity of ultrasound imaging, ultrasound can quickly gain access to the operating room, ICU, emergency rooms, and even under the bad environment of airway anatomy (11), and its simple, convenient, safe, real-time, and can be repeated measurement and has other advantages; thus, it is more widely applied in the pre-operative evaluation of patients requiring measurement of the airway and trachea diameter (11). To better apply to the selection of LDLT intubation in thoracic surgery during clinical anesthesia, reduce the patient's injury, and reduce complications, this study intends to explore the accuracy of the ultrasonic contrast CT MPR technique to measure the transverse diameter of the cricoid cartilage (TD-C) to guide the selection of the LDLT size.

MATERIALS AND METHODS

Design

This study was divided into the following two parts: the first part was an observational study, and the second part was a prospective, double-blind, randomized controlled intervention study, which was approved by the Ethics Committee of the First Affiliated Hospital of Shihezi University (2019-096-01), and written informed consent was obtained from all of the subjects participating in the trial and the study was registered in The Chinese Clinical Trial Registry (ChiCTR1900025963). From August 2019 to August 2020, 232 patients were enrolled at the First Affiliated Hospital of Shihezi University School of Medicine for elective thoracic surgery, and 222 patients were eventually enrolled in this study.

Sample

The participants were recruited by thoracic surgeons. The inclusion criteria were as follows: American Society of Anesthesiologists (ASA) Classes I-II, Cormack-Lehane views grade I-II, thoracic surgery under general anesthesia surgery, age from 18 to 80 years, pre-operative chest high-resolution CT examination within a month, LDLT was used during anesthesia, and the patient was informed about the study and he/she or his/her family signed the informed consent form. The exclusion criteria were as follows: predicted difficult intubation, difficulty in opening the mouth, small jaw deformity, ultrasonic detection of abnormal cartilage ring morphology, cricoid wall hyperplasia, attachment, tumor and shape change in the main airway, pre-operative hoarseness or sore throat, previous laryngeal or neck surgery, or diseases that cause shrinkage of the trachea (5).

The first part of the study was conducted from August 2019 to March 2020. A total of 124 patients were randomly enrolled, and 120 patients met the inclusion and exclusion criteria. In the second part of the study, 108 patients were enrolled from April 2020 to August 2020, and 102 patients were statistically analyzed.

According to the preliminary experimental results, we found that the accuracy rate of selecting the LDLT with conventional

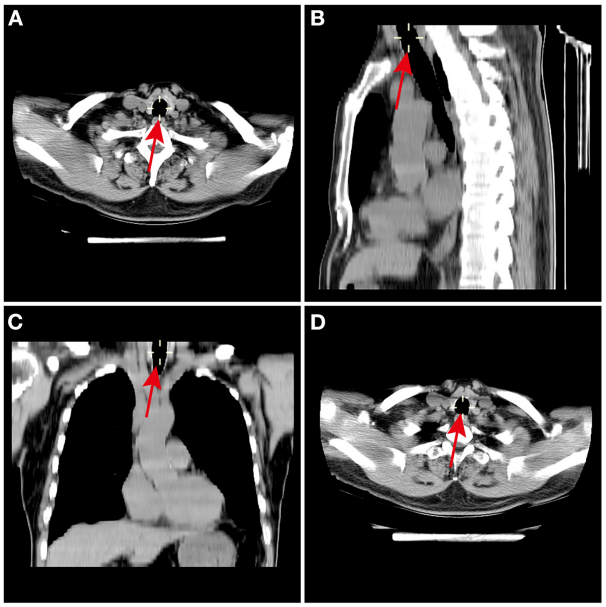

FIGURE 1 | Measurement of the cricoid cartilage using chest HRCT scan MPR. The MPR of the cricoid cartilage was performed using the **(A)** axial, **(B)** sagittal, and **(C)** coronal slices. The declination of TD-C was corrected in 3 dimensions to obtain a strictly orthogonal cut of the cricoid cartilage axis. **(D)** The TD-C were measured on the MPR at the lower border of the cricoid ring. TD-C, transverse diameter of cricoid cartilage.

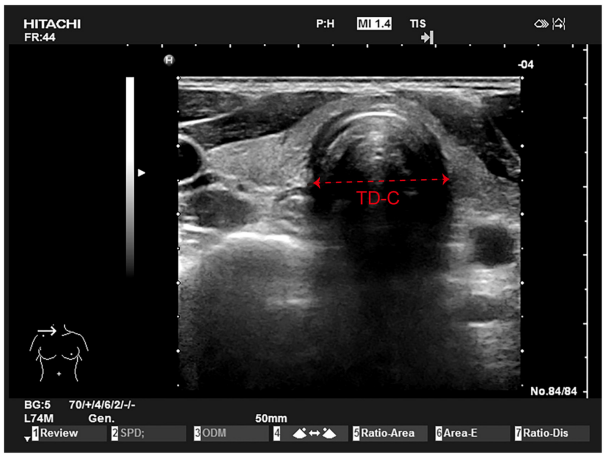

FIGURE 2 | Tracheal ultrasound examination. A linear 5 to 10 MHz probe is placed perpendicularly to the neck just above the sternoclavicular junction in transverse section (left). The outer tracheal diameter is measured on this transverse view (mm).

experience (height, gender) was about 60%. On examining the efficacy ($\alpha = 0.05$, $\beta = 0.1$), the accuracy rate of selecting the LDLT when measuring the TD-C was 90%, which was considered to be statistically significant. The sample size was calculated to be at least 50 patients in each group.

Randomization

Using computer-generated random numbers, continuous patients were randomly assigned to the ultrasound group or the CT MPR group in a 1:1 ratio. The researchers who measured the TD-C, the anesthesiologists who performed endotracheal intubation, and patients were unaware of the grouping.

The radiologists, who were not aware of the grouping, and they used the CarestreamPACS software to reconstruct and measure the patient's trachea in MPR using CT. The tilt of the cartilage was adjusted to obtain a strict vertical section of the cartilage's subsurface (**Figure 1**). The cursor was used to measure the TD-C and its shape. To reduce the measurement error, the image was enlarged to 400% for measurement, and the average value was taken after obtaining repeated measurements three times.

Patients get into the operating room, the jaw was slightly tilted back, the anesthesiologist, who was trained by professional physician and not know the study plan, will probe ultrasonic probe with coupling agent after long axis with the neck on the sternoclavicular articulation point 0.5 cm place to get the cricoid cartilage parallel plane image, obtain patients expiratory pause at the end of the clearance of cricoid cartilage ring diameter image (**Figure 2**), the average value was taken after obtaining repeated measurements 3 times.

Intervention

After entering the operating room, all of the patients were routinely monitored. Radial artery puncture was performed under local anesthesia, and invasive arterial pressure was monitored. After 3 min of pre-oxygenation (100% O_2, 5 L/min), intravenous injection of sufentanil 0.5 μg/kg and propofol 1.5–2.5 mg/kg was performed for anesthesia induction. After the patient's consciousness disappeared, cisatracurium 0.2 mg/kg was injected intravenously, and positive pressure ventilation by a face mask was performed. Bronchial intubation was performed after positive pressure ventilation 4 min. The tidal volume was 6–8 ml/kg during one-lung ventilation, positive end-expiratory pressure (PEEP) was 4–6 cmH_2O, and the respiratory rate was 12–20 times/min. Propofol, remifentanil, and cisatracurium were continuously pumped for anesthesia maintenance. While suturing the skin, the patients received self-controlled analgesia pump for post-operative pain management. At the end of the operation, the LDLT was retreated to the trachea and the patient was sent to the thoracic surgery ICU for mechanical ventilation and monitoring under anesthesia.

All of the bronchial intubations were performed by an anesthesiologist with at least 5 years of thoracic anesthesia experience. The anesthesiologist was not aware of the study method or grouping. First, select appropriate size of LDLT, the glottis was exposed with a video laryngoscope and the LDLT tip was inserted into the glottis under direct vision. advance the LDLT until a slight resistance is perceived, and the LDLT was continuously pushed to the expected depth. The expected depth (cm) of the LDLT = 12+ patient height (cm) /10. After adequate lubrication of the fiberoptic bronchoscope (FOB), introduce it into the tracheal lumen of the LDLT and identify the carina, and then verify the correct position of the bronchial lumen (the bronchial cuff must be barely visible). If the LDLT could not pass through the glottis due to severe resistance, the LDLT was continued to rotate anticlockwise 180° to continue the attempt

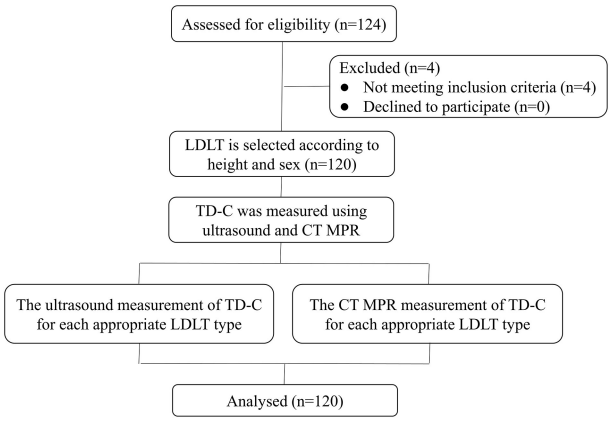

FIGURE 3 | Study flowchart of patients in the first part. TD-C, transverse internal diameter of cricoid cartilage; LDLT, left double lumen tube; MPR, multi-planar reconstruction.

to advance the LDLT. If the LDLT could not reach the trachea or bronchus due to severe resistance, intubation was performed with a smaller LDLT. After the intubation was complete, the anesthetist inserted the FOB to adjust the LDLT to the ideal location. Repeat the FOB control after patient position changes and throughout the intervention if necessary (12).

The First Part

Anesthesiologists selected the LDLT according to the conventional experience, such as the patient's height and gender, and recorded the optimal LDLT size (recorded the LDLT size and judged the LDLT as too large, too small, or appropriate according to the judgment standard). If the LDLT was too large, it was recorded as the adjacent smaller LDLT size; If the LDLT was too small, it was recorded as the adjacent larger LDLT size. The corresponding TD-C by ultrasound and CT MPR of the patient were collected. The data were statistically analyzed to obtain the different sizes of LDLT corresponding to ultrasound and CT MPR measurement of the TD-C range (**Figure 3**).

The Second Part

In the ultrasound group, the TD-C was measured by ultrasound. The range of TD-C in the first part was applied to select the corresponding size for intubation. In the CT MPR group, TD-C was measured by CT MPR, the range of TD-C obtained in the first part was applied to select the corresponding size for intubation, and the accuracy rate of the LDLT selected in the two groups was compared.

OBSERVATIONAL INDEX

Appropriate Standard for the LDLT

The main standard was that the LDLT was inserted smoothly (including the glottis, laryngeal, and bronchial areas) without resistance, the location of FOB inspection was correct and it arrived at the pre-determined bronchial level after adjustment, the intraoperative lung isolation was satisfactory, and the end-tidal carbon dioxide partial pressure ($PetCO_2$) was maintained at 35–45 mmHg. Objective criteria were injected air into the cuff. When the pressure inside the LDLT was 25 mmHg, it was stopped and connected to the anesthesia machine, when the peak pressure of positive pressure ventilation airway was below 30 cm H_2O, the air leakage phenomenon was adjusted (13).

Oversized Standard for the LDLT

There was obvious resistance when the LDLT entered the trachea or bronchus, or the LDLT tip could not enter the bronchus after being guided by a fiberoptic bronchoscope. Good pulmonary isolation could be achieved by injecting <1 ml of air into the bronchial cuff and <2 ml of air into the main tracheal cuff (13).

Undersized Standard for the LDLT

When the cuff pressure was adjusted to the standard value with the manometer after the LDLT was inserted successfully, the two lungs of the patients with airway leakage who needed injection of more than 3 or 6 ml of air into the two cuff could be satisfactorily isolated, and the LDLT size was considered to be too small (13).

Pulmonary Isolation Effect

Satisfactory isolation: clear breathing sound during ventilation of the two lungs separately, airway resistance increased < 10 cmH_2O after blocking ventilation of one side; Unsatisfactory isolation: incomplete respiratory isolation after blocking one side, or significantly increased ventilation resistance > 10 cm H_2O; No isolation: the two lungs could not be isolated at all, and no change was observed between blocking and not blocking.

Subglottic Resistance

Zero: no resistance; 1: Slight resistance; 2: Moderate resistance; the trachea met significant resistance under the glottis, but it could pass through the glottis by rotating the LDLT; 3: Heavy resistance, even by rotating the LDLT, it could not pass under the glottis, it must be replaced with a smaller LDLT.

Effects of Lung Collapse

Ten and 20 min after pleurotomy, a chest surgeon unaware of the grouping used a verbal rating scale (VRS) to evaluate the extent of lung collapse. Zero: Not collapsed at all; 10: Completely collapsed.

Hoarseness at 24 and 48 h After Surgery

An uninformed physician assessed the patient's hoarseness. Zero: no hoarseness; 1: The patient was aware of it; 2: Onlookers can detect; 3: Loss of voice.

Degree of Sore Throat at 24 and 48 h After Surgery

Zero: No sore throat; 1: Mild, sore throat only when swallowing; 2: Moderate, persistent sore throat, aggravated when swallowing; 3: Severe, throat pain affecting the patient's eating, and analgesic drugs were needed (11).

Other factors included age, gender, height, weight, Body Mass Index (BMI), the time required for intubation (it was defined as the time that the LDLT from the oral cavity to the expected depth), intubation times, LDLT changing conditions, Cormack-Lehane views grade I-II, the pressure and air in the trachea and bronchial cuff.

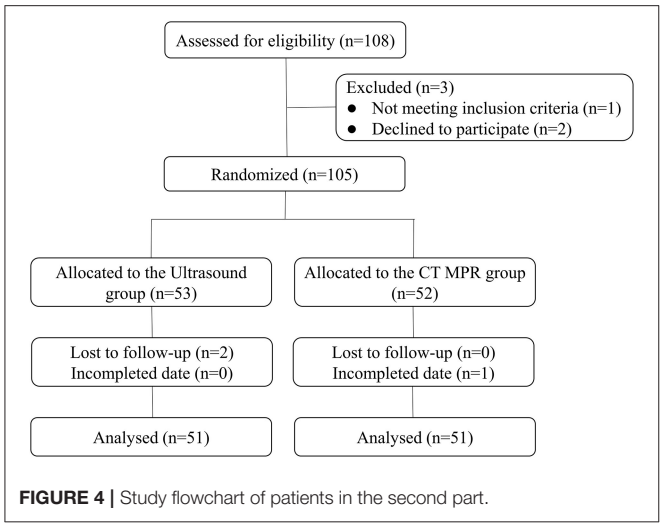

FIGURE 4 | Study flowchart of patients in the second part.

Statistical Analysis

SPSS 22.0 was used for statistical analysis of the data. The Kolmogorov-Smirnov test is used to check whether the data fits normal distribution, Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation, continuous variables not conforming to normal distribution were expressed as median and inter-quartile range, counting data were expressed as number and percentage, and the independent-samples *t*-test was used for inter-group analysis measurement date such as age, height, weight, TD-C between different genders. The χ^2 test was used to compare the enumeration data between the sexes and the intubation accuracy of the two groups. The classified variables were compared using Fisher exact test. Pulmonary isolation effect and subglottic resistance were analyzed using a non-parametric test because the variables did not satisfy the criteria for normality. In all of the statistical analyses, $P < 0.05$ was considered to be statistically significant.

RESULTS

In the first part, a total of 124 patients were assessed for eligibility. After exclusions (four patients did not meet the inclusion criteria), 120 patients were enrolled in this study (**Figure 3**). In the second part, among the 108 eligible patients, after exclusions, 102 patients were enrolled: 51 were randomized to the ultrasound group and 51 to the CT MPR group (**Figure 4**).

In the First Part

A total of 120 patients met the inclusion and exclusion criteria, and finally statistically analyzed. There were no statistically significant differences in age, BMI, operation time, surgical site, or ASA classification between the two groups ($P > 0.05$). Compared with female patients, height, weight, and TD-C values were significantly increased in male patients ($P < 0.05$). The intubation time and intubation times of female patients were significantly higher than those of male patients ($P < 0.05$).

TABLE 1 | Comparison of general conditions of male and female patients.

	Male ($n = 78$)	Female ($n = 42$)	*P*-value
Age (y)	54.2 ± 15.7	52.4 ± 10.4	0.631
Height (cm)	171.4 ± 6.2	160.5 ± 4.8	<0.001
Weight (kg)	72.0 ± 14.5	65.0 ± 7.6	0.011
Intubation time (s)	35.3 ± 11.0	46.4 ± 13.2	<0.001
Operating time (h)	3.3 ± 1.5	3.8 ± 1.4	0.128
BMI (kg/m²)	24.6 ± 4.4	25.1 ± 2.6	0.577
Ultrasound TD-C	17.62 ± 0.63	16.71 ± 0.63	0.000
CT MPR TD-C	17.42 ± 0.58	16.59 ± 0.62	0.000
Operating site			0.242
Right ($n = 86$)	55 (70.5%)	31 (73.8%)	
Left ($n = 34$)	23 (29.5%)	11 (26.2%)	
ASA classify			0.652
I ($n = 86$)	56 (71.8%)	30 (71.4%)	
II ($n = 34$)	22 (28.2%)	12 (28.6%)	
Appropriate LDLT			<0.001
39Fr ($n = 29$)	26 (33.3%)	3 (7.1%)	
37Fr ($n = 68$)	49 (62.8%)	19 (45.2%)	
35Fr ($n = 21$)	3 (3.9%)	18 (42.9%)	
SLT 7.0 ($n = 2$)	0 (0.0%)	2 (4.8%)	
Intubation times			0.003
1 ($n = 108$)	72 (92.3%)	36 (85.7%)	
2 ($n = 12$)	6 (7.7%)	6 (14.3%)	
The shape of TD-C			0.02
Round ($n = 76$)	68 (87.2%)	8 (19.0%)	
Oval ($n = 44$)	10 (12.8%)	34 (81.0%)	

Date are mean ± standard deviation or number (percentage). BMI, body mass index; TD-C, transverse internal diameter of cricoid cartilage; ASA, American Society of Anesthesiologist; LDLT, left double lumen tube; SLT, single lumen tube.

TABLE 2 | The range of appropriate LDLT.

Appropriate LDLT	Ultrasound TD-C	CT MPR TD-C
32Fr	<15.88	<15.74
35Fr	15.88∼16.80	15.74∼16.65
37Fr	16.75∼17.81	16.56∼17.68
39Fr	17.80∼18.88	17.65∼18.52

Values are expressed as 95% confidence interval [CI].MPR, multi-planar reconstruction.

In male patients, the shape of the cricoid cartilage was round (87.2%); while in female patients, the shape of the cricoid cartilage was oval (81.0%) ($P < 0.05$). Male patients had the maximum 37 Fr selection (62.8%), followed by 39 Fr selection (33.3%); and female patients had the maximum 37 Fr selection (45.2%), followed by 35 Fr selection (42.9%) (**Table 1**).

Ultrasonic measurement TD-C range: 32 Fr < 15.88; 35 Fr: 15.88 ∼ 16.80; 37 Fr: 16.75 ∼ 17.81; 39 Fr > 17.80. CT MPR measurement TD-C range: 32 Fr < 15.74; 35 Fr: 15.74 ∼ 16.65; 37 Fr: 16.56 ∼ 17.68; 39 Fr > 17.65 (**Table 2**).

Among the 120 patients, the LDLT size was too large in 22 patients (18.3%), suitable in 70 patients (58.3%), and too

TABLE 3 | Comparison of observation indexes among the three groups.

	Oversize ($n = 22$)	Appropriate ($n = 70$)	Undersize ($n = 28$)	*P*-value
Intubation time (s)	48.4 ± 9.2	32.2 ± 8.5	36.8 ± 11.2	<0.001
Intubation times				0.002
1	15 (68.2%)	70 (100.0%)	23 (82.1%)	
2	7 (31.8%)	0 (0.0%)	5 (17.9%)	
Subglottic resistance				0.004
0	1 (4.5%)	19 (27.1%)	22 (78.6%)	
1	10 (45.4%)	48 (68.6%)	6 (21.4%)	
2	6 (27.3%)	3 (4.3%)	0 (0.0%)	
3	5 (22.8%)	0 (0.0%)	0 (0.0%)	
Pulmonary isolation				0.009
Satisfactory isolation	10 (45.5%)	49 (70.0%)	6 (21.4%)	
Unsatisfactory isolation	9 (41.0%)	21 (30.0%)	21 (75.0%)	
No isolation	3 (13.5%)	0 (0.0%)	1 (3.6%)	
Effects of lung collapse				<0.001
No collapse	3 (13.6%)	0 (0.0%)	2 (7.1%)	
Mild collapse	2 (9.1%)	0 (0.0%)	7 (25.0%)	
Severe collapse	13 (59.1%)	44 (62.9%)	13 (46.4%)	
Completely collapse	4 (18.2%)	36 (37.1%)	6 (21.5%)	
Hoarseness at 24 h				<0.001
0	6 (27.3%)	37 (52.9%)	16 (57.1%)	
1	10 (45.4%)	33 (47.1%)	11 (39.3%)	
2	6 (27.3%)	0 (0.0%)	1 (3.6%)	
Hoarseness of 48 h				<0.001
0	11 (50.0%)	64 (91.4%)	22 (78.6%)	
1	11 (50.0%)	6 (8.6%)	6 (21.4%)	
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Sore throat at 24 h				<0.001
0	0 (0.0%)	19 (27.1%)	4 (14.3%)	
1	10 (45.5%)	46 (65.8%)	16 (57.1%)	
2	12 (54.5%)	5 (7.1%)	8 (28.6%)	
Sore throat at 48 h				<0.001
0	7 (31.8%)	53 (75.7%)	16 (57.1%)	
1	14 (63.6%)	17 (24.3%)	11 (39.3%)	
2	1 (4.6%)	0 (0.0%)	1 (3.6%)	

Date are mean ± standard deviation or number (percentage). Subglottic resistance: 0, no resistance; 1, slight resistance; 2, moderate resistance; 3, heavy resistance. Hoarseness: 0, no hoarseness; 1, the patient is aware of it; 2, onlookers can detect.

small in 28 patients (23.4%). The large group had the longest intubation time (48.4 ± 9.2 s), and 10 patients (45.4%) had slight resistance when intubation passed through the subglottic area; 48 patients (68.6%) in the appropriate group had slight resistance when intubation passed; and 22 patients (78.6%) in the subglottic group had no resistance. The effects of lung isolation, pulmonary collapse, hoarseness, and sore throat 24 and 48 h after surgery in the appropriate group were significantly better than those in the oversized and undersized groups ($P < 0.05$) (**Table 3**).

In the Second Part

A total of 102 patients were included and randomly divided into the ultrasound group and the CT MPR group. There were no

TABLE 4 | Comparison of general conditions of two groups.

	Ultrasound ($n = 51$)	CT MPR ($n = 51$)	*P*-value
Age (y)	53.3 ± 13.3	57.7 ± 15.3	0.124
Gender			0.836
Female	18 (35.3%)	17 (33.3%)	
Male	33 (64.7%)	34 (66.7%)	
Weight (kg)	68.7 ± 9.3	66.2 ± 10.4	0.214
Height (cm)	166.5 ± 8.9	165.5 ± 7.9	0.418
BMI (kg/m²)	25.2 ± 1.4	24.8 ± 1.4	0.171
ASA classify			0.562
I	41 (80.4%)	38 (74.5%)	
II	10 (19.6%)	13 (25.5%)	
Operating site			0.724
Right	35 (68.6%)	33 (64.7%)	
Left	15 (31.4%)	18 (35.3%)	
Operating time (h)	3.5 ± 1.5	3.6 ± 1.7	0.154
Intubation time (s)	28.2 ± 7.4	26.6 ± 7.0	0.752
Intubation times			
1	51 (100.0%)	51 (100.0%)	
2	0 (0.0%)	0 (0.0%)	

Date are mean ± standard deviation or number (percentage).

TABLE 5 | Comparison of LDLT accuracy between the two groups.

	Ultrasound ($n = 51$)	CT MPR ($n = 51$)	*P*-value
Oversized	2	2	0.128
Appropriate	46	48	0.846
Undersized	3	1	0.215
Accuracy rate	90.20%	94.10%	0.097

Date are number (percentage).

statistically significant differences in gender, age, height, weight, BMI, ASA classification, surgical site, duration of operation, and number of intubations between the two groups ($P > 0.05$), and the number of intubations in the two groups was once (**Table 4**).

In the ultrasound group, two cases were too large and three cases were too small with respect to choosing the LDLT, and the accuracy rate of choosing an appropriate LDLT was 90.2%. In the CT MPR group, 2 cases were too large and 1 case was too small, and the intubation accuracy was 94.1%. There was no statistically significant difference in the tube selection accuracy between the two groups ($P > 0.05$) (**Table 5**).

In the two groups of patients, choosing the number of each size of LDLT, TD-C value, the trachea and bronchus cuff volume, subglottic resistance, lung isolation effect, lung collapse effect, and post-operative 24 and 48 h hoarseness and sore throat showed no statistical difference ($P > 0.05$), and some patients (22 vs. 24) at 24 h after surgery had a mild sore throat, and only a few patients (3 vs. 5) at 24 h after surgery had mild hoarseness (**Table 6**).

In the first part, 28 (23.4%) patients' LDLT was too small, 22 (18.3%) patients' LDLT was too large, and 70 (58.3%)

TABLE 6 | Comparison of observation indexes among the two groups.

	Ultrasound ($n = 51$)	CT MPR ($n = 51$)	*P*-value
Appropriate LDLT			0.421
39Fr	14 (27.5%)	10 (19.6%)	
37Fr	24 (47.1%)	30 (58.8%)	
35Fr	12 (23.5%)	10 (19.6%)	
SLT7.0	1 (1.9%)	1 (2.0%)	
TD-C (mm)	17.45 ± 0.78	17.25 ± 0.71	0.182
Trachea cuff volume (ml)	4.12 ± 0.56	4.00 ± 0.53	0.275
Bronchial cuff volume (ml)	2.06 ± 0.31	2.00 ± 0.35	0.369
Subglottic resistance			0.687
0	45 (88.2%)	43 (84.3%)	
1	6 (11.8%)	8 (15.7%)	
2	0 (0.0%)	0 (0.0%)	
3	0 (0.0%)	0 (0.0%)	
Pulmonary isolation			0.246
Satisfactory isolation	46 (90.2%)	44 (86.3%)	
Unsatisfactory isolation	5 (9.8%)	7 (13.7%)	
No isolation	0 (0.0%)	0 (0.0%)	
Effects of lung collapse			0.091
No collapse	45 (88.2%)	47 (92.2%)	
Mild collapse	6 (11.8%)	4 (7.8%)	
Severe collapse	0 (0.0%)	0 (0.0%)	
Completely collapse	0 (0.0%)	0 (0.0%)	
Hoarseness at 24 h			0.239
0	48 (94.1%)	46 (90.2%)	
1	3 (5.9%)	5 (9.8%)	
2	0 (0.0%)	0 (0.0%)	
Hoarseness of 48 h			0.585
0	50 (98.0%)	49 (96.1%)	
1	1 (2.0%)	2 (3.9%)	
2	0 (0.0%)	0 (0.0%)	
Sore throat at 24 h			0.512
0	26 (51.0%)	22 (43.1%)	
1	22 (43.1%)	24 (47.1%)	
2	3 (5.9%)	5 (9.8%)	
Sore throat at 48 h			0.266
0	45 (88.2%)	42 (82.4%)	
1	5 (9.8%)	7 (13.7%)	
2	1 (2.0%)	2 (3.9%)	

Date are mean ± standard deviation or number (percentage).

patients' LDLT was appropriate. In the second part, according to the TD-C selection, the LDLT size was too large in four patients (3.9%), too small in four patients (3.9%), and suitable in 94 patients (92.2%), with a statistically significant difference ($P < 0.05$) (**Table 7**).

DISCUSSION

We found that in the first part of this study, by using ultrasonic and CT MPR, we could obtain the range of TD-C, then the second part was used to verify this method, as a result the success rate of intubation was more than 90%. Too large or too small of LDLT can increase the intubation time and the number of intubations, subglottic resistance, post-operative sore throat and hoarseness, can lead to lung failure isolation and one-lung collapse is not complete. The longer intubation duration and the more times of intubations in female patients than in male patients, we analyzed is due to the more constricted airway. In female, subglottic resistance is often encountered during intubation. The cricoid cartilage of female is oval, while in male, it is mostly round. In our study, the elliptic shape of the cricoid cartilage often leads to a larger choice of LDLT size, intraoperative lung isolation is not satisfactory, and post-operative complications, sore throat, and hoarseness. This is also where we need to pay attention in the future to continue our experiments with LDLT size selection.

At present, the LDLT is usually selected according to the conventional experience, such as gender, height, when the anesthesia department of most domestic hospitals conducts thoracic surgery, but it has low accuracy. Since there is no significant correlation between patient height and airway diameter, this approach tends to lead to inappropriate LDLT selection in Asians (14). According to Miller's anesthesiology, in female with height <152 cm, 32 Fr should be chosen, height <160 cm, 35 Fr should be chosen, and height > 160 cm, 37 Fr should be chosen. For male with height < 160 cm, the 37 Fr LDLT should be selected; with height < 170 cm, 39 Fr LDLT should be selected; with height > 170 cm, 41 Fr LDLT should be selected (15). The advantages of this method are as follows: it is simple and easy to use. The disadvantages of this method are as follows: the predicted by this method is the median value, and the LDLT size selected was not suitable for all patients due to the great individual variation of the airway size in patients with the same height range. Therefore, the specificity of this method is poor and the positive predictive value is low. This selection method is based on Europeans and Americans. Since Asians are generally smaller than Europeans and Americans, this method may not be applicable to Asians, especially Asian female.

It is generally believed that the correct LDLT size should be determined according to the LMB (16). However, LDLT selected according to the LMB often encounters significant subglottic resistance, especially in female patients (17). Since the cricoid cartilage is the narrowest part of the trachea, its diameter may be a determinant of the appropriate LDLT size (18). Since the shape of the LMB is not circular or elliptical, and it is not perpendicular to the cross section in space, it is difficult to measure it (12). Parab pointed out that the cricoid cartilage is almost always oval in shape and that in 75% of cases (19), the anterior and posterior diameter is longer. Kim D describes the circular shape of the lower margin of the cricoid cartilage (16). This difference may be caused by differences in race and method, and further research is needed to elucidate the factors influencing its structure. Similar to the LMB, the TD-C cannot be accurately predicted due to the poor correlation between height and the TD-C (17).

In recent years, the application of ultrasound technology in clinical anesthesia has developed rapidly, and it has become one

TABLE 7 | Comparison of accuracy between the first part and the second part.

		The first part (n = 120)			The second part (n = 102)			*P*-value
		Undersize	Appropriate	Oversized	Undersize	Appropriate	Oversized	
Male	32Fr	0	0	0	0	1	0	
	35Fr	1	1	0	1	6	0	
	37Fr	11	37	6	2	39	1	
	39Fr	0	13	9	0	20	0	
	All	12 (15.4%)	51 (65.4%)	15 (19.2%)	3 (4.3%)	66 (94.3%)	1 (1.4%)	<0.001
Female	32Fr	0	0	0	0	1	0	
	35Fr	12	11	2	1	9	1	
	37Fr	4	8	5	0	15	2	
	39Fr	0	0	0	0	3	0	
	All	16 (38.1%)	19 (45.2%)	7 (16.7%)	1 (3.1%)	28 (87.5%)	3 (9.4%)	<0.001
All		28 (23.4%)	70 (58.3%)	22 (18.3%)	4 (3.9%)	94 (92.2%)	4 (3.9%)	0.001

Date are number (percentage).

of the hot spots in clinical research (20). CT MPR technology has been proved to be able to accurately measure the diameter of the trachea and bronchus. Ultrasound and CT MPR have respective advantages in tracheal measurement and airway assessment (16), but few scholars at home and abroad have compared the two methods to evaluate the accuracy of the LDLT size. Kayashima K proved that ultrasonic measurement of the tracheal diameter combined with the patient height and gender could accurately guide the selection of the LDLT size (17). Nain and others experimented measuring the LMB by CT and the correlation between ultrasonic measurement of the tracheal diameter, the result is not encouraging, this means that the diameter of the LMB cannot be predicted by measuring the diameter of the trachea (21). Gu experimented measuring the trachea diameter by the neck ultrasound and CT; both with strong correlation, can better reflect the real situation of the trachea, but the disadvantage is not for the two kinds of measurement methods were compared (22). Although this experiment proves the LDLT in TD-C measurement accuracy, ultrasound and CT MPR show no difference, but CT MPR and its advantages, we can see the anteroposterior diameter of cricoid cartilage, when the patients' cricoid cartilage for the oval shape is irregular, we can even combine the transverse diameter and anteroposterior diameter to predict the size of LDLT.

The CT MPR technique can provide more accurate information needed for intubation. Chest CT can provide the following information: (1) the values of transverse diameters of the trachea and bronchus, their patency, changes in the inner diameter, stenosis, compression, distortion, and angulation; (2) whether the carina is shifted to the left or right, whether the plane of the left and right bronchi is consistent with the coronal plane, and how it is shifted; (3) the position of the bronchial opening of the upper lobe and its distance from the carina; (4) can clearly observe the bilateral lung structure and pulmonary vessels, especially the ventilatory side of the lung (23). Based on the advantages of CT, we found that the included angle between the trachea and the LMB was significantly different among different patients. Among them, patients with large angle formation had longer intubation time, increased intubation times, and were more likely to have sore throat and hoarseness on the first day after surgery.

Difficult airway management can be challenging for anesthesiologists, especially in thoracic anesthesia, the incidence of difficult airway was higher than that of the general patients, and the video laryngoscopy was successfully used in difficult intubation patients (24). Patients with normal size and shape of trachea and bronchial were enrolled in this study, however, in patients with difficult airways, measuring airway diameter alone is not sufficient, the LDLT with an embedded camera can confirm the LDLT's position and minimize the requirement for a bronchoscope and avoid the need to open the airway. Even when using tubes with embedded cameras, bronchoscopes can still occasionally be necessary (25).

Because LDLT has a large outside diameter and a pre-shaped tip, it can easily cause airway damage once the LDLT is not selected properly; thus, hoarseness and sore throat are common complications after bronchial intubation (26–28). The first part of this experiment with the LDLT size showed the probability of an oversized group of severe post-operative sore throat than the appropriate group, 12 cases of patients with severe post-operative sore throat suffered from serious resistance and the intubation time was more than 50 s, and eight cases of patients experienced more than two episodes of intubation; and in the second part, all of the patients did not develop severe post-operative sore throat.

There are still some deficiencies and improvements needed in this experiment. First, the TD-C was measured by ultrasound and CT MPR in this experiment, while the LMB and its shape were not measured. The accuracy of LDLT selection was analyzed by comparing the TD-C and LMB in subsequent

experiments. Second, all of the patients in this experiment came from the same region and visited the same hospital; thus, the sample representation was general. Third, in the second part of the experiment, two patients in the ultrasound group had difficulty in intubation, resulting in insufficient ventilation. CT images showed that the angle between the trachea and LMB was relatively large, and subsequent experiments would consider the image of the trachea and bronchus angulation for LDLT.

CONCLUSIONS

In summary, the conclusion of this experiment was that the TD-C range of ultrasonic measurement was as follows: 32 Fr $<$ 15.88, 35 Fr: 15.88–16.80, 37 Fr: 16.75–17.81, and 39 Fr $>$ 17.80. The CT MPR measurement TD-C range was as follows: 32 Fr $<$ 15.74, 35 Fr: 15.74–16.65, 37 Fr: 16.56–17.68, and 39 Fr $>$ 17.65. The accuracy rate of LDLT intubation in the ultrasound group was 90.2%, and that of LDLT intubation in the CT MPR group was 94.1%, with no significant difference in the intubation accuracy between the two groups.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of First Affiliated Hospital of Shihezi University (2019-096-01), and written informed consent was obtained from all of the subjects participating in the trial and the study was registered in The Chinese Clinical Trial Registry (ChiCTR1900025963). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JY, ZD, and CZ contributed to the study conception and design. Material preparation, data collection and analysis were performed by CZ, XQ, WZ, and AL. SH and YZ analyzed the data. The first draft of the manuscript was written by CZ and XQ. All authors read and approved the final manuscript.

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BRIEF RESEARCH REPORT
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Point-Of-Care Capillary Refill Technology Improves Accuracy of Peripheral Perfusion Assessment

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Background: Peripheral perfusion assessment is used routinely at the bedside by measuring the capillary refill time (CRT). Recent clinical trials have shown evidence to its ability to recognize conditions with decreased end organ perfusion as well as guiding therapeutic interventions in sepsis. However, the current standard of physician assessment at the bedside has shown large variability. New technology can improve the precision and repeatability of CRT affecting translation of previous high impact research.

Methods: This was a prospective, observational study in the intensive care unit and emergency department at a quaternary care hospital using a non-invasive finger sensor for CRT. The device CRT was compared to the gold standard of trained research personnel assessment of CRT as well as to providers clinically caring for the patient.

Results: Pearson correlations coefficients were performed across 89 pairs of measurements. The Pearson correlation for the device CRT compared to research personnel CRT was 0.693. The Pearson correlation for the provider CRT compared to research personnel CRT was 0.359.

Conclusions: New point-of-care technology shows great promise in the ability to improve peripheral perfusion assessment performed at the bedside in the emergency department triage and during active resuscitation. This standardized approach allows for better translation of prior research that is limited by the subjectivity of manual visual assessment of CRT.

Keywords: perfusion, sepsis, point of care, device, innovation

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INTRODUCTION

Approximately 1 million patients present annually to United States emergency departments with sepsis (1). The diagnosis, unfortunately, remains challenging with an 8% increase in mortality for every hour of delayed recognition (2). The mortal consequences of delayed diagnosis creates an imperative for improved early identification and intervention to meet the Surviving Sepsis goals of therapy. One measure that has been used in clinical practice for decades as a marker of perfusion is capillary refill time (CRT). In practice, however, there is a great deal of subjectivity and variability in how providers apply and interpret results of this simple, non-specific marker of oxygen delivery (3). Technology can standardize this measurement making it objective, reproducible and precise.

Through a problem-based innovation approach, a point-of-care bedside technology for CRT assessment (Promedix Inc.) has been developed (4); this opens the door to research evaluating CRT's ability to detect sepsis earlier and, hopefully, facilitate earlier diagnosis and more effective resuscitation of septic patients. The objective of this study was to evaluate the performance of a novel medical device to objectively measure CRT compared to both a rigorous manual method and unstructured usual practice as one of the first steps in validating the ability of the device.

METHODS

This was a prospective, observational study performed in a quaternary care university hospital across both an adult intensive care unit (ICU) and the emergency department (ED). The primary outcome of this convenience sample was evaluating the correlation between research personnel measurement of CRT relative to either the point of care technology prototype or provider CRT. This was a parallel study performed as part of a larger study evaluating the utility of CRT in sepsis diagnosis and monitoring of therapeutic interventions. This study had institutional review board approval. Patients and the public were not involved in the design, conduct, or reporting of this study. Patients were eligible if <17 years of age and with a known/suspected infection on intravenous antibiotics for sepsis in the ICU or if there was suspicion for sepsis in the ED. Patients were excluded if they had bilateral hand trauma, were either positive or had a pending COVID-19 test, cirrhosis, inability to consent, diabetic ketoacidosis, chronic liver disease or transplant, chronic kidney disease or transplant, pregnant, or a prisoner.

Following consent, a research assistant assessed CRT by applying manual pressure to a finger on the hand for 3 s and then releasing the pressure. Capillary refill duration was calculated with a chronometer and the stop point determined when the examiner determined the color of the nailbed was back to baseline. The research assistant underwent training by the study team and has extensive clinical research experience, but is not a trained medical practitioner. In the ED group of patients, the research personnel performed CRT manually with a chronometer and then asked the medical provider caring for the patient to assess CRT per standard of care without a chronometer. The current standard of care is to apply pressure to the nailbed to blanch the color and the provider simply counts to themselves until they visually determine the nailbed color is back to normal.

The research personnel performed the same procedure with the point of care technology as manual detection (Promedix Inc.) to measure CRT (4) (**Figure 1**). The technology is a grooved finger sensor that is applied to the distal phalanx of the patient. It connects *via* Bluetooth technology to an application that contains algorithms that detect manual application of pressure and then calculate exponential decay of the photodiode signal from the light source. The change in capillary blow flow timed with the pressure sensor is able to calculate the duration of capillary refill.

FIGURE 1 | Capillary refill device.

RESULTS

Pearson correlations coefficients were performed for each group of measurements. The ED cohort consisted of 29 patients with an average age of 46.2 years (stdev 15.1) and 41% male. The ICU consisted of 25 patients with an average age of 58.5 years (stdev 16.1) and 40% male. The ICU patients had sequential CRT over their admission resulting in a total of 69 measurements. The Pearson correlation for the device CRT compared to research personnel CRT was 0.693. The Pearson correlation for the provider CRT compared to research personnel CRT was 0.359 (**Figure 2**).

DISCUSSION

There is growing body of research examining the role of bedside peripheral perfusion monitoring via CRT to direct diagnosis and therapeutic interventions for sepsis and shock. This represents a paradigm shift away from serum testing and invasive monitoring; while these will remain crucial, the non-invasive nature and immediacy of CRT make it appealing in the diagnosis and treatment of a dynamic disease process like sepsis. Prior reviews have detailed the promise of peripheral perfusion monitoring with technology in shock states to improve outcomes (5).

There is potential for this technology to be integrated into standard hospital monitoring protocols to identify decompensating patients earlier. One recent study performed across 3 institutions examined 6,500 hospital rapid response team activations (6). The authors noted CRT was an independent

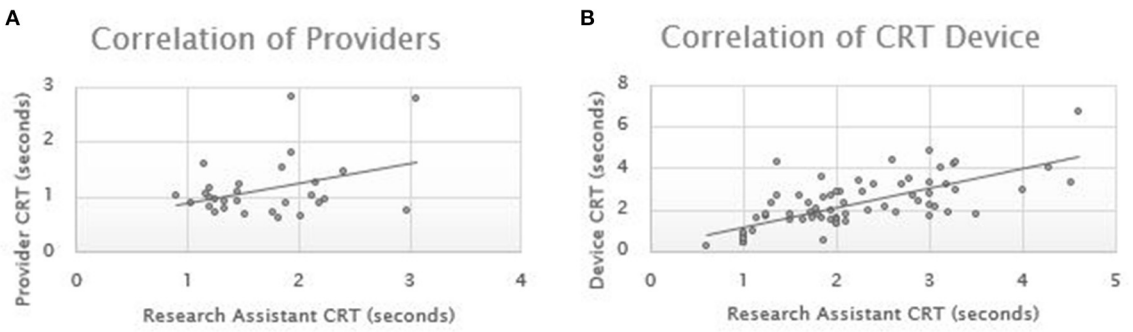

FIGURE 2 | Capillary refill time correlation. CRT, capillary refill time.

predictor of death, need for ICU transfer, and cardiac arrest. The ANDROMEDA shock trial randomized septic ICU patients to having their initial resuscitation guided by either CRT or blood lactate levels (7). The CRT group's outcomes were more favorable, in almost every category of morbidity and mortality, compared to the blood lactate group. Although it did not reach statistical significance ($p = 0.06$), when utilizing a pragmatic Bayesian analysis CRT was superior (8). A more recent study evaluated objective CRT measurement through a transmitted pulse oximetry light source and were able to show it significantly improved the test characteristics of standard sepsis screening scores in the ED (9). This type of technology has great promise for ED triage where studies have shown the ability to accurately triage sepsis patients can have significant impact on outcomes (10, 11).

This study had a number of limitations. The first is that there is no gold standard for CRT assessment to date. However, the best objective measure to date has been when CRT is performed by rigorous research personnel. For this reason this study used research assistants as the gold standard to compare the device to. Many factors can influence CRT including position, skin temperature, skin color, and hemoglobin concentration. However, the same protocol was used for each patient. In addition CRT were not compared to one another, but rather the CRT on the same patient using the device and gold standard. We believe this limits any confounding that would have been seen due to a patient differences, but future studies should evaluate these factors in further depth as we did not. A second limitation was the study was performed in two different hospital settings. However, this was done as capillary refill is measured in multiple places within healthcare and so the authors felt this was a pragmatic design. A single research assistant performed the manual and device measurements limiting the ability to assess inter-rater reliability. A third limitation is that this study was performed by a group that developed the technology. However, all study data was collected by research staff unrelated to the technology development. Further studies should be undertaken at multiple hospitals and will need to correlate CRT to outcomes including sepsis diagnosis, shock, lactate levels, and mortality.

This study demonstrates that CRT measured via light reflectance technology, is more highly correlated to a rigorous research standard measure than unstructured clinical measurement. This indicates the technology is a promising way to easily measure CRT in a rigorous and reproducible manner. Peripheral perfusion assessment by light reflectance has the potential to improve the care of sepsis and other shock states using point-of-care technology at the bedside.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Oregon Health & Science University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DS designed the study, data analysis, and drafted the manuscript. RC, RS, and MH revised it critically for important intellectual content. DS, RC, RS, and MH provide approval for publication of the content and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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A Novel Method for Measuring the Pupil Diameter and Pupillary Light Reflex of Healthy Volunteers and Patients With Intracranial Lesions Using a Newly Developed Pupilometer

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Background: Physicians currently measure the pupil diameter and the pupillary light reflex with visual observations using a ruler and a traditional penlight, leading to possibly inaccurate and subjective assessments. Although a mobile pupillometer has been developed and is available in clinical settings, this device can only assess one pupil at a time. Hence, an indirect pupillary light reflex, including those under irradiation to the opposite side of pupil, cannot be evaluated. Consequently, we have developed a new automatic mobile pupilometer, the Hitomiru®, with Hitomiru Co., Ltd. (Tokyo, Japan). This device is a two-glass type pupilometer with a video recording system. The pupil diameter and light reflex of both pupils can be measured simultaneously; therefore, both indirect and direct light reflexes can be assessed.

Purpose: To evaluate the clinical ability of the Hitomiru® pupilometer to assess the pupil diameter and the pupillary light reflex of healthy volunteers and patients with intracranial lesions in an intensive care unit (ICU).

Methods: Twenty-five healthy volunteers and five ICU patients with intracranial lesions on only the left side were assessed using the Hitomiru® pupilometer. The protocol was as follows: infrared light was applied to both pupils, followed by visible light to the right pupil, infrared light to both pupils, visible light to the left pupil, and then infrared light to both pupils. All the intervals were 2 s, and the dynamics of pupil diameters on both sides were continuously recorded.

Results: The healthy adults had approximately 0.5 mm anisocoria, miosis was harder, and mydriasis was less with increased age. There were several differences in miosis rates, miosis times, and mydriasis rates between the healthy adults and the patients with intracranial lesions with both direct irradiation and indirect irradiation.

Conclusions: The initial trial estimated and digitally recorded direct and indirect light reflexes, including rapidity of miosis after direct and indirect lights on, and mydriasis after direct and indirect lights off. The Hitomiru® pupilometer was a useful device to digitally record and investigate the relationship between pupil reflexes and intracranial diseases.

Keywords: mobile type pupilometer, digital record, direct and indirect irradiation, pupil diameter, pupil light reflexes, miosis, mydriasis, intracranial lesions

BACKGROUND

Prompt assessment of the pupil function in the clinical settings, such as during pre-hospital emergency care, in the emergency room, intensive care unit (ICU), or operation room, is critical to the evaluation of neurological function of critically ill patients who may have intracranial lesions. However, physicians currently measure the pupil diameter and the pupillary light reflex with visual observation using a ruler and a traditional penlight, leading to inaccurate and subjective assessment values [(1), Wilson (2), p. 897], and resulting in no digital records. This situation is in contrast to other vital sign recordings, such as information regarding respiratory and circulatory conditions that are evaluated and recorded digitally.

Although a mobile pupilometer has been developed and is available in the clinical setting (3–9), this device can only assess one pupil at a time. Hence, an indirect pupillary light reflex cannot be evaluated. Abnormal pupillary light reactivity such as time extension of light reflex is seen in the patients with intracranial disease such as increased intracranial pressure (2). In addition, evaluation of direct and indirect pupillary light reflex is necessary for differential diagnosis of optic nerve injury, oculomotor nerve damage, brain stem lesions, such as tumors, and medications (10) although the presence or absence of the difference between direct and indirect light reflex and the meaning of such difference in the patients with intracranial lesions have not been elucidated yet. Consequently, we have developed a new automatic mobile pupilometer, the Hitomiru® pupilometer, which is a two-glass type pupilometer incorporated with a video recording system, in cooperation with the University of Tokyo, Hyogo College of Medicine and Hitomiru Co., Ltd.

The Hitomiru® pupilometer has two characteristics: (1) the pupil diameter and light reflex of both pupils can be measured simultaneously; therefore, both indirect and direct light reflexes can be assessed, (2) the time of start of both miosis after direct and indirect lighting on, and mydriasis after direct and indirect lighting off, can be measured, (3) all the data are recorded digitally, leading to accurate and objective assessments, and (4) the instrument is a mobile type pupilometer, which can be easily transported to an ICU, emergency room, and pre-hospital care field.

The purpose of this study was to assess the pupil diameter and the direct and indirect pupillary light reflex in healthy volunteers using Hitomiru® pupilometer and investigate the relationship between these measurements and age because aging may influence neuro-activity involved in pupillary light reflex, and to investigate the differences in these parameters measured by Hitomiru® pupilometer between volunteers and patients with intracranial lesions in an ICU. This is the first trial to estimate and digitally record direct and indirect light reflexes, including the rapidity of miosis after direct and indirect lighting on, and mydriasis after direct and indirect lighting off, simultaneously.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Hyogo College of Medicine. It was conducted from January 2015 to October 2015 using healthy volunteers, and patients in the emergency ICU of Hyogo College of Medicine Hospital, which is a 20-bed maximum care unit.

Study Subjects

The healthy volunteers were included in the study after informed consent was received from them. They were 20–91 years of age (47.3 ± 18.7 years). The number of individuals (25 total) included five in each age group (in their teens, twenties, thirties, forties, fifties, and over 60 years of age), and consisted of 15 males and 10 females. The healthy volunteer group had neither intracranial lesions nor eye lesions, except for eyesight drops although they did not check precise ophthalmologic examinations. All of volunteers did not have past history, comorbidity, and medication that affect neurological response including pupil light reflex.

The patients in our ICU were included in the study after informed consent was received from the patients or their legal guardians. Inclusion criteria included the existence of intracranial lesions located on only the left side, to avoid confusion in the analysis of the results. The exclusion criteria included the existence of eye lesions such as cataract except for eyesight drop, past history like as diabetes mellitus that influenced the speed of pupil light reflex, preexistent pupillary abnormalities, active malignant disease, a do-not resuscitate decision, and/or refusal of study inclusion by the patient or the guardian or consent given too late for study inclusion. There were five patients, consisting of three males and two females. The ages ranged from 48 to 89 years (74.0 ± 14.5 years). All the patients except one were not given medicine that affects pupil light reflex including propofol, midazolam, and fentanyl. The patient characteristics, which included age, sex, disease type, treatment regimen, Glasgow Coma Scale, Factors that affect neurological response including past history, comorbidity, and medication, sedative and analgesics, midline shift on head CT, and time to measure from onset of the disease, are shown in **Table 1**.

TABLE 1 | Patients' characteristics.

No	Age	Sex	Disease	Lesion side	Treatment regimen	Glasgow coma scale		Factors that affect neurological response			Sedative and analgesics	Midline shift on head CT	Time to measurement from onset
						Initial	Worst	Past history	Comorbidity	Medication			
1	75	F	Middle cerebral artery occlusion	Left	Thrombectomy	4 5 6	3 4 6	None	None	None	None	None	Day 2
2	86	M	Lobar hemorrhage	Left	Endoscopic drainage	4 5 6	4 5 6	None	DM	None	None	None	Day 2
3	72	M	Middle cerebral artery occlusion	Left	Thrombectomy	1 1 1	1 T 1	None	DM	None	Midazolam (10 mg /h)	None	Day 2
4	47	F	Middle cerebral artery occlusion	Left	Conservative treatment	1 2 4	1 T 4	None	None	None	Fentanyl citrate (0.037 μg/kg/min)	None	Day 2
5	89	M	Acute subdural hematoma	Left	Conservative treatment	3 5 5	3 5 5	None	None	None	None	None	Day 3

Measurement Mechanism of the Hitomiru® Pupilometer

The Hitomiru® pupilometer evaluated the pupils with video recordings, regardless of the state of consciousness. When the patients could not open their eyes with obeying to the order because of depressed level of consciousness, we opened their eyelids by ourselves. Visible light was utilized to estimate the reactivity to light and infrared wavelength, which did not stimulate pupil reactivity, was often utilized to measure and monitor the size or diameter of a pupil. The Hitomiru® pupilometer shined visible light onto one side of the pupil to induce miosis, and then used infrared light to measure and monitor the size or diameter of both pupils by using infrared short-range sensors. Infrared short-range sensors were also used to gauge the distance between the camera and pupil to compensate for the measured diameter of each pupil. The boundary of each pupil was detected automatically. The area of each pupil was estimated and expressed as the number of pixels. The diameter of each pupil was regarded as a straight line that passed through the center of the pupil. The diameter of the pupil was calculated using the numerical value of the diameter and the coefficient of the distance between the camera and pupil (**Figure 1**). One session consisted of one 10-s interval. The detailed protocol was as follows: (1) infrared light exposure to both pupils for 2 s, (2) visible light exposure to the right pupil for 2 s, (3) infrared light exposure to both pupils for 2 s, (4) visible light exposure to the left pupil for 2 s, and (5) infrared light exposure to both pupils for 2 s.

Study Protocols

We evaluated three parameters of the direct and indirect pupillary light reflex; the miosis rate (the minimum pupil diameter during light irradiation/the maximum pupil diameter before light irradiation), the miosis time (the time until minimum pupil diameter during light irradiation), and a mydriasis rate (the minimum pupil diameter during light irradiation/the maximum pupil diameter until 2 s after discontinuation of light irradiation, which was usually a pupil diameter at 2 s after discontinuation of light irradiation). The measurements were performed with the Hitomiru® pupilometer under room light using a fluorescent lamp with a mean illumination of 1,049–1,133 lux during the daytime.

Study 1

We measured the pupil diameter and the direct and indirect pupillary light reflex of the right and left pupils of 25 healthy adult volunteers. The right pupil diameter and direct and indirect pupillary light reflexes of the left pupils were determined.

Study 2

The same measurement procedures were performed on 25 healthy adult volunteers (the same volunteers of Study 1). The data were analyzed for correlations between the measurement data (pupil diameter, and direct and indirect pupillary light reflex) and age.

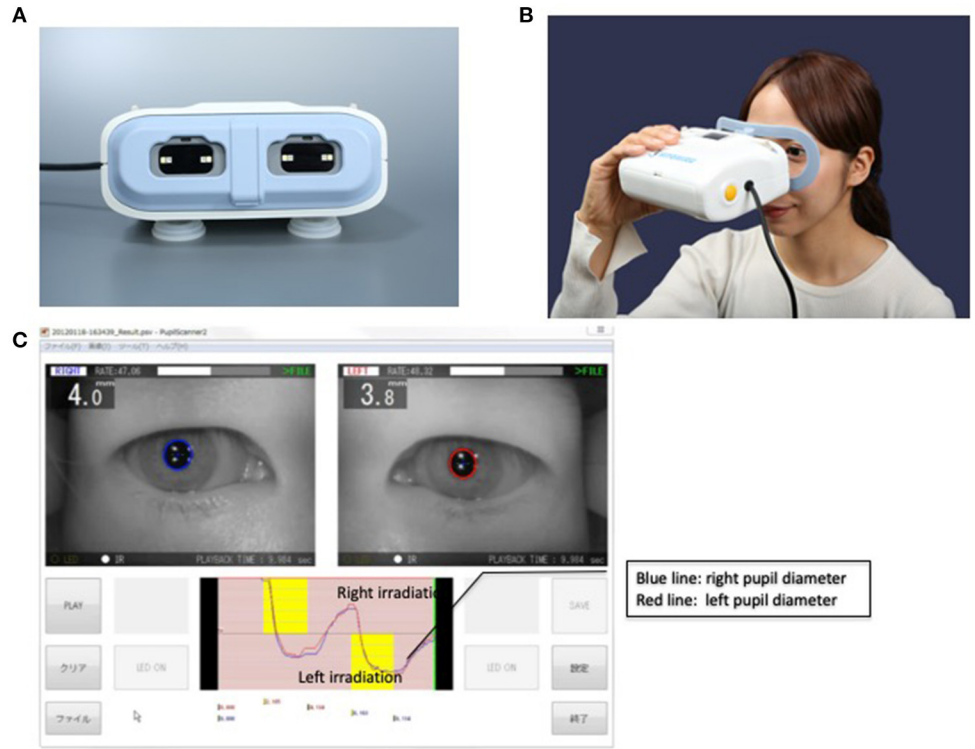

FIGURE 1 | The Hitomiru® pupillometer. **(A)** The shape of the Hitomiru® device is like a glass with light sources and a video camera which allows automatically captures the image of pupils. The captured data is sent to the computer, which is connected to the pupillometer, then the diameters are recorded and analyzed with included proprietary software. **(B)** The Hitomiru® pupillometer used on a volunteer. **(C)** Measurement screen of the device. In the upper image, the right and left pupil is captured with a blue and red circle, respectively. In the lower image, the blue and red line shows a right and left pupil diameter, respectively. The yellow zone in the upper and lower section of the graph shows the right and left eye irradiation, respectively. When the irradiation induces miosis, the lines go downward. Conversely, when the cessation of irradiation induces a mydriasis, the lines go upward.

Study 3

The same measurement procedures were used for the patients with intracranial lesions. The patients' pupil reflexes were measured when we obtained informed consent from the patients' family and these were Day 2 or Day 3.

The data were compared with that of the volunteer group (measurement of the pupil diameter and pupillary light reflex). For the purpose of integrating the average age of the volunteer group and the patient group, we choose five subjects who were over 60 years of age among the 25 volunteers. All data compared the five volunteers with five patients.

Statistical Analyses

Differences in continuous variables, including pupil diameter, miosis rate, miosis time, and mydriasis rate, between the two groups were compared using Student's *t*-test after first verifying the normal distribution of the data by the Shapiro–Wilk test; otherwise, the Mann–Whitney U-test was used. The associations between age and spontaneous pupil diameters, miosis rate, miosis time, and mydriasis rate in healthy volunteers were assessed with a correlation coefficient (r). All statistical analyses were performed using JMP® 9 software (SAS Institute Inc., Cary, NC, USA). The column scatter plots shown in **Figures 2–6** were generated using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA).

RESULTS

Study 1

The spontaneous pupil diameters were significantly smaller in the left eyes than the right eyes (**Figure 2**). However, there were no significant differences in miosis rates (**Figures 3A,B**), miosis times (**Figures 3C,D**), and/or mydriasis rates (**Figures 3E,F**) in both the right and left pupils between direct and indirect irradiation.

Study 2

There was a strong negative correlation between age and spontaneous pupil diameters (right: $r = -0.70$, $p < 0.001$ and left $r = -0.81$, $p < 0.001$: **Figure 4**). There was a moderate positive linear relationship between age and miosis rates in right eye irradiation (right, direct irradiation: $r = 0.40$, $p < 0.05$ and left, indirect irradiation: $r = 0.61$, $p < 0.01$, **Figure 5A**), but not in left eye irradiation (**Figure 5B**). As shown in **Figures 5C,D**, there were weak or negligible negative correlation between age and miosis time. There was a moderate positive correlation between

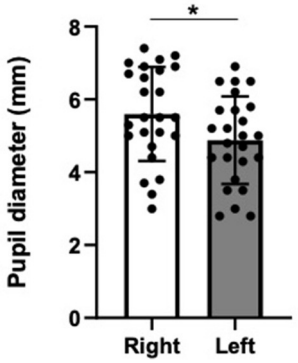

FIGURE 2 | Spontaneous pupil diameters without irradiation in healthy volunteers. Data are presented as the mean ± SD. Closed circles show data distribution. *$P < 0.05$. $N = 25$/group.

age and mydriasis rates in right eye irradiation (right, direct irradiation: $r = 0.67$, $p < 0.01$ and left, indirect irradiation: $r = 0.57$, $p < 0.01$, **Figure 5E**). Similar tendencies were observed in left eye irradiation (right, indirect irradiation: $r = 0.46$, $p < 0.05$ and left, direct irradiation: $r = 0.37$, $P = 0.07$, **Figure 5F**). These results suggest that the mydriasis after irradiation was easier or earlier in the older groups. This may be due to the pupil diameters were smaller with increased age.

Study 3

The average age was 74.0 ± 14.5 years old and 77.8 ± 10.0 years of age for the patient group and the volunteer group, respectively. The spontaneous pupil diameter without irradiation tended to be smaller in the left eye than in right eye in both the volunteer group and patient group (**Figure 2**), although this was not significant (**Figure 6**). There was no statistical difference in spontaneous pupil diameter between the volunteer group and the patient group in both the right and left eyes.

The miosis rate (**Figures 6B,C**), miosis time (**Figures 6D,E**), and mydriasis rate (**Figures 6F,G**) of the right and left pupils under right and left eye irradiation in the volunteer group and the patient group are shown in **Figure 6A**.

Miosis Rate

Under right eye irradiation (opposite side of the lesion in the patient group), the miosis rate of the right pupil (direct irradiation), and the left pupil (indirect irradiation) showed no significant difference between the volunteer group and the patient group. After left eye irradiation (side of lesion in the patient group), the miosis rate of the right pupil (indirect irradiation) also showed no difference between the volunteer group and the patient group. However, the miosis rate of the left pupil (direct irradiation) was significantly higher in the patient group than in the volunteer group, indicating that the pupil on the side of the lesion had more difficulty undergoing miosis.

Miosis Time

After right eye irradiation (opposite side of lesion in the patient group), the miosis time of the right pupil (direct irradiation) showed no difference between the volunteer group and the patient group. However, the miosis time of the left pupil (indirect irradiation) was significantly shorter in the patient group than in the volunteer group. After left eye irradiation (side of lesion in the patient group), the miosis time of the right pupil (indirect irradiation) showed no significant difference between the volunteer group and the patient group. However, the miosis time of the left pupil (direct irradiation) was significantly shorter in the patient group than in the volunteer group. These results indicated that the miosis response of the pupil on the side of the lesion in the patient group was quicker than that of the volunteer group, regardless of direct or indirect irradiation use.

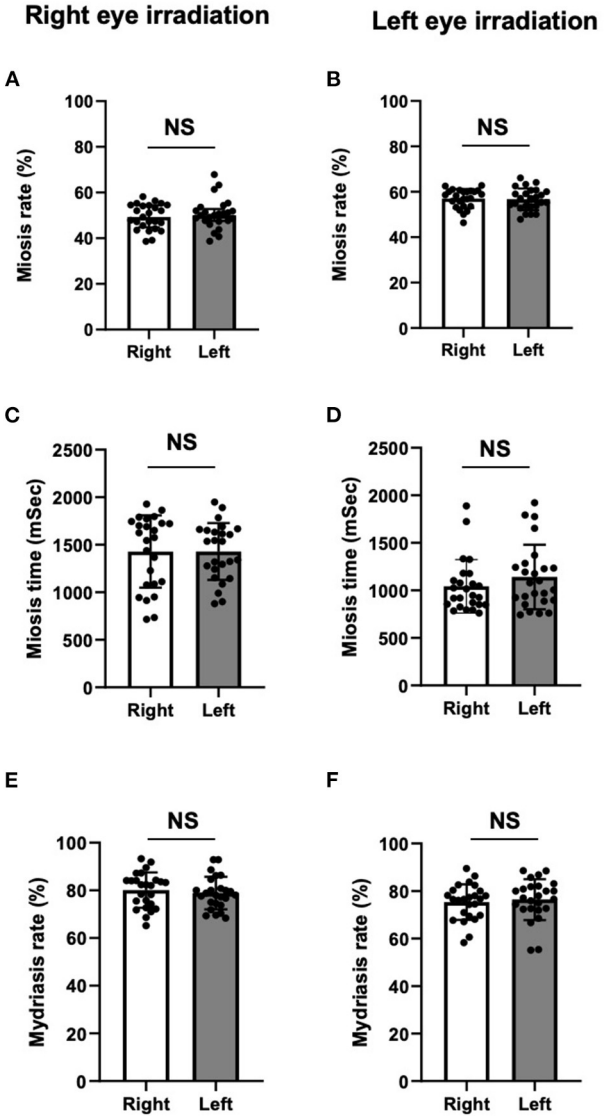

FIGURE 3 | Miosis rates **(A,B)**, miosis times **(C,D)**, and mydriasis rates **(E,F)** in healthy volunteers. There were no significant differences in miosis rate **(A,B)**, miosis time **(C,D)**, and mydriasis rate **(E,F)** in both right and left pupils between direct and indirect irradiation. For all panels, Data are presented as the mean ± SD. Closed circles show data distribution. NS, not significant. $N = 25$/group.

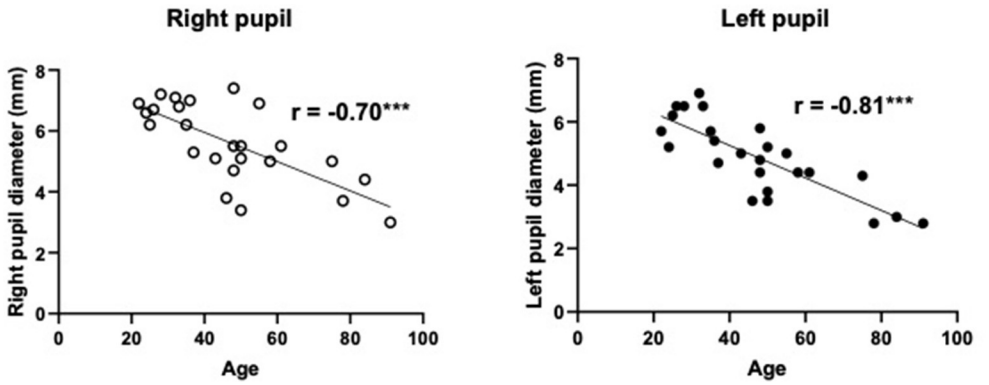

FIGURE 4 | The relationship between spontaneous pupil diameters and age in healthy volunteers. The pupil diameters were significantly smaller with increased age in both the right and left eyes. *r*, correlation coefficients. ***$P < 0.001$. $N = 25$/group.

Mydriasis Rate

After both right and left eye irradiation (both were on the opposite side of the lesion and lesion sites in the patient group), the mydriasis rates of both the right and left pupil (both direct and indirect irradiation) were significantly lower in the patient group than in the volunteer group, indicating that the mydriasis responses of the pupils on both the opposite and lesion site in the patient group were significantly more exaggerated than those in the volunteer group, irrespective of direct or indirect irradiation use.

DISCUSSION

The use of pupillometry has been limited by the lack of a uniform standard for assessment and the unavailability of easily obtained quantitative measurements of pupillary function (11). Although pupillometry has been accomplished with a penlight, variable factors, such as the amount of ambient light in the room, the observer's visual acuity, the distance of the penlight bulb from the patient's pupil, and the strength of the penlight batteries, could change the results of pupillometry measurements (1). Larson and Muhiudeen reported that routine clinical examinations performed with a penlight were unable to detect the presence of a pupillary light reflex when the light amplitude was <0.3 mm and the maximum constriction velocity was <1 mm/s (1). Several quantitative pupillometry devices have been developed since 1981, and a study using a quantitative pupilometer device has been reported (12). However, our study was novel, because the bilateral pupil diameter and pupillary light reflex were evaluated simultaneously and quantitatively using a mobile automatic pupillometer.

Regarding the anisocoria in healthy adults, Lam et al. reported that approximately 20% of normal adults had anisocoria of 0.4 mm or greater (13). They also reported that the number of adults with anisocoria increased with age, and anisocoria was seen in one-third of the normal adult group >60 years of age. In Study 1, the average age of the volunteers was younger than 60 years (47 years of age), and the healthy adults without intracranial lesions had anisocoria of approximately 0.7 mm. When we evaluated the anisocoria in the 27–39-year-old healthy volunteer group, many of them had anisocoria of approximately 0.5 mm. These results suggested that the anisocoria existed in healthy adults more than that previously reported (13). A literature search of the reason(s) why the right pupil diameter tended to be larger than the left one, however, found no studies.

Regarding miosis in healthy adults, it has been reported that the pupil diameter of the normal adult showed a miosis tendency that increased with age. This was called "Senile Miosis," and it was hypothesized that the autonomic nervous system participated in the process (14). Specifically, it was suggested that the parasympathetic nerve function changes with age. However, there was no report examining the relationship of mydriasis rate, time, and miosis rate after light irradiation with age or the laterality of these parameters. The results in Study 2 showed significant relationships between miosis rates and age, as well as the laterality of this tendency. This further suggests that with the right eye irradiation it was more difficult to induce miosis, and it was easier to induce pupil dilation, in both the direct and indirect pupillary light reflexes, with age. However, most of the results of left eye irradiation did not show significant differences. If age-related parasympathetic nerve superiority has an influence on the pupillary light reflex, it should become easy to undergo miosis and harder to dilate with age. However, the results were not in agreement with this hypothesis. Generally, it was shown that the autonomic nerve function decreases with age for a long time (15, 16). Hence, it was suggested that the results from Study 2 (becoming easy to undergo miosis and hard to dilate with age) were not due to age-related parasympathetic nerve superiority, but to decreased autonomic nerve function, because the results of Study 1 suggested that the pupillary light reflex showed less physiological changes. In addition, our results suggested that the direct/indirect pupillary light reflex had greater accuracy than the pupil diameter, because the light reflex data did not reflect the change of physiological characteristics.

To our knowledge, this study was the first to present data regarding the indirect pupillary right reflex of patients with intracranial lesions in an ICU (Study 3). When comparing the patient group with the volunteer group, the pupil diameter

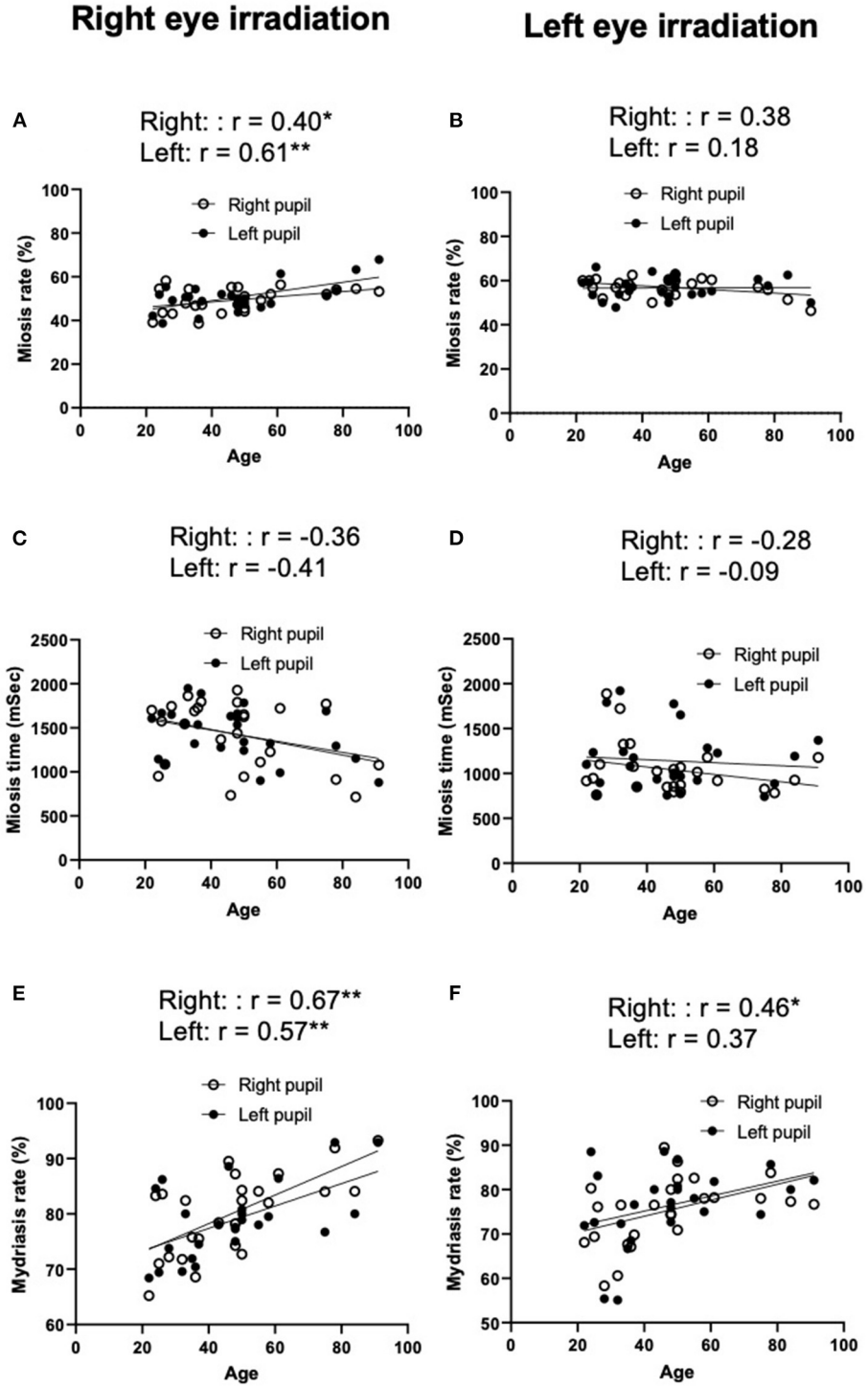

FIGURE 5 | Relationship between age and miosis rate **(A,B)**, miosis time **(C,D)**, and mydriasis rate **(E,F)** in healthy volunteers. *r*, correlation coefficients. $^{**}P < 0.01$, $^{*}P < 0.05$. $N = 25$/group.

did not show a significant difference between the volunteer group and the patient group in both the right and left eyes. However, the miosis times of the left pupils (i.e., the pupils on the side of the lesion) were significantly shorter in the patient group than in the volunteer group regardless of direct or indirect irradiation. One possible explanation may be following; in the patient group, the pupil diameters were smaller and the miosis rate of the left pupils were larger or tended to be larger

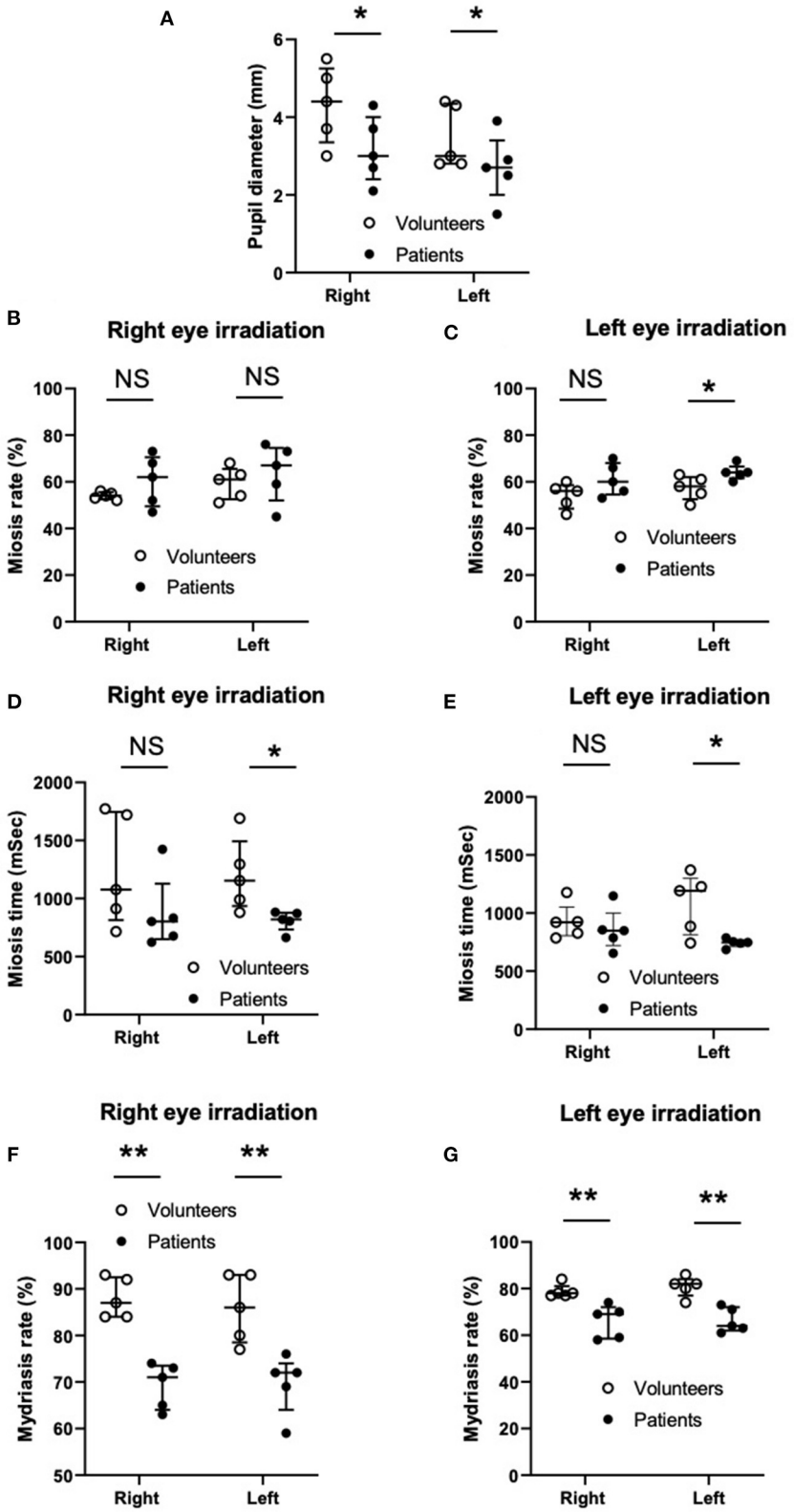

FIGURE 6 | Comparison of spontaneous pupil diameters **(A)**, miosis rate **(B,C)**, miosis time **(D,E)**, and mydriasis rate **(F,G)** between the volunteers and patients. Column scatter plots representing the data distribution (open and closed circles), median (horizontal bar), and interquartile range (vertical bar). NS, not significant. $^{**}P < 0.01$, $^{*}P < 0.05$. $N = 5$ in each group.

(direct light reflex shown in **Figure 6C**, indirect light reflex shown in **Figure 6B**, respectively) indicating that substantial miosis distances were shorter. However, the mechanism(s) by which these phenomena were seen in the pupils only on the lesion sites needs to be further investigated. Furthermore, the mydriasis rate in both the left and right pupils (i.e., the pupils on both the opposite side and the same side of the lesion) were significantly lower in the patient group than in the volunteer group, indicating that the pupils of both sides of the patient groups were more exaggerated, irrespective of direct or indirect irradiation. These results suggested that we may be able to provide more meaningful information with not only pupil diameter but also the miosis time and mydriasis rate under direct and indirect irradiation. However, these direct and indirect light reflexes and the relationship between the light reflexes and the state of the disease need to be further investigated. The Hitomiru® pupillometer is a novel, more convenient and useful device to measure pupil responses under indirect and indirect irradiation simultaneously, with digitally recorded results leading to faster measurement and accurate and objective assessments. In addition, because the instrument is a mobile type pupilometer, it can be easily transported to anywhere such as an ICU, emergency room, and pre-hospital care field.

Our study had several limitations. The time interval from the first measurement (light irradiation for the right side) to the next measurement (light irradiation for the left side) was only 2 s. The pupil diameters in many subjects may not return to baseline during the 2-s time interval just before the beginning of left eye irradiation. Therefore, the results of the left eye irradiation should be different from the results obtained when the time interval is longer than 2 s or when the left eye irradiation is done first. Second, although we selected patients with intracranial lesions on only the left side, the type of disease, onset, and severity varied. Third, volunteers did not check precise ophthalmologic examinations before starting this experiment even though they had neither intracranial lesions nor eye lesions based on the hearing investigation. Fourth, mydriasis rates of left pupils at the end of 2-s visible light off after right eye irradiation, which was the beginning of left eye irradiation, were $<100\%$ in both volunteers and patients, indicating that 2-s interval was not enough for the pupils to return to the baseline. This might affect the measurements during left eye irradiation. Finally, because we only examined Japanese patients, these findings may not translate to patients of other ethnicities or races.

In conclusion, our studies showed that healthy adults may have approximately 0.5 mm anisocoria, miosis was harder, and mydriasis was easier with increased age, and there were differences in miosis rates, miosis times, and mydriasis rates between the healthy adult and the patient groups with intracranial lesions under both direct irradiation and indirect irradiation. The Hitomiru® pupillometer, a newly developed instrument used to measure pupil responses under direct and indirect irradiation, simultaneously and digitally recorded the data, and could be a useful device to further investigate the relationship between pupil reflexes and the state of intracranial diseases.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of Hyogo College of Medicine. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JK: direction of the study and editing the manuscript. HN: practice of the study. IY, AM, and NM: acquisition and analysis of data for the work. YO: substantial contributions to the conception or design of the work and analysis and interpretation of data for the work. All authors contributed to the article and approved the submitted version.

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Effect of Dynamic Circuit Pressures Monitoring on the Lifespan of Extracorporeal Circuit and the Efficiency of Solute Removal During Continuous Renal Replacement Therapy

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Objective: To observe the effects of dynamic pressure monitoring on the lifespan of the extracorporeal circuit and the efficiency of solute removal during continuous renal replacement therapy (CRRT).

Materials and Methods: A prospective observational study was performed at the West China Hospital of Sichuan University in the ICU. Analyses of the downloaded pressure data recorded by CRRT machines and the solute removal efficiencies, calculated by 2*Ce/(Cpre+Cpost), where Ce, Cpre, and Cpost are the concentrations of the effluent, pre-filter blood, and post-filter blood, respectively, were performed. Samples were collected at 0, 2, 6, 12, and 24 h when continuous veno-venous hemodiafiltration (CVVHDF) was used after the initiation of CRRT. Measurements in concentrations of creatinine, blood urea nitrogen, and β2-microglobulin in the plasma and effluent were recorded.

Results: Extracorporeal circuits characterized by moderate-to-severe (M–S) access outflow dysfunction (AOD) events, defined as access outflow pressure less than or equal to −200 mmHg for more than 5 min, had shorter median lifespans with no anticoagulation (32.3 vs. 10.90 h, $P = 0.001$) compared with the no M–S AOD events group. The significant outcome also existed in regional citrate anticoagulation (RCA) (72 vs. 42.47 h, $P = 0.02$). Moreover, Cox regression analysis revealed that the lack of M–S AOD events, RCA, or CVVHDF independently prolonged the circuit lifespan. All tested solutes removal efficiencies started to decline at 12 h. Furthermore, efficiencies of all solutes removal dropped obviously at 24 h when TMP $\geq$ 150 mmHg.

Conclusion: RCA and CVVHDF predicted a longer circuit lifespan. M–S AOD events were associated with a shorter circuit lifespan when RCA or no anticoagulant was used. Replacement of extracorporeal circuit could be considered when running time of filter lasted up to 24 h with TMP $\geq$ 150 mmHg.

Keywords: continuous renal replacement therapy, circuit pressures, extracorporeal circuit failure, access outflow dysfunction, solute removal efficiency

INTRODUCTION

Continuous renal replacement therapy (CRRT) slowly and effectively removes water and solutes from critically ill patients (1). Prolonging the lifespan of CRRT circuits is fundamental for better use of the extracorporeal circuit. The extracorporeal circuit, which is the key part of CRRT, consists of a vascular access outflow lumen, pre-filter tubing, a filter, post-filter tubing, an air-trap chamber, pre-vascular inflow tubing, and a vascular access inflow lumen. Frequent clotting in the extracorporeal circuit may lead to blood loss, shorter effective treatment times, and increased medical costs (2). Many factors might influence circuit survival, including anticoagulation, vascular access, CRRT treatment parameters (e.g., modality, filter membrane, blood flow rate), hematocrit, and blood coagulation (3–9). However, the mechanisms of extracorporeal circuit failure (ECF) are still not clear.

In the past, pressure data were obtained by manual recording every hour. With developments in science and technology, mainstream CRRT machines can continuously record changes in pressure, such as access outflow pressure (AOP), pre-filter pressure (PFP), effluent pressure (EP), and return inflow pressure (RIP), every minute during therapy and store the data on internal storage. A few trials have investigated the pressure changes during CRRT (10, 11), and stored pressures data can be downloaded into an Excel spreadsheet to obtain the detailed pressure data and the precise circuit lifespan (12).

Continuous renal replacement therapy removes waste and maintains the electrolyte and acid–base balance via various techniques, so it is logical to believe that the removal efficiencies of diverse sizes of solutes are different due to their distinct characteristics and removal methods. Previous studies that focused on solute removal predominantly focused on modality and pre-/post-dilution. Many influencing factors remain unknown. In addition, no trials have investigated the relationship between dynamic pressure monitoring and solute removal efficiency hindered by the extraction method. We hypothesized that continuous pressure changes during CRRT affect the extracorporeal circuit lifespan and solute removal efficiency.

MATERIALS AND METHODS

Study Design

This prospective, observational, cohort study was performed in the ICU of the West China Hospital of Sichuan University, Chengdu China. The data were recorded from October 2018 to December 2019. The study was approved by the Institutional Review Board of West China Hospital, Sichuan University (2017-06). Informed consent was obtained from the patient or a responsible surrogate.

Study Population

A total of 395 episodes of CRRT in 131 patients were included. These episodes represented 16,244.1 h of treatment. Eligibility criteria included patients age 18 years or greater who had received at least one episode of CRRT with CVVHDF or continuous veno-venous hemofiltration (CVVH) modality in the ICU. All circuits had been provided using a Prismaflex machine (Baxter, United States), because this device is the main equipment in hospitals for CRRT. Patients were excluded if using other blood purification therapies, such as plasma exchange. CRRT circuits that were side arms of an extracorporeal membrane oxygenation circuit were also excluded.

CRRT Protocol

The choice of anticoagulant is determined by the clinical situation. RCA was the first option when there were no contraindications (e.g., severe acidosis, liver failure, severe hypoxemia) against the use of it in this center with low-molecular weight heparin (LMWH) or no anticoagulant as the alternative. Meanwhile, LMWH is preferred for anticoagulation in patients with existing diseases (such as thrombosis) needing heparin. No anticoagulant use should be considered in patients at high risk of bleeding and with contraindications of citrate. For all the patients, double-lumen venous catheters were used for vascular access. All femoral vascular access was achieved via 13-Fr dual-lumen catheters (Baxter, United States), and jugular access was achieved via 11.5-Fr catheters (Baxter, United States). The blood rate was maintained at 150–200 mL/min. CVVH was performed in the pre-dilution mode. CVVHDF was performed in the post-dilution mode, and the ratio of dialysate to replacement fluid was 1:1. The replacement fluid used was the standard bicarbonate-based solution (QINGSHAN LIKANG, China); details of the components are presented in the **Supplementary Material**. Extracorporeal circuit cessation occurred when the extracorporeal circuit clotted or clotting. Meanwhile, the circuit reaching the maximum recommended use (72 h) should also be changed. A total of 395 episodes of CRT in 131 patients were included. These episodes represented 16,244.1 h of treatment. Eligibility criteria included patients of age 18 years or greater who had received at least one machine-recorded episode of CRRT and used CVVHDF or CVVH. All circuits had been provided using a Prismaflex machine (Baxter, United States) with the AN69 ST150 filter (Baxter, United States). Patients were excluded if using other blood purification therapies, such as plasma exchange, or if CRRT circuits that were side arms of an extracorporeal membrane oxygenation circuit were used.

Measurement of Pressure Dynamics in the Extracorporeal Circuit

The methods used to extract, store, and analyze the continuous pressure data were similar to those described in a previous publication (12). The pressure variables included minute access outflow pressure (AOP), effluent pressure (EP), pre-filter pressure (PFP), and return inflow pressure (RIP) from relevant circuit points. Transmembrane pressure (TMP), corresponding to the pressure of the filter membrane, was calculated from these data using the equation: $TMP = (PFP + RIP)/2 - EP$. Access outflow dysfunction (AOD) was defined as an AOP −200 mmHg according to a previous study (10). We defined three types of AOD events on the basis of total minutes of AOD: mild ($\leq$5 min), moderate (5 min $<$ timing $\leq$ 60 min), and severe (time $>$ 60 min).

Sample Collection in the Extracorporeal Circuit During CRRT and Measurement

Samples (blood and effluent) were obtained at 2, 6, 12, and 24 h when CRRT was used in the post-dilution CVVHDF modality. The concentrations of blood urea nitrogen (BUN), creatinine (Cr), and β2-microglobulin in the plasma and effluent were measured in the clinical laboratory of West China Hospital of Sichuan University. Solute removal efficiency = 2*Ce/(Cpre+Cpost), where Ce, Cpre, and Cpost are the concentrations of the effluent, blood pre-filter, and post-filter, respectively. The data of solute removal efficiency were matched with the accurate pressures data at the same timepoint.

Collection of Characteristics

Baseline patient demographics, including gender, age, diagnosis, weight, and height were established from existing hospital databases. Laboratory parameters and the sequential organ failure assessment (SOFA) score (13) before initiation of every episode of CRRT were conducted, including hemoglobin, platelets, prothrombin time (PT), indexed normalized ratio (INR), and activated partial thromboplastin time (APTT). If no blood test was realized at the start of the circuit, the closest blood test realized was considered. We collected the following CRRT treatment characteristics, including blood flow, dose, anticoagulation, modality, vascular access site, circuit survival, and the reason for extracorporeal circuit change as reported in the ICU charting system.

Statistical Methods

Continuous variables were expressed as mean with standard deviation if normally distributed, or median with interquartile range (IQR) if non-normally distributed. Categorical variables are reported as count with percentage. Variability of pressures was defined as the standard deviation for all pressures. Comparisons of data from groups were analyzed using the one-way analysis of variance, Mann–Whitney-test, Chi-square test, or Fisher's test. Variables associated with extracorporeal circuit lifespan were analyzed using the Cox regression model. A p-value <0.05 was considered to be statistically significant. Data were analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL, United States). **Figures 3**, **4** were drawn by Graphpad prism version 7.0 (Graphpad, United States).

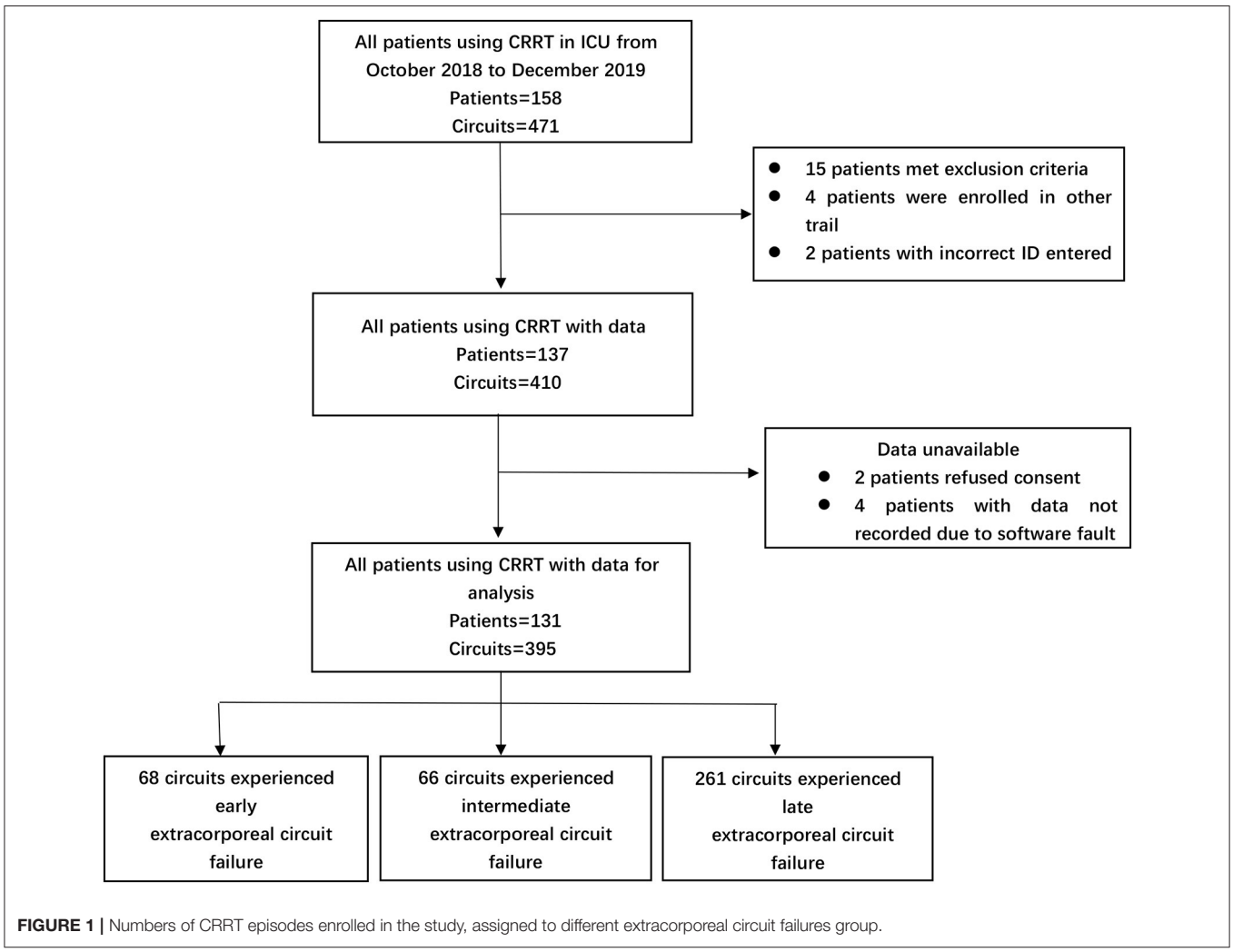

FIGURE 1 | Numbers of CRRT episodes enrolled in the study, assigned to different extracorporeal circuit failures group.

RESULTS

Patients and Extracorporeal Circuits

A total of 395 episodes (**Figure 1**) in 131 patients, accounting for 16,244.1 h of effective treatment time, were included in the study. Over the course of our study, 96 cases (24.3%) were electively ended (i.e., the circuit had been used for 72 h). Clotting of the filter or air-trap chamber occurred in 299 cases (75.7%). The median lifespan of the extracorporeal circuit was 39.7 h. For anticoagulation, RAC was the primary choice (48.6%), followed by no anticoagulation (31.1%), and LMWH (20.3%). In the cluster of modality, the proportion of CVVHDF was 81.3%, and CVVH was 18.7%. The average prescribed dose of CRRT was 31.3 ± 3.2 ml/kg/h. The dominant access site was the femoral vein (368 circuits, 93.2%) with the remaining 27 circuits (6.8%) via a jugular vein. Two hundred twenty-seven circuits used the right side femoral vein as access and 141 circuits used the left side femoral vein. The details are reported in **Tables 1a,b**.

Dynamic Pressure Changes During CRRT With Different Extracorporeal Circuit Failures

For further analysis, according to the circuit lifespan we defined three types of ECFs (10), including early (≤12 h), intermediate (>12 h, ≤24 h), and late (>24 h). The median circuit life of these circuits was 7.0 h (IQR, 5.86–9.53 h) in the early ECFs group compared with 16.70 h (IQR, 13.97–20.60 h) in the intermediate group and 60.98 h (IQR, 39.78–72 h) in the late group. Overall, 134 circuits (33.9%) experienced early-intermediate failure, and 261 circuits (66.1%) experienced late failure. The mean changes in the AOP, PFP, EP, RIP, and TMP data were completely distinct in the different groups. The dynamic mean pressure curve graphs are shown in **Figure 2**. The negative value of AOP was smallest in the early group (−62.87 ± 2.31 mmHg), which was 23.5 and 4.87 mmHg lower than that in the late and intermediate groups, respectively. The overall changes in the PFP were also varied among the different types of ECFs: the mean value in the early, intermediate, and late groups were 133.43 ± 21.95, 150.47 ± 28.09, and 104.92 ± 3.89 mmHg, respectively. About EPs, the intermediate group had the smallest value of mean extracorporeal circuit data, followed by the late and early groups. In data of RIPs, the lowest and highest mean values were 46.38 ± 1.11 and 61.22 ± 7.74 mmHg in the late group and the intermediate group, respectively. In the curve graph of TMP, the line in the early and intermediate groups increased rapidly, with mean data of 98.12 ± 34.48 and 120.15 ± 38.891 mmHg, respectively. Moreover, the variability of the late groups was statistically smaller than that compared to the other groups ($P < 0.05$) in all totally different extracorporeal circuit pressure cluster (AOP, PFP, EP, RIP, TMP). The detailed variability data are shown in **Table 2**.

Access Outflow Dysfunction Events Under Different Anticoagulants

A total of 225 circuits experienced at least one AOD episode, and no significant difference was found (38.81 vs.40.38 h, $P = 0.66$) in the median lifespan of the circuits in which no AOD event occurred. However, the median circuits survival without M–S AOD events were associated with a longer circuit lifespan (42.50 vs. 17.14 h, $P = 0.001$). About anticoagulation, the median circuit survival for the filter using RCA was significantly longer compared with non-RCA [RCA (69.41 h: IQR, 37.29–72) vs.

TABLE 1a | Demographics, clinical characteristics, and the extracorporeal circuit.

Age (years)	56.7 ± 14.0
Gender (male/female)	86/45
SOFA score	14 ± 2
Diagnosis	
Respiratory disease	33
Cardiovascular disease	30
Digestive diseases	43
Neurological disorders	5
Sepsis	20
Episodes of CRRT	395
Reason for changing extracorporeal circuit	
Clotting or clotted of extracorporeal circuit	299 (75.7%)
Elective circuit change	96 (24.3%)
CRRT prescription	
CVVH	74 (18.7%)
CVVHDF	321 (81.3%)
Dose of CRRT (ml/kg/h)	31.4 ± 3.1
Flow of blood (mL/min)	180.3 ± 10.1
Laboratory data before the initiation of every episode of CRRT	
Hemoglobin (g/L)	85.0 ± 19.0
Platelet (*10^9/L)	113.0 ± 89.4
PT, s	18.0 ± 7.42
INR	1.5 ± 0.6
APTT, s	45.1 ± 21.7

SOFA, the sequential organ failure assessment; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration.

TABLE 1b | Lifespan of extracorporeal circuit in different groups.

Variable	Circuits	Circuit life (h)
All circuits	395	39.7 (6.91–72)
Anticoagulation		
Low molecular weight heparin	80 20.3%)	16.7 (8.5–33.0)
Regional citrate anticoagulation	192 (48.6%)	69.33 (37.29–72)
No anticoagulation	123 (31.3%)	29.42 (14.05–44.3)
Vascular access		
Internal jugular	27 (6.8%)	57.28 (33.73–72)
Right femoral	227 (57.4%)	33.43 (15.7–71.87)
Left femoral	141 (35.8%)	43.63 (18.55–72)
Classification of extracorporeal circuit failure		
Early	58 (14.7%)	7.0 (5.86–9.53)
Intermediate	76 (19.2%)	16.70 (13.97–20.60)
Late	261 (66.1%)	60.98 (39.78–72)

First column expressed as absolute numbers, parentheses denote percentage of total. Second column expressed as median (interquartile range).

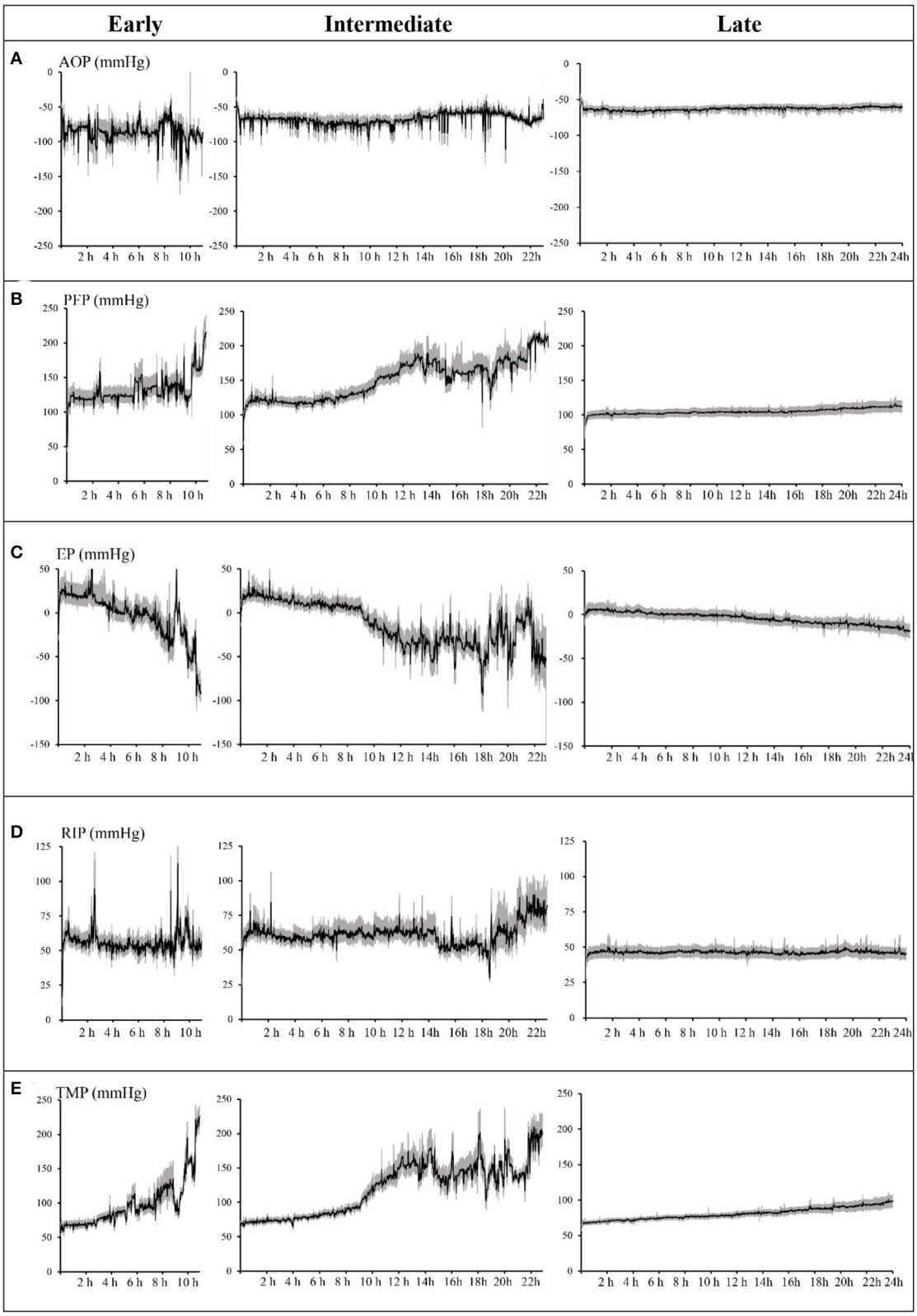

FIGURE 2 | Dynamic mean pressure curve of every minute over time by early, intermediate, and late extracorporeal circuit failures. **(A)** Access outflow pressure (AOP). **(B)** Pre-filter pressure (PFP). **(C)** Effluent pressure (EP). **(D)** Return inflow pressure (RIP). **(E)** Transmembrane pressure (TMP). Shaded areas = 95% confidence of the mean. Lifespan of the early group ended at 11 h, the intermediate group ended at 23 h, and the late group ended at 24 h. AOP, PFP, EP, RIP, and TMP are the average values of each pressure minute.

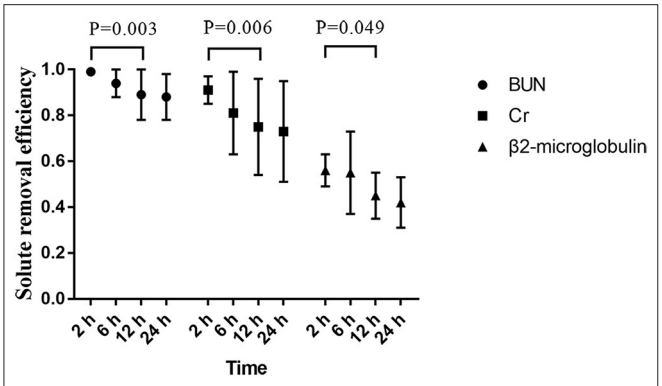

FIGURE 3 | Solute removal efficiency at different times.

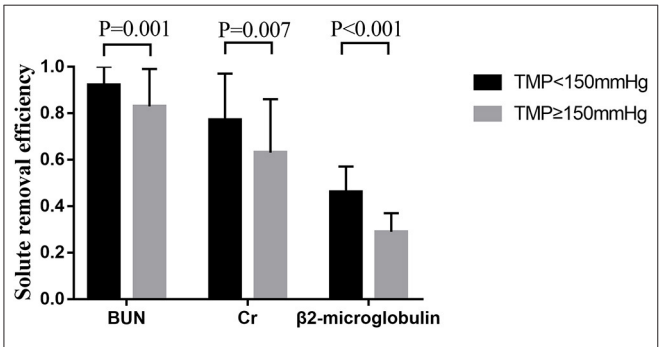

FIGURE 4 | Solute removal efficiency in different TMPs groups at 24 h.

TABLE 2 | Pressure data of different extracorporeal circuit failures.

Pressure (mmHg)	Early ECF	Intermediate ECF	Late ECF
AOP	−86.37 ± 13.03	−67.69 ± 8.20	−62.87 ± 2.31
AOP variability	37.73 ± 23.28	20.31 ± 14.33	13.79 ± 10.21
PFP	133.43 ± 21.95	150.47 ± 28.09	104.91 ± 3.89
PFP variability	32.86 ± 12.33	37.89 ± 15.20	12.67 ± 8.12
EP	−3.52 ± 26.07	−13.49 ± 25.03	−4.30 ± 6.44
EP variability	26.05 ± 13.73	37.04 ± 15.60	15.91 ± 9.81
RIP	55.82 ± 7.25	61.22 ± 7.74	46.37 ± 1.11
RIP variability	14.88 ± 8.39	15.53 ± 9.14	9.97 ± 5.99
TMP	98.12 ± 34.48	120.15 ± 38.89	80.79 ± 8.11
TMP variability	32.40 ± 16.12	46.40 ± 20.75	14.38 ± 11.64

ECF, extracorporeal circuit failure; AOP, access outflow pressure; PFP, pre-filter pressure; EP, effluent pressure; RIP, pre-filter pressure; TMP, transmembrane pressure.

LWMH (16.7 h: IQR, 8.5–33.0) vs. none (29.42 h: IQR, 14.05–44.3, $P < 0.05$)]. Moreover, the effects of the interaction of anticoagulant and M–S AOD events on circuit survival were distinct. When no anticoagulant was used, the median lifespan of circuits without M–S AOD events was significantly prolonged compared with M–S occurred (32.3 h: IQR, 16.79–44.78 vs.10.90 h: IQR, 6.23–19.19, $P = 0.001$). The same effect existed while using RCA (72 h: IQR, 39.67–72 vs. 42.47 h: IQR, 19.79–68.13, $P = 0.02$). However, the effect of M–S AOD events on circuit survival disappeared with LMWH (11.80 h: IQR, 6.23–22.24 vs.11.27 h: IQR, 6.97–19.24, $P = 0.61$).

TABLE 3 | Comparisons between the early-to-intermediate and late ECF groups.

	Early-to-intermediate ECF, $N = 134$	Late ECF, $N = 261$	*P*-value
With AOD	83 (61.9%)	142 (54.4%)	0.22
With mild AOD	54 (40.3%)	121 (46.4%)	0.34
With M-S AOD	30 (22.4%)	21 (8.0%)	<0.001
Hemoglobin	82.67 ± 18.04	86.23 ± 19.40	0.17
Platelet (*10^9/L)	133.46 ± 84.86	102.67 ± 90.11	0.01
PT, s	16.93 ± 6.07	17.85 ± 14.42	0.58
INR	1.54 ± 0.54	1.51 ± 0.74	0.73
APTT, s	41.48 ± 19.26	45.55 ± 24.40	0.20
Modality (CVVHDF)	85 (63.4%)	236 (90.4%)	<0.001
Vascular access (femoral)	129 (96.3%)	239 (91.6%)	0.14
Location of femoral vein (right)	79 (61.2%)	132 (55.4%)	0.38

AOD, access outflow dysfunction; M-S AOD, moderate-severe access outflow dysfunction; PT, prothrombin time; INR, international normalized index; APTT, activated partial thromboplastin time; CVVHDF, continuous veno-venous hemodiafiltration.

Risk Factors of Circuit Survival for First Circuit, Subsequent Circuits, and All Circuits

Comparison between the early-intermediate and the late groups revealed that M–S AOD episodes (22.4 vs. 8.0%, $P < 0.001$), platelet level (102.67 ± 90.11 vs. 133.46 ± 84.86 *10^9/l, $P = 0.011$), and CVVHDF modality (90.4 vs. 63.4%, $P < 0.001$) were different. However, mild AOD events, hemoglobin, PT, INR, APTT, and vascular access were not different between these two groups (**Table 3**). For the first circuit from each patient, there were 131 circuits for analysis. The study revealed that CRRT with the use of RCA was more likely to prolong circuit survival compared with use of no anticoagulant [HR, 0.44 (0.25–0.79), $P = 0.006$]. CVVHDF [HR, 0.38 (0.20–0.74), $P = 0.004$] was associated with longer circuit lifespan. Meanwhile, M–S AOD event [HR, 3.80 (1.50–9.62), $P = 0.005$] was highly in connection with ECF. Excluding the first filter, for subsequent circuits to analyze, no M-S AOD event, RCA, and CVVHDF were still intensively associated with longer lifespan of extracorporeal circuit. However, higher hemoglobin was slightly associated with longer circuit survival [HR, 0.91 (0.84–0.97), $P = 0.006$]. The analysis involved all circuits that showed no M–S AOD event, RAC, CVVHDF, lower platelets levels, higher hemoglobin were independently associated with longer circuit lifespan (detailed data shown in **Table 4**). In summary, no M–S AOD even t, RAC, and CVVHDF remained associated with greater circuit survival.

TABLE 4 | Cox regression analysis of variables associated with shorter circuit survival.

Variables	First circuit		Subsequent circuits		All circuits	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
AOD	0.92 (0.53–1.61)	0.76	0.99 (0.71–1.40)	0.96	0.95 (0.72–1.27)	0.75
Moderate-severe AOD	3.79 (1.5–9.62)	0.005	1.66 (1.10–2.55)	0.02	1.88 (1.28–2.74)	0.001
Anticoagulation (relative to none)						
Regional citrate anticoagulation	0.44 (0.25–0.79)	0.006	0.41 (0.27–0.62)	<0.001	0.42 (0.30–0.58)	<0.001
LWMH	1.35 (0.68–2.67)	0.39	1.34 (0.86–2.08)	0.20	1.30 (0.90–1.88)	0.17
CVVHDF	0.38 (0.20–0.74)	0.004	0.47 (0.29–0.74)	0.001	050 (0.34–0.72)	<0.001
Platelets (per 100 G/L increase)	1.09 (0.80–1.50)	0.58	1.11 (0.97–1.28)	0.13	1.13 (1.0–1.28)	0.048
Hemoglobin (per 10 g/L increase)	0.99 (0.90–1.08)	0.75	0.91 (0.84–0.97)	0.006	0.94 (0.90–0.99)	0.02

AOD, access outflow dysfunction; LWMH, Low molecular weight heparin; CVVHDF, continuous veno-venous hemodiafiltration; HR, hazards ratio.

Solute Removal Efficiency and Dynamic Pressure Changes

The removal efficiency of middle-molecular solute (β_2-microglobulin) was significantly lower than that of BUN and creatinine at different time points during CRRT. All efficiencies of tested solutes removal (BUN, creatinine, and β2-microglobulin) dropped gradually with operation time prolonged (**Figure 3**). According to the precise TMP data which was matched with sample collection time, groups of TMP data were clustered into four (TMP $<$ 100 mmHg, 100 $\leq$ TMP $<$ 150 mmHg, 150 $\leq$ TMP $<$ 200 mmHg, TMP $\geq$ 200 mmHg), details presented in the **Supplementary Material**. In the comparison of different TMPs, two groups were formed: TMP $<$ 150 mmHg and TMP $\geq$ 150 mmHg. The solute removal efficiency in the lower TMP group showed a greater clearance ability than that in the higher TMP group. Moreover, this phenomenon significantly occurred between the TMP $<$ 150 mmHg and TMP $\geq$ 150 mmHg group for BUN (0.92 ± 0.10 vs. 0.83 ± 0.16, $P = 0.001$), creatinine (0.77 ± 0.20 vs. 0.63 ± 0.23, $P = 0.007$), and β2-microglobulin (0.46 ± 0.11 vs. 0.29 ± 0.08, $P < 0.001$) at 24 h (**Figure 4**).

DISCUSSION

Main Findings

We analyzed continuous pressure data from CRRT and found that, after classifying the different types of circuit failures, M–S AOD was associated with a shorter lifespan of extracorporeal circuit compared to mild dysfunction. Moreover, when anticoagulation was performed with citrate or when anticoagulation was not performed, M–S was associated with shorter circuit survival compared to that observed when LMWH was used. We found that the use of CVVHDF and citrate and the absence of M–S AOD events prolonged the lifespan of the extracorporeal circuit. Our study demonstrated a distinct downtrend in small-molecule and middle-molecular solutes in removal efficiency under different anticoagulation modalities. Solutes removal efficiency declined significantly at 24 h or TMP $\geq$ 150 mmHg. Meanwhile, removal efficiency declined when circuit survival up to 24 h while TMP $\geq$ 150 mmHg compared with those in TMP $<$ 150 mmHg at 24 h.

Relationship to Previous Studies

Lifespan of Extracorporeal Circuit

Recently published studies (3, 4) suggested that RCA was superior to heparin for circuit survival and anticoagulation-related bleeding risk. However, the lifespan of the extracorporeal circuit still varied greatly in studies despite whatever anticoagulant was applied. A multicenter, randomized controlled study (14) of 174 patients compared circuit survival when different anticoagulants were used, namely, citrate and heparin, during CRRT. The lifespan of the two groups was 37.5 ± 23 h and 26.1 ± 19 h, respectively. The standard deviation confirmed the variability in circuit survival. Brain et al. (9) reported a meta-analysis about non-anticoagulant factors (such as vascular access, dialysis membrane, and modality) on the lifespan of the extracorporeal circuit, but the value of this article decreased because most of the studies were observational or reported circuit factors in sub-analysis. Factors influencing the lifespan of the extracorporeal circuit are not exactly definite, so further studies are needed. AOP is a major concern in circuit pressures monitoring on the lifespan of the extracorporeal circuit. AOP is measured between the catheter and the blood pump. Since the inner blood is sucked by the extracorporeal circuit, the AOP is generally negative and < -50 mmHg (15). A recently published observational study (10) was the first study to acquire continuous pressure data accurately during CRRT, and these pressures accurately reflect the real state of each part of the extracorporeal circuit. This study suggested that an AOP ≤ -200 mmHg could be considered a dysfunction, and AOD events can shorten the survival of the extracorporeal circuit. The study still had some limitations, such as the inclusion of a narrow population (most were post-operative patients) and the lack of RCA data. A recent retrospective study (11) suggested that the occurrence of an AOD event within 4 h after the initiation of CRRT significantly reduced the lifespan of the extracorporeal circuit by 12.9 h compared with the absence of an AOD event. COX analysis of two studies (10, 11) suggested that AOD events were independent risk factors for circuit survival, which indicates that AOP status warrants concern.

AOD events are quite common in the clinic, and these events are an indirect indicator of the quality and function

of the vascular access. Several causes of AOD were proposed: 1. The patient's body position may change frequently due to the needs of nursing or other therapy. The catheter may be suddenly bent or folded, which results in a sharp decrease in AOP and an extremely negative value. This interference is the most common reason for an AOD event in the clinic (16, 17). 2. The formation of thrombus or fibrous sheath in the lumen of a catheter or the collapse or thrombosis of the central vein where the catheter was placed may cause an AOD event. 3. Blood flow exceeding the maximum allowable range of the double-lumen catheter (>350 or 400 ml/min) may also cause an AOD event. The occurrence of M–S AOD events should be avoided as much as possible. The results of our study suggested that short-term AOD is not enough to affect the lifespan of the extracorporeal circuit. Only AOD that lasted a sustainable time (≥5 min), such as an M–S AOD event, affected the extracorporeal circuit, especially circuits with citrate and no anticoagulation. Notably, this phenomenon did not indicate that heparin were superior to RCA and no anticoagulation but only indicated that M–S AOD events should be a concern. The possible explanation for this result is that different anticoagulants play distinct roles. Citrate prevents coagulation by complexing ionized calcium in the extracorporeal circuit. The part entering the human body is metabolized from one molecule of citrate into three molecules of bicarbonate in the mitochondria of the liver, skeletal muscle, and kidney (18). Notably, complexed calcium is released, and lost calcium is supplemented in post-filter. Therefore, citrate is an ideal regional anticoagulant that effectively maintains an anticoagulation effect in the extracorporeal circuit and avoids bleeding in the body. LMWH exerts systemic anticoagulant effects by enhancing antithrombin III activity and inhibiting thrombin (factor IIa) and factor Xa. The pharmacokinetics are complex. Therefore, the variability in the high risk of bleeding individuals is a disadvantage. In addition, COX analysis showed that M–S AOD events were a risk factor for circuit survival.

Solute Removal Efficiency

The use of RCA has been verified to prolong the circuit survival and avoid a system "shutdown" because of the early clotting of the circuit. Nevertheless, a decrease in solute clearance occurs even if the extracorporeal circuit functions properly. From now on when we should replace the extracorporeal circuit accurately is a mystery and even the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines do not have a suggestion about that point, and how and when do solute removal efficiency decay are still indeterminate. Therefore, it is very valuable to find an indicator to determine whether to replace the extracorporeal circuit. Clogging of hemofilter membranes and clotting of the circuit are associated with the rise in TMP (15). Compared with other pressures data, TMP is particularly important in the study of solute removal efficiency. The relationship between TMPs and solute removal efficiency has not been investigated. Previous trials have studied the effects of diverse filter membranes and dilution methods on removal efficiency (19, 20). A large multicenter randomized controlled (RENAL) study (21) of 1,508 patients investigated the effect of high dose (40 ml/kg*h) and low dose (25 ml/kg*h) on 90-day survival rate during CRRT and suggested no difference. A uniform CRRT dose was used in our study to exclude its effect on solute removal efficiency. A study (19) focused on the effect of membrane materials (Sureflux150E vs. AV-400) on solute clearance; however, the results showed no difference between cellulose triacetate membranes and synthetic membranes on the removal of solutes (urea nitrogen and creatinine). Our study only used ST150 membrane (polyacrylonitrile material) to decrease the interference of materials. A small multicenter randomized controlled study (22) recently focused on the effects of different modalities (CVVH *vs*. CVVHD), convection and diffusion, on solute clearance using similar doses. The results showed no significant difference at 0 h and 4 h ($P > 0.05$) for small solutes (urea nitrogen and creatinine) and medium-to-macromolecules (inflammatory mediators, such as IL-6). No study has analyzed the solute removal efficiency and continuous pressure in the extracorporeal circuit because of the prior lack of effective data extracting methods. Therefore, our study is innovative.

Solutes have distinct removal efficiencies due to unique characteristics. The kidney is the only excretory organ of β2-microglobulin (11.8 kDa). A previous study (23) showed that the risk of death increased 11% when the concentration of β2-microglobulin increased by 10 mg/L in blood. Therefore, this study selected it as a representative medium-molecular solute. It has been thought that small molecules, such as urea nitrogen, freely pass through the dialysis membrane for 100% removal. However, a randomized controlled study conducted by Lyndon et al. (24) revealed that the measured clearance rates of urea nitrogen and creatinine in a high-dose group during CRRT were significantly different from the achieved clearance rates of 7.1 and 13.9% ($P < 0.001$), respectively. The results showed that the clearance of urea nitrogen and creatinine was not 100%, and the ability to remove creatinine was significantly overestimated compared with urea nitrogen. However, this study had some limitations, such as the lack of a downward trend in the removal effects for diverse solutes. A recent prospective cohort study (25) investigated the effect of high-flux filters (surface area 1.8 m^2) on the clearance of various solutes during CRRT. The results showed that the clearance of small molecule solutes (Cr and BUN) was not different at 72 h (0.99 ± 0.03 vs. 0.91 ± 0.16, $P = 0.074$; 1 ± 0 vs. 0.95 ± 0.17, $P = 0.5$), but β2-microglobulin changed substantially (0.61 ± 0.09 vs. 0.48 ± 0.13, $P = 0.002$). The results of this study are higher than our results at every sample collection time. The explanation for this phenomenon may be that the removal efficiency of the high-flux filter was higher than an ordinary filter. In addition, the lifespan of all the circuits was extreme (72 h), and no filter coagulation occurred with the use of citrate as the anticoagulation. Therefore, solute removal may decrease more slowly when the extracorporeal circuit is running well.

Strengths and Limitations

This study has important clinical significance because continuous pressures data are still not completely utilized. In our

study, we collected various modalities of anticoagulation and multiple RCA data (48.6%) compared to other trials (10, 11). Moreover, we creatively combined the dynamic pressure monitoring with the solute removal efficiency during CRRT and offered a new idea for circuit replacement.

Our study also has several limitations. First, it was a single-center observational study, so that its discoveries do not demonstrate causality. Also, the findings require verification by larger multicenter studies. In addition, our study used data from a single type of machine, dose, dialyzer membrane, so risk factors of circuit survival and the results of AOD need more various data to confirm the results. Besides, data lacked adjusting for the effect of within-patients repeated measurements. Finally, this study was short of data about solute removal efficiency of other middle molecular weight molecules (e.g., cytokines), so further study should be undertaken to corroborate these findings.

CONCLUSION

RCA and CVVHDF prolonged circuit survival during CRRT. M–S AOD events should be of a concern, especially when RCA or no anticoagulant is used. With the prolonged use of the extracorporeal circuit, all tested solutes removal efficiency started to significantly decline at 12 h. Besides, with the increase of TMP, solute removal efficiency descended dramatically. Moreover, extracorporeal circuit might consider to be replaced at 24 h when TMP $\geq$ 150 mmHg because of the decline of solute removal efficiency.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZ mainly responsible for program design and modification. PL, LL, XT, MG, TW, and LC were involved in this clinical trial and vouch for the adherence of the trial to the protocol, for the accuracy of the data. PL conducted the statistical analysis and wrote the first draft. All authors reviewed, revised, and approved the final version of the manuscript and agreed to the submission of this paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.621921/full#supplementary-material

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MINI REVIEW
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Plethysmographic Peripheral Perfusion Index: Could It Be a New Vital Sign?

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The plethysmographic peripheral perfusion index (PPI) is a very useful parameter with various emerging utilities in medical practice. The PPI represents the ratio between pulsatile and non-pulsatile portions in peripheral circulation and is mainly affected by two main determinants: cardiac output and balance between sympathetic and parasympathetic nervous systems. The PPI decreases in cases of sympathetic predominance and/or low cardiac output states; therefore, it is a useful predictor of patient outcomes in critical care units. The PPI could be a surrogate for cardiac output in tests for fluid responsiveness, as an objective measure of pain especially in un-cooperative patients, and as a predictor of successful weaning from mechanical ventilation. The PPI is simple to measure, easy to interpret, and has continuously displayed variables, making it a convenient parameter for detecting the adequacy of blood flow and sympathetic-parasympathetic balance.

Keywords: peripheral perfusion index, plethysmography, critically ill, anesthesia, shock

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INTRODUCTION AND AIM OF THE WORK

The pulse oximeter is a basic monitor in medical practice with an essential role to evaluate the peripheral oxygen saturation and heart rate using plethysmography technology. Pulse oximetry-derived peripheral perfusion index (PPI) is another variable that is measured by pulse oximeters using relatively advanced technology, namely, co-oximetry. The PPI represents the ratio between the portions of the blood in the peripheral tissue, namely, the pulsatile and the non-pulsatile blood flow. The PPI is measured by different types of monitors (e.g., Masimo Corporation, Irvine, CA, USA).

Peripheral perfusion index values depend on the blood flow in the peripheral circulation and the vascular tone; thus, it reflects two main determinants, which are the cardiac output and the balance between the sympathetic and the parasympathetic nervous systems. Being a representative of those two major hemodynamic parameters, the PPI could provide very useful information during the initial evaluation, risk stratification, and follow-up. The normal value of PPI was suggested to range between 0.2 and 20%; however, an observational study showed a median (quartiles) normal value of PPI of 4.3 (2.9–6.2) (1). The values of PPI are highly skewed and therefore, it is more commonly used for follow-up in comparison to the baseline readings of each individual (2).

This review is aimed to clarify the different benefits of monitoring the PPI and the pitfalls and the limitations of its measurements. An overview of its uses in emergency departments, intensive care units, and operating theaters will be also provided.

PPI AS SEVERITY INDICATOR IN CRITICALLY ILL PATIENTS

Being a representative of sympathetic-parasympathetic balance, the PPI decreases in conditions with sympathetic overactivity, which is predominant in critical illness and circulatory failure (3). The PPI decreases when there is sympathetic stimulation; therefore, although septic shock is characterized by vasodilatory and distributive nature, this vasodilatation does not apply to peripheral blood vessels (2). Thus, the more the more severe the shock, the lower the PPI is (4). Low PPI predicted poor outcomes in various groups of critically ill patients, such as patients with sepsis (5) and post-cardiac arrest patients (1). In patients with severe sepsis or septic shock, a PPI < 0.3 can predict the need for vasopressor therapy. Furthermore, a PPI < 0.2 can predict patient mortality (5, 6). In patients with post-return of spontaneous circulation (ROSC) after an out-of-hospital arrest, the mean PPI in the first 30 min was independently associated with patient outcomes, i.e., 30-day mortality or poor neurologic outcome (1). Patients with the lower tertile PPI showed double-fold mortality compared to those with higher PPI values (1). As higher PPI reflects better peripheral tissue perfusion, it is linked to good patient outcomes.

Recent evidence also suggests that PPI could be used to guide and titrate vasopressor pressor therapy (7).

PPI AS A GUIDE FOR FLUID THERAPY

As PPI is affected by both cardiac output and vasomotor tone, PPI could be an indicator of the cardiac output in case there is no change in the sympathetic activity. Furthermore, PPI showed a good ability to detect changes in the cardiac output in patients with septic shock (8).

Hence, PPI was used in fluid responsiveness tests as a surrogate for cardiac output in various maneuvers (9). An increase of 9% in the PPI after a passive leg raising test (10) and 2.5% after end-expiratory occlusion (11) test could predict fluid responsiveness with fair predictive value. An increase of 5% in the PPI after a 200-ml fluid bolus can predict fluid responsiveness in patients with septic shock (12). A decrease of 26% in the PPI after the lung recruitment maneuver can also predict fluid responsiveness in the operating room (13). This use represents a great achievement in guiding fluid therapy in settings where a cardiac output monitor is not available (13). It should be noted that the value of PPI in different tests of fluid responsiveness is more prominent in the positive predictive value than the negative predictive value; therefore, the increase in the PPI with preload challenge can detect responders while the failure of the PPI to increase does not confidently rule out fluid responsiveness.

PPI AS AN OBJECTIVE MEASURE FOR PAIN

Pain assessment usually relies on subjective scores, which require patient cooperation. Therefore, evaluation of pain in un-cooperative patients, such as critically ill patients, is usually challenging and requires a cumbersome scoring system. Finally, there are no tools to provide real-time measurement of pain. Various studies used the relation between PPI and sympathetic activity as an indirect method for pain evaluation (14, 15). There was a correlation between the change in PPI and the change in the behavioral pain scale in non-intubated patients (15). A decrease in the PPI value by 0.7 could accurately detect a 3-point change in the behavioral pain scale in non-intubated patients (15).

PPI IN THE OPERATING ROOM

Various uses were reported for the PPI in the operating room. Some uses of the PPI in the operating room rely on its relationship with the vasomotor tone, such as discrimination of failed and successful peripheral nerve blocks (16) and neuraxial blocks (17). An increase in the PPI value by 40% from the baseline value can detect successful supraclavicular brachial plexus block (16). Other authors reported that the PPI can trace the changes in central hemodynamics under general anesthesia where the sympathetic activity is commonly reduced (18). PPI was also found a predictor of postoperative complications after major surgeries (19, 20). Furthermore, intraoperative PPI could be used to tailor the use of vasoactive drugs to provide safe hypotensive anesthesia (21).

OTHER USES OF PPI IN CRITICALLY ILL PATIENTS

In critically ill patients, the PPI was evaluated for predicting several outcomes. Relying on its relation to the sympathetic tone, low PPI was able to predict hypotension during intermittent and continuous haemodialysis (22). A pre-dialysis PPI ≤ 1.8 can predict hypotension during dialysis with a positive predictive value of 80% and a negative predictive value of 100% (22). During weaning of mechanical ventilation, there is a usual increase in the cardiac output due to shifting the patient from positive to negative thoracic pressure (23). This increase in cardiac output is considered one of the predictors of successful weaning (23, 24). This fact might explain the recent finding of the ability of the PPI to predict successful weaning (25). Furthermore, weaning failure might be associated with stress and sympathetic overactivity, which contributed to the relation of the PPI and weaning outcome. Failure of the PPI to increase by 40% by the end of the spontaneous breathing trial can predict reintubation with a negative predictive value of 95% (25).

LIMITATIONS

The use of PPI in clinical practice has some limitations. (1) PPI is characterized by skewness and a wide range of measurements among normal persons; therefore, it is better to evaluate its changes in comparison to the bassline readings from the same person. (2) Care should always be paid to the possibility of poor signals especially in cold extremities low temperature and high doses of vasopressors. (3) Being a ratio between the pulsatile and non-pulsatile portions of peripheral blood flow, the PPI is not feasible for use in patients who receive extra-corporeal membrane oxygenation. (4) Being affected by two variables, namely, the cardiac output and the autonomic activity, evaluation of the change in the PPI should be performed over short intervals where one of these two variables is relatively constant so that the PPI could be closely correlated to only one variable. However, even if it was affected by the two variables, the PPI could provide a good idea of patient prognosis because both variables affect the PPI in the same direction.

The utility of PPI in clinical practice is still a subject of ongoing research. Future studies are needed to evaluate the correlation between PPI and brain perfusion.

From the currently available evidence, we can conclude that PPI is an irreplaceable vital sign with many important uses, such as a prognostic marker in critically ill and surgical patients, guiding fluid and vasopressor management, assessing the success of weaning from mechanical ventilation, and can be used as an objective measure for the assessment of regional anesthesia and pain.

AUTHOR CONTRIBUTIONS

MME, MM, and RG contributed to the conception of the idea, literature search, collecting material, and drafting the manuscript. AH contributed to the conception of the idea, literature search, collecting materials, and drafting and revising the manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Association of Frailty With the Risk of Mortality and Resource Utilization in Elderly Patients in Intensive Care Units: A Meta-Analysis

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Background: The associations of frailty with the risk of mortality and resource utilization in the elderly patients admitted to intensive care unit (ICU) remain unclear. To address these issues, we performed a meta-analysis to determine whether frailty is associated with adverse outcomes and increased resource utilization in elderly patients admitted to the ICU.

Methods: We searched PubMed, EMBASE, ScienceDirect, and Cochrane Central Register of Controlled Trials through August 2021 to identify the relevant studies that investigated frailty in elderly (≥ 65 years old) patients admitted to an ICU and compared outcomes and resource utilization between frail and non-frail patients. The primary outcome was mortality. We also investigated the prevalence of frailty and the impact of frailty on the health resource utilization, such as hospital length of stay (LOS) and resource utilization of ICU.

Results: A total of 13 observational studies enrolling 64,279 participants (28,951 frail and 35,328 non-frail) were finally included. Frailty was associated with an increased risk of short-term mortality (10 studies, relative risk [RR]: 1.70; 95% CI: 1.45–1.98), in-hospital mortality (five studies, RR: 1.73; 95% CI: 1.55–1.93), and long-term mortality (six studies, RR: 1.86; 95% CI: 1.44–2.42). Subgroup analysis showed that retrospective studies identified a stronger correlation between frailty and hospital LOS (three studies, MD 1.14 d; 95% CI: 0.92–1.36).

Conclusions: Frailty is common in the elderly patients admitted to ICU, and is associated with increased mortality and prolonged hospital LOS.

Trial registration: This study was registered in the PROSPERO database (CRD42020207242).

Keywords: frailty, elderly intensive care unit patients, mortality, hospital length of stay, meta-analysis

INTRODUCTION

With the aging of the population, the number of elderly patients admitted to the intensive care unit (ICU) has been growing (1). Recently, approximately 20% of the ICU admissions are elderly patients, and this proportion is expected to increase in the next decade (2). During hospitalization in the ICU, elderly patients are considered to be more vulnerable to the stress induced by acute illnesses, since they have age-related physiological changes, are more likely to have chronic diseases and have a higher prevalence of frailty. In the context of the rational allocation of medical resources, especially during the COVID-19 epidemic, appropriate intensive care resource utilization is essential, and many physicians have doubts if elderly patients are benefitted from the ICU admission. It is challenging to identify elderly patients who may benefit from intensive treatment.

The concept of frailty originated in the field of geriatrics and has been introduced to critical care medicine. Frailty is used to describe a biological syndrome or state associated with aging that is characterized by decreased functioning of multiple physiological systems, accompanied by an increased vulnerability to stress (3). Characteristic physiologic and molecular features, such as increased oxidative stress and inflammatory markers, are observed in frail individuals (4–6). For the frail individuals, functional aging represented by frailty is more important than biological aging (7), and there is emerging evidence that frail individuals are more vulnerable to adverse outcomes and increased resource utilization across different disease states (8–17). Frailty has been indicated proven to be associated with increased mortality but not increased service utilization in patients who were critically ill (18). However, some results have been controversial concerning the elderly patients admitted to ICU, who are more vulnerable to frailty (19, 20). Thus, it is crucial to investigate the impact of frailty on the elderly patients admitted to ICU.

In this study, we conducted a meta-analysis to assess whether frailty in elderly ICU patients is predictive of adverse outcomes and increased resource utilization. We hypothesized that frailty was associated with an increased mortality and resource utilization in the elderly patients admitted to ICU.

METHODS

Protocol and Registration

Our study was reported according to the Meta-analysis Of Observational Studies Epidemiology (MOOSE) guidelines (21), and the protocol was registered in PROSPERO (CRD42020207242).

Information Sources and Searches

We initially searched electronic databases, including PubMed and EMBASE, in February 2020. Our search used keywords including "frailty" OR "frail" OR "frail elderly" AND "intensive care" OR "intensive care unit" OR "critical care" OR "critically ill" OR "critical ill" OR "critical illness." The reference lists of selected articles were searched manually to identify additional studies. The literature search was updated in August 2021, adding the other research electronic databases of ScienceDirect, Cochrane Central Register of Controlled Trials.

Study Selection

Two authors (FPX and JZ) carried out the literature search independently. We first removed duplicate records and then screened the titles and abstracts of all the articles for potential relevance. Records were identified as included, uncertain, or excluded. For uncertain records, the full text of the article was further investigated to determine its eligibility. The inclusion criteria were as follows: i) participants: elderly (every individual $\geq$65 years old) patients admitted to ICU; ii) exposure: frailty; iii) outcome: mortality or resource utilization; and iv) study design: prospective or retrospective cohort studies. We resolved disagreements by the discussion.

Data Extraction

A data extraction sheet was developed in Excel to collect the following data: author, year, study design, country, frailty identification method, the sample sizes of frail, and non-frail patients, and the outcomes of interest. We chose outcomes that indicated the mortality of the patients and health services utilization. Outcomes maximally adjusted for available covariates were collected in our meta-analysis. The primary outcome was mortality, including short-term mortality ($\leq$1 month after ICU admission), in-hospital mortality, and long-term mortality ($\geq$6 months after ICU admission). Secondary outcomes were focused on health resource utilization, including hospital length of stay (LOS), use of mechanical ventilation, use of vasoactive agents, and use of renal replacement therapy. These data were independently extracted by FPX and JZ and later checked by SSM.

Quality Assessment

We used the Newcastle–Ottawa Scale (NOS) to evaluate the quality of the studies included (22). The NOS is a validated scale for assessing the quality of observational studies, and it has the following three domains: selection of the study groups, comparability of the groups, and assessment of the outcomes. The NOS is a 9-point scale awarding a maximum of four stars for selection, two stars for comparability, and three stars for outcomes. Studies scoring 0–3 were deemed low quality; those scoring 4–6 were considered to be of moderate quality; and those scoring 7–9 were classified as high quality.

Statistical Analysis

We calculated the relative risk (RR) with the corresponding 95% CI for mortality, use of mechanical ventilation, use of vasoactive agents, and use of renal replacement therapy with a random-effects model. In our meta-analysis, the RR was considered to be equivalent to the hazard ratio and the odds ratio (OR) (23). The weighted mean difference with 95% CI was calculated for the hospital LOS. We converted data to means and SDs when they were reported as medians (24). We conducted subgroup analyses with stratification by study type, age, frailty measure, and adjustment for confounders. Statistical heterogeneity among

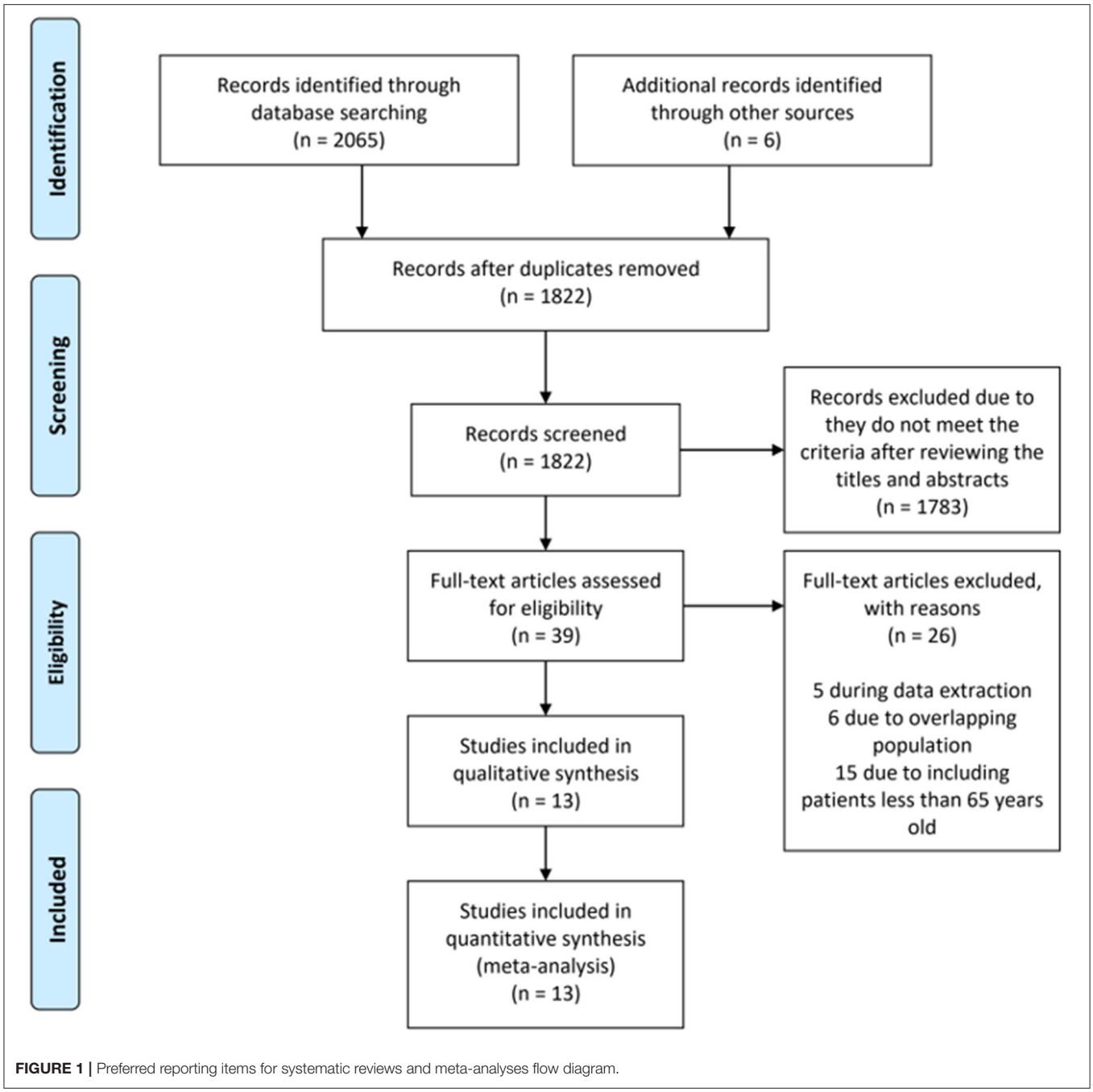

FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses flow diagram.

studies was determined with the Mantel–Haenszel (M–H) chi-squared test and the I^2 statistic. Significant heterogeneity was defined as I^2 value greater than 50% (25). An unadjusted, two-sided $p < 0.05$ was considered statistically significant. We performed the analyses using Review Manager 5.3 software (The Cochrane Collaboration, Copenhagen Denmark).

RESULTS

Study Selection

The initial search identified 2,071 articles and abstracts. After the removal of duplicate articles, 1,822 remained. A further 1,783 records were excluded because they did not meet the criteria after the titles and abstracts were reviewed. A total of 39 full-text articles were assessed in detail. According to the inclusion criteria, 26 studies were excluded, leaving 13 studies (19, 20, 26–36) that were eligible for inclusion in the meta-analysis (**Figure 1**).

Study Characteristics

We summarized the characteristics of the included studies in **Table 1**. The studies in our meta-analysis were published between 2014 and 2021. Nine of them were prospective observational studies, and the remaining four were retrospective cohort studies.

TABLE 1 | Characteristics of included studies.

Author	Study design	Country	Sample size	Frailty [*n*(%)]	Age (years)	Frailty definition	Outcomes assessed	Variables adjustment of adjusted mortality reported
Darvall et al. (19)	Retrospective cohort	Australia and New Zealand	15613	6203(39.7%)	84.6 ± 4.2	CFS > 4	Mortality/morbidity/ health service utilization	Sex, region, hospital type, and severity of illness
Fernando et al. (20)	Prospective cohort	Canada	1510	507(33.6%)	75.4 ±7.4	CFS > 4	Mortality/morbidity/ health service utilization	Age, sex, MODS, origin from long-term care, and comorbidity
Ferrante et al. (26)	Prospective cohort	USA	353	213(60.3%)	85.2 ±5.2	FI ≥ 3	Mortality/morbidity/ health service utilization	Age, gender, SOFA score, type of ICU admission
Flaatten et al. (27)	Prospective cohort	21 European countries	5021	2156(42.9%)	84.0 ± 3.7	CFS > 4	Mortality/morbidity	Age, gender, SOFA score, type of ICU admission
Guidet et al. (28)	Prospective cohort	22 European countries	3903	1568(40.2%)	84.0 ± 4.4	CFS > 5	Mortality/morbidity	Age, habitat, SOFA score, CPS and CFS
Hamidi et al. (29)	Retrospective cohort	USA	34854	17427(50.0%)	76.7 ± 7.0	NA	Mortality/morbidity/ health service utilization	NA
Heyland et al. (30)	Prospective cohort	Canada	609	193(31.7%)	85.0 ± 3.0	CFS > 4	Mortality/morbidity/ health service utilization	NA
Jung et al. (35)	Prospective cohort	28 countries	1346	279(20.7%)	75.0 ± 4.4	CFS ≥ 5	Mortality/morbidity/ health service utilization	Age, sex, comorbidities, SOFA score, BMI, PaO_2/FiO_2
Le Maguet et al. (31)	Prospective cohort	France	196	46(23.5%)	75.0 ± 6.0	FP>2; CFS > 4	Mortality/morbidity/ health service utilization	Sex, brain injury, SAPS II, glasgow coma scale, memory disorders, severe sepsis, septic shock, dialysis, ARDS, corticosteroid treatment
López et al. (32)	Prospective cohort	Spain	132	46(34.8%)	78.7 ± 6.7	CFS > 4	Mortality/morbidity/ health service utilization	APACHE II
Pasin et al. (36)	Retrospective cohort	Italy	302	167(55.3%)	84.0 ± 3.70	CFS ≥ 5	Mortality/morbidity/ health service utilization	Age, gender, BMI, CFS, MAP, chronic condition, cause of admission, need for suport treatment
Silva-Obregón et al. (33)	Retrospective cohort	Spain	285	53(18.6%)	77.6 ± 4.1	CFS > 5	Mortality/morbidity/ health service utilization	Gender, number of comorbidities, severity scores, treatment intensity and complications
Zeng et al. (34)	Prospective cohort	China	155	93(60.0%)	82.7 ± 7.1	FI > 0.22	Mortality/morbidity/ health service utilization	Age, sex

CFS, clinical frailty scale; FI, frailty index; FP, frailty physical phenotype; ICU, intensive care unit; NA, not available.

Our meta-analysis enrolled 64,279 participants. Among them, 28,951 patients were frail, and 35,328 patients were classified as non-frail. The pooled data showed that the prevalence of frailty in the elderly population admitted to ICU studied was 0.37 (0.33, 0.41) (**Figure 2**). Nine studies assessed frailty with the clinical frailty scale (CFS) (37), two used the frailty index (FI) (38), one used the modified frailty index (mFI) (29), and one study used both the CFS and the frailty phenotype (FP) (39). The quality of the included studies ranged from 6 to 9 stars on the NOS, denoting that the studies were of high or moderate quality (**Supplementary File 1**).

Mortality

All 13 studies reported the association between frailty and the risk of mortality. We extracted hospital mortality data from five studies, short-term mortality from 10 studies, and long-term mortality from six studies. The pooled unadjusted data revealed that frailty was associated with increased short-term mortality (RR: 1.70; 95% CI: 1.45–1.98; $I^2 = 88.0\%$; **Figure 3A**), in-hospital mortality (RR: 1.73; 95% CI: 1.55–1.93; $I^2 = 11.0\%$; **Figure 3B**), and long-term mortality (RR: 1.86; 95% CI: 1.44–2.42; I2 = 75.0%; **Figure 3C**). Eleven studies reported outcomes adjusted for different covariates, including age, sex, region,

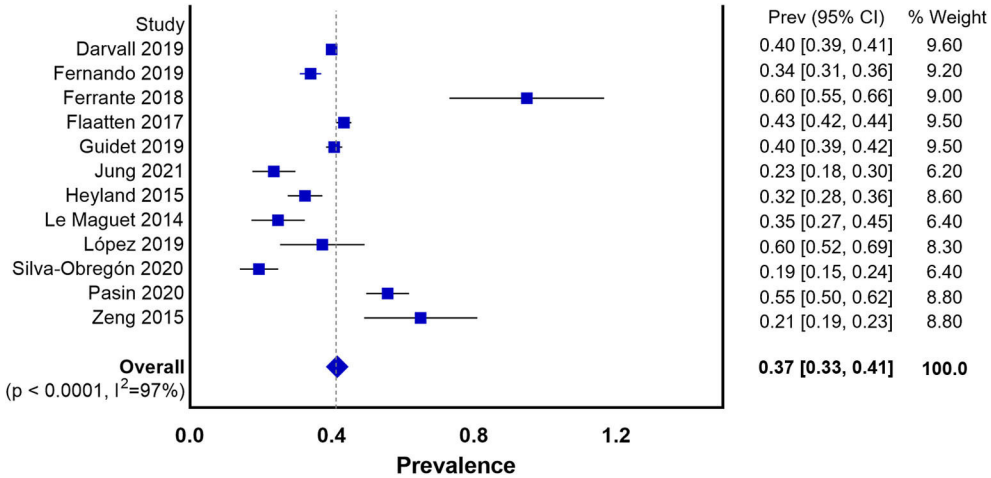

FIGURE 2 | Prevalence of frailty in the elderly patients admitted to ICU according to all the measures of frailty.

hospital type, severity of illness, treatment, and type of ICU admission (**Table 1**).

Subgroup analysis was conducted to determine the association of frailty with short-term and long-term mortality. The results showed that neither short-term nor long-term mortality was significantly affected by study location, age, the frailty measure, or adjustment for confounders (**Table 2**).

Resource Utilization

Six studies reported the hospital LOS. The pooled results showed that frail and nonfrail patients did not have significantly different hospital LOSs (MD 1.52 days; 95% CI−0.40–3.43, $p < 0.001$, $I^2 = 93\%$; **Supplementary File 2**). A subgroup analysis was conducted for the study type, and frailty was associated with a longer LOS (MD 1.14 days; 95% CI: 0.92–1.36, $p = 0.63$, $I^2 = 0\%$) in the retrospective studies. In the three prospective studies, the MD for short-term mortality was 1.76 d; 95% CI−1.94–5.46; $p = 0.06$, $I^2 = 65\%$ (**Supplementary File 2**).

Seven of the 13 studies compared the use of mechanical ventilation. There was no difference in the use of mechanical ventilation between frail and non-frail patients (RR: 0.91; 95% CI 0.80–1.04; $p < 0.001$; $I^2 = 80\%$; **Supplementary File 3**). In addition, five of the 13 studies reported the use of vasoactive therapy between frail and non-frail patients. There was no difference between the groups (RR: 0.95; 95% CI 0.85–1.06; $p = 0.08$; $I^2 = 52\%$; **Supplementary File 4**). There was also no difference in the use of renal replacement therapy between frail and non-frail patients in six of the 13 studies (RR: 1.07; 95% CI 0.76–1.51; $p = 0.006$; $I^2 = 69\%$; **Supplementary File 5**).

DISCUSSION

In this meta-analysis of 11 observational studies, we found that frailty was identified in approximately 40% of the elderly patients admitted to the ICU. We also found that frailty was associated with increased risks of short-term, in-hospital, and long-term mortality. In the retrospective studies, we found that frail patients were likely to have a prolonged hospital LOS. There was no significant difference between the frail and non-frail groups in the use of mechanical ventilation, use of vasoactive therapy, or the use of renal replacement therapy.

Our data showed that the prevalence of frailty in the elderly patients admitted to ICU was higher than that reported in a previous study (18), which included the adult ICU hospital population and was not specifically focused on the elderly patients. The VIP2 study (28) suggested that the prevalence of frailty was 40.2% in very old patients admitted to ICU, and our result appeared consistent with this finding. Meanwhile, most of the published data (40–43) showed that frail patients were likely to be more susceptible to coronavirus disease 2019 (COVID-19) with a prevalence of frailty as high as 51.1% (40). This result provided empirical evidence of the widely held belief that frail patients are relatively more susceptible to the pathogens.

Frailty was recognized initially in the field of geriatric medicine, and it has recently been increasingly identified as an essential determinant of prognosis in patients admitted to ICU. Our results were consistent with those of a previous study which showed that frail patients were at higher risk than non-frail patients of poor outcomes in different settings (44–46). The explanation for this finding involves the changes in pathophysiology in frail patients. Frail ICU patients have neuromuscular weakness, inflammation, and immunosenescence (47), which cause molecular and cellular deficits (48). These factors may increase susceptibility to pathogens in patients admitted to ICU. Furthermore, a diminished reserve in the multiple systems in frail patients might increase adverse outcomes such as mortality and the use of mechanical ventilation. Furthermore, frail patients have reduced resilience making their recovery more difficult (44) and prolonging their hospital LOS. In our meta-analysis, we found that elderly frail ICU patients

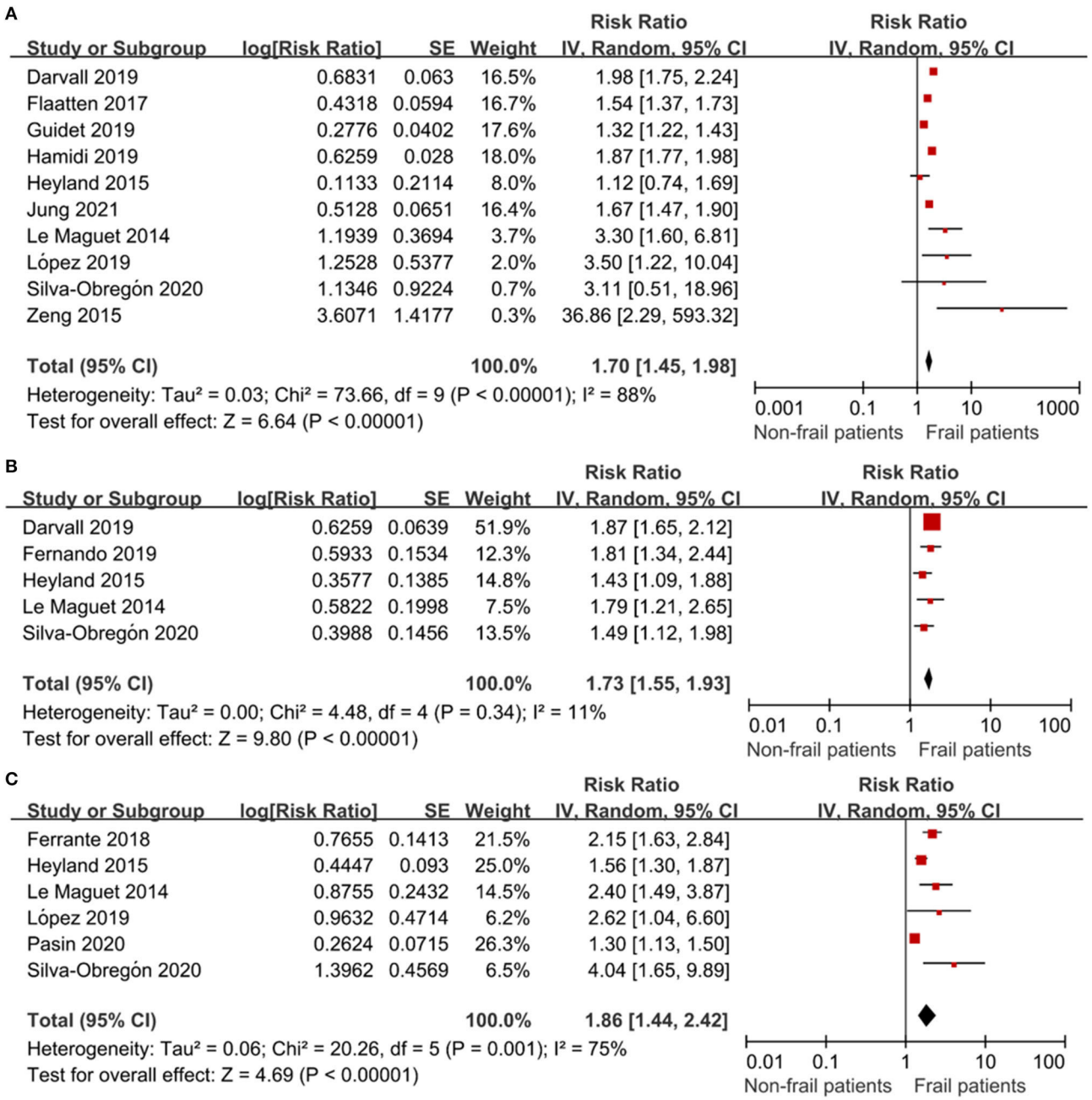

FIGURE 3 | The association of frailty and mortality in elderly patients admitted to ICU. RR = relative risk. **(A)** The association of frailty and short-term mortality in elderly patients admitted to ICU. **(B)** The association of frailty and in-hospital mortality in the elderly patients admitted to ICU. **(C)** The association of frailty and long-term mortality in the elderly patients admitted to ICU.

had longer hospital LOSs, although this was only reported in the retrospective studies.

There was no significant difference between frail and non-frail patients in the use of mechanical ventilation, vasoactive agents, or renal replacement therapy, and we did not find a significant difference in hospital LOS in the prospective studies. The study by Heyland reported a higher rate of mechanical ventilation in non-frail patients than in frail patients (30). This result is unexpected because diminished resilience would be likely to increase the possibility of the need for advanced ICU support in frail patients. Critically ill frail patients may be more likely to receive mechanical ventilation due to decreased oxygen uptake and weakness. Furthermore, because of immunosenescence, it may take more time for

TABLE 2 | Subgroup analysis on the association between frailty and mortality.

Variable	Short-term mortality				Long-term mortality			
	N	RR (95% CI)	I^2 (%)	*Pheterogeneity*	N	RR (95% CI)	I^2 (%)	*Pheterogeneity*
Research type								
Retrospective	3	1.89 [1.80, 1.99]	0	0.61	2	2.09 [0.70, 6.27]	83	0.01
Prospective	7	1.56 [1.31, 1.86]	77	< 0.01	4	1.94 [1.51, 2.49]	50	0.11
Age								
>65 years old	5	1.84 [1.62, 2.09]	41	0.15	3	2.68 [1.83, 3.93]	0	0.60
>80 years old	5	1.54 [1.23, 1.92]	89	< 0.01	3	1.60 [1.24, 2.06]	81	< 0.01
Frailty measure								
CFS	7	1.59 [1.34, 1.88]	85	< 0.01	5	1.77 [1.34, 2.34]	59	< 0.01
Other	3	2.88 [1.29, 6.43]	70	0.03	1	2.15 [1.63, 2.84]	Not applicable	Not applicable
Adjustment for confounders								
Severity scores Yes	6	1.55 [1.33, 1.81]	70	< 0.01	4	2.32 [1.85, 2.90]	0	0.60
No	4	1.81 [1.51, 2.16]	73	0.01	2	1.41 [1.18, 1.68]	59	0.12

CFS, clinical frailty scale; RR, relative risk.

critically ill frail patients to recover (47). During the COVID-19 epidemic, data (40) have shown that frail patients had prolonged hospital LOSs, which was not consistent with the data from the prospective studies in our meta-analysis. Possible explanations for these results are the limitations of medical care influenced by frailty, the incomplete reporting of data, the discharge pattern, and survival bias. Critically ill frail patients are likely to die earlier than non-frail patients, which may have reduced their hospital LOS and use of advanced organ support.

To reduce the heterogeneity due to the use of different methods to assess frailty, we performed a subgroup analysis according to the assessment method. The use of various methods to assess frailty should be considered. The FP (39) model and the cumulative deficit model (38) were developed to provide a theoretical framework for research on frailty. The FP model was first validated by Fried et al. The FP identifies frailty on the basis of five biological phenomena that result from the functional decline of multiple physiological systems (slow walking speed, low physical activity level, impaired grip strength, unintended weight loss, and self-reported exhaustion), while the cumulative deficit model calculates the FI on the basis of a range of health deficits (signs, symptoms, disabilities, impairments, and diseases). In our meta-analysis, two studies (26, 34) used the FI, and one study (31) used both the FP and CFS. To improve the ease of assessment of frailty in routine clinical practice, other tools have been developed, such as the CFS (37) and mFI. The CFS is an easy-to-use frailty measure with nine items with scores ranging from fit to terminally ill. The patients are considered to be frail when the CFS is more than 5 points. Eight studies included in our analysis used the CFS in the context of critical illness, enabling practitioners to rapidly screen for frailty, and the mFI (29) has also been validated in patients admitted to ICU. Future studies on the reliability, validity, and feasibility of frailty measures in the setting of the ICU are required.

There are several potential limitations of our meta-analysis. First, the included elderly patients had a range of underlying conditions; therefore, the prognostic significance of frailty in patients with acute respiratory distress syndrome, shock, and other types of organ failure should be confirmed in the future studies. Second, various frailty assessment tools were adopted in the included studies, leading to unavoidable heterogeneity. At last, it should be noted that the studies included in our meta-analysis were observational and may have been prone to bias.

CONCLUSIONS

In conclusion, frailty is common in the elderly patients admitted to ICU, and it is associated with an increased risk of mortality. Furthermore, in the retrospective studies, elderly frail patients had a prolonged hospital LOS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

FX was responsible for the conception and design of the study, acquisition, the analysis and interpretation of the data, the drafting and revision of the article, and gave final approval of the version to be published. JZ and SM were responsible for the acquisition and analysis of data. HQ participated in the data analysis and the interpretation of the results. FG was responsible for the conception and design of the

study, the analysis and interpretation of the data, the drafting and revision of the article, and gave final approval of the version to be published. All authors read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.637446/full#supplementary-material

Supplementary File 1 | Quality assessment of included studies with the Newcastle–Ottawa Scale.

Supplementary File 2 | The association of frailty with the hospital length of stay in elderly patients admitted to ICU.

Supplementary File 3 | The association of frailty with the use of mechanical ventilation in elderly patients admitted to ICU.

Supplementary File 4 | The association of frailty with the use of vasoactive therapy in elderly patients admitted to ICU.

Supplementary File 5 | The association of frailty with the use of renal replacement therapy in elderly patients admitted to ICU.

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Superiority of Supervised Machine Learning on Reading Chest X-Rays in Intensive Care Units

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Purpose: Portable chest radiographs are diagnostically indispensable in intensive care units (ICU). This study aimed to determine if the proposed machine learning technique increased in accuracy as the number of radiograph readings increased and if it was accurate in a clinical setting.

Methods: Two independent data sets of portable chest radiographs ($n = 380$, a single Japanese hospital; $n = 1{,}720$, The National Institution of Health [NIH] ChestX-ray8 dataset) were analyzed. Each data set was divided training data and study data. Images were classified as atelectasis, pleural effusion, pneumonia, or no emergency. DenseNet-121, as a pre-trained deep convolutional neural network was used and ensemble learning was performed on the best-performing algorithms. Diagnostic accuracy and processing time were compared to those of ICU physicians.

Results: In the single Japanese hospital data, the area under the curve (AUC) of diagnostic accuracy was 0.768. The area under the curve (AUC) of diagnostic accuracy significantly improved as the number of radiograph readings increased from 25 to 100% in the NIH data set. The AUC was higher than 0.9 for all categories toward the end of training with a large sample size. The time to complete 53 radiographs by machine learning was 70 times faster than the time taken by ICU physicians (9.66 s vs. 12 min). The diagnostic accuracy was higher by machine learning than by ICU physicians in most categories (atelectasis, AUC 0.744 vs. 0.555, $P < 0.05$; pleural effusion, 0.856 vs. 0.706, $P < 0.01$; pneumonia, 0.720 vs. 0.744, $P = 0.88$; no emergency, 0.751 vs. 0.698, $P = 0.47$).

Conclusions: We developed an automatic detection system for portable chest radiographs in ICU setting; its performance was superior and quite faster than ICU physicians.

Keywords: machine learning technique, chest radiographs, ICU, computer-aided detection, deep convolutional neural network, adaptive ensemble learning

INTRODUCTION

Critically ill patients often have organ dysfunction and require frequent and intense monitoring. Portable chest radiography is key to assessing cardiopulmonary function in the intensive care unit (ICU), allowing clinicians to identify pathological findings such as pneumonia, pneumothorax, pleural effusion, and atelectasis (1–7). A review of a large number of portable chest radiographs with high accuracy is important for the improvement of ICU patient outcomes; however, this can be challenging, primarily due to a lack of manpower (8, 9). Machine learning technology is effective in analyzing a large amount of data, including image data (10–14). Therefore, this promising technique potentially supports interpretations of radiographs, which may improve quality of care and patient safety by reducing physician's workload in ICU.

Substantial investigations have documented computer-aided detection (CAD) systems for medical images (15–21). Advances in machine learning enhance the potential utility of ICU care. Among various medical images, chest radiographs have been the most investigated; however, insufficient accuracy limits its clinical use. In addition, investigations on chest radiographs in the ICU have not been well elucidated.

Therefore, we developed a new algorithm using supervised machine learning with two independent datasets. We hypothesized that the accuracy of our supervised machine learning technique would increase as the number of radiograph readings increased; we also hypothesized that the technique would accurately and quickly identify pathological findings from portable chest radiographs in a clinical setting.

METHODS

Data Collection

We Collected Two Independent Data Set From Institutions in Different Regions

Data set 1 (a single Japanese center intensive care unit data): Consecutive portable chest radiographs (Sirius Starmobile tiara Airy; HITACHI, Tokyo, Japan) of a hospital based radiographic database for ICU patients who admitted between April 2017 and December 2018 were retrospectively extracted and used by the study team member from the ICU at Chiba University Hospital, Japan. This tertiary referral hospital ICU where approximately 1,800 patients admitted in a year had 22 beds and was utilized by patients following emergency room admission and after elective surgery, accounting for approximately 80% of ICU beds. Of 3,351 screened patients, we selected 380 chest radiographs, in which a single diagnosis could be made from one of the following categories: atelectasis, pneumonia, pleural effusion, and no emergency. The diagnosis was made on the basis of clinical signs, laboratory data, and other images, including computed tomography (CT) with a radiologist report and bedside ultrasound. Two board-certified ICU physician with the specialty of interventional radiology reviewed all radiographs and labeled each imaging with one of the diagnoses in a comprehensive and coherent manner. If there was any doubt in diagnosis, the radiograph was excluded from further analysis.

Data set 2 (National Institute of Health [NIH] repository, US multi centers data): ChestX-ray8 dataset provided by the NIH clinical center, which contains 8,508 weak supervised multi-label methods to classify and locate the text-mined 14 common thorax diseases, mined from the text radiological reports via natural language processing techniques were used (**Figure 1**). Because the accuracy of this dataset is estimated to be >90%, we identified erroneous labels and cleaned up the images according to previous reports (22); we excluded images with magnification or those deemed to be of poor quality by three experts including two board-certified radiology physicians.

All clinical datasets were provided with DICOM format. The resolution of the original images in the single center ICU datasets sizes 2,430 pixels height and 1,994 pixels width and that of original images in the NIH datasets sizes 1,024 pixels height and 1,024 pixels width. To align them, all images in the single center ICU datasets are cropped and resized into 1,024 pixels height and 1,024 pixels width.

This study was approved by the Institutional Review Board of Chiba University Graduate School of Medicine (No. 2972; Feb, 2018) and was performed in accordance with the committee's guidelines.

Two-Stage Classification Model

We used two different deep convolutional neural network architectures. Dense convolutional network 121 (DenseNet 121), which connects each layer to every other layer in a feed-forward fashion named DenseBlock. DenseNet121 has several compelling advantages and details are found in the supplemental digital content [see **Appendix** (Supplemental Digital content)].

The area under the curve (AUC) for atelectasis and pneumonia was particularly low at 0.574 and 0.499, respectively, in the four-class simultaneous classification of atelectasis, pneumonia, pleural effusion, and no abnormalities in DenseNets 121 conducted in a preliminary experiment. Therefore, we developed a two-stage classification method in which the combination of atelectasis and pleural effusion, and pneumonia and pleural effusion were once classified as the same class, and then separated them into each class in the second stage. The proposed network model of this study runs on Keras 2.1.5 with Python 3.4 on Ubuntu 16.04.4 LTS.

Adaptive Ensemble Learning

In adaptive ensemble learning, an arbitrary number of models are selected from 10 models generated by iterative learning, and the average of the certainty output values of each model is calculated. For model selection, the optimum number and optimum combination were determined from 10 models. We found that it was optimal to select 4 out of 10 models in the proposed two-stage classification method. Using this adaptive ensemble learning, the average AUC improved to 0.672.

Diagnostic Performance by Physicians vs. Machine Learning

To compare the accuracy and efficiency of the machine learning algorithm, five board-certified critical care physicians and three senior emergency residents voluntarily annotated images from

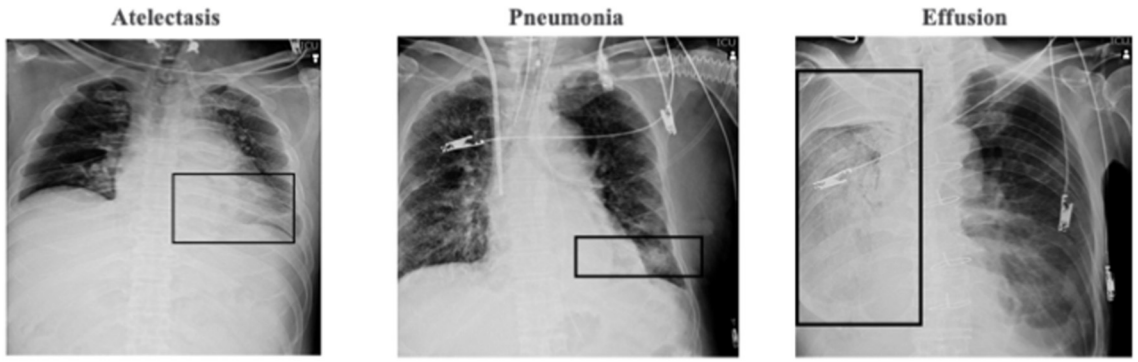

FIGURE 1 | NIH repository test image sample.

TABLE 1 | Accuracy comparison of four algorithms.

Comparison of AUC	Atelectasis	Pneumonia	Effusion	Not emergency	Four classes average
Four-class simultaneous classification	0.574	0.499	0.700	0.625	0.600
Two-stage classification 1	0.605	0.551	0.599	0.518	0.568
Two-stage classification 2	0.672	0.686	0.676	0.561	0.649
Two-stage classification 2 and adaptive ensemble learning	0.711	0.698	0.718	0.634	0.690

AUC, area under the curve.

the clinical samples which were dedicated data and part of the Chiba university hospital collected. To test physician's diagnostic accuracy, we developed a web-based software which was developed originally in our laboratory based on Java Script and can show a portable chest radiograph to a physician and the physician can input the diagnosis adjusting the dial of for categories (Not emergency, Pleural effusion, atelectasis, pneumonia) according to the physician's confidence from 0 to 100. We chose 53 chest radiographs which were randomly selected from Dataset 1. In a test, one physician successively reviewed 53 chest radiographs one by one using the developed software which automatically record the duration to diagnose a single portable chest radiograph (**Supplementary Figure 1**, **Supplementary Material**). The diagnostic accuracy calculated by AUC of receiver operator characteristic (ROC) analysis and the time for completing the images were compared with those obtained using the machine algorithm.

Outcome Measures and Statistical Analysis

The sensitivity and specificity for the ability of the CNN to classify atelectasis, pneumonia, pleural effusion, and no emergency were calculated. The ROCs were plotted by varying the operating threshold. For the ROC curves, standard error, 95% confidence intervals, and comparisons between AUCs were made using a non-parametric approach. The adjusted Wald method was used to determine 95% confidence intervals for sensitivity and specificity. *P*-values < 0.05 were considered to be statistically significant. All statistical analyses were performed using R® (ROCR, version 3.2.4) and PRISM® version 7 (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

Table 1 depicts the process of our algorithm development using Data set 1(a single Japanese center intensive care unit data). As shown in the table, our two-stage classification model improved its performance as compared to that of a four-class simultaneous classification model.

We next tested Data set 2 (NIH repository data, US multi center data, which is a larger and independent data set from different region, includes 1,120 for training, 120 for validation and 480 for test). In atelectasis, the AUC increased as the number of training data points increased, with a significant difference between 25 (280 images) and 100% (1,120 images) of the samples ($P < 0.05$) (**Figure 2A**). In pleural effusion, the AUC increased with an increase in the amount of data from 25 to 50% ($P < 0.01$) and from 75 to 100% of the samples ($P < 0.01$) (**Figure 2B**). In pneumonia, the AUC increased from 25 to 50% ($P < 0.05$) and 75% ($P < 0.01$) of the samples with an increase in the number of data points, respectively (**Figure 2C**). For no emergency, the AUC showed an increase in the number of data points from 25 to 50% ($P < 0.05$) and 25 to 100% of the samples ($P < 0.05$)

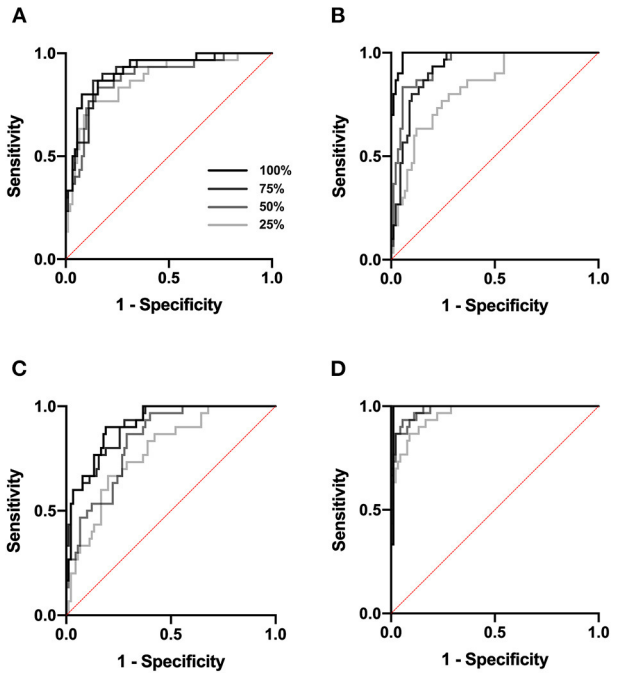

FIGURE 2 | ROC curve. ROC analysis was performed at a sample size of 25, 50, 75, and 100%. **(A)** ROC analysis for atelectasis. **(B)** for pleural effusion. **(C)** for pneumonia. **(D)** for no emergency.

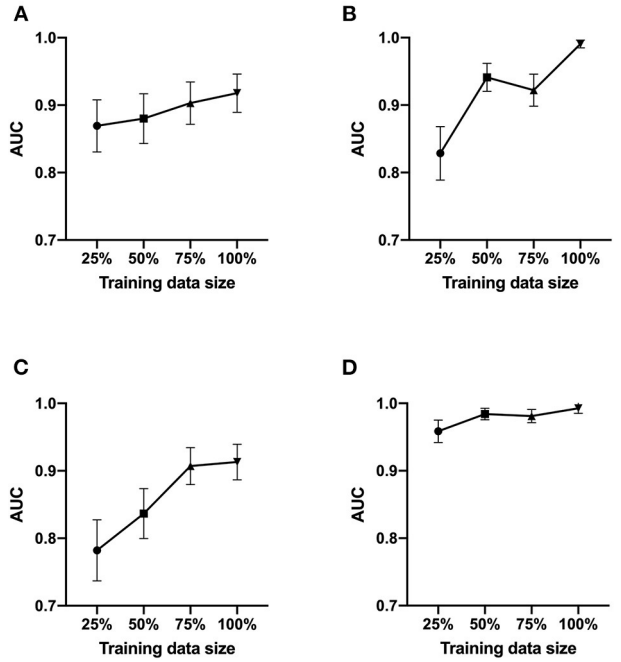

FIGURE 3 | AUC values as a function of the sample size. The AUC of ROC analysis was shown at a sample size of 25, 50, 75, and 100%. **(A)** for atelectasis. **(B)** for pleural effusion. **(C)** for pneumonia. **(D)** for no emergency.

(**Figure 2D**), with an increase in the number of data points. **Figures 3A–D** depicts the trend of AUC improvement with the increase in sample numbers.

The average time for ICU physicians to complete a review of 53 chest radiographs was 12 min (median, interquartile range 9–14). The algorithm finished the same dataset within 9.66 s. The diagnostic accuracy represented by AUC was higher by machine learning compared to those physicians in all categories: atelectasis, AUC 0.744 (95%CI 0.583–0.904) vs. 0.557 (95%CI 0.507–0.636), $P = 0.030$; pleural effusion, AUC 0.856 (95%CI 0.754–0.958) vs. 0.706 (95%CI 0.657–0.752), $P = 0.007$; pneumonia, AUC 0.702 (95%CI 0.571–0.869) vs. 0.744 (95%CI 0.643–0.829), $P = 0.881$; no emergency, AUC 0.751 (95%CI 0.597–0.906) vs. 0.698 (95%CI 0.615–0.792), $P = 0.476$).

DISCUSSION

In the present study, we developed a novel automatic detection system to aid ICU physicians in identifying pathological findings from portable chest radiographs. In the case of atelectasis and pleural effusion, the system performed extremely well compared to board-certified ICU physicians. Another advantage that should be highlighted is that the supervised machine learning technology had an extremely fast diagnostic time. The system could interpret one image per 0.18 s. Since the proposed model can run on the general deep learning framework, it can be adapted to widely other environments.

In this study, we validated that the diagnostic accuracy improved as the sample size increased with a large sample size (NIH repository data). The accuracy of this dataset is considered to be >90%, and so it would be sufficient to test our hypothesis. However, because of the uncertainty of the diagnosis randomly lurk under a cloak of the provided chest radiographs, we used our own in-hospital dataset to develop the machine learning algorithm, which is key to improving the accuracy of our system. We developed a novel two-stage classification method from this dataset. Incorporating machine learning into diagnostic imaging could lead to rapid therapeutic interventions by determining image results quickly with fewer errors. As for the cost, it is unknown since the business has not yet been developed.

It is important to aim for higher sensitivity to rule out acute pathology. Sensitivity is referred to as recall in the machine learning field. The sensitivity of our system for acute pathology was 0.846 for atelectasis, 0.846 for pneumonia, and 1.00 for pleural effusion. On the basis of our findings, the clinical application of this system is wide; the technology allows for reducing the risk of misdiagnosis and saving physician's efforts. The system requires true diagnosis; correct labels of radiographs need to be provided by clinicians. However, our data indicate that, after a period of training, once the system has taken a sufficient sample size, an end-user will experience high satisfaction in the diagnoses; the diagnoses would be consistent with their own at high accuracy (AUC >0.9) and at an extremely fast processing time.

While detecting pneumonia, machine learning had a poorer performance compared to the other abnormal findings. Poor performance in machine learning is either due to overfitting or underfitting of the data. Overfitting occurs when the trained model does not generalize well to unseen cases but fits the training data well. Assessment of the training curves can be used to evaluate the possibility of overfitting. In our study setting, it was apparent that the data loss on the validation data was much greater than that on the training datasets, which suggested the possibility of overfitting. The trend becomes more prominent when the training sample size is small. This is one of the main limitations of this study.

Since the present study developed algorithms with high predictive value, the future direction of research would be clinical application. The COVID-19 pandemic would require the speedy X-ray diagnosis system with high processing capability which detect the severe pneumonia in the shortage of the specialist physician (23–26). This system may be helpful for the screening of these patients with pulmonary opacity.

The study had other limitations that should be addressed. First, the number of learning images needed to be reduced by removing duplicate labels from the dataset. For example, for pneumonia, the ChestX-ray14 database had 1,107 pneumonia images; however, those included other labels such as pneumonia/atelectasis, pneumonia/pleural effusion/, and pneumonia/mass. We chose 300 images that were solely labeled as pneumonia to avoid the double count of diagnosis. It is plausible that the system performance decreased because the number of learning images was limited in pneumonia. Second, the resolution of image samples was lower than that of normal X-ray images. In our hospital, physicians usually use images with a resolution higher than 2,000 pixels; however, the images needed to be resized to 1,024 pixels in the training and validation datasets. Further studies are warranted to test the effect of image resolutions on diagnostic accuracy by comparing physicians and machine learning techniques. Third, this study lacked the topographic diagnoses within the chest X-rays (pathology by lobes, or by segments), and other pathologies or information that can be read in the radiographs, such as positioning of devices. However, this would not be a problem except for the increase in the amount of information that would have to be contributed to the learning system or for the addition of other layers of neurons to the model. Furthermore, this study did not have the data of the baseline demographic and clinical characteristics of participants including patients age, sex, BMI, diagnosis, and SOFA score. However, the machine learning without patient's characteristics would be versatile and increase the ability of accuracy form the images with limited information. Finally, this study has several limitations including sources of potential bias, statistical uncertainty, the limited number of cases, the number of investigators from the same geographical area, and generalizability in another environment (different types of patients, races, pathologies). Statistical uncertainty is important since the sample size calculation was not performed in this study. Since we developed new prediction algorithms using machine learning approaches and could not speculate a proper sample size, we did perform sample size estimation and analyzed available data. However, the strength of this study is comparison of the software performance with human chest x-ray readers. Expansive study, which is statistically built using this study results and add new images, in particular from different geographical regions to improve performances and generalizability of the model with multicenter even international collaborations, would be desirable.

CONCLUSIONS

We developed an automatic detection system for portable chest radiographs of ICU patients using two-stage classification method which performed superior to board-certified ICU physicians in the case of atelectasis and pleural effusion. The diagnostic accuracy improved as the sample size increased. The diagnostic time of the machine learning system was significantly shorter than that of physicians.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Chiba University Graduate School of Medicine. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

KT and TNakad designed the conception of the study. KT, TD, and TNakag performed acquisition of data. KT, NT, TD, and TNakag analyzed statistics. KT and KS drafted the manuscript. All authors made interpretations of data, added intellectual content of revisions to the paper, and gave final approval of the version to be published.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.676277/full#supplementary-material

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Development and Validation of a Simple-to-Use Nomogram for Predicting In-Hospital Mortality in Patients With Acute Heart Failure Undergoing Continuous Renal Replacement Therapy

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Background: Patients with acute heart failure (AHF) who require continuous renal replacement therapy (CRRT) have a high risk of in-hospital mortality. It is clinically important to screen high-risk patients using a model or scoring system. This study aimed to develop and validate a simple-to-use nomogram consisting of independent prognostic variables for the prediction of in-hospital mortality in patients with AHF undergoing CRRT.

Methods: We collected clinical data for 121 patients with a diagnosis of AHF who underwent CRRT in an AHF unit between September 2011 and August 2020 and from 105 patients in the medical information mart for intensive care III (MIMIC-III) database. The nomogram model was created using a visual processing logistic regression model and verified using the standard method.

Results: Patient age, days after admission, lactic acid level, blood glucose concentration, and diastolic blood pressure were the significant prognostic factors in the logistic regression analyses and were included in our model (named D-GLAD) as predictors. The resulting model containing the above-mentioned five factors had good discrimination ability in both the training group (C-index, 0.829) and the validation group (C-index, 0.740). The calibration and clinical effectiveness showed the nomogram to be accurate for the prediction of in-hospital mortality in both the training and validation cohort when compared with other models. The in-hospital mortality rates in the low-risk, moderate-risk, and high-risk groups were 14.46, 40.74, and 71.91%, respectively.

Conclusion: The nomogram allowed the optimal prediction of in-hospital mortality in adults with AHF undergoing CRRT. Using this simple-to-use model, the in-hospital

mortality risk can be determined for an individual patient and could be useful for the early identification of high-risk patients. An online version of the D-GLAD model can be accessed at https://ahfcrrt--d-glad.shinyapps.io/DynNomapp/.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT0751838.

Keywords: acute heart failure, continuous renal replacement therapy, nomogram, prognostic model, mortality

INTRODUCTION

Acute heart failure is life-threatening and one of the most common causes of hospitalization worldwide. It is characterized by a high risk of in-hospital mortality and re-hospitalization, which may result from acute myocardial dysfunction (ischemia, inflammation, or toxicity), arrhythmia, uncontrolled hypertension, non-adherence to medication/diet, or volume overload, and requires timely treatment (1). Patients with acute heart failure (AHF) require admission to intensive care units (ICUs) and are usually critically ill with multiorgan failure, in which the kidneys are most frequently involved (2). The goals of the treatment for AHF in the ICU are to improve hemodynamic stability and organ perfusion, alleviate symptoms, and limit cardiac and renal damage (1), which can be achieved by continuous extracorporeal blood purification, known as continuous renal replacement therapy (CRRT) (3). The CRRT can mimic urine output by slowly and continuously removing the plasma water of the patient (4) and achieving accurate volume control and hemodynamic stability (5). The 2016 European Society of Cardiology guidelines recommended the consideration of renal replacement therapy (RRT) in patients with AHF with refractory volume overload and acute kidney injury (AKI) (1).

Continuous renal replacement therapy is the most commonly used mode of renal replacement therapy (RRT) and has been used increasingly on patients with AHF in the ICU in recent years (5). The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) study showed that the in-hospital mortality rate of the patients with AHF in the ICU was ∼17.8% (6), which was three times higher than those in the general ward. However, when an indicator for CRRT is confirmed in critically ill patients, the mortality rate is already up to 45–62.1% (7–9), which is twice that in patients with AHF in the ICU. Therefore, there is a need for an early scoring model or screening system that can help clinicians to intervene rapidly and ameliorate the disease outcome in patients with AHF undergoing CRRT, who are at high risk of mortality. The tools most widely used to predict mortality in critically ill patients are the Acute Physiology Assessment and Chronic Health Evaluation II (APACHE II), the Mortality Probability Model II, and the Simplified Acute Physiologic Score II (SAPS II) (10–12). However, the variables included in these scoring systems are too complex and inconvenient for routine use. The Modified Early Warning Score (MEWS) and SUPER score, SpO_2, urine volume, pulse, emotional state, and respiratory rate are more concise than the APACHE II or SAPS II and can be used for the early warning of the onset of AHF in at-risk patients (13, 14). The APACHE II, SAPS II, and MEWS scores have some predictive value for the risk of death but their ability to predict in-hospital mortality in patients with AHF receiving CRRT is not known. To the best of our knowledge, there are no specialized scores or models that can predict in-hospital mortality in these patients.

This study aimed to develop and validate a simple-to-use nomogram model consisting of independent prognostic variables for the prediction of in-hospital mortality in adults with AHF undergoing CRRT. Meanwhile, the effectiveness of APACHE II, SAPS II, and MEWS in predicting the in-hospital mortality of AHF patients receiving CRRT was verified, and the most suitable model was selected and compared with the nomogram model to be widely popularized and applied.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of the Qilu Hospital of Shandong University (approval number KYLL-202011-114).

Data Source

The patient data used in this study was sourced from two databases. The first database was the Acute Heart Failure Unit (AHFU) at the Qilu Hospital of Shandong University, which opened on August 5, 2014, and was the first AHFU in China to advocate the concept of "early warning, early intervention" under the guidance of the SUPER score. Using this score, the onset of AHF can be predicted 2–6 h earlier than previously, and the rate of in-hospital mortality was decreased by more than 10% from 2012 to 2014 (13). The second was the medical information mart for intensive care III (MIMIC-III, version 1.4) database, a freely accessible, single-center, large online international database, which is approved by the institutional review boards of the Massachusetts Institute

Abbreviations: AHF, acute heart failure; AHFU, acute Heart Failure Unit; AKI, acute kidney injury; ALT, alanine transaminase; APACHE II, acute Physiology Assessment and Chronic Health Evaluation II; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C-index, the Harrell concordance index; CAD, coronary artery disease; CIs, confidence intervals; CKD, chronic kidney disease; CIC, clinical impact curve; CPR, cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; DBP, diastolic blood pressure; DCA, decision curve analysis; DM, diabetes mellitus; DN, diabetic nephropathy; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; MAP, mean arterial pressure; MEWS, modified early warning score; MIMIC-III, the medical information mart for intensive care III; MV, mechanical ventilation; NEU%, neutrophils ratio; NT-proBNP, N-terminal precursor B-type diuretic peptide; NRI, Net Reclassification Index; ORs, odds ratios; RRT, renal replacement therapy; ROC, receiver-operating characteristic curve; SAPS II, Simplified Acute Physiologic Score II; SBP, systolic blood pressure; SNS, sympathetic nervous system; WBC, white blood cell.

TABLE 1 | The baseline characteristics of the survivor cohort and the non-survivor cohort.

	Overall	Non-Survivor	Survivor	*P*
N	**226**	**98**	**128**	
Sex = Male (%)	123 (54.4)	56 (57.1)	67 (52.3)	0.56
Age (%)				<0.001
<45	23 (10.2)	4 (4.1)	19 (14.8)	
>70	98 (43.4)	60 (61.2)	38 (29.7)	
45~70	105 (46.5)	34 (34.7)	71 (55.5)	
Non-DM (%)	113 (50)	45 (45.9)	68 (53.1)	0.347
Non-HP (%)	123 (54.4)	50 (51.0)	73 (57)	0.445
Non-CAD (%)	105 (46.5)	39 (39.8)	66 (51.6)	0.105
Non-CKD (%)	94 (41.6)	48 (49)	46 (35.9)	0.066
Non-DN (%)	158 (69.9)	68 (69.4)	90 (70.3)	0.997
Non-CPR (%)	205 (90.7)	84 (85.7)	121 (94.5)	0.042
MV (%)				0.079
Without MV	99 (43.8)	35 (35.7)	64 (50)	
IMV	83 (36.7)	43 (43.9)	40 (31.2)	
non IMV	44 (19.5)	20 (20.4)	24 (18.8)	
Temperature = 35–38.5°C (%)	203 (89.8)	92 (93.9)	111 (86.7)	0.123
Heart Rate (%)				0.339
<90 beats/min	122 (54)	54 (55.1)	68 (53.1)	
>140 beats/min	7 (3.1)	1 (1.0)	6 (4.7)	
90–140 beats/min	97 (42.9)	43 (43.9)	54 (42.2)	
Respiration (%)				0.625
<20 breaths/min	103 (45.6)	42 (42.9)	61 (47.7)	
≥30 breaths/min	15 (6.6)	8 (8.2)	7 (5.5)	
20–30 breaths/min	108 (47.8)	48 (49.0)	60 (46.9)	
SBP >120 mmHg (%)	81 (35.8)	26 (26.5)	55 (43.0)	0.016
DBP >60 mmHg (%)	107 (47.3)	35 (35.7)	72 (56.2)	0.003
MAP ≥70 (%)	149 (65.9)	58 (59.2)	91 (71.1)	0.084
SPO2 (%)				0.016
≤94	39 (17.3)	25 (25.5)	14 (10.9)	
≥99	115 (50.9)	44 (44.9)	71 (55.5)	
94–98	72 (31.9)	29 (29.6)	43 (33.6)	
UA (%)				0.143
≤30	136 (60.2)	62 (63.3)	74 (57.8)	
≥50	48 (21.2)	15 (15.3)	33 (25.8)	
30–50	42 (18.6)	21 (21.4)	21 (16.4)	
WBC > 10*10^9/L (%)	117 (51.8)	53 (54.1)	64 (50)	0.635
NEU% >75% (%)	141 (62.4)	67 (68.4)	74 (57.8)	0.138
Hemoglobin >90 g/L (%)	121 (53.5)	55 (56.1)	66 (51.6)	0.585
Platelet >130*10^9/L (%)	151 (66.8)	58 (59.2)	93 (72.7)	0.047
Potassium 3.5–5.5 mmol/L (%)	169 (74.8)	68 (69.4)	101 (78.9)	0.139
Sodium = 137–147 mmol/L (%)	93 (41.2)	35 (35.7)	58 (45.3)	0.188
Calcium = 2.0–2.6 mmol/L (%)	130 (57.5)	51 (52)	79 (61.7)	0.186
ALT >40 U/L (%)	87 (38.5)	45 (45.9)	42 (32.8)	0.062
AST >60 U/L (%)	101 (44.7)	53 (54.1)	48 (37.5)	0.019
Creatinine >430 umol/L (%)	85 (37.6)	22 (22.4)	63 (49.2)	<0.001
BUN >20 mmol/L (%)	138 (61.1)	55 (56.1)	83 (64.8)	0.232
Blood glucose >10 mmol/L (%)	68 (30.1)	38 (38.8)	30 (23.4)	0.019
Lactic acid>1.8 mmol/L (%)	92 (40.7)	50 (51.0)	42 (32.8)	0.009
NT-proBNP [n (%), median (IQR)]	126 (55.75%), 20725.00 (10018.25, 35,000)	70 (71.43%), 27008.50 (10766.50, 35,000)	56 (43.75%), 19,843 (8843.25, 35,000)	0.423

(Continued)

TABLE 1 | Continued

	Overall	Non-Survivor	Survivor	*P*
Troponin I [n (%), median (IQR)]	52 (23%), 0.23 (0.03, 1.32)	32 (32.65), 0.30 (0.04, 1.75)	20 (15.63%), 0.08 (0.03, 1.20)	0.402
Troponin T [n (%), median (IQR)]	85 (37.61%), 0.22 (0.09, 0.98)	38 (38.78%), 0.18 (0.06, 0.62)	47 (36.72%), 0.34 (0.12, 1.19)	0.164
Days after admission before CRRT (%)				<0.001
≤3d	107 (47.3)	30 (30.6)	77 (60.2)	
>10d	44 (19.5)	33 (33.7)	11 (8.6)	
4–10d	75 (33.2)	35 (35.7)	40 (31.2)	
MEWS (mean ± SD)	3.16± 2.02	3.54 ±1.93	2.88 ±2.05	0.014
SUPER Score (mean ± SD)	3.45 ±1.59	3.73 ±1.60	3.23 ±1.55	0.019

ALT, alanine transaminase; aST, Aspartate aminotransferase; DM, diabetes mellitus; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; DN, diabetic nephropathy; IMV, invasive mechanical ventilation; IQR, interquartile range; MAP, mean arterial pressure; MEWS, modified early warning score; MV, mechanical ventilation; NEU%, neutrophils ratio; NT-proBNP, N-terminal precursor B-type diuretic peptide; SBP, systolic blood pressure; WBC, white blood cell.

of Technology and Beth Israel Deaconess Medical Center (15) and contains data collected from more than 38,000 adults between 2001 and 2012. All the data from the MIMIC-III database were extracted by one of the investigators (Luyao Gao) after the completion of the collaborative institutional training initiative (CITI) program course with certification (ID 36599230).

Study Population and Design

Patients with a diagnosis of AHF who underwent CRRT in the AHFU and those whose data were included in the MIMIC-III database were eligible for inclusion in the study. Patients who died before CRRT and those with missing information on the primary endpoint events were excluded. The eligible patients were randomly (7:3) allocated to the training cohort ($n = 159$) or the validation cohort ($n = 67$).

All the patients were categorized according to whether they were survivors or non-survivors at the time of discharge from the hospital. In principle, the time point of the clinical data collection of our model was when the physicians decided to initiate CRRT on the patients with AHF; the variables adopted were the newest ones we can acquire before the CRRT. If CRRT was needed to be initiated on the patient upon admission, we can refer to the laboratory reports in the emergency rooms or junior hospitals. An extensive list of baseline variables related to in-hospital mortality was identified (**Table 1**). The interval between the admission to the hospital and the start of the CRRT was also named days after the admission. For the study, in-hospital mortality was defined as all-cause mortality. We then developed novel clinical prediction models to predict the risk of in-hospital mortality.

If the proportion of the missing values was <5%, it was replaced with mean or median values; if the proportion was more than 5%, the missing values were imputed using multiple linear regression. Some values, such as those for the N-terminal precursor B-type diuretic peptide (NT-proBNP) and troponin, for which the missing proportion was over 60%, were only analyzed using the existing data.

Statistical Analysis

The categorical variables were expressed as a percentage and compared using the chi-squared test or Fisher's exact test. The continuous variables were summarized as the mean and SD or the median [interquartile range (IQR)] and compared using the *t*-test and Kruskal–Wallis test, respectively.

The magrittr package was used to randomly divide the eligible patients into the training and validation cohort. Univariate logistic regression analyses were performed to determine the independent risk factors for the in-hospital all-cause deaths in the training cohort. The odds ratios (ORs) and 95% CIs were calculated for these variables to quantify the strength of the associations. All the variables that showed a relationship with in-hospital mortality in the univariate analysis or were considered clinically relevant were candidates for the stepwise multivariate analysis in the training cohort. A nomogram model, produced using the rms package, was formulated based on the results for the independent risk factors identified in the multivariate logistic regression. Based on the nomogram model, the total scores and prediction of the in-hospital mortality risk for each patient were added for each eligible variable and then converted to predicted probabilities in both the training and validation cohorts.

To evaluate the ability of the model to predict in-hospital mortality, we first calculated the calibration of the model using 1,000 bootstrap samples to decrease the overfit bias. The Hosmer–Lemeshow test was used to evaluate the goodness of the fit. Second, the Harrell concordance index (C-index) and receiver-operating characteristic curve (ROC) analysis were used to evaluate the predictive performance and discrimination ability of the nomogram. A ROC analysis was used to calculate the optimal cutoff values, which were determined by maximizing the Youden index. Third, the clinical effectiveness of the resulting model was evaluated by a decision curve analysis (DCA) and clinical impact curve (CIC), which is a method for evaluating diagnostic or prognostic tools that potentially have advantages over others (16, 17). The increase in the discriminative value of the MEWS and the resulting model

TABLE 2 | Univariate logistic regression analysis of in-hospital mortality in the training cohort.

Variable	OR	95% CI		*P*-value
Sex Female vs. Male	0.95	0.50	1.79	0.8723
Age				
<45	Ref.			
45–70	2.46	0.73	11.30	0.1826
>70	8.89	2.63	41.13	0.0013
DM	1.53	0.82	2.90	0.1852
Hypertension	1.17	0.62	2.21	0.6268
CAD	1.62	0.86	3.08	0.1396
CKD	0.76	0.40	1.44	0.3943
DN	1.12	0.57	2.20	0.7475
CPR	3.41	1.06	13.08	0.0492
MV				
Without MV	Ref.			
non-IMV	1.41	0.60	3.28	0.4304
IMV	1.81	0.89	3.73	0.1056
T (°C)				
35–38.5	Ref.			
<35 or >38.5	0.43	0.09	1.52	0.2223
Heart Rate (beats/min)				
<90	Ref.			
90–140	0.87	0.46	1.66	0.6820
>140	0.00	NA	0.00	0.9891
Respiration (beats/min)				
<20	Ref.			
20–30	0.95	0.49	1.81	0.8686
≥30	1.08	0.25	4.38	0.9189
SBP (mmHg)				
>120	Ref.			
≤120	2.50	1.28	5.00	0.0082
DBP (mmHg)				
>60	Ref.			
≤60	3.04	1.59	5.95	0.0009
MAP (mmHg)				
>70	Ref.			
≤70	1.91	0.98	3.78	0.0595
SpO_2 (%)				
≥99	Ref.			
95–98	0.83	0.40	1.71	0.6176
≤94	2.84	1.11	7.72	0.0328
Urine volume (ml/h)				
≥50	Ref.			
30–50	2.38	0.86	6.91	0.1013
≤30	2.59	1.13	6.41	0.0299
WBC (10^9/L)				
≤10	Ref.			
>10	1.52	0.81	2.88	0.1965
NEU% (%)				
≤75	Ref.			
>75	1.21	0.63	2.32	0.5737
HGB (g/L)				
>90	Ref.			
≤90	0.63	0.33	1.19	0.1540
Platelet (10^9/L)				
>130	Ref.			
≤130	1.63	0.84	3.17	0.1513
Potassium (mmol/L)				
3.5–5.5	Ref.			
<3.5 or >5.5	1.89	0.87	4.13	0.1078
Sodium (mmol/L)				
137–147	Ref.			
<137 or >147	1.35	0.71	2.59	0.3600
Calcium (mmol/L)				
2.0–2.6	Ref.			
<2.0 or >2.6	1.12	0.59	2.11	0.7268
ALT (U/L)				
≤40	Ref.			
>40	1.35	0.70	2.58	0.3685
AST (U/L)				
≤60	Ref.			
>60	2.18	1.15	4.18	0.0179
Creatinine (umol/L)				
≤430	Ref.			
>430	0.33	0.16	0.65	0.0020
BUN (mmol/L)				
≤20	Ref.			
>20	0.90	0.47	1.70	0.7356
Blood glucose (mmol/L)				
≤10	Ref.			
>10	2.78	1.38	5.72	0.0048
Lactic acid (mmol/L)				
≤1.8	Ref.			
>1.8	2.68	1.40	5.19	0.0031
Days after admission before CRRT				
≤3d	Ref.			
4–10d	2.59	1.24	5.53	0.0123
>10d	6.84	2.78	18.08	<0.0001
MEWS	1.11	0.95	1.30	0.1855
SUPER score	1.23	1.00	1.53	0.0514

ALT, Alanine transaminase; AST, Aspartate aminotransferase; DM, diabetes mellitus; BUN, blood urea nitrogen; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; DN, diabetic nephropathy; IMV, invasive mechanical ventilation; MAP, mean arterial pressure; MEWS, modified early warning score; MV, mechanical ventilation; NEU%, neutrophils ratio; OR, odds Ratio; SBP, systolic blood pressure; WBC, white blood cell.

for mortality were assessed using the Net Reclassification Index (NRI).

All statistical analyses were performed using STATA version 15.0 (StataCorp LLC, College Station, TX, USA) and R language software (v4.0.3, http://www.r-project.org/). The packages used in the study were tableone, foreign, rms, broom, magrittr, pROC,

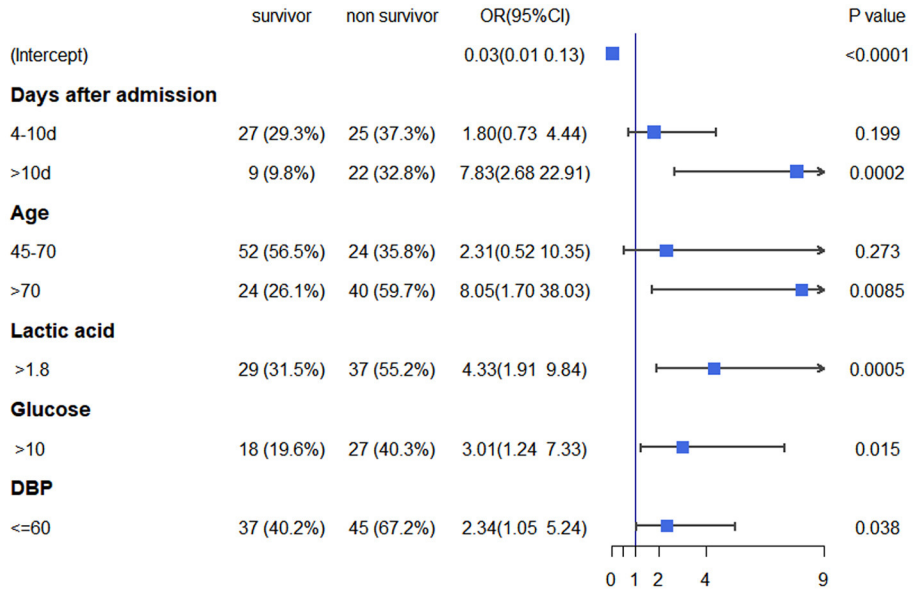

FIGURE 1 | Multivariate logistic regression analysis of in-hospital mortality based on pre-CRRT data in the training cohort. CRRT, continuous renal replacement therapy.

rmda, blorr, PredictABEL, ResourceSelection, and ggplot2. The $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Study Population

A total of 226 patients with AHF who underwent CRRT during the study period were enrolled and grouped according to whether they were discharged from the hospital as non-survivors ($n = 98$, 43.4%) or survivors ($n = 128$, 56.6%). The mortality rate in the validation cohort was 46.3 and 42.1% in the training cohort; both these values were lower than the previously reported rate of 58.1% (7). The demographics and clinical characteristics of the patients in the non-survivors and survivors' cohort are summarized in **Table 1**. Compared with the survivors, the non-survivors were older and more likely to receive more cardiopulmonary resuscitation (CPR), have lower systolic blood pressure (SBP) and diastolic blood pressure (DBP), lower creatinine and platelet levels, lower oxyhemoglobin saturation (SpO_2), more likely to have higher aspartate aminotransferase (AST), blood glucose, and lactic acid, and to have a longer interval between the admission to the hospital and starting the CRRT. The NT-proBNP was only collected in 126 patients as more than half of the patients had renal insufficiency and nearly 30% of the test value of the patients exceeds the upper limit (35,000 ng/L). The troponin was also missing up to 50% of the data, so both values were not included in the model building. The demographics and clinical characteristics of the training cohort are detailed in **Supplementary Table 1**. There was no significant difference in any of the clinicopathological data except for the potassium level and SUPER score, which were more abnormal in the validation cohort and may explain why the mortality was slightly higher in that cohort. The details can be found in **Supplementary Table 2**.

Logistic Regression Analyses

All the variables used in these analyses were based on retrospectively obtained data. The results of the univariate logistic analysis are presented in **Table 2**. In addition to the variables that were statistically significant in univariate analysis ($p < 0.05$), namely, age, need for CPR, SBP, DBP, SpO_2, urine volume, AST, creatinine, blood glucose, and lactic acid levels, and the interval between admission to the hospital and starting CRRT, the variables considered as clinically related to in-hospital mortality, such as mechanical ventilation (MV), mean arterial pressure (MAP), and SUPER score, were candidates for the stepwise multivariate analysis in the training cohort.

The analyses showed that the factors independently associated with in-hospital mortality were age (45–70 years vs. <45 years [OR 2.31, 95% CI 0.52–10.35; $p = 0.273$] and >70 years vs. <45 years [OR 8.25, 95% CI 1.7–38.03; $p = 0.0085$]), days after admission (4–10 days vs. <3 days [OR 2.31, 95% CI 0.52–10.35; $p = 0.199$] and >10 days vs. <3 days [OR 7.83, 95% CI 2.68–22.91; $p = 0.002$]), lactic acid (OR 4.33, 95% CI 1.91–9.84; $p = 0.0005$), blood glucose (OR 3.01, 95% 1.24–7.33; $p = 0.015$), and DBP (OR 2.34, 95% CI 1.05–5.24; $p = 0.038$; **Figure 1**).

Nomogram Model and Webserver

The independently associated risk factors (age, days after admission, lactic acid, blood glucose, and DBP) were used to form an in-hospital mortality risk estimation nomogram (**Figure 2A**). To allow clinicians to use this tool, which we have named the D-GLAD model, more conveniently and easily, we used the DynNom package and shinyapps (https://

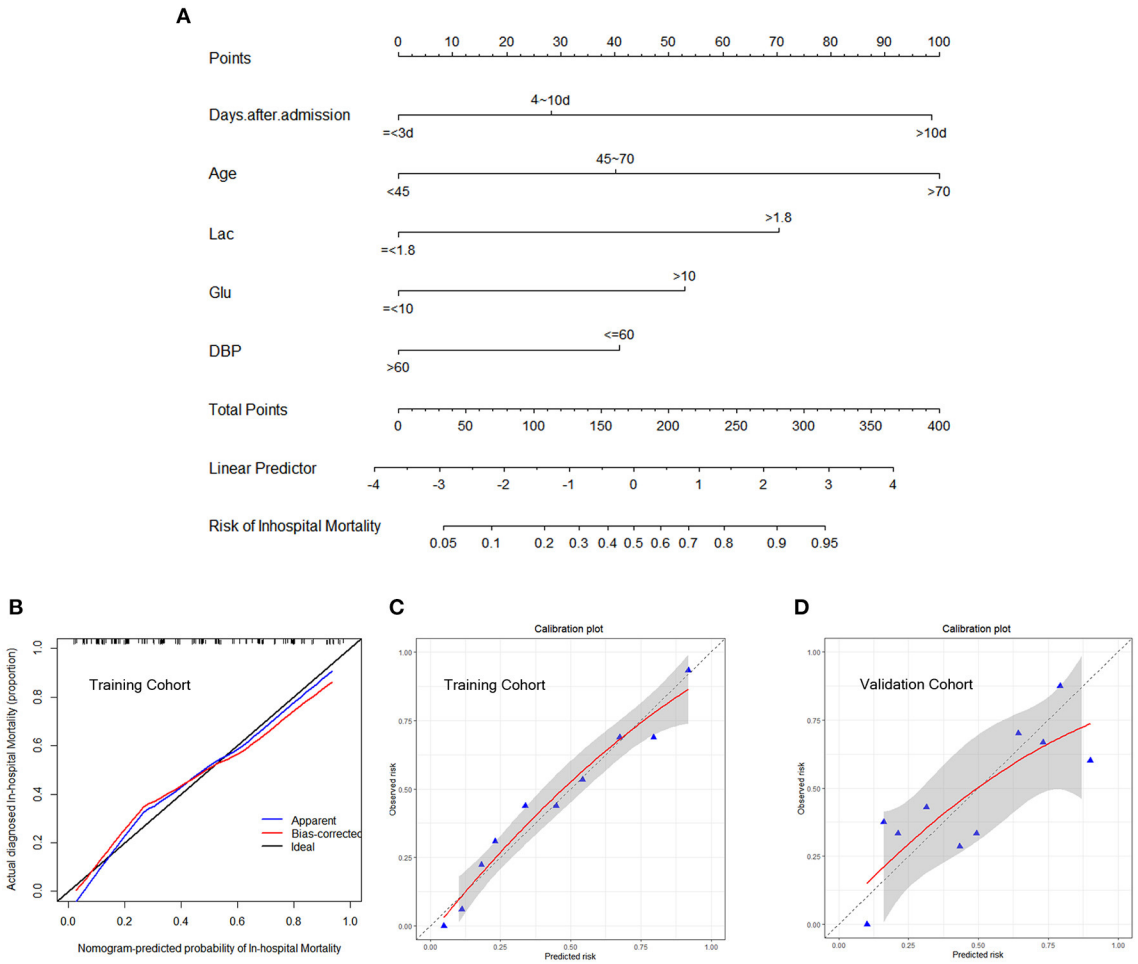

FIGURE 2 | Development predicting nomogram model. **(A)** The nomogram includes significant clinical characteristics for predicting in-hospital mortality in AHF patients undergoing CRRT. To estimate the in-hospital mortality rate of an individual patient, the value of each included significant clinical characteristic is acquired and divided into the different groups, followed by a line drawn straightly downward to determine the points. The sum of these five numbers is located at the Total Points axis, then a line is drawn downward to the risk of in-hospital mortality axes to determine the likelihood of in-hospital mortality. The calibration curve of the nomogram model for predicting in-hospital mortality was internally validated using the bootstrap validation method **(B)** and Hosmer–Lemeshow test **(C)** in the training cohort and externally validated using the Hosmer–Lemeshow test **(D)** in the validation cohort. The nomogram-predicted probability of in-hospital mortality is plotted on the x-axis, and the actual in-hospital mortality is plotted on the y-axis. The gray area both in c and d represents a 95% confidence interval. AHF, acute heart failure; CRRT, continuous renal replacement therapy; DBP, diastolic blood pressure; Lac, lactic acid.

www.shinyapps.io) to build an online webserver (https://ahfcrrt--d-glad.shinyapps.io/DynNomapp/), which can show the individualized prediction dynamically by inputting the clinical features. Clinicians and researchers can predict in-hospital mortality by reading the output figures and tables generated by the webserver (**Supplementary Figure 1**).

Validation of the Nomogram Model

The calibration of the nomogram model was internally validated using the bootstrap method and the Hosmer–Lemeshow test ($p = 0.868$); the externally validated Hosmer–Lemeshow test ($p = 0.1043$), showed good agreement with the concordance of the nomogram (**Figures 2B–D**). The nomogram demonstrated good accuracy in estimating the risk of the in-hospital all-cause mortality, with an unadjusted C-index of 0.829 (95% CI 0.767–0.891) in the training cohort, which was significantly higher than that of the MEWS (C-index 0.578, 95% CI 0.491–0.666; $p < 0.001$; **Figure 3A**). The C-index for the D-GLAD model was 0.740 (95% CI 0.620–0.860) in the validation cohort and was 0.685 (95% CI 0.558–0.813) for the MEWS. Although there was no statistically significant difference in the C-index value between the D-GLAD model and MEWS, the value was much larger for D-GLAD (**Figure 3B**).

Compared with the MEWS, the results of the DCA and the CIC demonstrated that the D-GLAD model had good clinical effectiveness in both the training and validation cohorts (**Figures 3C–F**). All the results indicated that the accuracy, discrimination ability, and clinical effectiveness of the D-GLAD model were superior to those of the MEWS.

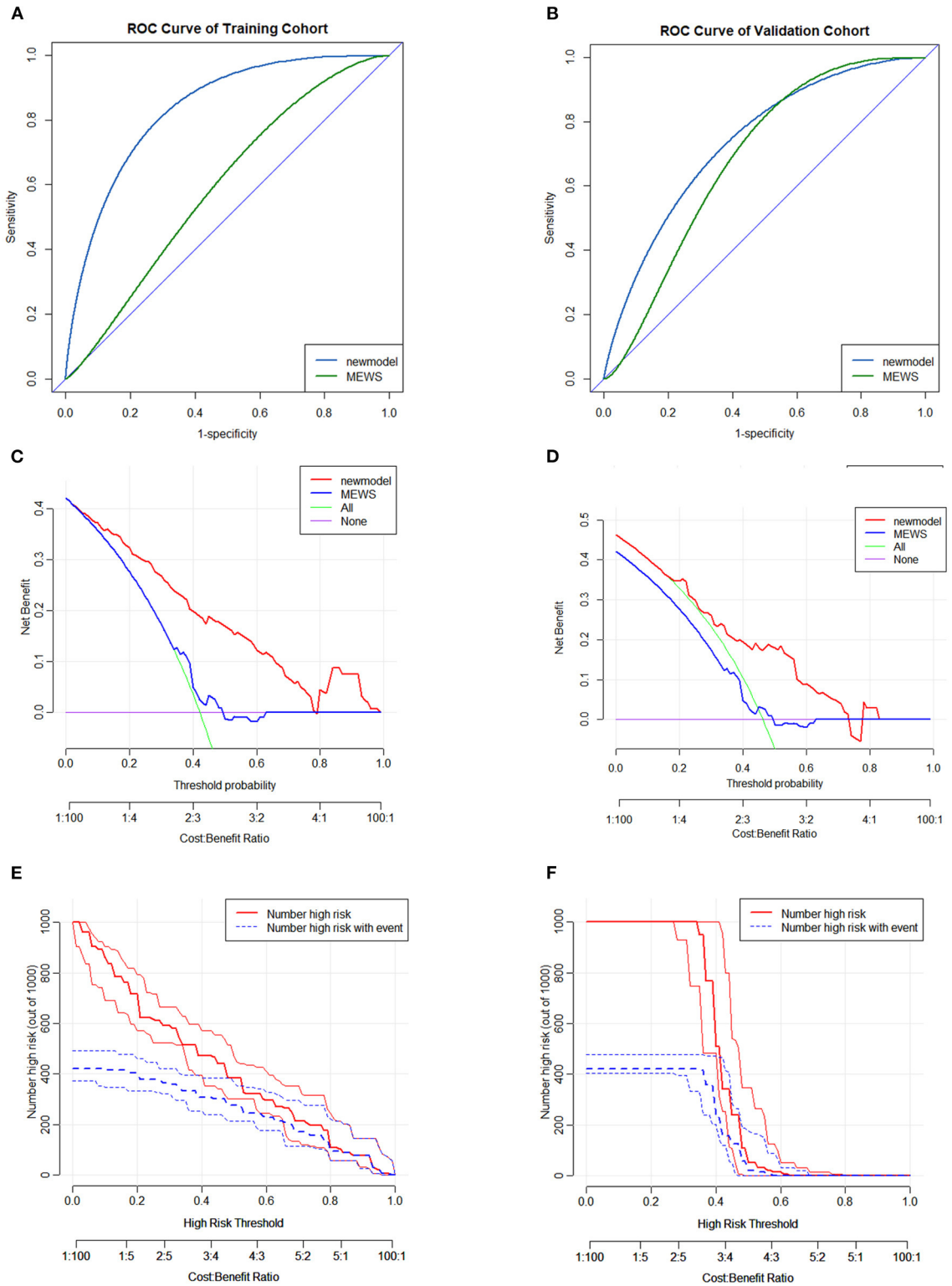

FIGURE 3 | Discrimination and clinical effectiveness validation of predicting nomogram model. The ROC analyses of in-hospital mortality of the nomogram model and MEWS in the training cohort **(A)** and validation cohort **(B)**. DCA curve for in-hospital mortality in the training cohort **(C)** and validation cohort **(D)**. CIC for in-hospital mortality in nomogram model **(E)** and MEWS **(F)** in the training cohort. CIC, clinical impact curve; DCA, decision curve analyses; MEWS, Modified Early Warning Score; ROC, receiver operating characteristic curve.

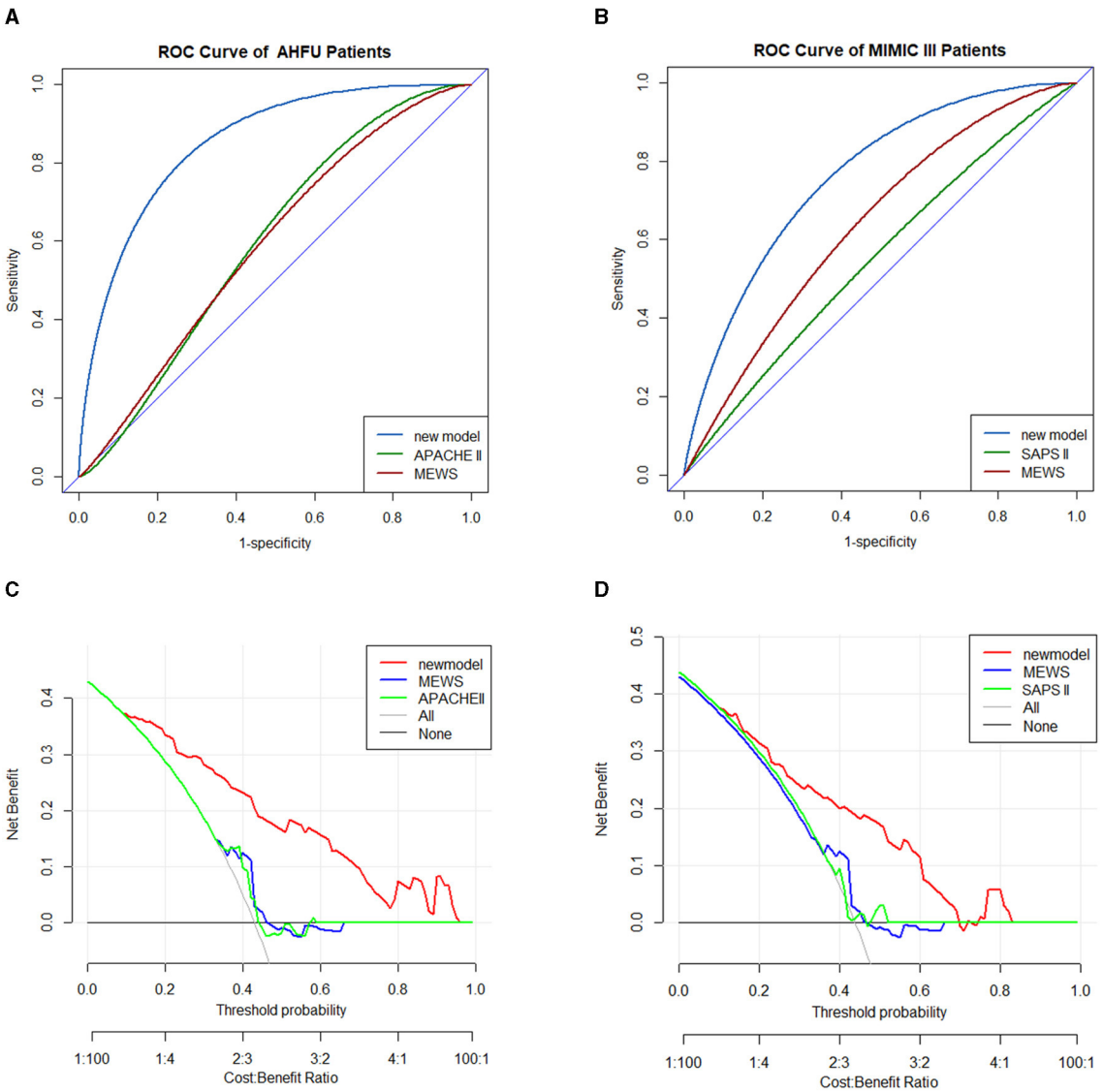

FIGURE 4 | Validation of predicting nomogram model in AHFU and MIMIC III patients. The ROC analyses of in-hospital mortality of the nomogram model and MEWS in the AHFU cohort **(A)** and MIMIC III cohort **(B)**. DCA curve for in-hospital mortality in the AHFU cohort **(C)** and MIMIC III cohort **(D)**. AHFU, acute heart failure unit; DCA, decision curve analyses; MEWS, Modified Early Warning Score; MIMIC III, medical information mart for intensive care III; ROC, receiver operating characteristic curve.

D-GLAD in AHFU and MIMIC-III

Only the APACHE II data could be extracted from the AHFU database and only the SAPS II data could be extracted from the MIMIC-III database.

In the AHFU cohort, the C-index for the D-GLAD model was 0.845 (95% CI 0.779–0.912), which was significantly different ($p < 0.001$) from that of the APACHE II (0.579, 95% CI 0.478–0.680) and MEWS (0.604, 95% CI 0.505–0.704; **Figure 4A**). The clinical effectiveness was similar for the MEWS and APACHE II but was much better for the D-GLAD model (**Figure 4B**).

In the MIMIC-III cohort, the C-index for the D-GLAD model was 0.759 (95% CI 0.667–0.851), which was significantly different ($p = 0.0025$) from that of the SAPS II (0.535, 95% CI 0.422–0.647) but not from that of the MEWS (0.618, 95% CI 0.512–0.724, $p = 0.0564$; **Figure 4C**). The clinical effectiveness of the D-GLAD model was much better than that of the MEWS and SAPS II (**Figure 4D**).

D-GLAD Model Predict In-Hospital Mortality

The ROC curve showed that the optimal cutoff value for predicting in-hospital mortality was 0.266, with a corresponding total nomogram score of ∼122. We used the prediction and total score for the risk stratification, where <125, 125–170, and >170 corresponded to low risk, moderate risk, and high risk, respectively. The NRI showed that the resulting model had better prognostic discrimination ability than the MEWS for the in-hospital mortality in both the training cohort (NRI,

TABLE 3 | Predictive value of D-GLAD model and SUPER score for in-hospital mortality.

		D-GLAD model					
		Low-risk <125		Moderate-risk 125–170		High-risk >170	
SUPER Score	Low-risk	6.67%	(1/15)	50.00%	(2/4)	57.14%	(4/7)
	Moderate-risk	9.38%	(3/32)	39.13%	(9/23)	72.73%	(24/33)
	High-risk	13.79%	(4/29)	34.78%	(8/23)	75.00%	(30/40)
	Extremely high-risk	57.14%	(4/7)	75.00%	(3/4)	66.67%	(6/9)
	All	14.46%	(12/83)	40.74%	(22/103)	71.91%	(64/89)

59.14%; $p < 0.001$) and the validation cohort (NRI, 23.84%; $p = 0.187$). Using the D-GLAD model, the in-hospital mortality rate was ∼14.46% in the low-risk group and up to 40.74% in the moderate-risk group. The in-hospital mortality was up to 71.91% in the high-risk group using the D-GLAD model and up to 65% in the extremely high-risk group using the SUPER score (**Table 3**). When used for screening high-risk patients, the sensitivity, specificity, positive predictive value, and negative predictive value were 73.5, 76.6, 57.2, and 87.2%, respectively, in the training cohort and 83.87, 44.44, 56.52, and 76.19% in the validation cohort.

DISCUSSION

In this study, we not only clarified the clinical features of patients with AHF undergoing CRRT and their risk factors for mortality but also developed and validated a nomogram model that could predict in-hospital mortality in these patients based on the data from the Qilu Hospital AHFU and MIMIC-III database. Patient age, days after admission, lactic acid level, blood glucose concentration, and DBP were the independent predictors of in-hospital mortality and were used to form a D-GLAD model that performs better than the APACHE II, SAPS II, and MEWS, and can help clinicians for the early screening of high-risk patients.

Acute heart failure is a severe disease with high mortality and hospital readmission rates and is characterized by the rapid onset or worsening of symptoms of heart failure, mostly associated with systemic congestion (18). Several observational studies in patients with AHF have demonstrated that fluid overload is independently associated with increased morbidity and mortality (19, 20). One reason was that patients with AHF are at risk of death not only from cardiovascular disease (CVD) but also from multiorgan failure, such as AKI. Acute kidney injury was more common in patients with AHF (nearly 24.3%), compared with those without AKI, and the risk of in-hospital mortality was more than 2-fold higher in patients with AKI (21). Continuous renal replacement therapy is the predominant RRT modality used for critically ill patients in ICUs (5) and can address congestion, reduce fluid overload, and maintain acid-base balance to improve the survival rate.

The predictors of in-hospital mortality in patients with AHF undergoing CRRT have been reported to include older age, lower SBP and DBP, and a decreased serum creatinine level (22), which is consistent with our research. We found that age was an undoubtedly hazardous factor for AHF in that the older the patient, the higher the mortality rate, which is consistent with previous research (23). The age-related structural and functional changes in the body, along with reduced compensatory capacity, are irreversible. Diastolic blood pressure and SBP also play an important role in AHF patients (24). The perfusion of the coronary arteries occurs during diastole, and when the DBP becomes too low to maintain the perfusion, the blood flow to the coronary arteries is reduced and the heart cannot obtain enough oxygen to function, which causes damage to the heart. Our results showed that a DBP ≤60 mmHg was an independent risk factor for in-hospital mortality, similar to previous studies in which intradialytic hypotension during the 1st h after initiation of CRRT has been identified as an independent predictor of high in-hospital mortality (25). However, this does not mean that a higher DBP is necessarily beneficial once hypertension does occur and the risk of stroke increases, so we advocate maintaining the DBP at 60–90 mmHg using vasoactive or antihypertensive agents or not.

The activation of the sympathetic nervous system (SNS), usually caused by cardiac output reduction in AHF patients, is one of the major neurohormonal mechanisms of the development or progression of AHF and promotes cardiomyocyte hypertrophy and fibrosis, impairing the diastolic and systolic functions of the heart (26). The activation of the SNS also causes the inhibition of glucose-stimulated insulin secretion and the increase of glucagon secretion *via* the α-receptor, caused hyperglycemia (27). In AHF patients, hyperglycemia may be the response to the danger and is a reflection of an activated SNS. Hyperglycemia in the hospitalized patients may be caused not only by the poor glycemic control in diabetes but also by a transient stress response to current disease states, named stress hyperglycemia (28). Hyperglycemia upon admission was independently associated with in-hospital and short-term mortality in AHF patients and was an independent predictor of 1-year mortality in non-diabetes Mellitus (DM) patients with AHF (27, 29). Several studies have consistently shown that relative hyperglycemia is more strongly associated with in-hospital mortality than absolute hyperglycemia in patients with diabetes (28, 30, 31). Blood glucose needs to maintain stability in the body, although our results only showed that a blood glucose ≤10 mmol/L was a positive factor. Hypoglycemia can lead to an insufficient energy supply to the brain and heart, which leads to neuropsychiatric

symptoms, palpitations and tremors, and even comatose, sudden death, and other adverse events in severe cases. It was reasonable to control blood glucose in the range of 5–10 mmol/L or strictly 8–10 mmol/L to reduce the side effects of hyperglycemia and hypoglycemia.

Lactic acid is the mesostate of blood glucose and is produced mainly by glycolysis due to stress or hypoxia (for example, shock or arterial embolism) when the aerobic metabolism of blood glucose is reduced and then goes through glycolysis to produce energy. Breaking the balance between lactic acid production and elimination can promote lactate accumulation, called hyperlactatemia. In the setting of AHF, several mechanisms, such as peripheral hypoperfusion, low cardiac output, activation of AHF, hypoxemia, and liver or renal dysfunction (elimination lactate), can alter the lactate homeostasis (32). It is well-documented that elevated lactate levels and their continued elevation are useful for identifying high-risk patients and for predicting worse outcomes and the high risk of mortality in patients with AHF (33, 34). The elevated blood lactate acid, $\geq$2 mmol/L, predicted nearly 1.8-folds on 1-year mortality than low blood lactate acid ($<$2.5 mmol/L) (33). In our study, elevated lactate levels were a strong risk factor for death, which is consistent with the results of previous studies.

In patients with AHF with refractory volume overload and AKI, CRRT was recommended to alleviate the cardiac load and release condition. However, the time to initiate RRT in AHF remains controversial due to the lack of targeted research. Bart et al. compared ultrafiltration with diuretic-based therapy in patients with acute decompensated heart failure and worsened renal function, and found that the rates of death and rehospitalization did not differ significantly between the two treatments strategies (35). Our study showed that the interval between the admission in the hospital and starting CRRT was an independent predictor of in-hospital mortality, possibly because the early initiation of CRRT can allow the better control of metabolic abnormalities and other complications associated with increased mortality (36). This finding is consistent with previous reports. However, patients could be needlessly exposed to iatrogenic complications, such as hypotension, bleeding, infection, and hypothermia, which might explain why there was no statistically significant difference between 4–10 and $<$3 days in our study. When more than 10 days have elapsed before the initiation of CRRT, the patient mortality was higher because the conditions were mostly severe even after meticulous medical care. However, there was an inevitable selection bias in our research because those who died before meeting the criteria for initiation of CRRT or improved without the need for RRT were excluded (37). Follow-up data were not available for eligible patients in our study and could be investigated by clinicians or researchers of future studies.

We found that early treatment with intravenous loop diuretics (38), improved SBP, mechanical ventilation (39), and urine volume were associated with in-hospital mortality in AHF patients, and whether these variables could be used to improve the model is still unclear.

To our knowledge, the D-GLAD model is the first nomogram developed from data collected from more than one center that can be used to screen for patients with AHF at high risk of needing CRRT. Moreover, this is the first study to use the APACHE II score, SAPS II score, and MEWS to predict the risk of in-hospital mortality in patients with AHF receiving CRRT and to compare the results with those obtained using the D-GLAD model. However, the study had several limitations. First, we only recorded the in-hospital mortality of eligible patients and did not include further follow-up of survivors. A large, well-designed prospective study with a long-term follow-up is needed to validate and perfect the model. Second, we could only identify 226 patients who met the inclusion criteria; an addition of a greater number of eligible patients to the database will allow us to construct a more stable and accurate model. Third, we only analyzed patients who received CRRT, so whether the D-GLAD model can be used to guide the initiation of CRRT in patients who are hesitant to accept it is still unknown. Finally, this model is mostly based on the data from Caucasian and Asian populations, and the extent to which it can be adapted for use in other ethnic populations is unclear.

In conclusion, the D-GLAD model is the first nomogram to be derived from data obtained from more than one center (an AHFU database and the MIMIC-III database) and allowed the optimal prediction of in-hospital mortality in patients with AHF undergoing CRRT. The validation results in our training cohort and external cohort demonstrated that the nomogram performed well and had high accuracy, discrimination ability, and clinical effectiveness. Using this simple-to-use model, the risk of in-hospital mortality can be determined for an individual patient, which can be useful to guide the early screening of high-risk patients. Combined with the SUPER score, the D-GLAD model can more accurately assess the risk of in-hospital mortality in the AHF patients receiving CRRT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Qilu Hospital of Shandong University (KYLL-202011-114). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LG and YB conception of the study and writing of the manuscript. LG collected the data from the MIMIC III. WS and QZ collection of the data from the Qilu Hospital Acute Heart Failure Unit and analysis of all data. QY and SC revision of the manuscript. FX and YC critical revision of the

manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.678252/full#supplementary-material

Supplementary Figure 1 | Development webserver of predicting nomogram model.

Supplementary Table 1 | The baseline characteristics of the survivor cohort and the non-survivor cohort in the training cohort.

Supplementary Table 2 | The demographics and clinical characteristics of the validation cohort and the training cohort.

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Mid-Regional Proadrenomedullin (MR-proADM) and Microcirculation in Monitoring Organ Dysfunction of Critical Care Patients With Infection: A Prospective Observational Pilot Study

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Introduction: Microvascular alterations are involved in the development of organ injury in critical care patients. Mid-regional proadrenomedullin (MR-proADM) may predict organ damage and its evolution. The main objective of this study was to assess the correlation between MR-proADM and microvascular flow index (MFI) in a small cohort of 20 adult critical care patients diagnosed with infection, sepsis, or septic shock. Further objectives were to evaluate the correlation between the clearance of MR-proADM and the variables of microcirculation and between MR-proADM and the Sequential Organ Failure Assessment (SOFA) score.

Materials and Methods: This is a prospective observational pilot study. Inclusion criteria: consecutive adult patients admitted to intensive care unit (ICU) for or with infection-related illness. Daily measurement of MR-proADM and calculation of the SOFA score from admission in ICU to day 5. Repeated evaluations of sublingual microcirculation, collection of clinical data, and laboratory tests.

Results: Primary outcome: MR-proADM was not significantly correlated to the MFI at admission in ICU. A clearance of MR-proADM of 20% or more in the first 24 h was related to the improvement of the MFIs and MFIt [percentual variation of the MFIs + 12.35 (6.01–14.59)% vs. +2.23 (−4.45–6.01)%, $p = 0.005$; MFIt +9.09 (4.53–16.26)% vs. −1.43 (−4.36–3.12)%, $p = 0.002$].

Conclusion: This study did not support a direct correlation of MR-proADM with the MFI at admission in ICU; however, it showed a good correlation between the clearance of MR-proADM, MFI, and other microvascular variables. This study also supported the prognostic value of the marker. Adequately powered studies should be performed to confirm the findings.

Keywords: mid-regional proadrenomedullin, microcirculation, sepsis, septic shock, infection, organ failure

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INTRODUCTION

Sepsis is a life-threatening syndrome characterized by a widespread tissue and microvascular injury (1, 2).

Organ failure is one of the main challenges of septic patients and hemodynamic optimization is a cornerstone of adequate organ perfusion for prevention and treatment of organ dysfunction (3).

However, organ sufferance may occur even after restoration of systemic hemodynamics. The mechanisms underlying this phenomenon are multifactorial and not completely clear, but there is increasing evidence that alterations of the microvascular blood flow are strongly implicated. Sepsis affects endothelial cell function; it determines endothelial barrier disruption and leakage and it leads to microcirculatory alterations that directly contribute to organ dysfunction (4–7).

Adrenomedullin (ADM) is an endogenous peptide hormone of 52 amino acids synthesized widely through tissues (including bone, adrenal cortex, kidney, lung, blood vessels, and heart). ADM is biologically active and its effects include vasodilator, positive inotropic, diuretic, natriuretic, and bronchodilator actions; ADM is also an inhibitor for the secretion of insulin, aldosterone, and adrenocorticotropic hormone (8, 9). Previous studies showed that ADM increases in inflammatory diseases, including sepsis and septic shock, in order to stabilize the microcirculation and to protect against endothelial hyperpermeability (10–14); they also suggested that the variation in plasmatic levels of ADM may act as a marker of severity of the endothelial damage (15, 16).

Mid-regional proADM (MR-proADM) is a fragment of ADM with no known function. It is produced in ratio of 1:1 to ADM. Its half-life is numerable in hours and it proportionally reflects the activity of ADM (8).

Mid-regional proADM was already described as biomarker in community-acquired pneumonia and it has been proposed as a prognostic marker with potential clinical role in sepsis (17, 18). In the study of Valenzuela-Sánchez et al. (19), MR-proADM showed good correlation with organ dysfunction related to infection and to mortality in critical care patients. The authors evaluated the clearance of MR-proADM during the first days of intensive care unit (ICU) admission and they demonstrated an enhanced clearance of MR-proADM in survivor patients.

In our small-scale preliminary study, we aimed to investigate if MR-proADM, as biomarker of organ failure and of endothelial damage, could be correlated with microvascular alterations in critical care patients admitted in ICU for or with different degrees of infection-related illness.

MATERIALS AND METHODS

Population, Enrolment, and Data Collection

This is a prospective observational pilot study performed in the 14-bed General and Traumatic ICU of Azienda Ospedaliera Universitaria Ospedali Riuniti of Ancona (Italy).

Inclusion criteria: 20 adult (age equal or superior to 18 years old) critically ill patients, consecutively admitted in ICU for or with different degrees of infection-related illness (infection, sepsis, and septic shock), with a length of stay (LOS) in ICU inferior to 24 h before the enrollment in this study. Infection, sepsis, and septic shock were determined according to the Third International Consensus Definitions for Sepsis and Septic Shock (20).

Exclusion Criteria to enrollment were: age inferior to 18 years old, LOS in hospital longer than 48 h, conditions that prevented adequate monitoring of sublingual microcirculation, end-of-life care, and refusal to consent.

The primary objective of this study was to study a correlation between plasma levels of MR-proADM and the microcircular flow index (MFI) at admission in ICU. Sample size was calculated on the primary endpoint. It was also purpose of the study to examine the relationship between MR-proADM in the 5-day period of observation and other microvascular variables [total vessel density (TVD), De Backer score, perfused vessel density (PVD), and proportion of perfused vessels (PPV)] and to verify the association of MR-proADM with the Sequential Organ Failure Assessment (SOFA) score (as marker of organ dysfunction) and between the SOFA score and the microvascular indices. We predetermined to calculate the clearance of MR-proADM and to evaluate the relation between the first 24 h clearance and the evolution of microvascular parameters.

The study was articulated in 5 days of monitoring (day 1 to day 5) from admission in ICU.

Plasmatic levels of MR-proADM were dosed for all the timepoints. The Simplified Acute Physiology Score (SAPS) II and the Acute Physiologic Assessment and Chronic Health Evaluation Classification System II (APACHE II) scores were calculated at admission in ICU. The SOFA score was evaluated at admission (day 1) and daily to day 5.

Anthropometric and demographic data were collected at baseline including age, sex, weight, and height of the patients.

Microbiological parameters were assessed to categorize patients [infection, sepsis, or septic shock; source of infection; and presence of multidrug resistance (MDR)].

For each of the five timepoints, we recorded clinical, hemodynamic, and laboratory parameters [systolic, diastolic, and mean arterial pressure; heart rate; cardiac output where available; respiratory parameters and mechanical ventilation; venous and arterial blood gas variables; vasoactive therapy; main parameters for renal, hepatic, and hematological function; and procalcitonin (PCT)].

At day 1 (<24 h from ICU admission), day 2 (24 h after the first assessment), and day 5, the sublingual microcirculation was assessed by using incident dark field (IDF) technology.

Microvascular Assessment

Sublingual microcirculation was registered by using a high-resolution video microscopy camera (CytoCam, Braedius Medical BV, Huizen, Netherlands, UK) with IDF technology and the microcirculatory parameters were, then, derived offline with the Automated Vascular Analysis (AVA) software (version 3.2; Microvision Medical, Amsterdam, Netherlands, UK).

Microvascular assessment and analysis were performed by experienced operators and in compliance with the "second consensus on the assessment of sublingual microcirculation in

critically ill patients" and "the microcirculation image quality score" (21, 22).

The MFI, TVD, PVD, and PPV were calculated for both the small-size vessels and total vessels in all the videos analyzed. The De Backer score was analyzed for total vessels.

The MFI is a semi-quantitative measure of perfusion quality; it is calculated by dividing the image into four quadrants in which the observer reports the predominant type of flow by using an ordinal scale (0 for absent flow, 1 for intermittent flow, 2 for sluggish flow, and 3 for normal flow).The average of the four quadrants is the final MFI.

Total vessel density and De Backer score are indices of vessel density. The first is the total length of vessels divided by the total surface of the analyzed area, while the second one is calculated as the number of vessels crossing horizontal and the vertical arbitrary grid lines divided by the total length of the lines. PPV is the percentual number of perfused vessels divided by the total number of vessels; PVD is derived by multiplying vessel density by the PPV and reflects the functional vessel density.

Measurement of MR-proADM

Arterial blood samples were collected and immediately centrifuged. Plasma samples were, then, stored at −80°C for subsequent measurement of MR-proADM.

Plasmatic levels of MR-proADM were measured by using Time Resolved Amplified Cryptate Emission (TRACE) technology with Thermo Scientific™ B·R·A·H·M·S™ KRYPTOR Compact PLUS (Dasit). The reference limit for this method was 0.55 nmol/l.

Ethics

In compliance with national applicable laws, informed consent was obtained from the subject before inclusion by signing the appropriate informed consent paperwork. Patients temporarily unable to consent were included in the study with deferred subject consent in a later phase and written informative for the next of kin. The study protocol was approved by the Local Ethics Committee [Comitato Etico Regione Marche (CERM); protocol number 212639, NCT03931967] and it conformed to the principles of Helsinki declaration (last revision, Edinburgh 2000).

Sample Size Calculation

Sample size calculation was calculated on the basis of the primary endpoint of the study (correlation between plasma levels of MR-proADM and the MFI at admission in ICU-T1): 19 patients were shown to be sufficient to detect a statistically significant correlation coefficient (higher than 0.6) with a power of 80% and an alpha error of 0.05.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS statistic software (version 17.0) (IBM Corporation, New York, USA).

According to the distribution of the main variables (assessed with the Kolmogorov–Smirnov test) and to the limited size of the sample, non-parametric statistics predominated. Data are presented as median and interquartile ranges (IQRs) for continuous variables and number and percentage for discrete variables.

The Spearman's rank correlation coefficient was used to summarize the strength and direction (negative or positive) of the relationship between MR-proADM and the MFI as primary outcome measure with further parameters of microcirculation and with the severity scales. The non-parametric Mann–Whitney *U* test was used for comparisons between independent samples. The Friedman test with the Dunn's *post-hoc* pairwise comparison was used for repeated measures of the same variable. In order to take into account the factor "time" in the comparison between groups, the two-way ANOVA for repeated measures was also performed (after normalization of the data through Box-Cox transformation) for the parameter of microcirculation with the Sidack's *post-hoc* test. The area under the receiver operating characteristic (ROC) curve was calculated to sample the ability of MR-proADM to discriminate the severity of patients.

Differences were considered significant at $p < 0.05$.

RESULTS

Descriptive of the Sample

From November 2018 to June 2019, a total of 29 patients were screened for the study and 20 of them were enrolled after obtaining the informed consent. A total of 9 patients were not enrolled for exclusion criteria.

Patients were predominantly males (65%) with a median age of 70 (51–74) years. At admission in ICU, the SAPS II score was 52.5 (35.50–75.05), the APACHE II score was 19.5 (12.25–30.00), and the SOFA score was 11 (8–14). The SOFA score at admission corresponded to SOFA score at time of enrollment, as all the patients were enrolled in the first 24 h of ICU stay (**Table 1**).

TABLE 1 | Descriptive of the study population.

Age, years	70 [51–74]
Males	13 (65)
SAPS II score, AU	52.50 [35.50–75.05]
APACHE II score, AU	19.50 [12.25–30.00]
SOFA score, AU	11 (8–14)
Source of infection	
Respiratory	13 (65)
Abdominal	3 (15)
Genito-urinary	2 (10)
CNS	2 (10)
Septic shock	10 (50)
Sepsis	5 (25)
Infection without sepsis	5 (25)
PCT at admission, ng/ml	6.42 [1.01–24.08]
WBC at admission, cell * $10^3/mm^3$	9.71 [7.7–13.06]
LOS in ICU, days	12.50 [9.00–16.75]
Mortality	3 (15)

Median (IQR), n (%), AU.
IQR, interquartile range; SAPS II, Simplified Acute Physiology II; APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment; PCT, procalcitonin; WBC, white blood cell; LOS, length of stay.

Half of the 20 patients were in septic shock at recruitment and 5 of 20 patients were septic. The origin of infection was respiratory in the vast majority of them (65%). Of 13 patients with low respiratory tract infections, five patients were diagnosed with type 1 influenza virus. Mortality rate was 15% and all the non-survivors were in septic shock. The LOS in ICU was 12.50 (9.00–16.75) days, but 11 of 20 patients were transferred to other ICUs for further treatments (**Table 1**). Median LOS for patients who did not survive was 21 (9–21) days.

Mid-regional proADM was 3.42 (1.73–4.17) nmol/l at day 1, 3.02 (1.55–3.73) nmol/l at day 2, 2.05 (1.35–3.59) nmol/l at day 3, 1.8 (1.34–3.10) nmol/l at day 4, and 1.62 (1.27–3.20) nmol/l at day 5.

We calculated the clearance of MR-proADM (daily clearance in percentage) during the 5 days of recruitment: the median clearance of MR-proADM was 11.44 (−12.29–23.90)% at day 2, 10.79 (0.16–26.94)% at day 3, 1.80 (−6.82–16.38)% at day 4, and 8.82 (−2.35–20.61)% at day 5.

In **Table 2** we report the median values of MR-proADM and of PCT at admission in ICU (day 1 of enrollment) according to the diagnosis (infection, sepsis, and septic shock). No significant difference was evidenced for MR-proADM and PCT in the comparison between infected, septic, and septic shock patients.

The median values of MR-proADM at admission were higher in septic shock confronted to sepsis and of sepsis confronted to infection; these differences are not statistically significant. PCT did not show a linear increase in the three subgroups and resulted in very wide IQRs. MR-proADM and PCT showed a weak linear correlation in the population, when evaluated at T1 (Spearman's rank correlation coefficient + 0.672, $p = 0.001$). The correlation was more solid in the subgroup of patients with septic shock (Spearman's rank correlation coefficient + 0.758, $p = 0.011$).

TABLE 2 | Day 1 plasmatic values of MR-proADM and procalcitonin (PCT).

	Infection	Sepsis	Septic shock	p value
MR-proADM, nmol/l	1.44 [0.94–1.84]	2.16 [1.35–4.00]	3.99 [3.58–7.04]	ns
PCT, ng/ml	1.20 [0.52-6.93]	0.8 [0.59-3.73]	25.95 [1.79-86.62]	ns

Median (IQR).
MR-proADM, mid-regional proadrenomedullin.

Mid-Regional proADM and Microvascular Flow Index

Table 3 presents median values of the parameters of microcirculation in the general population at the three timepoints.

The MFI of small vessels (MFIs) at admission in ICU was lower in the subgroup of septic shock patients [2.72 (2.5–2.85)], but not statistically different from that of septic [2.83 (2.83–2.96)] and infected [2.83 (2.58–2.87)] patients. Similar results were evident for MFI of total vessels (MFIt).

Both the MFIs and MFIt at admission in ICU were not correlated to MR-proADM (the Spearman's rank correlation coefficient not statistically significant) in the general population nor in the three subgroups of patients (infected, septic, and shocked).

We determined an arbitrary cutoff of 20% of the clearance of MR-proADM in the first 24 h of recruitment by dividing the patients in two groups: patients who showed a clearance of MR-proADM higher and equal-to-lower than 20%.

We measured the percentage of variation of the MFI of small and total vessels in the same time frame. The MFI improved significantly more in patients that showed a clearance of MR-proADM > 20% compared to those patients where the clearance of MR-proADM was ≤ 20% [the Mann–Whitney *U* test, percentual variation of the MFIs +12.35 (6.01–14.59)% vs. +2.23 (−4.45–6.01)%, $p = 0.005$; percentual variation of MFIt + 9.09 (4.53–16.26)% vs. −1.43 (−4.36–3.12)% $p = 0.002$] (**Figure 1**).

Patients with reduced clearance of MR-proADM showed lower clearance also at T5 (clearance T5 to T2 19.2 vs. 24.3%) and deterioration in the MFIs [negative variation of −6.1% (−10.5–0) vs. 0% (−6.33–(+3.1); $p = 0.017$]. The trend was similar for MFIt, but not statistically significant ($p = 0.06$).

TABLE 3 | Descriptive of microvascular parameters at day 1, day 2, and day 5.

	Day 1	Day 2	Day 5	*p* value
MFIs, AU	2.83 [2.67–2.83]	2.92 [2.75–2.00]	2.75 [2.58–2.92]	ns
MFIt, AU	2.87 [2.75–2.92]	2.92 [2.86–3.00]	2.83 [2.75–2.96]	ns
TVDs, mm/mm^2	21.20 [17.07–23.85]	18.98 [16.99–23.11]	20.31 [18.29–23.17]	ns
TVDt, mm/mm^2	21.87 [18.21–25.38]	19,60 [18.33–23.68]	20.94 [19.15–24.10]	ns
PVDs, mm/mm^2	20.10 [16.55–23.04]	18.88 [16.88–23.00]	18.70 [17.49–22.72]	ns
PVDt, mm/mm^2	20.85 [17.70–24.86]	19.41 [18.21–23.57]	20.72 [18.83–23.52]	ns
PPVs, %	97.01 [95.47–98.01]	98.57 [96.26–99.39]	96.86 [95.14–98.71]*	0.023
PPVt, %	97.04 [96.53–98.35]	98.65 [96.61–99.41]	97.11 [95.05–98.59]	ns
De Backer score, 1/mm	12.99 [10.29–13.96]	11.28 [10.18–13.27]	11.77 [11.14–13.83]	ns

*Median (IQR) [Friedman test with Dunn's post-hoc test. *$p < 0.05$ in the comparison $t_{(5)}$ on $t_{(2)}$].*
MFIs, microvascular flow index of small vessels; MFIt, microvascular flow index of total vessels; TVDs, total vessel density; TVDt, total vessel density of total vessels; PVDs, perfused vessel density; PVDt, perfused vessel density of total vessels; PPVs, proportion of perfused small vessels; PPVt, proportion of perfused vessels for total vessels.

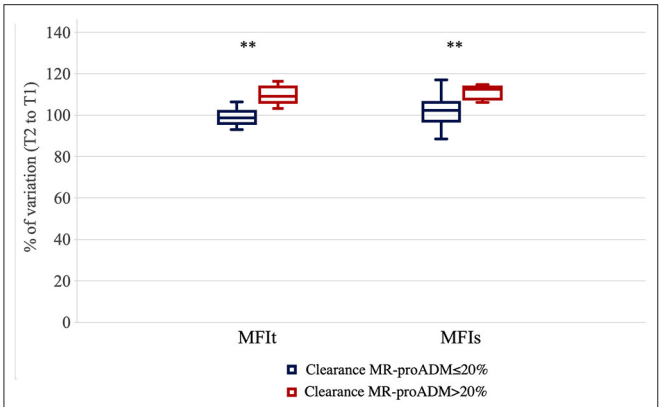

FIGURE 1 | Percentage of variation for microvascular flow index of total vessels (MFIt) and MFI of small vessels (MFIs) in the first 24 h of evaluation in the two groups of patients [clearance of mid-regional proadrenomedullin (MR-proADM) inferior-to-equal or higher than 20%]. $^{**}p < 0.01$.

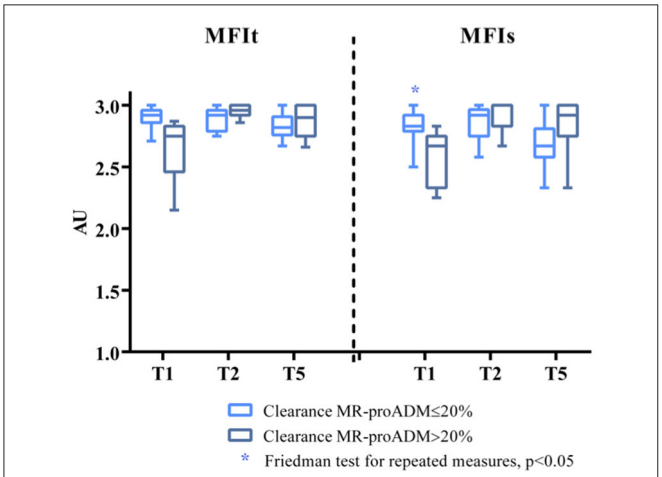

FIGURE 2 | MFIs and MFIt at T1, T2, and T5 in the two groups of patients (clearance of MR-proADM inferior-to-equal or higher than 20%). The Friedman test for repeated measures statistically significant for MFIs in the group of patients with clearance of MR-proADM ≤ 20%. $^{*}p < 0.05$.

The Friedman test for repeated measures was statistically significant for the MFIs in the group of patients with clearance of MR-proADM ≤ 20% ($p = 0.035$, Dunn's *post-hoc* test not significant; $p = 0.057$ for patients with clearance of MR-proADM > 20%) (**Figure 2**).

The two-way ANOVA for repeated measures, performed after normalization of the data through Box-Cox transformation, showed for the MFIs a significant interaction between time and group ($p = 0.015$), but no significant effect of time ($p = 0.611$) or group ($p = 0.836$) *per se*. The Sidack's multiple comparisons test revealed a significant difference at baseline between the two groups ($p = 0.043$) and no other differences at the other time points [$t_{(2)}$: $p = 0.848$; $t_{(5)}$: $p = 0.419$]. Moreover, there was a significant increase in the MFIs at day 5 only in the group of patients with clearance of MR-proADM > 20% ($p = 0.045$ vs. baseline). The two-way ANOVA was also performed on the percentage of variation of the MFIs from baseline and it showed a significant interaction between time and group ($p = 0.005$) and a significant effect of both the time ($p = 0.008$) and group ($p = 0.004$). The Sidack's multiple comparisons test revealed a significant difference between the two groups at 24 h ($p = 0.009$) and at day 5 ($p < 0.001$). A significant increase in the MFIs was found only in the group of patients with a clearance of MR-proADM > 20% either at 24 h ($p = 0.002$ vs. baseline) and 5 days ($p = 0.017$ vs. baseline), while the MFIs did not significantly change over time in patients with a clearance of MR-proADM ≤ 20% (**Figure 3**).

For MFIt, the two-way ANOVA test showed a significant interaction between time and group ($p = 0.004$). No significant effect of time ($p = 0.561$) or group ($p = 0.937$) was noticed. There was a significant difference at baseline between the two groups ($p = 0.029$; Sidack's multiple comparisons test) and no other differences at the other time points [$t_{(2)}$: $p = 0.273$; $t_{(5)}$: $p = 0.780$]. Moreover, there was a significant increase in MFIt at day 2 only in the group of patients with clearance of MR-proADM > 20% ($p = 0.018$ vs. baseline). The analysis performed on percentage of variation of MFIt from baseline showed a significant interaction between time and group ($p = 0.001$) and a significant effect of both the time ($p = 0.003$) and group ($p = 0.006$). The difference between the two groups was significant at 24 h ($p < 0.001$) and at day 5 ($p = 0.002$) and a significant increase in MFIt was found only in the group of patients with clearance of MR-proADM > 20% either at 24 h ($p < 0.001$ vs. baseline) and 5 days ($p = 0.002$ vs. baseline) (**Figure 3**).

Mid-Regional proADM and Other Parameters of Sublingual Microcirculation

Mid-regional proADM was not correlated to the parameters of sublingual microcirculation at admission in ICU. The proportion of perfused small and total vessels were weakly correlated to MR-proADM at day 2 (Spearman's rho correlation coefficient for PPVs−0.648, $p = 0.002$; for PPVt−0.578, $p = 0.008$).

The Mann–Whitney *U* test showed a difference in the percentual variation of PVDs and PVDt day 2 to day 1 between patients with a clearance of MR-proADM > 20% and ≤ 20%, respectively; the percentual variation of PVDs was +10.51 [−9.28–(+)15.09]% vs. −9.93 [−19.32–(−)3.94]%; $p = 0.024$] and the percentage of variation of PVDt was 6.94 [−8.98–(+)23.12]% vs. −9.65 [−16.15–(−)4.35]%; $p = 0.024$].

The difference between the two groups was shown also in the interval day 5 to day 1 [percentage of variation of PVDs +20.19 (2.26–33.57)% vs. −14.24 [−27.05–(+)0.17]%; $p = 0.005$] [PVDt + 15.43 (0.68–32.67)% vs. −11.27 [−23.23–(+)3.42]%; $p = 0.01$].

The Friedman test for repeated measures was statistically significant for PVDs and PPVs in the group that showed a reduced clearance of MR-proADM ($p = 0.039$ for PVDs, the Friedman test for repeated measures, the Dunn's *post-hoc* test significant in the comparison T5 to T1, $p = 0.043$; $p = 0.027$ for PPVs, the Dunn's *post-hoc* test significant in the comparison T5 to T2, $p = 0.024$) (**Supplementary Figure 1**).

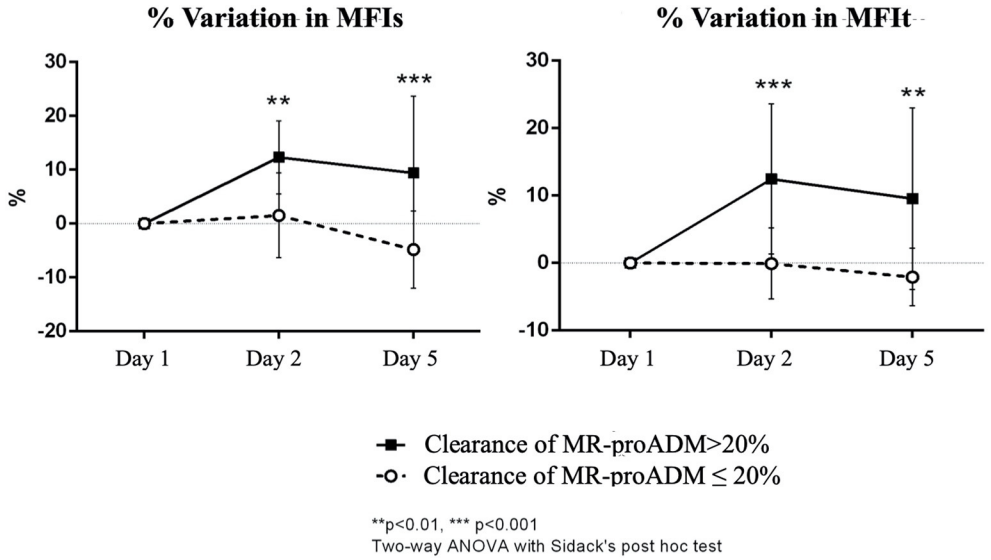

FIGURE 3 | Percentual variation of MFIs and MFIt from baseline in the two groups of patients (clearance of MR-proADM inferior-to-equal or higher than 20%). The two-way ANOVA with the Sidack's *post-hoc* test. $^{**}p < 0.01$. $^{***}p < 0.001$.

The two-way ANOVA for repeated measures (Box-Cox transformation) showed for PVDs a significant interaction between time and group ($p = 0.004$). The Sidack's test was not significant at any time points; however, there was a significant increase in PVDs at day 5 in the group of patients with clearance of MR-proADM > 20% ($p = 0.024$ vs. baseline) and a significant decrease in PVDs at day 5 in the group of patients with clearance of MR-proADM ≤ 20% ($p = 0.035$ vs. baseline). The two-way ANOVA performed on percentage of variation of PVDs from baseline found a significant interaction between time and group ($p = 0.002$) and a significant effect of group ($p < 0.001$). A difference between the two groups was evident at 24 h ($p = 0.012$) and at day 5 ($p < 0.001$). A significant increase in PVDs was found in the group of patients with clearance of MR-proADM > 20% at 5 days ($p = 0.022$ vs. baseline), while a significant decrease was found in patients with clearance of MR-proADM ≤ 20% at day 5 ($p = 0.021$ vs. baseline) (**Figure 4**).

For PVDt, a significant interaction was evidenced between time and group ($p = 0.015$); the Sidack's multiple comparisons test was not significant. PVDt tended to increase at day 5 in the group of patients with clearance of MR-proADM > 20% ($p = 0.066$ vs. baseline) and decrease at day 5 in the group of patients with clearance of MR-proADM ≤ 20% ($p = 0.088$ vs. baseline); however, the changes were not statistically significant. There was a significant interaction between time and group ($p = 0.006$) and a significant effect of group ($p = 0.001$) in the two-way ANOVA performed on percentage of variation of PVDt from baseline with a significant difference between the two groups at 24 h ($p = 0.007$) and at day 5 ($p < 0.001$). A significant increase in PVDt was only found in the group of patients with clearance of MR-proADM > 20% at 5 days ($p = 0.019$ vs. baseline) (**Figure 4**).

For PPVs and PPVt, no significant interaction between time and group and no significant effect of time were found. The Sidack's multiple comparisons test revealed no significant difference between the two groups at any time points. Moreover, there was no significant change over time in PPVs or PPVt in either group.

The test also showed a significant interaction between time and group for De Backer score ($p = 0.022$) and for TVDs ($p = 0.018$); the Sidack's test was not statistically significant.

No other correlation was evidenced between MR-proADM and the De Backer score or TVD of total and small vessels.

Mid-Regional proADM and the SOFA Score

A clearance of MR-proADM ≤ 20% in the first 24 h of ICU stay discriminated a worsening of the SOFA score from T2 to T5 (AUC 0.938, CI 0.776–1, $p = 0.025$) with the median SOFA score at day 5 of 13 (9–15) in the group where MR-proADM clearance was lower than 20 vs. 8% (6–11) in the group with higher clearance.

The SOFA Score and Microvascular Variables

The SOFA score was correlated to microvascular variables at admission in ICU only in septic shock patients with the Spearman's rho correlation coefficient for MFIs of −0.698 ($p = 0.025$) and for PPVs of −0.720 ($p = 0.017$).

At day 2, the SOFA score was weakly correlated to PPVs (the Spearman's rho correlation coefficient −0.459; $p = 0.042$) also in the general population. The correlation was stronger in the group with clearance of MR-proADM > 20% (the Spearman's rho correlation coefficient −0.893; $p = 0.007$) than in the group with clearance of MR-proADM ≤ 20% (the Spearman's rho correlation coefficient −0.663; $p = 0.014$). Similar correlation was evident at day 2 between the SOFA score and PPVt (the Spearman's rho correlation

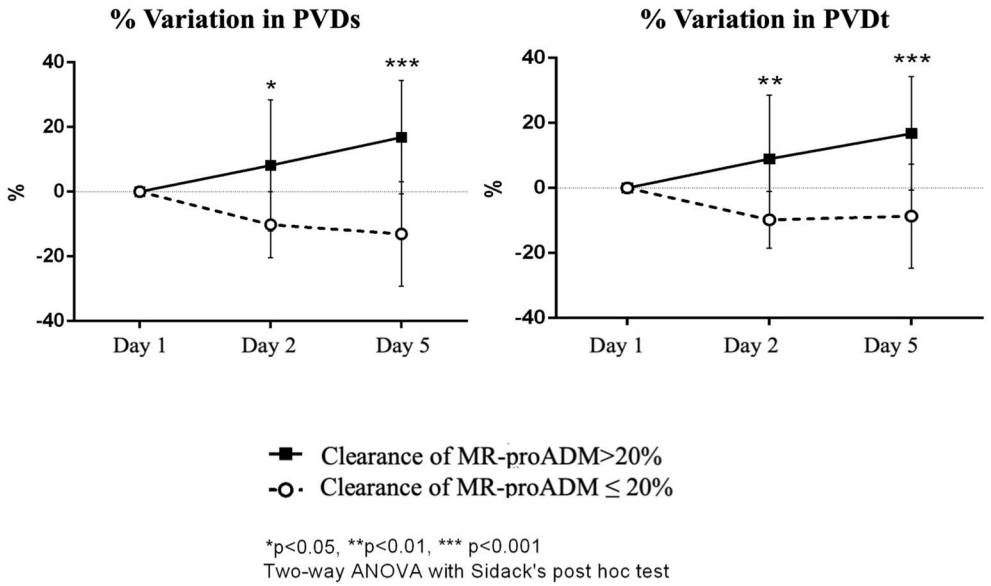

FIGURE 4 | Percentual variation of perfused vessel density of small vessels (PVDs) and PVD of total vessels (PVDt) from baseline in the two groups of patients (clearance of MR-proADM inferior-to-equal or higher than 20%). The two-way ANOVA with the Sidack's *post-hoc* test. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

coefficient −0.461; $p = 0.041$ (−0.883, $p = 0.08$ in the group with clearance of MR-proADM > 20% and −0.682, $p = 0.01$ for the group with clearance of MR-proADM ≤ 20%, respectively).

The SOFA score was not correlated to microvascular variables at day 5.

DISCUSSION

In this small-scale preliminary study, we consecutively recruited 20 adult patients admitted in ICU with or for infection, sepsis, or septic shock. We monitored them for 5 consecutive days, analyzing the plasmatic levels of MR-proADM, the main clinical parameters, and the scores of severity. We evaluated the sublingual microcirculation to understand if MR-proADM, as biomarker of organ failure and of ADM-activity on the endothelium, could be associated with alterations of the variables of microcirculation and in particular to the MFI at admission in ICU. We calculated the clearance of MR-proADM over the first 24 h of recruitment and we compared it to the evolution over time of microvascular variables and of the SOFA score.

Mid-regional proADM at recruitment (and admission in ICU) tented to be higher in septic shock patients, than in septic and infected ones, but the difference was not statistically significant. The first 24 h clearance showed relation with the SOFA score. Although MR-proADM was not statistically related to the MFI at admission in ICU, the reduction of plasmatic levels of MR-proADM in the first 24 h of intensive care treatment was associated with an improvement of the MFI that was more evident than in patients with reduced or no clearance of the marker. Patients in which MR-proADM cleared showed a substantial stability of the MFI toward the first 5 days and an improvement in the SOFA score, while the opposite group suffered a deterioration of sublingual microcirculation in terms of the MFI and showed the statistically higher SOFA score at day 5. Similar evolution was evident for other parameters of microcirculation, in particular PVD and PPV of small vessels that relate to the quality of the flow and to microvascular perfusion. The proportion of perfused vessels was inversely correlated to the SOFA score at day 2, strongly in patients with higher clearance of MR-proADM. The SOFA score was correlated to microvascular variables at admission in ICU, but just in the small group of patients with septic shock.

Sepsis and septic shock are characterized by increased endothelial permeability, endothelial barrier dysfunction, proinflammatory activation of endothelial cell, reduced deformability of red blood cells, alterations of the glycocalyx, and leukocyte adhesion and rolling; further mechanisms lead to microcirculatory flow disturbance in septic pattern (23–25). Damaged microcirculation is involved in the pathophysiology of organ dysfunction: it compromises tissue perfusion through the impairment of both the diffusion (reduced and heterogeneous capillary density) and convection (altered capillary flow) of oxygen and nutrients; the altered blood flow furtherly acts as trigger to tissue inflammation (23–25).

In this situation, as in further inflammatory diseases, ADM increases and MR-proADM parallelly to ADM (10, 23). The increase of ADM participates to stabilize the endothelial barrier and to optimize the junctional integrity; it protects endothelial cells and the microcirculation (9, 10, 26–29). This effect was demonstrated on endothelial cells from different vascular beds (lung pulmonary artery, umbilical vein, and brain) in *ex-vivo* and

in-vivo models and on the ileal microcirculation of experimental rat model of *Staphylococcus aureus* alpha-toxin-induced sepsis (13, 26, 29). The relevance of ADM on the integrity of the microvasculature in sepsis is the trigger for this study.

In this study, the single value of MR-proADM was not correlated to microvascular variables at admission in ICU, but the 24 h clearance of MR-proADM was correlated with the quality of the microvascular perfusion, the density of microcirculation, and with the severity of organ dysfunction.

From the results of this study, we could hypothesize that patients who showed enhanced clearance of MR-proADM and where organ dysfunction and microcirculation both improved could be considered as patients who controlled the inflammatory source that triggered production of ADM (ratio 1:1 with MR-proADM) and in which the endothelial damage of microcirculation resolved (or was more controlled). The opposite result in the group where MR-proADM cleared more slowly may indicate persistence of synthesis and release of ADM due to an active organ dysfunction and also of microvascular dysfunction.

Full-scale prospective studies will be needed to confirm the hypothesis, but it would be consistent with previous studies and in particular with the study of Valenzuela-Sánchez et al. (19), where they reported that ongoing MR-proADM levels at 48 h following admission in ICU and clearance of the marker on day 5 following admission helped to determine unfavorable evolution in 104 patients with severe sepsis.

As a pilot study on a small number of patients, our investigation cannot provide any conclusive answer on the correlation between MR-proADM and the microvascular and organ perfusion for several and important limitations. As the estimation of the sample size was aimed to the primary objective of this study (correlation of the single value of MR-proADM and the MFI at admission in ICU), the population could be statistically underpowered for the secondary analysis performed on the clearance of MR-proADM and the MFI, the SOFA score, and other microvascular parameters. The decision to choose an arbitrary cutoff of the 24 h clearance of MR-proADM could influence the results of this study and the use of a different cutoff could lead to different results. There is limited literature about the clearance of MR-proADM; none about the cutoff of clearance at 24 h and this threshold value requires further validation (8, 30, 31).

These factors should be carefully considered when extrapolating the data reported. The results could be also affected by the difference in the rate of disappearance of MR-proADM and the rate of changes in the microcirculation. Moreover, this study was intentionally designed to include a heterogeneous population of patients with wide different degrees of infection-related illness and, therefore, different expression of MR-proADM and degrees of microvascular alterations. The two groups analyzed showed baseline differences and this determinant influences the reliability of the results. Some of the patients enrolled presented sepsis related to viral origin in which MR-proADM could have performed within given limits, if considered just as single value (admission value) without examining a trend, although few studies suggest it as effective prognostic tool (8, 32) and the advanced average age of our population may also have affected the results and should be cautiously considered in the limitations of our data.

The microvascular damage in our population was, indeed, less severe of what we can expect in a population of septic and septic shock patients (in particular for the MFI and PPV), as we also included patients with infection, but without sepsis where the microvascular impairment is less studied and less homogeneous; most of the patients presented with an MFI < 3 at admission in ICU and this result was consistent with our previous study, the MicroDAIMON study (33), where we reported an abnormal MFI on day 1 of admission in 20.6% of the patients and in 55.7% of cases during ICU stay; on the other hand, the median value of the MFI was still acceptable even in septic shock patients and the damage of the microcirculation was expressed heterogeneously among patients. The density of vessels (that is more strongly related to outcome in septic patients) was less impaired than expected, while the dominant alteration was the quality of the perfusion (6, 34).

For all the limits of this study explained, future full-scale studies should be performed in a more homogeneous population.

Although we suggest caution in reading our findings for the limitations that we already explained, we believe that our results may justify further research projects to evaluate if the trend of MR-proADM toward days could be able to relate to the evolution of microvascular dysfunction and of organ injury. If MR-proADM confirms the correlation found, it may play a clinical role as a biomarker in predicting the microvascular response to infections, sepsis, or septic shock. There are limited publications on the usefulness of MR-proADM in the field of critical care; we suggest this will be a field of interest (15, 32, 35–38).

CONCLUSION

In our small cohort of adult patients admitted in ICU with infections, sepsis, and septic shock, MR-proADM and the MFI were not correlated at admission in ICU; however, a correlation existed between the first 24 h clearance of MR-proADM and the MFI and between the clearance of the molecule and other indices primarily connected with the quality of perfusion of the sublingual microcirculation. We believe that the relation between the expression of MR-proADM and the infection-related microvascular impairment merits further investigation: the clearance of MR-proADM could be a variable of interest in a comprehensive evaluation of this type of patients, but full-scale studies are needed to confirm our findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Regione Marche - CERM; protocol

number 212639, NCT03931967. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RD: formal analysis, investigation, methodology, and writing. ED: investigation, methodology, and review and editing. CS, AC, EC, JM, VG, and EA: investigation. PG: investigation and analysis. MB and MM: analysis. AD: conceptualization, methodology, writing—review and editing, and project administration. All the authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.680244/full#supplementary-material

Supplementary Figure 1 | Total vessel density (TVD), proportion of perfused small vessel (PVD), and PPV of small and total vessels, De Backer score in the two groups of patients (clearance of MR-proADM inferior-to-equal or higher than 20%). The Friedman test with the Dunn's *post-hoc* test. $*p < 0.05$ for the Dunn's *post-hoc* test.

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The Utility of a Point-of-Care Transcranial Doppler Ultrasound Management Algorithm on Outcomes in Pediatric Asphyxial Out-of-Hospital Cardiac Arrest – An Exploratory Investigation

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Background: Transcranial Doppler ultrasound is a sensitive, real time tool used for monitoring cerebral blood flow; it could provide additional information for cerebral perfusion in cerebral resuscitation during post cardiac arrest care. The aim of the current study was to evaluate the utility of a point-of-care transcranial Doppler ultrasound management algorithm on outcomes in pediatric asphyxial out-of-hospital cardiac arrest.

Methods: This retrospective cohort study was conducted in two tertiary pediatric intensive care units between January 2013 and June 2018. All children between 1 month and 18 years of age with asphyxial out-of-hospital cardiac arrest and a history of at least 3 min of chest compressions, who were treated with therapeutic hypothermia and survived for 12 h or more after the return of circulation were eligible for inclusion.

Results: Twenty-one patients met the eligibility criteria for the study. Sixteen (76.2%) of the 21 children were male, and the mean age was 2.8 ± 4.1 years. Seven (33.3%) of the children had underlying disorders. The overall 1-month survival rate was 52.4%. Twelve (57.1%) of the children received point-of-care transcranial Doppler ultrasound. The 1-month survival rate was significantly higher ($p = 0.03$) in the point-of-care transcranial Doppler ultrasound group (9/12, 75%) than in the non-point-of-care transcranial Doppler ultrasound group (2/9, 22.2%).

Conclusions: Point-of-care transcranial Doppler ultrasound group was associated with a significantly better 1-month survival rate compared with no point-of-care transcranial Doppler ultrasound group in pediatric asphyxial out-of-hospital cardiac arrest.

Keywords: point-of-care, transcranial Doppler ultrasound, asphyxial, pediatric, out-of-hospital cardiac arrest

BACKGROUND

Asphyxia is the most common cause of pediatric out-of-hospital cardiac arrest (OHCA). Despite advances in resuscitation, patients who survive pediatric OHCA often suffer from high mortality and severe neurological sequelae (1–3). The neurological prognosis after pediatric OHCA depends on the duration and severity of global brain ischemia and hypoxia (4, 5). Effective cerebral perfusion after resuscitation has a notable influence on neurological outcomes (6–8). However, the return of spontaneous circulation (ROSC) does not automatically restore adequate cerebral perfusion. Actual cerebral blood flow is difficult to measure in children with critical illness because accurate measurement methods, including single-photon emission computed tomography, positron emission tomography, and radionuclide angiography are complex techniques, which are not suitable for routine use in clinical practice. The identification of a more immediate, non-invasive, bedside approach to complement these existing methods is therefore of importance.

Transcranial Doppler ultrasonography (TCD) provides an easily applicable, bedside technique for the evaluation and monitoring of cerebral blood flow in the main cerebral arteries. Point-of-care TCD has many useful applications in the day-to-day bedside assessment of cerebral hemodynamic status in neurocritical care practice, including post cardiac arrest care (9–14). A patient's cerebral hemodynamic status after resuscitation can be determined using the pattern of Doppler spectral waveform, the pulsatility index (PI) and the mean flow velocity of the main cerebral arteries following TCD examination (9–12). Using serial TCD examinations, changes in the Doppler spectral waveform, PI and mean flow velocity strongly reflect hemodynamic fluctuations during post-cardiac arrest care (10, 11, 13–16).

Therefore, point-of-care TCD might guide cerebral resuscitation to improve the patient's cerebral hemodynamic status during post cardiac arrest care. However, only a few studies have reported on point-of-care TCD guided cerebral resuscitation in pediatric asphyxial OHCA survivors (14). A consensus stepwise management algorithm was designed, based on the experiences described in the authors previously published article, for the intensive care of unconscious pediatric asphyxial OHCA cases (10). This was available for use in the author's pediatric intensive care unit since 2013. The aim of the present exploratory analysis was to evaluate the effect of point-of-care TCD guided cerebral resuscitation on patient outcomes in pediatric asphyxial OHCA survivors.

Abbreviations: PCPC, Pediatric Cerebral Performance Category; ROSC, recovery of spontaneous circulation.

METHODS

Patient Population

The present investigation was a retrospective cohort study using chart reviews of asphyxial OHCA at two pediatric intensive care units of Chang Gung Children's Hospital (Linkou and Kaohsiung branches), between January 1st 2013 and June 30th 2018 (**Figure 1**). OHCA was defined as patients who had successfully been resuscitated with ROSC following cardiac arrest, and for whom chest compressions were initiated before arriving at the hospital (1, 2, 10). Asphyxial cardiac arrest was defined as resuscitation secondary to preceding acute respiratory failure.

Patients were eligible for the study if they met the following criteria: (1) aged between 1 month and 18 years; (2) duration of cardiac arrest was at least 3 min and they survived for 12 h or more after the ROSC; (3) comatose status (Glasgow coma scale [GCS] score) $\leq$8 after ROSC; (4) receiving therapeutic hypothermia (1, 2, 10). Patients were excluded if they met any of the following criteria: (1) were older than 18 years; (2) had hemodynamic instability refractory to intensive care and died within 12 h; (3) were not in a coma after resuscitation (GCS >8); (4) were known to have pre-existing degenerative neurological diseases; and (5) had ventricular fibrillation, a history of congenital heart disease or were on extracorporeal membrane oxygenation. If a patient experienced more than one resuscitation during the study period, only the first resuscitation meeting the eligibility criteria was included. The present study was approved by the Chang Gung Memorial Hospital Institutional Review Board (IRB numbers: 201700975B0, 201700976B0, 201700977B0 and 201900302B0).

Post-cardiac Arrest Care

The two study institutions follow general principles of post cardiac arrest care after resuscitation (2, 10). In general, systolic and mean arterial blood pressure are maintained at or above the lower limit in children. All patients were intubated with mechanical ventilation to maintain an arterial oxygen saturation of $\geq$94% and normocarbia ($PaCO_2$ 35–40 mmHg). The hemoglobin level was also maintained above 10 gdL^{-1} (1, 2, 10). With regard to the treatment of increased ICP, the head of the bed was routinely elevated to >30°. Hyperosmolar therapy with mannitol and/or 3% hypertonic saline was used to lower ICP. The goal osmolality was between 300 and 320 mosm/KgH_2O and the goal serum sodium was between 145 and 155 mEq/L (17, 18). All

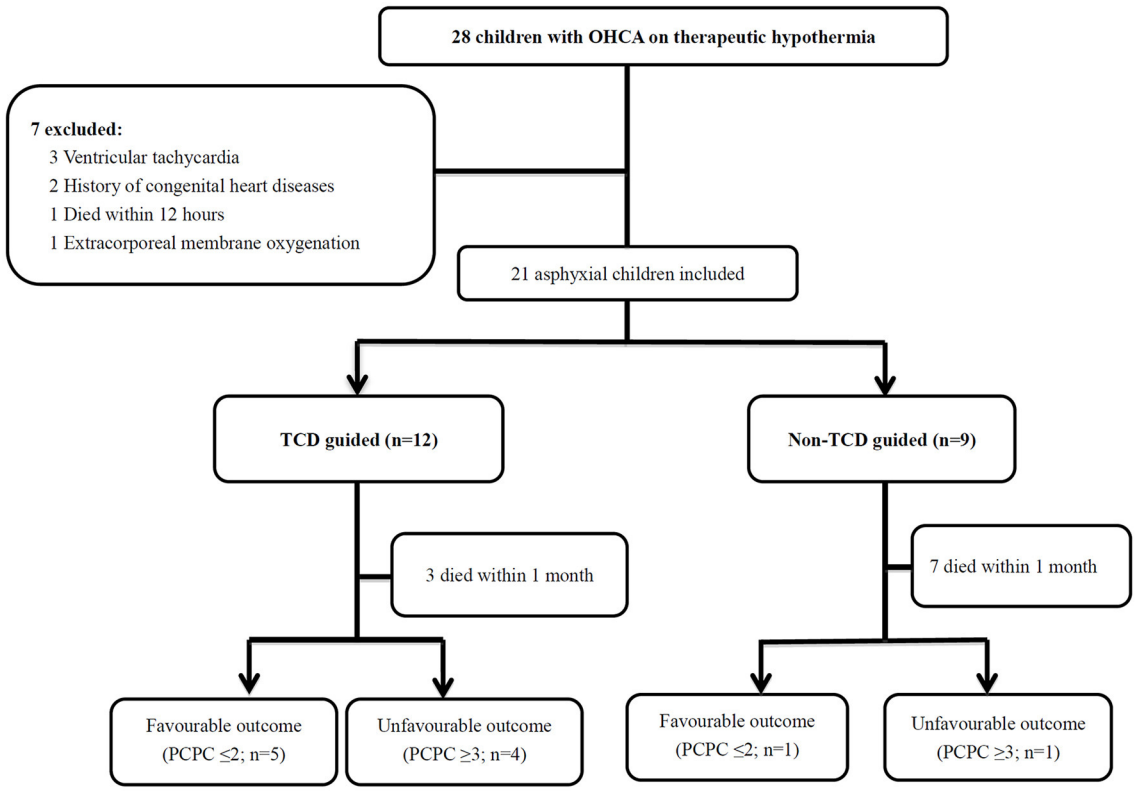


FIGURE 1 | Twenty-eight patients with OHCA with therapeutic hypothermia were identified. A total of 7 children were excluded, and 21 asphyxial OHCA comatose patients were enrolled, including 12 patients who received the TCD guided cerebral resuscitation protocol and 9 patients without the TCD guided cerebral resuscitation protocol. The patients with 6-month neurological outcomes included those who died during the follow-up period. The survival rate was significantly higher ($p = 0.03$) in the TCD guided group (9/12, 75%) compared with the non-TCD guided group (2/9, 22.2%). OHCA, out-of-hospital cardiac arrest; PCPC, pediatric cerebral performance category; TCD, Transcranial Doppler ultrasound.

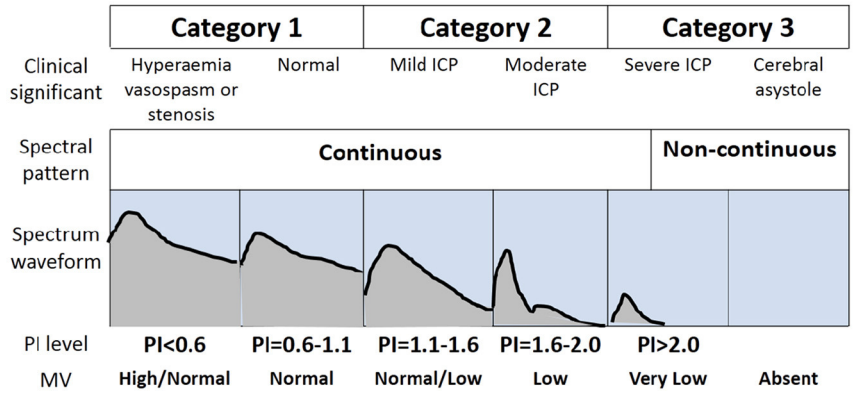
patients also received therapeutic hypothermia, and were sedated with midazolam and/or received neuromuscular blockers.

Point-of-Care TCD Guided Cerebral Resuscitation Protocol

The point-of-care TCD guided cerebral resuscitation protocol was performed at the Linkou branch of the hospital. Serial TCD examinations of the bilateral middle cerebral arteries (MCAs) were performed using a 2 MHz probe (128XP; Acuson, Mountain View, CA, USA) or an S5-1 MHz probe (Philips, Andover, MA, USA). Point-of-care TCD was performed in three phases of therapeutic hypothermia: a pre-hypothermia phase, hypothermia phase (72 h when the body temperature reached 33°C), and a rewarming phase. TCD findings were provided to the clinical teams at least once every day, or more often if any changes occurred. For each TCD investigation, the pattern of Doppler spectral waveform, values of the peak, end diastolic and mean flow velocity were recorded and the PI was calculated (9–12). The pattern of Doppler spectral waveform was divided into discontinuous and continuous patterns. A discontinuous pattern was defined as a pattern with the loss of diastolic flow, the appearance of retrograde diastolic flow, or no detectable flow. The normal values and defined abnormal values for PI and mean flow velocity in the MCA used in the current study are summarized in **Figure 2** (10). The TCD findings were scored as the most severe findings in different phases. If the PI and mean flow velocity were different in bilateral MCA, the most severely abnormal values were used as the severity of this phase.

According to TCD data and the prognosis in previous literature, the TCD finding was divided into three categories: category (1) continuous waveform with PI <1.1 and normal or high mean flow velocity, category (2) continuous waveform with PI between 1.1 and 2.0 with low or normal mean flow velocity, category (3) discontinuous waveform or continuous waveform with PI >2.0 and low mean flow velocity (**Figure 2**) (10).

Hypertonic saline sliding scale protocol was used to achieve target sodium levels at 3 different categories, which was modified from previously published stepwise protocol for intracranial pressure control in head-injured pediatric patients (19, 20). The goal of hyperosmolar therapy for category 1 was maintenance of serum osmolality between 290 and 300 mOsm/kg H_2O and serum sodium between 145 and 150 mEq/L, and systolic and mean arterial blood pressures at or above the lower limit in children (19, 20). For category 2, the goal of hyperosmolar therapy was maintenance of serum osmolality between 300 and 320 mOsm/kg H_2O and serum sodium between 150 and



ICP: Intracranial pressure; PI: pulsatility index; MV: mean velocity

The normal values and defined abnormal values for transcranial Doppler used in this study

	Normal	Abnormal
MCA TAMX Velocities (cm/s)		
3–12 months	74 (±14)	>88 or <60
1–3 years	85 (±10)	>95 or <75
4–6 years	94 (±10)	>104 or <84
7–10 years	97 (±9)	>106 or <88
11–18 years	81 (±11)	>92 or <70

MCA: middle cerebral artery; TAMX: time-averaged mean of the maximal velocities;
(*): The standard deviation (SD) velocities
Table is modified from the data in reference 10.

FIGURE 2 | The category of transcranial Doppler ultrasound findings according to spectral pattern, PI and mean flow velocities after the ROSC. The figure was modified from references 9 and 11. ICP, Intracranial pressure; PI, pulsatility index; MV, mean velocity; ROSC, return of spontaneous circulation.

155 mEq/L (19, 20), and achieving the lower limit of mean flow velocity on TCD by increasing vasoactive medications or administering fluids and blood products (19–21). For category 3, vasoactive medications combined with fluids or blood products were administered to achieve higher systolic and mean arterial blood pressures (8, 19–21). The goal of the intensive care guided by TCD findings were: (1) to achieve a continuous waveform and at least the lower limit of mean flow velocity; (2) to maintain the serum osmolality at 320–340 mOsm/kg H_2O and serum sodium at 155–160 mEq/L (19, 20) (**Figure 3**).

Data Collection

The following information was collected for all patients: (1) demographics and pre-existing diseases; (2) event characteristics, such as first-monitored rhythm during arrest and the duration of cardiopulmonary resuscitation; (3) variables after resuscitation. The primary outcome was the survival rate at 30 days following cardiac arrest.

The primary cause of death within 1 month was categorized into 3 groups: (1) brain death and withdrawal for poor neurological prognosis, (2) cardiovascular failure/futility, and (3) and respiratory failure/futility (2). The secondary outcome was duration of hospitalization and neurological outcome, which was assessed using Pediatric Cerebral Performance Category (PCPC) scores according to the recommendations for outcome assessments in comatose cardiac arrest patients in children who survived for 6 months after the events and in those who died during follow-up (1, 2, 10). Neurological outcomes were dichotomized as either a favorable prognosis (PCPC $\leq$2) or an unfavorable prognosis (PCPC $\geq$3).

Statistical Analysis

The patient characteristics in each study group are represented as descriptive statistics, and the data are presented as the mean $\pm$ standard deviation (SD). The effects of point-of-care TCD guided cerebral resuscitation on the 1-month survival rate and 6-months neurological outcomes were analyzed. Between group differences

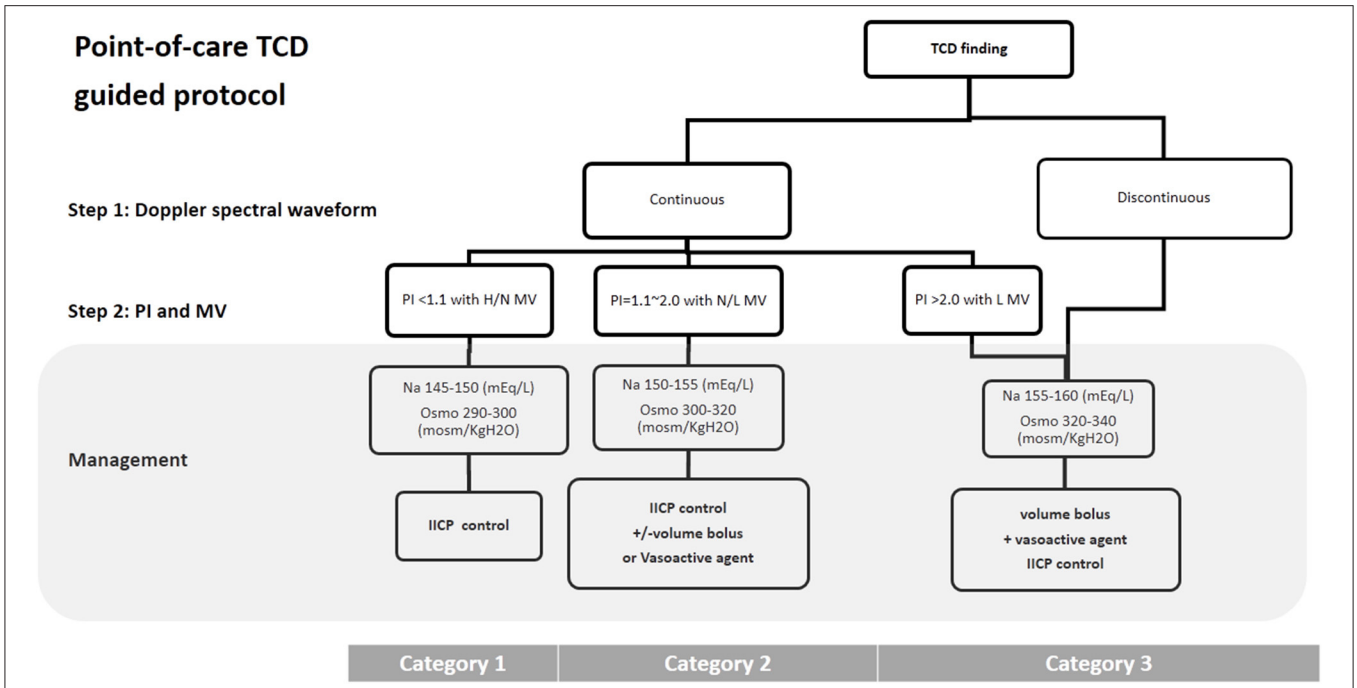


FIGURE 3 | TCD guided cerebral resuscitation protocol. A stepwise management algorithm shows the clinical treatment strategy according to the pattern of Doppler spectral waveform, PI and MV of middle cerebral artery on TCD examination. H, high; N, Normal; L, low; IICP, increased intracranial pressure; TCD, Transcranial Doppler ultrasound; PI, pulsatility index; MV, mean velocity; Osmo, osmolality.

were analyzed using the chi-squared test or Fisher's exact test for categorical variables, and the Student's *t*-test for normally distributed continuous variables. The Mann-Whitney U test was used for non-normally distributed data. Associations between the outcomes of patients in the point-of-care TCD guided and no point-of-care TCD guided groups were determined using univariate analysis. Statistical analyses were performed using SPSS statistical software, version 23.0 (IBM, Inc., Chicago, IL). A two-sided $p < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Patient Profile

During the 5.5-year study period, 74 OHCA patients were identified, of whom 28 (37.8%) children were treated with therapeutic hypothermia. Twenty-one (75%) of the 28 children treated with therapeutic hypothermia met the study inclusion criteria. Seven children were excluded, including 3 with ventricular tachycardia, 2 with a history of congenital heart disease, 1 who died within 12 h due to refractory cardiogenic shock despite the use of vasopressor and/or inotropic agents, and 1 who received extracorporeal membrane oxygenation (**Figure 1**).

Twelve (57.1%) of the 21 patients received point-of-care TCD guided cerebral resuscitation and the remaining 9 (42.9%) received no point-of-care TCD guided cerebral resuscitation. Thirteen (61.9%) of the 21 events were bystander-witnessed cardiac arrest, however only 7 (33.3%) of the 21 bystanders performed cardiopulmonary resuscitation (CPR). The first documented arrest rhythm was described as asystole in 19 (90.5%) patients and bradycardia/pulseless electrical activity in 2 (9.5%) patients. There were no significant differences in the demographic data between the point-of-care TCD guided and no point-of-care TCD guided groups (**Table 1**).

Variables and Treatment During and After Resuscitation

The mean duration of cardiac arrest before the return of ROSC was 23.1 min (range 8–81 min), and there was a longer duration of cardiac arrest in the point-of-care TCD guided group (mean ± SD, 27.33 ± 19.61 min) compared with the no point-of-care TCD guided group (17.44 ± 8.66 min), but this difference was not statistically significant ($p = 0.176$). Serum lactate and glucose levels immediately after resuscitation were similar between the two groups. The baseline patient characteristics were also similar between the two groups, suggesting a similar severity of illness after resuscitation. The event characteristics during resuscitation are listed in **Table 1**. Detailed clinical data and characteristics observed during resuscitation of the 21 patients with asphyxia OHCA are listed in **Additional Table 1**.

Post-cardiac Arrest Care

In terms of treatment, all patients received therapeutic hypothermia and vasoactive and/or inotropic medications. All patients in both groups also received anti-increased intracranial

TABLE 1 | Characteristics of the 21 children with asphyxial out-of-hospital cardiac arrest receiving therapeutic hypothermia.

Characteristic	Point-of-care TCD guided ($n = 12$)	No point-of-care TCD guided ($n = 9$)	*p*-value
Gender			1.000
Female	3 (25%)	2 (22.2%)	
Male	9 (75%)	7 (77.8%)	
Age			0.120
1 month-11 months	9 (75%)	5 (55.6%)	
1–4 years	2 (16.7%)	0 (0%)	
5–8 years	1 (8.3%)	1 (11.1%)	
9–18 years	0 (0%)	3 (33.3%)	
Chronic pre-existing illness			0.670
No	8 (66.7%)	6 (66.7%)	
Respiratory	1 (8.3%)	2 (22.2%)	
Neurologic	2 (16.7%)	1 (11.1%)	
Other	1 (8.3%)	0 (0%)	
Bystander-witnessed cardiac arrest	7 (58.3%)	6 (66.7%)	1.000
Bystander performed CPR	3 (25%)	4 (44.4%)	0.397
Initial rhythm			1.000
Asystole	11 (91.7%)	8(88.9%)	
Bradycardia/PEA	1 (8.3%)	1 (11.1%)	
Characteristics during resuscitation			
Interval of CPR to ROSC (min)	27.33 ± 19.61	17.44 ± 8.66	0.176
Serum pH	7.047 ± 0.217	7.093 ± 0.162	0.617
Initial glucose (mg/dL)	259.25 ± 135.31	239.43 ± 138.74	0.764
Initial lactate (mmol/L)	84.89 ± 46.86	82.56 ± 51.17	0.919
Post-cardiac arrest GCS	3.50 ± 1.16	3.00 ± 0.00	0.166
PRISM III	37.08 ± 7.44	42.33 ± 3.20	0.063
PELODS	38.25 ± 8.83	43.77 ± 4.40	0.078
Treatments			
VIS[#]	19.87 ± 8.96	25.83 ± 14.25	0.291
Ventilator duration (days)	21.42 ± 19.06	10.67 ± 9.08	0.106
IICP control (mannitol+3% NaCL)			
Serum sodium (mEq/L)[##]	157.0 ± 6.49	153.55 ± 6.48	0.244
Serum osmolality (mOsm/kg H_2O)[##]	324.27 ± 17.36	326.20 ± 26.46	0.863
Outcomes			
Hospital length of stay (days)	32.17 ± 19.82	11.67 ± 9.12	0.006*
1-month survival	9 (75%)	2 (22.2%)	0.030*
Cause of 1-month death			
Brain death or withdrawal for poor neurologic prognosis	2 (66.7%)	5 (71.4%)	
Cardiovascular failure/futility	1 (33.3%)	1 (14.3%)	
Respiratory failure/futility	0 (0%)	1 (14.3%)	
6-month neurological outcomes ($n = 21$)[a]			
Favorable prognosis (PCPC score ≤2)	5 (41.7%)	1 (11.1%)	0.177
Unfavorable prognosis (PCPC score ≥3)	7 (58.3%)	8 (88.9%)	

TCD, transcranial Doppler ultrasound; CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; GCS, Glasgow Coma Scale; PRISM, pediatric risk of mortality; PELODS, pediatric logistic organ dysfunction scores; TTM, Targeted temperature management; VIS, Vasoactive-Inotropic score; IICP, increased intracranial pressure; PCPC, pediatric cerebral performance category.

[#]The maximum vasoactive-inotropic score level during the first 5 days.

[##]The maximum serum level of sodium and osmolality during the first 5 days.

[a]The patients with 6-month neurological outcomes included those who died during the acute and follow-up period. In the TCD guided group, one patient died during the follow-up period. In the Non-TCD guided group, no patient died during the follow-up period.

**$p < 0.05$: statistically significant.*

pressure drugs, such as mannitol and/or hypertonic saline. There was a trend of lower maximum vasoactive-inotropic score (19.87 ± 8.96) and a higher serum sodium level (157.0 ± 6.49 mEq/L) during the first 5 days in the point-of-care TCD guided group compared to the no point-of-care TCD guided group (25.83 ± 14.25 and 153.55 ± 6.48 mEq/L), but this difference was not statistically significant ($p = 0.291$ and 0.244, respectively). There were also no significant differences in the additional treatment strategies used in both groups (**Table 1**).

Survival Rate and Functional Outcomes

The primary cause of death within 1 month was brain death or withdrawal of life-sustaining therapy owing to a poor neurological prognosis (66.7% in the point-of-care TCD guided group and 71.4% in the no point-of-care TCD guided group) (**Table 1**). The overall 1-month survival rate was 52.4%. The survival rate was significantly higher ($p = 0.03$) in the point-of-care TCD guided group (9/12, 75%) compared with the no point-of-care TCD guided group (2/9, 22.2%). The duration of hospital stay was significantly longer in the point-of-care TCD guided group compared with the no point-of-care TCD guided group (32.17 ± 19.82 vs. 11.67 ± 9.12 days, $p = 0.006$). Of the 11 survivors, 6 (54.5%) had PCPC scores of 1 or 2 at 6 months follow-up.

The 6-month neurological outcomes were significantly better (PCPC ≤2) in the point-of-care TCD guided group compared with the no point-of-care TCD guided group; however, this difference was not statistically significant (5/9, 55.6% vs. 1/2, 50%, $p = 1.000$) (**Table 1**). Treatment details and outcomes of the 21 patients with asphyxial OHCA are listed in **Additional Table 2**.

TCD Findings

The pattern of Doppler spectral waveform, PI and the mean blood velocity of bilateral middle cerebral artery in the point-of-care TCD guided group are shown in **Additional Table 3**. The TCD categories of the MCA at days 1 and 3 did not significantly influence the 1-month mortality or 6-month neurological outcomes. However, a category 1 in the MCA at day 5 led to a significantly better survival compared with category 3 (9 of 9 children in the 1-month survival group vs. 1 of 3 children in the 1-month mortality group; $p = 0.045$), but not in the 6-month neurological outcomes. The maximum category of TCD findings during the first 5 days was also not associated with the 1-month survival or 6-month neurological outcomes. TCD findings of the MCA during the different treatment phases, in the 12 patients receiving point-of-care TCD guided cerebral resuscitation protocol between 1-month survival and 6-month neurologic outcomes, are listed in **Table 2**.

DISCUSSION

Sustained intracranial hypertension and inadequate cerebral reperfusion after resuscitation can lead to catastrophic irreversible neurological injury and death. Serial point-of-care TCD examinations allow clinicians to assess the effectiveness of cerebral perfusion after resuscitation (10–16). The prognostic value of TCD for children after resuscitation in the study hospital have been previously published (10). Based on this previous TCD report, a consensus management protocol was achieved in the pediatric intensive care units. After following this algorithm in the present study, point-of-care TCD guided cerebral resuscitation was associated with a significantly better 1-month survival rate compared with no point-of-care TCD guided group in pediatric patients with asphyxial OHCA ($p = 0.03$).

The first step in TCD examinations after resuscitation is to distinguish the pattern of Doppler spectral waveform (9–12). A discontinuous Doppler spectral waveform can be regarded as a lethal sign, which indicates cerebral circulatory arrest (22–24). In addition, the presence of PI >2.0 with a low mean blood velocity indicated severe inadequate reperfusion (ischaemia/hypoperfusion), related to increased ICP. In these situations, aggressive systemic haemodynamic support by volume loading and vasoactive agents (19, 21), combined with hyperosmolar therapy with serum sodium 155–160 mEq/L and serum osmolality 320–340 mOsm/kg H_2O, should be utilized to improve the increased ICP and produce sufficient diastolic flow on TCD examination (19, 20, 25).

The second step of TCD examination after resuscitation is to distinguish the PI and mean flow velocity. The predominant TCD findings after resuscitation were low mean flow velocity. An effective cerebral perfusion after resuscitation has a notable influence on the final neurological prognosis (6–8). Recently, Lovett et al. reported using TCD to evaluate cerebral blood flow velocity in children with global hypoxic ischemic (HI) events (26). They found the patients with favorable neurologic outcomes had a flow velocity near normal, whereas those with unfavorable outcomes had more extreme flow velocity, defined as 2 standard deviations above normal cerebral blood flow velocity (26). In the current study, a different goal for hyperosmolar therapy and mean arterial blood pressure was used according to the TCD finding. A normal or high mean flow velocity (category 1) TCD finding on day 5 led to significantly better 1-month survival compared with a category 3 finding ($p = 0.045$).

As the intracranial cerebral pressure was not available, there is no consensus on an optimal mean arterial blood pressure in children. In this study, we used a point-of-care TCD guided cerebral resuscitation protocol, and found that there was a lower maximum vasoactive-inotropic score and a higher serum sodium level in the point-of-care TCD guided group compared with the no point-of-care TCD guided group, although this did not reach statistical significance. However, point-of-care TCD guided cerebral resuscitation to achieve adequate cerebral perfusion by systematic haemodynamic optimization, using volume loading and vasoactive agents combined with different goals of hyperosmolar therapy, may improve the outcomes of comatose survivors after resuscitation.

Furthermore, impaired cerebral autoregulation has been associated with worse outcomes. Lovett et al. also investigated cerebral autoregulation with transient hyperaemic response ratio (THRR) using TCD in children with global HI events and concluded that the children with favorable outcomes seemed to have more periods of intact cerebral autoregulation compared to those with unfavorable outcomes (26). Sundgreen et al. found

TABLE 2 | The parameters of the middle cerebral artery during different time points in 12 patients receiving point-of-care transcranial Doppler ultrasound guided cerebral resuscitation protocol.

Characteristic	1 month outcome			6 month neurological outcome		
	Survival ($n = 9$)	Death ($n = 3$)	*p*-value	Favorable outcome ($n = 5$)	Unfavorable outcome ($n = 7$)	*p* value
Doppler spectrum waveform			0.250			1.000
Continuous	9	2		5	5	
Discontinuous	0	1		0	1	
TCD Finding						
Day 1			0.360			0.237
Category 1	3	2		1	4	
Category 2	4	0		3	1	
Category 3	2	1		1	2	
Days 2–3			0.193			0.454
Category 1	4	1		3	2	
Category 2	5	1		2	4	
Category 3	0	1		0	1	
Days 4–5			0.045*			0.470
Category 1	9	1		5	5	
Category 2	0	0		0	0	
Category 3	0	2		0	2	
Maximum TCD finding during the first 5 days			0.211			0.539
Category 1	2	1		1	2	
Category 2	5	0		3	2	
Category 3	2	2		1	3	

TCD, transcranial Doppler; MCA, middle cerebral artery; ROSC, Return of spontaneous circulation.
$p < 0.05$: statistically significant.

mean arterial pressure should be maintained at a higher level to secure cerebral perfusion in abnormal cerebral autoregulation (8). These studies suggest that TCD with individualized goal-directed therapy can be used to manage blood pressure and maintain cerebral autoregulation. Future research should focus on the potential clinical applications of point-of-care TCD guided cerebral hemodynamic status and optimal mean arterial blood pressure.

There were some limitations to the present study. First, it was a retrospective study in a limited cohort of children after resuscitation. Therefore, it is difficult to make a strong conclusion about point of care TCD guided management algorithm on outcome. In term of this issue, it needs a prospective, randomized and large sample study. However, there have been few reports in pediatric literature regarding point-of-care TCD guided management after resuscitation, and the novelty of this study may outweigh the limitation of small numbers. Second, it is difficult to investigate every possible confounder separately, such as the use of vasopressors, the strategy of ventilator support, and sedation and anesthesia, with respect to the cerebral blood flow and outcomes of post-cardiac arrest care. Finally, the TCDs were performed by one operator and the treating clinicians were aware of the results. Therefore, there is a risk of favorable/unfavorable neurological outcomes being a self-fulfilling prophecy. Nonetheless, exploring the potential of point-of-care TCD in this population is an important avenue for further research.

CONCLUSIONS

A stepwise management algorithm based on the pattern of Doppler spectral waveform, PI and mean flow velocity of MCA on TCD examinations could guide the cerebral hemodynamic status of cerebral resuscitation during post cardiac arrest care. Adjust neurocritical care by point-of-care TCD guided protocol, therefore, may improve the outcomes of pediatric asphyxial OHCA. A large randomized controlled trial of point-of-care TCD guided cerebral resuscitation should be considered for pediatric OHCA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Chang Gung Memorial Hospital Institutional Review Board (IRB numbers: 201700975B0, 201700976B0, 201700977B0, and 201900302B0). Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: Retrospective study.

AUTHOR CONTRIBUTIONS

J-JL conceived the study and drafted the manuscript. J-JL, H-CK, Y-JL, M-HH, M-CC, O-WC, and E-PL participated in data collection. S-HH, H-SW, and K-LL participated in the study's design and coordination. K-LL critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.690405/full#supplementary-material

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Pharmacokinetics of Esomeprazole in Critically Ill Patients

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Background: Esomeprazole, a potent proton pump inhibitor (PPI), is widely used for the prevention of stress ulcers in intensive care unit (ICU) patients.

Objective: This study investigates the pharmacokinetics (PK) of esomeprazole in critically ill patients.

Methods: The study included eligible adult ICU patients who received endotracheal intubation assisted mechanical ventilation for more than 48 h and had at least an extra risk factor for stress ulcers. All enrolled patients received once-daily intravenous (IV) esomeprazole 40 mg. After the first dose of esomeprazole was administrated, serial blood samples were collected at 3, 5, 15, 30 min and 1, 2, 4, 6, 8, and 10 h. The total sample concentrations of esomeprazole were measured by UPLC-MS/MS. Esomeprazole PK parameters were analyzed using noncompartmental analysis.

Results: A total of 30 patients were evaluable. Mean age and body mass index (BMI) were 61.97 years and 23.14. PK sampling on the first dose resulted in the following median (IQR) parameters: $AUC_{0-\infty}$ 8.06 (6.65–9.47) mg·h/L; $MRT_{0-\infty}$ 4.70 (3.89–5.51) h; $t_{1/2}$ 3.29 (2.7–3.87) h; V 24.89 (22.09–27.69) L; CL 6.13 (5.01–7.26) L/h; and C_{max} 2.56 (2.30–2.82) mg/L.

Conclusions: According to the label of esomeprazole, our study showed different esomeprazole PK parameters in ICU patients compared with healthy volunteers. Esomeprazole has unique pharmacokinetic parameters in critically ill patients.

Keywords: esomeprazole, PK parameters, proton pump inhibitors, CYP2C19, ICU patients

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INTRODUCTION

Stress-induced ulcers are extremely common in ICU patients. Because these patients usually have risk factors for stress ulcers, such as coagulopathy, mechanical ventilation for at least 48 h, a Glasgow Coma score of ≤10, or multiple organ dysfunction syndrome (MODS) (1, 2). Approximately 75–100% of ICU patients experience mucosal injury within 24 h of ICU admission. Among them, 5–25% of ICU patients may have obvious bleeding if they do not receive drugs to prevent stress ulcers (3). Multiple studies have reported that stress-related ulcer bleeding may increase the mortality risk of ICU patients (4, 5). Therefore, stress ulcer prophylaxis (SUP) is recommended by many guidelines and expert consensuses, such as the Surviving Sepsis, Stress Ulcer Prophylaxis Campaign, and the Expert Suggestions of Prevention and Treatment of Stress Ulcer (2, 6).

PPIs and histamine 2 receptor antagonists (H2RA) are the two kinds of acid-suppressive agents most commonly used in SUP. However, Meta-analyses show that the PPIs used for SUP can significantly reduce the rate of ulcer bleeding compared with H2RA (7). Esomeprazole is the first (*S*)-isomer of the PPIs family approved for listing in the United States and major European countries in 2001 with oral and intravenous formulations (8). Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. In CYP2C19 extensive metabolizers, esomeprazole is inactivated at a faster rate. In contrast, CYP2C19 poor metabolizers have approximately twice the level of exposure to esomeprazole. Although genetic variation in CYP2C19 influences the plasma concentration of esomeprazole, the Dutch Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) recommends that esomeprazole dosage is not changed when CYP2C19 is normal, intermediate, or poorly metabolized (9). Patients with severely impaired hepatic function had a lower rate of metabolism. The AUC was 76% higher than in patients with Gastro-Oesophageal Reflux Disease (GORD) (10).

Numerous clinical trials have demonstrated that esomeprazole has a more pronounced acid-suppressive effect and fewer adverse events than other PPIs (11–13). According to several comparative studies of the acid suppressant efficacy of PPIs, the pharmacokinetic parameters of PPIs are positively correlated with their acid-suppressive effect. Among all PPIs products on the market, esomeprazole has superior pharmacokinetic characteristics and had been proven to be the best acid control effect in the clinical application (10). One study shows that the AUC of esomeprazole was almost 2-fold higher than that of omeprazole at the same dosage (14). The result showed that esomeprazole has a better acid-suppressive effect with a longer duration of intragastric pH $>$ 4 (14). Previous studies on the pharmacokinetics of esomeprazole were carried out in healthy, elderly, patients with symptomatic GORD and patients with hepatic impairment. However, fewer PK parameters of esomeprazole in ICU patients were reported. ICU patients were critically ill with multiple-organ dysfunction, hypoalbuminaemia, and extracorporeal clearance techniques. Drug pharmacokinetic characteristics are often different from healthy subjects. Therefore, the objective of this trial was to describe the PK of a single dose of i.v. esomeprazole in critically ill patients.

MATERIALS AND METHODS

Study Design

This open-label, single-treatment exploratory trial of IV esomeprazole was conducted in an Intensive Care Unit with critically ill patients with at least one additional risk factor for stress ulcer (Clinical Trial Registry, *ChiCTR1800018516*). The study protocol was approved by the Ethics Committee of Lishui Hospital of Zhejiang University (*Ethical Review of Clinical Research-2016-43*) and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from the patients or the patients' legally authorized representative.

Patients aged 18–89 years who were admitted to ICU and receiving esomeprazole for the prophylaxis of stress-related mucosal disease were eligible to participate. Exclusion criteria included lactation or pregnancy, clinical diagnosis of treat peptic ulcer bleeding, peptic/stomach ulcer, gastroesophageal reflux disease, and Zollinger-Ellison syndrome, or the dosage of esomeprazole $>$40 mg in 1 day for other purposes. Patients also were excluded if they had a history of treated peptic ulcer bleeding, peptic/stomach ulcer, gastroesophageal reflux disease, and Zollinger-Ellison syndrome. All eligible patients received IV esomeprazole 40 mg once a day by the site nurse from the central vein. Each dose was injected slowly with 5 min. After IV esomeprazole 40 mg was administered, blood samples of 1.0 mL were drawn from the basilic vein: at 3, 5, 15, 30 min and 1, 2, 4, 6, 8, and 10 h. All blood samples were stored at room temperature for 30 min after collection and then centrifuged at 1500 *g* for 10 min at room temperature. Plasma was aspirated and transferred into a labeled 1.5 mL Eppendorf tube and stored at −80°C immediately after aspiration until drug assay. Patients were eligible if the PK curve was completed.

Baseline Parameters

Upon inclusion, the baseline parameters of each patient were registered: gender, age, weight, BMI, alanine transaminase (ALT), aspartate transaminase (AST), blood urine nitrogen (BUN), creatinine clearance rate (CCR), APACHE II score (within 24 h of ICU admission), and Child-Pugh class.

Sample Measurement

Blood samples were collected according to the scheduled time and the concentration of esomeprazole in plasma and were determined by UPLC-MS/MS according to a previous method [15]. The chromatographic column was the ACQUITY UPLC BEH C18 column (2.1× 50 mm, 1.7 um). Esomeprazole was separated by gradient elution, which consisted of mobile phase A acetonitrile and A 0.1% formic acid and 5 mM ammonium formate in water. Gradient condition was detailed as follows: total run time was 3 min. Initially, mobile phase A was sustained as 20% from 0 to 0.7 min. Ten, A was reached to 80% for the 0.9 min. Ten 80% of mobile phase A was maintained for 0.5 min. Next, the mobile phase A was drawn back to 20% for 0.7 min and equilibrated as 20% for the 2 min. The flow rate was 0.40 ml/min, and the column was 40°C. Detection was conducted with a triple quadrupole tandem mass spectrometer equipped with positive electrospray ionization (ESI) by multiple reactions monitoring (MRM) of the transitions. The ion transitions were m/z 346.2 $>$198.0 for esomeprazole and m/z 285.1 $>$ 193.1 for diazepam (internal standard).

CYP2C19 Genetic Analysis

Genetic polymorphism of cytochrome CYP2C19 was detected by DNA microarray, which was reported in our previous study (15). In brief, 4 mL of whole blood samples were collected from each patient; the DNA was extracted from the blood using a Blood

Genomic DNA Extraction Kit, then the concentration and purity of extracted DNA was determined by spectrophotometry. The variants of the CYP2C19 gene were detected by a commercially available kit (BaiO Technology Co, Ltd., Shanghai, China). Six genotypes of CYP2C19 were classified as three metabolic phenotypes. CYP2C19 genotype of *1/*1 is a normal metabolizer (NM). The intermediate metabolizer (IM) includes the CYP2C19 genotype of *1/*2 and *1/*3. The poor metabolizer (PM) includes CYP2C19 *2 /*2, *2/*3 or *3/*3.

Pharmacokinetic Analyzes

PK parameters of esomeprazole were calculated according to the plasma concentration-time profiles, which were analyzed by a noncompartmental model analysis in DAS 3.2.8 (Drug and Statistics 3.2.8, Shanghai China). Pharmacokinetic analyses were performed with evaluable data from patients who were eligible for the study and had a sufficient number of data points. The areas under the concentration of esomeprazole in the plasma vs. the time curve from time zero to infinity ($AUC_{0-\infty}$) and the area under the respective first moment-time curve from time zero to infinity ($AUMC_{0-\infty}$) were calculated by the linear trapezoidal rule and the standard area extrapolation method. MRT was calculated as $AUMC_{0-\infty}/AUC_{0-\infty}$. The plasma clearance (CL) was estimated as $Dose/AUC_{0-\infty}$. Plasma terminal half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda z$, while λz is the terminal slope of the log plasma esomeprazole concentration-time profile. V was calculated as MRT× CL. The maximum esomeprazole concentration (C_{max}) was directly determined from the plasma esomeprazole concentration-time curves.

Statistical Analysis

The values for pharmacokinetic variables were stated as estimates with 95% confidence intervals for the true geometric means. All continuous variables were tested for normality by the Kolmogorov-Smirnov test. The data of skewed distribution were transformed into the log-normal distribution. After normal testing, statistical analysis was conducted by SPSS 20.0 using ANOVA. The changes of six main pharmacokinetic parameters of both liver function classification and CYP 2C19 polymorphism were analyzed by multivariate analysis of variance. $P < 0.05$ was considered to be significantly significant.

RESULTS

Patients

All 30 participants completed the study. Baseline characteristics are summarized in **Table 1**. The patients were two/thirds of men, aged 18–88 years, and had a mean APACHE II score of 21.10. Other baseline characteristics were: mean body mass index 23.14 kg/m^2, mean Child-Pugh score 6.37, mean creatinine clearance rate 91.32 mL/min, and mean albumin 29.90 g/L. 63.33% of participants had three or more additional stress ulcer risk factors.

Esomeprazole PK

The geometric means (95% CI) of the PK parameters are presented in **Table 2**. **Figure 1** shows the mean esomeprazole concentration profiles of a single i.v. dose of 40 mg over 10 h after administration.

TABLE 1 | Baseline characteristics of all participants.

	Participants ($n = 30$)
Demographics	
Gender, n(%)	
Male	20 (66.67)
Female	10 (33.33)
Age(years), Mean(range)	61.97 (18–88)
Elderly (≥65 years), n(%)	15 (50.00)
Weight(kg), Mean(range)	63.10 (42.50–80.00)
BMI(kg/m^2), Mean(range)	23.14 (18.16–26.67)
Clinical characteristics	
APACHE II, Mean(range)	21.10 (11–30)
Child-Pugh score, Mean(range)	6.36 (5–9)
CCR(mL/min), Mean(range)	91.32 (10.67–207.82)
Albumin(g/L), Mean(range)	29.90 (16.50–38.50)
Additional stress ulcer risk factor, n (%)	
Respiratory failure	22 (73.33)
Coagulation dysfunction	2 (6.67)
Severe craniocerebral trauma	12 (40.00)
Multiple trauma	11 (36.67)
Post-major surgical procedure	19 (63.33)
Sepsis	10 (33.33)
Shock or persistent hypotension	5 (16.67)
Acute renal or liver failure	2 (6.67)
Multiple organ dysfunction syndrome (MODS) and/or multiple organ failure (MOF)	6 (20.00)

BMI, body mass index; APACHE II, acute physiologic and chronic health evaluation II; CCR, creatinine clearance rate.

TABLE 2 | The pharmacokinetic parameters of esomeprazole.

	Variable	Mean	95% CIs
$AUC_{0-\infty}$	The area under the plasma concentration-time curve, mg·h/L	8.06	6.65–9.47
$MRT_{0-\infty}$	Mean retention time of the drug in the organism, h	4.70	3.89–5.51
$t_{1/2}$	Half-life, h	3.29	2.71–3.87
V	Volume of drug distribution, L	24.89	22.09–27.69
CL	Clearance, L/h	6.13	5.01–7.26
C_{max}	Maximum plasma drug concentration, mg/L	2.56	2.30–2.82

Effect of CYP2C19 Metabolic Phenotype

The pharmacokinetic results were analyzed according to the CYP2C19 metabolic phenotype in **Table 3**. The PK parameters except for C_{max} were slightly different between NM, IM, and PM. NM and IM individuals had higher values of $AUC_{0-\infty}$, $MRT_{0-\infty}$, $t_{1/2}$, and V. However, PM individuals had higher CL values than NM and IM individuals.

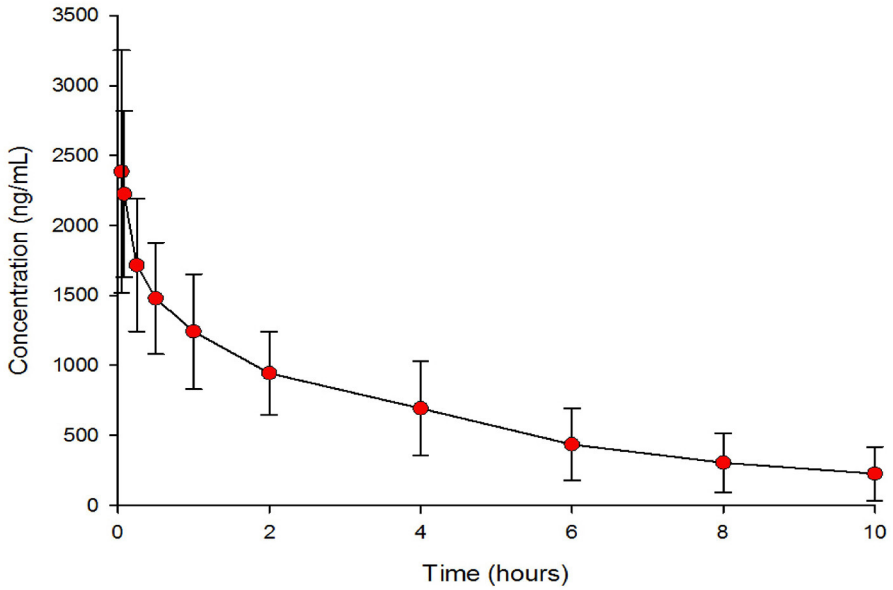

FIGURE 1 | Esomeprazole plasma concentration after intravenous administrations of 40 mg dose age.

TABLE 3 | Comparison of esomeprazole PK parameters with various CYP2C19 metabolic phenotype.

Variable	Normal metabolizers (NM, $n = 12$)	Intermediate metabolizers (IM, $n = 15$)	Poor metabolizers (PM, $n = 3$)	*P*-value
$AUC_{0-\infty}$	8.29 (6.07–10.50)	8.34 (5.97–10.71)	5.76 (1.09–10.42)	0.56
$MRT_{0-\infty}$	5.08 (3.70–6.46)	4.58 (3.32–5.83)	3.84 (-1.27–8.96)	0.66
$t_{1/2}$	3.67 (2.61–4.73)	3.18 (2.31–4.05)	2.33 (0.45–4.21)	0.40
V	26.30 (19.88–32.71)	24.00 (20.87–27.13)	23.73 (14.17–33.29)	0.72
CL	5.57 (4.07–7.08)	6.29 (4.33–8.25)	7.59 (0.23–14.95)	0.58
C_{max}	2.56 (2.07–3.06)	2.53 (2.24–2.83)	2.67 (-0.45–5.78)	0.96

Effect of Child-Pugh Grade

The Pharmacokinetic results were analyzed according to Child-Pugh grade in **Table 4**. According to Child-Pugh scoring criteria, 18 participants were in class A and 12 participants were in class B. The PK parameters of $AUC_{0-\infty}$, $MRT_{0-\infty}$, $t_{1/2}$, and V were slightly different between Child A and Child B groups. Compared with the Child B group, values of $AUC_{0-\infty}$, $MRT_{0-\infty}$, $t_{1/2}$, V, and C_{max} in the Child A group were low, but the CL value was high.

Effect of Both Liver Function Classification and CYP 2C19 Polymorphism

The Pharmacokinetic results were analyzed with both Child-Pugh grade and CYP2C19 metabolic phenotype in **Table 5**. **Table 6** showed that the variables of $AUC_{0-\infty}$, $MRT_{0-\infty}$, $t_{1/2}$, V, CL, and C_{max} in Child-Pugh grade, CYP2C19 metabolic phenotype, and their interaction had no significant difference ($P > 0.05$).

DISCUSSION

According to the instructions of esomeprazole, the results of this study indicated that the esomeprazole PK parameters in critically ill patients were different from those in healthy volunteers. We observed highly variable PK parameters, in particular for the observed volume of drug distribution (V) and clearance (CL). Compared with the values reported for Chinese healthy volunteers, the value of V 24.89 (22.09–27.69) L in critically ill patients was 1.88 times higher and the value of CL 6.13(5.01–7.26) L/h was 35.85% lower (16).

Compared with healthy volunteers, many factors such as increased total body water and interstitial or 'third space' fluid volumes, decreased albumin concentration, plasma pH changed, peripheral tissue penetration changed during septic shock, and increased permeability of the blood-brain barrier (BBB) that may influence drug distribution among critically ill patients (17). Therefore, V for hydrophilic drugs such as β-lactam antibiotics was increased in critically ill patients (18). The value of V (24.89 L) was nearly double that of healthy volunteers (13.32 L) (16), suggesting that esomeprazole was distributed more extensively in critically ill patients. Esomeprazole is a high protein binding drug and its protein binding rate is 97%. Therefore, unbound esomeprazole plasma concentration is increased in hypoproteinemia patients. According to the baseline characteristics of all participants, the mean albumin concentration was 29.90 g/L lower than normal values. Hypoproteinemia is one reason for high V. There were 10 participants of sepsis. High peripheral tissue penetration during septic shock also is one reason for high V. In addition, critically ill patients often have increased total body water and interstitial or "third space" fluid volumes were the most common factors that led to elevated V.

TABLE 4 | Comparison of esomeprazole pharmacokinetic parameters with various Child-Pugh grade.

	Variable	Child A ($n = 18$)	Child B ($n = 12$)	*P*-value
$AUC_{0-\infty}$	The area under the plasma concentration-time curve, mg·h/L	7.74 (6.07–9.40)	8.55 (5.70–11.39)	0.58
$MRT_{0-\infty}$	Mean retention time of the drug in the organism, h	4.25 (3.41–5.10)	5.38 (3.69–7.07)	0.17
$t_{1/2}$	Half-life, h	2.91 (2.31–3.50)	3.86 (2.65–5.08)	0.10
V	Volume of drug distribution, L	23.51 (20.16–26.85)	26.97 (21.61–32.32)	0.22
CL	Clearance, L/h	6.29 (4.70–7.87)	5.90 (4.08–7.73)	0.74
C_{max}	Maximum plasma drug concentration, mg/L	2.72 (2.34–3.10)	2.32 (2.00–2.65)	0.13

TABLE 5 | Comparison of esomeprazole pharmacokinetic parameters with various Child-Pugh grade and CYP2C19 metabolic phenotype.

PK		Child A	Child B
$AUC_{0-\infty}$	Normal metabolizers	8.62 (8.49–9.20)	7.31 (4.70–7.47)
	Intermediate metabolizers	6.97 (4.71–10.62)	10.81 (4.89–13.25)
	Poor metabolizers	6.40 (3.64–7.23)	/
$MRT_{0-\infty}$	Normal metabolizers	4.82 (3.75–6.61)	4.84 (3.27–7.32)
	Intermediate metabolizers	3.46 (2.73–5.55)	5.95 (2.93–8.67)
	Poor metabolizers	3.41 (2.03–6.08)	/
$t_{1/2}$	Normal metabolizers	3.71 (2.35–4.82)	3.65 (2.17–5.94)
	Intermediate metabolizers	2.62 (1.63–3.63)	4.31 (2.20–5.83)
	Poor metabolizers	2.15 (1.68–3.16)	/
V	Normal metabolizers	24.82 (15.20–31.59)	28.82 (18.01–36.04)
	Intermediate metabolizers	24.57 (16.90–28.85)	23.50 (22.67–28.79)
	Poor metabolizers	25.21 (19.36–26.62)	/
CL	Normal metabolizers	4.64 (4.35–4.71)	5.47 (5.35–8.51)
	Intermediate metabolizers	5.76 (3.94–8.72)	3.70 (3.11–8.40)
	Poor metabolizers	6.25 (5.53–10.99)	/
C_{max}	Normal metabolizers	2.84 (2.50–3.87)	2.20 (1.63–2.50)
	Intermediate metabolizers	2.45 (2.14–2.90)	2.71 (2.13–2.85)
	Poor metabolizers	2.08 (1.82–4.10)	/

The CL in this study was 6.13 L/h, which was far lower than Chinese healthy volunteers 17.1 L/h (16). This means that esomeprazole was slowly cleared with longer residence time *in vivo*. Esomeprazole was the drug mainly metabolized by the liver CYP2C19 isoenzyme and nearly 80% was excreted from urine in the form of metabolites according to its drug instructions. CL could be affected by liver dysfunction, renal dysfunction, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) (17). There were 12 participants of Child-Pugh grade B, individuals with mild to moderate hepatic dysfunction could affect the reduced CL. CCR was 10.67–207.82 mL/min with high individual variability. Moderate-to-severe renal impairment also caused the reduced CL. In addition, the elevated V of esomeprazole was widely distributed in critically ill patients, which could lead to low clearance.

As $t_{1/2}$ is proportional to V and inversely proportional to CL, the impact of a change in V during critical illness on the overall pharmacokinetics of esomeprazole likely depends on whether CL is affected. The mean $t_{1/2}$ of esomeprazole in this study (3.29 h) was much higher than that reported in healthy volunteers (mean, 0.85 h) (10). This observation was consistent with the fact that clearance was reduced while the volume of distribution was increased, which would result in an increased elimination half-life (elimination rate constant $k = CL/V$) (15). This indicated that the retention time of esomeprazole in critically ill patients is prolonged.

$AUC_{0-\infty}$ is another important PK parameter in these special patients. The mean $AUC_{0-\infty}$ in this study (8.06 mg·h/L) was nearly more than three times the value described in healthy volunteers after a single intravenous dose of 40 mg (6.84 μmol·h/L) (16), when they were converted into unified units. Similarly, C_{max} was increased in critically ill patients. C_{max} of healthy volunteers (5.53 μmol/L) was only 74.6% of the value in critically ill patients (18). This was in line with the elevated V and reduced CL we observed. According to a previous report (10), esomeprazole had a clear AUC-effect relationship. AUC was correlated to the inhibitory effect on stimulated gastric acid secretion. Therefore, we speculated that the increased esomeprazole concentration exposure in blood with high AUC and C_{max} in critically ill patients could have a more effective acid control effect. The special pathological characteristics of critically ill patients caused AUC and C_{max} to change. Furthermore, the increased unbound fraction resulting from the low plasma albumin levels means that more free-drug was available for elimination, which is consistent with the increased C_{max} we observed in this study.

Esomeprazole is extensively metabolized in the liver by the human cytochrome P450 (CYP) enzyme system. According to the label for esomeprazole (Nexium IV), in patients with liver impairment, the dosage of esomeprazole should be adjusted based on Child-Pugh grade when esomeprazole was used to rebleeding of gastric or duodenal ulcers following therapeutic endoscopy. In order to evaluate the effect of the liver impairment on esomeprazole PK, we divided the participants into Child A group or Child B group according to their Child-Pugh score. Compared with the Child A group, $AUC_{0-\infty}$, $MRT_{0-\infty}$, $t_{1/2}$, and V of esomeprazole in the Child B group were increased by 1.10, 1.27, 1.32, and 1.15-fold, but CL and C_{max} in Child B group were decreased to 94.80% and 85.29%. These PK parameters showed critically ill patients with severe liver impairment had wider distribution and longer retention of esomeprazole in the body. However, for the PK parameters, there was no significant difference between the two groups. This was because many factors could affect the metabolism of

TABLE 6 | Tests of between Child-Pugh grade and CYP2C19 metabolic phenotype Effects.

Source	Type III sum of squares	df	Mean square	*F*-value	Sig.
Dependent variable: $AUC_{0-\infty}$					
Corrected model	28.746	4	7.187	0.464	0.761
Intercept	1325.392	1	1325.392	85.624	0.000
Child-Pugh grade	0.858	1	0.858	0.055	0.816
CYP2C19 metabolic phenotype	16.855	2	8.427	0.544	0.587
Child-Pugh grade* CYP2C19	9.754	1	9.754	0.630	0.435
Dependent variable: $MRT_{0-\infty}$					
Corrected model	15.920	4	3.980	0.826	0.521
Intercept	493.836	1	493.836	102.459	0.000
Child-Pugh grade	5.203	1	5.203	1.080	0.309
CYP2C19 metabolic phenotype	1.302	2	0.651	0.135	0.874
Child-Pugh grade* CYP2C19	5.768	1	5.768	1.197	0.284
Dependent variable: $t_{1/2}$					
Corrected model	10.768	4	2.692	1.117	0.371
Intercept	234.154	1	234.154	97.125	0.000
Child-Pugh grade	3.271	1	3.271	1.357	0.255
CYP2C19 metabolic phenotype	2.006	2	1.003	0.416	0.664
Child-Pugh grade* CYP2C19	2.397	1	2.397	0.994	0.328
Dependent variable: V					
Corrected model	110.896	4	27.724	0.454	0.768
Intercept	13605.724	1	13605.724	222.913	0.000
Child-Pugh grade	64.075	1	64.075	1.050	0.315
CYP2C19 metabolic phenotype	16.530	2	8.265	0.135	0.874
Child-Pugh grade* CYP2C19	10.168	1	10.168	0.167	0.687
Dependent variable: CL					
Corrected model	26.159	4	6.540	0.686	0.608
Intercept	842.319	1	842.319	88.402	0.000
Child-Pugh grade	0.167	1	0.167	0.018	0.896
CYP2C19 metabolic phenotype	10.757	2	5.378	0.564	0.576
Child-Pugh grade* CYP2C19	15.641	1	15.641	1.642	0.212
Dependent variable: C_{max}					
Corrected model	2.654	4	0.663	1.478	0.239
Intercept	143.061	1	143.061	318.650	0.000
Child-Pugh grade	1.382	1	1.382	3.078	0.092
CYP2C19 metabolic phenotype	0.120	2	0.060	0.134	0.875
Child-Pugh grade* CYP2C19	1.402	1	1.402	3.122	0.089

esomeprazole during critical illness, such as CYP2C19 genotype difference, administration of a CYP2C19 inhibitor or two drugs metabolized by the same CYP2C19 resulting in competitive inhibition, administration of an agent that induces CYP2C19, reduced hepatic or splanchnic blood flow as a result of shock, acute renal failure or increased protein binding to albumin or α_1-acid glycoprotein, Gram-negative sepsis associated with the production of LPS and increased global or locoregional production of proinflammatory cytokines, surgical interventions and so on (17). In this study, the combined drugs of the enrolled cases were vasoactive drugs (norepinephrine), opioid analgesics (morphine, fentanyl), sedatives (midazolam, dexmedetomidine), antibiotics (imipenem cilastatin, piperacillin tazobactam, cefoperazone sulbactam, vancomycin), albumin and crystalloid fluid. These combined drugs with no clear reports of drug interaction with EPZ.

According to the label for esomeprazole (Nexium IV), CYP2C19 is the major metabolic enzyme, while the CYP2C19 poor metabolizers (PM) genotype is common in Asian populations with a ratio of 15–20%. The difference of the individual CYP2C19 genotype resulted in different PK and PD. At a steady state, the ratio of AUC in Poor Metabolizers to the rest of the population (Extensive metabolizers) is approximately 2 (14). In the current study, six genotypes of CYP2C19 were classified into three metabolic phenotypes, normal metabolizer (NM), intermediate metabolizer (IM), and poor metabolizer (PM). Compared with the PM group, the mean $AUC_{0-\infty}$ of esomeprazole were 1.44 and 1.45-fold higher than NM and IM groups. However, the ratio of $AUC_{0-\infty}$ between different CYP2C19 phenotypes was much lower than that reported in healthy volunteers (19). $t_{1/2}$ in NM and IM groups were longer than PM group, while CL in NM and IM groups were lower

than the PM group. The results of $t_{1/2}$ and CL were inconsistent with the previous study (20). We speculated that the main reason was the small sample size with only three patients in the PM group.

There are two limitations of this study. One limitation is the small sample size of the PM group. Given the adequate sample size of the NM, IM, and PM groups, we can obtain the pharmacokinetic characteristics of critical patients with different CYP phenotypes. The other limitation is that the pharmacodynamics of the anti-acid effect and effective maintenance time at target pH after intravenous administration of esomeprazole were not designed. Further PK/ PD model clinical studies of esomeprazole plasma concentration with effects on 24 h intragastric pH levels are necessary to establish the scientific dosage regimen of critically ill patients. We recommend that further studies based on the population PK and PD are essential, for more data are required to promote the rational use of esomeprazole in critically ill patients.

CONCLUSIONS

The PK of a single dose of 40 mg i.v. esomeprazole in critically ill patients was different from the PK data reported by previous studies in healthy volunteers receiving the same i.v. dose of 40 mg.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Figshare (https://doi.org/10.6084/m9.figshare.13141406.v2 and https://doi.org/10.6084/m9.figshare.17019536).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Lishui Municipal Central Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CS, YX, and XT participated in the design of this study and they both performed the statistical analysis. WT and QZ tested the blood concentration. YX and WT carried out pharmacokinetic analyzes. WW, TZ, and JS managed patients and collected data. YX drafted the manuscript. All authors read and approved the final manuscript.

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Definition of Acute Respiratory Distress Syndrome on the Plateau of Xining, Qinghai: A Verification of the Berlin Definition Altitude-PaO_2/FiO_2-Corrected Criteria

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Background: Acute respiratory distress syndrome (ARDS) is a common critical respiratory illness. Hypoxia at high altitude is a factor that influences the progression of ARDS. Currently, we lack clear diagnostic criteria for high-altitude ARDS. The purpose of this study was to determine the value of the application of the Berlin Definition altitude-PaO_2/FiO_2-corrected criteria for ARDS in Xining, Qinghai (2,261 m).

Methods: We retrospectively analyzed the clinical data of patients with ARDS admitted to the Department of Critical Care Medicine of the Affiliated Hospital of Qinghai University from January 2018 to December 2018. The severity of ARDS was categorized according to the Berlin Definition, Berlin Definition altitude-PaO_2/FiO_2-corrected criteria, and the diagnostic criteria for acute lung injury (ALI)/ARDS at high altitudes in Western China (Zhang criteria). In addition, the differences between the three criteria were compared.

Results: Among 1,221 patients, 512 were treated with mechanical ventilation. In addition, 253 met the Berlin Definition, including 49 (19.77%) with mild ARDS, 148 (58.50%) with moderate ARDS, and 56 (22.13%) with severe ARDS. A total of 229 patients met the altitude-PaO_2/FiO_2-corrected criteria, including 107 with mild ARDS (46.72%), 84 with moderate ARDS (36.68%), and 38 (16.59%) with severe ARDS. Intensive care unit (ICU) mortality increased with the severity of ARDS (mild, 17.76%; moderate, 21.43%; and severe, 47.37%). Twenty-eight-day mortality increased with worsening ARDS (mild 23.36% vs. moderate 44.05% vs. severe 63.16%) ($p<0.001$). There were 204 patients who met the Zhang criteria, including 87 (42.65%) with acute lung injury and 117 (57.35%) with ARDS. The area under receiver operating characteristics (AUROCs) of the Berlin Definition, the altitude-P/F-corrected criteria, and the Zhang criteria were 0.6675 (95% CI 0.5866–0.7484), 0.6216 (95% CI 0.5317–0.7116), and 0.6050 (95% CI 0.5084–0.7016), respectively. There were no statistically significant differences between the three diagnostic criteria.

Conclusion: For Xining, Qinghai, the altitude-PaO_2/FiO_2-corrected criteria for ARDS can distinguish the severity of ARDS, but these results need to be confirmed in a larger sample and in multicenter clinical studies.

Clinical Trial Registration: ClinicalTrials.gov, identifier: NCT04199650.

Keywords: acute respiratory distress syndrome, high altitude, Berlin Definition, ARDS, P/F

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a severe disease that has received considerable attention due to its high mortality rate (35–40%) (1). Proposed in 2012 (2), the Berlin Definition of ARDS is currently used to diagnose ARDS from the time of onset, the cause of pulmonary edema, and chest X-ray findings and stratify data according to PaO_2/FiO_2.

The Qinghai-Tibet Plateau, which has an average elevation exceeding 4,500 m, is the world's highest and China's largest plateau with an area of 2,500,000 km^2. Nearly 6 million people live in Qinghai Province, and 3 million people live in high-altitude areas.

Due to the hypoxic conditions on the plateau, patients with ARDS have special pathophysiological changes and clinical manifestations (3). If the definition of ARDS is completely followed in the plateau area, it may lead to treatment errors in these patients. For example, the incorrect setting of mechanical ventilation parameters or the use of invasive mechanical ventilation in patients who would otherwise have been treated with non-invasive ventilation or a mask to improve oxygenation. In Zhang et al. (4) proposed the diagnostic criteria for acute lung injury (ALI)/ARDS at high altitudes in Western China, which has been widely used in these areas. However, the Zhang criteria are proposed according to the American-European Consensus Conference (AECC) standard, which has certain limitations. Since the Berlin Definition was proposed, the diagnostic criteria of ARDS for altitudes above 1,000 m should be updated.

For the plateau area, the Berlin Definition indicates that in areas with altitudes above 1,000 m, the PaO_2/FiO_2 should be calculated according to the correction formula [$PaO_2/FiO_2 \times$ (atmospheric pressure/760)] (2). However, there is no clear evidence to prove whether the "Berlin Definition altitude-PaO_2/FiO_2-corrected criteria" is suitable for patients with ARDS in high-altitude areas. The objective of this study was to update the definition using new data (epidemiological, physiological, and clinical trial data) to address the current limitations of the diagnostic criteria for ALI/ARDS at high altitudes in Xining in Western China and explore other defining variables.

MATERIALS AND METHODS

Study Design

The study was a single-center, retrospective, observational study. The objective of the study was to verify the value of the application of the Berlin Definition altitude-PaO_2/FiO_2-corrected criteria for ARDS in Xining, Qinghai (altitude: 2,261 m). Because the data were de-identified, the hospital institutional review board waived the need for informed consent and approved the study. The trial was registered at clinicaltrials.gov (NCT04199650).

Definition of ARDS

The Berlin Definition: All enrolled patients met the Berlin Definition of ARDS. PaO_2/FiO_2 is as follows: mild ARDS, 200 mmHg $< PaO_2/FiO_2 \leq$ 300 mmHg; moderate ARDS, 100 mmHg $< PaO_2/FiO_2 \leq$ 200 mmHg; and severe ARDS, $PaO_2/FiO_2 \leq$ 100 mmHg.

For the Berlin Definition altitude-PaO_2/FiO_2-corrected criteria (hereafter, altitude-PaO_2/FiO_2-corrected criteria; note that all patients met the Berlin Definition except for the PaO_2/FiO_2 criterion), the PaO_2/FiO_2 was calculated according to the plateau correction formula [PaO_2/FiO_2^*(barometric pressure)/760)]. PaO_2/FiO_2 was combined with the Xi'ning atmospheric pressure (581 mmHg), and the altitude-PaO_2/FiO_2-corrected criteria for ARDS severity are as follows: mild ARDS, 153 mmHg $< PaO_2/ FiO_2 \leq$ 230 mmHg; moderate ARDS, 76 mmHg $< PaO_2/ FiO_2 \leq$153 mmHg; and severe ARDS, $PaO_2/FiO_2 \leq$76 mmHg.

With the diagnostic criteria for ALI/ARDS at high altitudes in Western China [following Zhang criteria (4)], patients with ALI or ARDS were classified according to PaO_2/FiO_2, altitude (2,200 m), and the AECC diagnostic criteria. Patients with $PaO_2/FiO_2 \leq$150 mmHg were diagnosed with ARDS, whereas those with PaO_2/FiO_2 between 150 and 200 mmHg were diagnosed with ALI.

Study Population

Patients who were undergoing mechanical ventilation and entered the Department of Intensive Medicine of the Affiliated Hospital of Qinghai University between January 2018 and December 2018 were screened. The patients had to meet the Berlin Definition altitude-PaO_2/FiO_2-corrected criteria, the Zhang criteria, or all of the above. We excluded patients younger than 18 years and those with an Intensive Care Unit (ICU) length of stay $<$ 24 h.

Data Collection

For every enrolled patient, clinical data were assessed to detect whether the patient fulfilled the Berlin Definition, the altitude-P/F-corrected criteria, the Zhang criteria, or all of the above. Demographic data, underlying diseases, risk factors for ARDS, and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were recorded during the first 24 h of ICU admission. FiO_2, blood gases, and illness severity were recorded on the first day. The first day was defined as the first day on which the

patients met the ARDS or ALI criteria. Given the difficulty of comparing noninvasive ventilation settings with invasive modes, we excluded patients with noninvasive ventilation from the analysis of ventilator management. Interventions and treatments during the ICU stay and patient outcomes were recorded.

Outcome Measures

The primary outcome measures were ICU mortality, 28-day mortality, and 28-day mechanical-ventilation-free days. The secondary outcome measures were the duration of mechanical ventilation, length of ICU stay, and length of hospital stay.

Statistical Analysis

Normally distributed data are presented as the mean ± SD, and non-normally distributed data are presented as the median (interquartile range, IQR). *p*-values for categorical variables were calculated with the χ^2-test, while *p*-values for continuous variables were estimated with the *t*-test, the Mann–Whitney test, ANOVA, or the Kruskal–Wallis test depending on the distribution and number of variables. The receiver operating curve (ROC) statistical analyses were performed by using GraphPad Prism for Windows version 8.1, and other statistical tests were performed with SPSS for Windows version 19.0. Statistical significance was assessed at the 2-sided $p < 0.05$ level.

RESULTS

Since the patients were from high-altitude areas, we analyzed the enrolled patients and their characteristics, blood gases, and mechanical ventilation data based on the altitude-P/F-corrected criteria.

Characteristics of Enrolled Patients

Among the 1,221 patients who were admitted to the ICU from January 1, 2018 to December 31, 2018, 512 had invasive mechanical ventilation after admission during the study period. Among them, 253 patients met the Berlin Definition, 229 met the altitude-P/F-corrected criteria, and 204 patients met the Zhang criteria (**Figure 1**).

General Information

There were 229 patients who met the altitude-P/F-corrected criteria, of whom 107 (46.72%) had mild ARDS, 84 (36.68%) had moderate ARDS, and 38 (16.59%) had severe ARDS.

Patients with severe ARDS had fewer chronic hepatic dysfunctions than those with mild to moderate ARDS ($p = 0.017$), and APACHE II scores at presentation were slightly higher for patients with severe ARDS ($p < 0.001$). The most common risk factors were infection, pneumonia, aspiration, and trauma (**Table 1**).

Blood Gases and Mechanical Ventilation Practices

Regarding pH indicators and arterial carbon dioxide partial pressure ($PaCO_2$), the three groups had similar values. Lactate values (Lac) were significantly higher in patients with increased ARDS severity (**Table 1**).

The ventilator parameters were recorded during the first 24 h, during which the patients met the altitude-P/F-corrected criteria (**Table 1**). There was an absence of a statistical difference in applied positive end-expiratory pressure (PEEP) between the severity groups ($p = 0.358$). Patients with more severe ARDS had a higher ventilator setting for inspired oxygen concentration, and the difference was statistically significant ($p < 0.001$).

Outcomes in Patients With ARDS

The Berlin Definition

A total of 253 patients met the Berlin Definition, of whom 49 (19.37%) had mild ARDS, 148 (58.50%) had moderate ARDS, and 56 (22.13%) had severe ARDS. The ICU mortality rates of patients with ARDS who had mild, moderate, and severe cases were 6.12, 18.92, and 42.86%, respectively ($p < 0.001$). With worsening ARDS, 28-day mortality increased (mild 6.12% vs. moderate 33.11% vs. severe 60.71%), and the median (IQR) number of ventilator-free days over a 28-day period decreased [mild ARDS, 26.17 (20.00–27.21) days; moderate ARDS, 18.73 (0.00–25.30) days; severe ARDS, 0.00 (0.00–18.26) days].

The Altitude-P/F-Corrected Criteria

Among the 229 patients who met the altitude-P/F-corrected criteria, 107 (46.72%) were diagnosed with mild ARDS, 84 (36.68%) were diagnosed with moderate ARDS, and 38 (16.59%) were diagnosed with severe ARDS. ICU mortality increased with the severity of ARDS (mild, 17.76%; moderate, 21.43%; and severe, 47.37%). Twenty-eight-day mortality increased with worsening ARDS (mild 23.36% vs. moderate 44.05% vs. severe 63.16%; $p<0.001$). The median (IQR) number of ventilator-free days in a 28-day period declined with the severity of ARDS [mild, 21.42 (3.75–26.50) days; moderate, 16.53 (0.00–24.28) days; and severe, 0.0 (0.00–16.02) days ($p < 0.001$)].

The duration of mechanical ventilation in survivors slightly increased with the severity of ARDS [mild, 3.88 (1.04–9.13) days; moderate, 4.46 (1.40–9.45) days; and severe, 5.11 (2.73–11.85) days], but the difference was not statistically significant ($p = 0.132$). Differences between the length of ICU stay and the length of hospital stay across the Berlin Definition categories (mild, moderate, and severe) were statistically significant.

Diagnostic Criteria for ALI/ARDS at High Altitudes in Western China

There were 204 patients who met the Zhang criteria. Among the 204 enrolled patients, 87 (42.65%) had ALI and 117 (57.35%) had ARDS. The ICU mortality was 18.39% for those with ALI vs. 30.77% for those with ARDS ($p = 0.045$), and the 28-day mortality (51.28%) was higher for patients with ARDS than for patients with ALI (26.44%) ($p<0.001$). The median (IQR) number of ventilator-free days over a 28-day period was higher in patients with ALI [19.50 (0.00–26.04)] than in patients with ARDS [4.21(0.00–23.31)] ($p = 0.03$). There were no significant differences in the length of ICU stay, the duration of invasive ventilation, and the length of hospital stay between patients with ALI and patients with ARDS (**Table 2**).

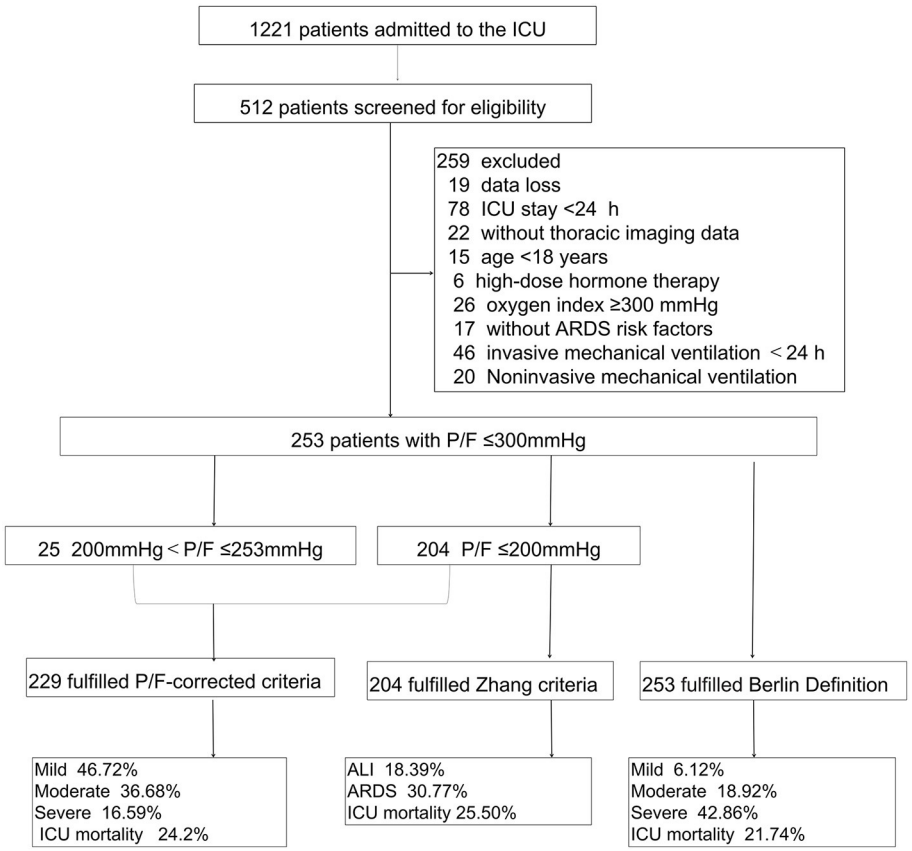

FIGURE 1 | Flow diagram of patient screening and enrollment. P/F, PaO_2/FiO_2; P/F-corrected criteria, The Berlin Definition altitude-PaO_2/FiO_2-corrected criteria; Zhang criteria, The diagnostic criteria for ALI/ARDS at high altitudes in Western China; Berlin Definition, The Berlin Definition of acute respiratory distress syndrome; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

Area Under ROC Curve

The area under the receiver operating characteristic (AUROCs) of the Berlin Definition, the altitude-P/F-corrected criteria, and Zhang criteria were 0.6675 (95% CI Power 0.5866–0.7484), 0.6216 (95% CI Power 0.5317–0.7116), and 0.6050 (95% CI power 0.5084–0.7016), respectively. There were no statistically significant differences between the three diagnostic criteria (**Figure 2**).

Characteristics of the Misclassifications of Patients With Altitude-P/F-Corrected Criteria and Berlin Definition

There were 24 patients with mild ARDS according to the Berlin Definition, but they did not meet the altitude-P/F-corrected criteria. All these patients were admitted to the surgery or emergency department and had almost no serious underlying diseases. In particular, only one patient had a history of chronic lung disease. The condition of these patients improved quickly after treatment, and all of them survived the ICU stay and were discharged from the ICU (**Table 3**).

There were 82 patients who met the Berlin Definition of moderate ARDS, but according to the plateau-P/F-corrected criteria, these patients were considered only to have mild ARDS. Sixteen of these patients died in the ICU (19.51%). Seventeen patients with severe ARDS, as defined by the Berlin Definition, met the altitude-P/F-corrected criteria of moderate ARDS, and the ICU fatality rate of these patients was 35.29%.

Characteristics of the Misclassifications of Patients With Altitude-P/F-Corrected Criteria and Zhang Criteria

There were 25 patients with mild ARDS according to the altitude-P/F-corrected criteria, but they did not meet the Zhang criteria. The oxygenation index of this part of patients is between 200 and 230 mmHg. Three of these patients died in the ICU (12%). Five patients with moderate ARDS, defined by the altitude-P/F-corrected criteria, met the Zhang criteria of ALI, and the ICU fatality rate of these patients was zero. The characteristics of these patients are shown in **Table 4**.

The Distribution of Patients Across the Different Criteria

The P/F was < 200 mmHg in 204 patients who met both Zhang criteria and Berlin Definition and altitude-P/F-corrected criteria. There were 25 patients with a P/F between 200 and 253 who

TABLE 1 | General information of 229 patients who met the altitude-P/F-corrected criteria.

	Mild	Moderate	Severe	*P* values
No(%)	107(46.72%)	84(36.68%)	38(16.59%)	
Age (years, $\bar{x} \pm$ SD)	50.45 ± 15.40	56.85 ± 16.83	59.05 ± 14.64	0.290
Male (n,%)	74(69.16%)	55(65.47%)	26(68.42%)	0.859
Source of ICU entry (n,%)				
Surgery	39(36.45%)	40(47.62%)	10(26.32%)	0.064
Internal medicine	10(9.35%)	10(11.90%)	12(31.58%)	0.003
Emergency	58(54.21%)	34(40.47%)	16(42.11%)	0.134
ARDS risk factors (n,%)				
Pneumonia	16(14.95%)	18(21.43%)	8(21.05%)	0.463
Infection	37(34.58%)	35(41.67%)	11(28.95%)	0.355
Aspiration	15(14.02%)	12(14.29%)	5(13.16%)	0.986
Trauma	22(20.56%)	15(17.86%)	4(10.53%)	0.383
Basic diseases (n,%)				
Hypertension	33(30.84%)	27(32.14%)	8(21.05%)	0.434
Diabetes mellitus	15(14.02%)	15(17.86%)	1(2.63%)	0.073
Chronic pulmonary disease	14(13.08%)	21(25.00%)	6(15.79%)	0.096
Chronic cardiac insufficiency	25(23.36%)	25(29.76%)	9(23.68%)	0.574
Chronic renal dysfunction	19(17.76%)	15(17.86%)	2(5.26%)	0.153
Chronic liver dysfunction	29(27.10%)	17(20.24%)	2(5.26%)	0.017
APACHE II score ($\bar{x} \pm$ SD)	12.45 ± 5.11	13.24 ± 5.28	17.55 ± 5.52	<0.001
PaO_2/FiO_2 ($\bar{x} \pm$ SD)	183.49 ± 20.04	118.15 ± 20.97	52.31 ± 12.39	<0.001
pH ($\bar{x} \pm$ SD)	7.37 ± 0.31	7.29 ± 0.81	7.37 ± 0.11	0.572
$PaCO_2$(mmHg, $\bar{x} \pm$ SD)	36.52 ± 18.21	41.17 ± 18.26	42.10 ± 12.03	0.098
PaO_2(mmHg,$\bar{x} \pm$ SD)	82.25 ± 35.70	66.2 ± 22.92	43.86 ± 14.28	<0.001
FiO_2(%,$\bar{x} \pm$ SD)	63.92 ± 22.37	71.87 ± 21.41	89.47 ± 15.93	<0.001
PEEP (cmH_2O,$\bar{x} \pm$ SD)	5.11 ± 0.86	5.36 ± 1.59	5.26 ± 0.86	0.358
Lac (mmol/L, median IQR)	1.90(1.30–3.40)	2.40(1.40–4.85)	3.30(2.05–5.63)	0.030

APACHE II, Acute Physiology and Chronic Health Evaluation II; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; Lac, lactic acid; IQR, Inter Quartile Range.

met the Berlin Definition and altitude-P/F-corrected criteria for mild ARDS. Twenty-four patients with only $253 \geq P/F < 300$ met the Berlin Definition and were considered to have mild ARDS (**Figure 3**).

DISCUSSION

The main manifestations of ARDS are persistent hypoxemia due to the pathophysiological changes of decreased lung volume (5), decreased compliance, and a decreased proportion of ventilatory blood flow (6). Although an increasing number of clinical studies in recent years have confirmed that some biomarkers are associated with ARDS (7), there is no evidence that they can be used in diagnosis (8, 9). The diagnosis of ARDS still focuses on the function of the lung, including the time of onset, oxygenation index, and imaging findings (10). P/F is the most important parameter to determine the severity of ARDS (11).

As mentioned earlier, high-altitude areas have characteristics of low oxygen pressure, strong radiation, cold climate, and so on (12). As altitude increases, the atmospheric pressure and the partial pressure of inhaled oxygen decrease (3). The low-oxygen environment in high-altitude areas has significant effects on the human body (13). Some studies have highlighted that the arterial blood partial pressure of healthy adults at high altitudes is significantly lower than that of healthy adults of the same age group in the plain area (14). Acute and chronic hypoxia at high altitudes can induce a variety of diseases and affect the quality of life and work capacity of people residing at high altitudes (15). People living at high altitudes for a long time have different tolerances for hypoxic environments, resulting in pathophysiological changes in patients with ARDS in high-altitude areas that are different from those in plain areas (16).

Studies have confirmed that ARDS associated with high altitude is characterized by hypoxemia that is difficult to treat and significantly increased pulmonary hypertension. In addition, the inflammatory response is more serious than what occurs in the plains. Hence, we need to update the criteria for ARDS in areas with altitudes above 1,000 m (17).

According to the AECC criteria, some patients with mild ARDS are diagnosed with ALI, and when clinicians lack awareness of this subgroup, they fail to provide appropriate support and treatment. In Zhang et al. (4) proposed the diagnostic criteria of ALI/ARDS in high-altitude areas of Western China on the basis of the AECC diagnostic criteria. Since then,

TABLE 2 | Comparison of outcomes according to the three criteria.

	Berlin Definition (253 cases)				Altitude-P/F-corrected criteria (229 cases)				Zhang criteria (204 cases)		
	Mild	Moderate	Severe	*P* values	Mild	Moderate	Severe	*P* values	ALI	ARDS	*P* values
No(%)	49(19.37)	148(58.50)	56(22.13)		107(46.72)	84(36.68)	38(16.59)		87(42.65)	117(57.35)	
ICU mortality, No(%)	3(6.12)	28(18.92)	24(42.86)	<0.001	19(17.76)	18(21.43)	18(47.37)	0.001	16(18.39)	36(30.77)	0.045
28-day mortality, No(%)	3(6.12)	49(33.11)	34(60.71)	<0.001	25(23.36)	37(44.05)	24(63.16)	<0.001	23(26.44)	60(51.28)	<0.001
No of ventilator-free days over a 28-day period, d, median (IQR)	26.17 (20.00–27.21)	18.73 (0.00–25.30)	0 (0.00–18.26)	<0.001	21.42 (3.75–26.50)	16.53 (0.00–24.28)	5.6 (0.00–16.02)	<0.01	19.5 (0.00–26.04)	4.21 (0.00–23.31)	0.03
ICU length of stay, d, median (IQR)	6 (2.23–12.32)	8.71 (4.63–18.10)	6.69 (3.53–14.18)	0.024	7.67 (3.67–14.92)	8.23 (3.71–16.96)	7.69 (4.30–14.77)	0.929	8.08 (4.63–16.42)	7.79 (3.63–15.17)	0.246
Duration of invasive ventilation, d, median (IQR)	1.79 (0.73–4.98)	4.75 (1.50–10.62)	4.23 (2.16–9.92)	0.003	3.88 (1.04–9.13)	4.46 (1.40–9.45)	5.11 (2.73–11.85)	0.132	5.08 (1.46–9.83)	4.67 (2.15–10.63)	0.945
Hospital length of stay, d, median (IQR)	24 (19.00–38.00)	22 (13.25–35.75)	16 (6.00–25.75)	0.001	23 (14.00–37.00)	18.5 (9.25–30.00)	18 (8.00–26.00)	0.036	23 (14.00–38.00)	18 (9.00–29.50)	0.059

IQR, Inter Quartile Range.

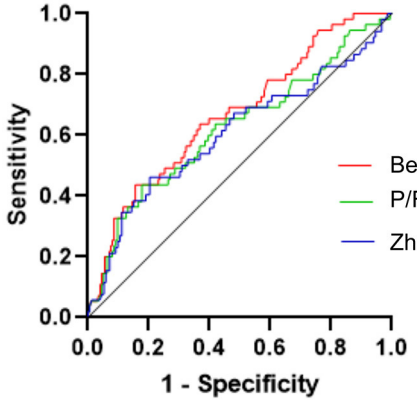

FIGURE 2 | Comparison of the area under the receiver operating characteristic (ROC) curve of three different ARDS criteria for the ICU case fatality rate. Here were no statistically significant differences between the three diagnostic criteria. Berlin Definition, The Berlin Definition of acute respiratory distress syndrome; P/F-corrected criteria, The Berlin Definition altitude-PaO_2/FiO_2-corrected criteria; Zhang criteria, The diagnostic criteria for ALI/ARDS at high altitudes in Western China.

the Zhang criteria have been widely used to diagnose ARDS in Western China. Since the Berlin Definition in 2012, the diagnosis criteria of ARDS in areas with altitudes above 1,000 m have not been updated. Therefore, we need to update the Zhang criteria (4). From this study, we know that when diagnosing patients with ARDS in Xining, Qinghai Province, according to the diagnostic criteria of ALI/ARDS in high-altitude areas of Western China, the case fatality rate of patients with ARDS is significantly lower than that of patients with ARDS in China and other parts of the world. This may be due to how the criteria exclude some patients with mild ARDS, that is, patients with P/F between 200 and 253 mmHg. Hence, no significant difference can be found between the groups.

According to the results of this study, the incidence rate of ARDS in the Affiliated Hospital of Qinghai University's intensive care unit was 16.70–20.72%, which is higher than that of the 2018 Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study (1, 18). This confirms that the incidence rate of ARDS increases in hypoxic environments at high altitudes. In the future, we will perform more clinical trials, which are necessary to confirm the findings of this study.

In this study, in Xining, Qinghai, the overall ICU mortality of patients diagnosed with ARDS according to the altitude-P/F-corrected criteria was 24.02%, and the ICU mortality of patients with mild, moderate, and severe ARDS was 17.76, 21.43, and 47.37%, respectively. The 28-day mortality was 37.56%, specifically, 23.36% for mild ARDS, 44.05% for moderate ARDS, and 63.16% for severe ARDS. The results are similar to the results of international and domestic large-scale epidemiological studies of patients with ARDS in recent years. In contrast, according to the Berlin Definition for the severity of ARDS, in Xining, Qinghai, the ICU mortality of patients with mild ARDS is only

TABLE 3 | Characteristics of the misclassifications of patients with altitude-P/F-corrected criteria and Berlin Definition.

Parameter	Patients with P/F 200–230	Patients with P/F 200–153	Patients with P/F 100–76
No	24	82	18
APACHE II score ($\bar{x} \pm SD$)	8.67 ± 3.82	12.20 ± 5.31	4.22 ± 14.56
ICU mortality: No(%)	0	19.51%	33.33%
Duration of invasive ventilation, d, median (IQR)	1.75(0.70–8.06)	4.92(1.51–10.43)	3.15(1.05–4.29)
ICU length of stay, d, median (IQR)	6.75(2.98–14.61)	8.48(4.64–16.27	4.02(2.72–7.80)
Hospital length of stay, d, median (IQR)	26.5(20–40.25)	23(14.00–36.50)	14(5.00–20.75)
ARDS risk factors (n,%)			
Trauma	12(50)	19(23.17)	2(11.11)
Pneumonia	5(20.83)	12(14.63)	4(22.22)
Infection	12(50.00)	16(19.51)	3(16.67)
Aspiration	5(20.83)	11(13.41)	3(16.67)
Other	3(12.50)	24(29.27)	6(33.33)

APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, Inter Quartile Range.

TABLE 4 | Characteristics of the misclassifications of patients with altitude-P/F-corrected criteria and Zhang criteria.

Parameter	Patients with P/F 200–230	Patients with P/F 200–153
No	25	5
APACHE II score ($\bar{x} \pm SD$)	13.28 ± 4.14	15.6 ± 5.08
ICU mortality: No(%)	12%	0
Duration of invasive ventilation, d, median (IQR)	1.83(0.83–4.29)	6.79(1.08–8.08)
ICU length of stay, d, median (IQR)	4.42(1.96–9.42)	12.67(6.13–21.54)
Hospital length of stay, d, median (IQR)	24(16.00–35.00)	22(13.00–28.00)
ARDS risk factors (n,%)		
Trauma	3(12.00%)	2(40.00%)
Pneumonia	4(16.00%)	0
Infection	7(28.00%)	2(40.00%)
Aspiration	4(16.00%)	0
Other	7(28.00%)	1(20.00%)

APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, Inter Quartile Range.

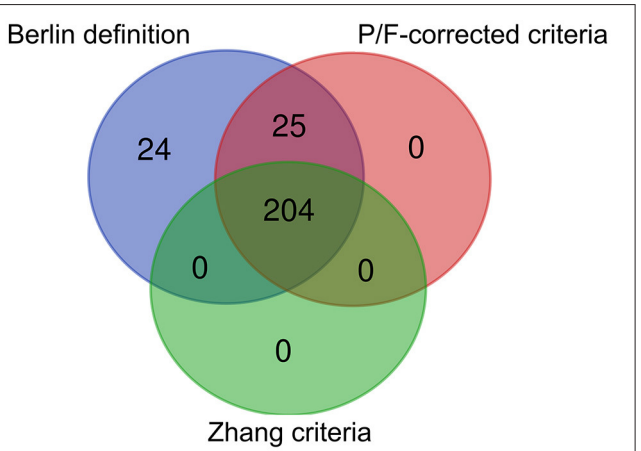

FIGURE 3 | Venn diagram of patient distribution for different criteria. Berlin Definition, The Berlin Definition of acute respiratory distress syndrome; P/F-corrected criteria, The Berlin Definition altitude-PaO_2/FiO_2-corrected criteria; Zhang criteria, The diagnostic criteria for ALI/ARDS at high altitudes in Western China; The P/F was < 200 mmHg in 204 patients, 25 patients with a P/F between 200 and 253 mmHg, and 24 patients with 253 ≥ P/F < 300.

6.12%, which is significantly lower than that reported in other epidemiological studies.

At high altitude, the oxygen content and partial pressure of oxygen in the air were lower than those in the plain area, and when the partial pressure of oxygen was < 300 mmHg in patients at high altitude, there were no other serious pulmonary pathological changes. Even if the patients had lung infiltration shadows and other characteristics consistent with an ARDS diagnosis, they could not be regarded as having ARDS.

The concept of ARDS has been put forward for 50 years, and progress in the care of patients with ARDS has been limited to refinement in supportive care such as lung protection ventilation, prone position, and even extracorporeal membrane oxygenation (ECMO). Delays or missed diagnosis of ARDS will cause clinicians to use wrong mechanical ventilation strategies, such as using the wrong PEEP, for patients. According to our research, patients with mild ARDS identified by the uncorrected Berlin Definition are very mild. Despite this, we think this is a false positive. These patients had a low APACHE II score and left the ICU after a short time with a good prognosis. In addition, they can quickly improve through routine oxygen therapy, therefore, these patients should not be diagnosed with ARDS.

According to the Berlin Definition, the length of ICU stay and the duration of invasive ventilation differed among the groups with mild, moderate, and severe ARDS. Despite this, no such difference was found according to the altitude-P/F-corrected criteria and Zhang criteria. After analyzing the results, we found that the between-group differences in the Berlin Definition were mainly due to the fact that the parameters of mild ARDS were very different from those of moderate to severe ARDS. This is also a false positive change caused by the inclusion of a large number of patients with the Berlin Definition.

This preliminary study confirmed that the altitude-P/F-corrected criteria can be used to classify the severity of ARDS in the Xining area of Qinghai Province. With the Zhang criteria, clinicians may fail to recognize the severity of ARDS in some patients, resulting in a delay in the diagnosis. On the other hand, the application of the Berlin Definition criteria in high-altitude areas may lead to a false-positive diagnosis of ARDS in a large number of patients, resulting in overtreatment.

This study has some limitations. 1) This study is a single-center retrospective study. Hence, the sample size is small and the sample source is limited, resulting in the sample not being very representative. The results must later be verified by multicenter clinical studies. 2) According to the results of this study, the altitude-P/F-corrected criteria for ARDS are applicable in Xining, Qinghai, but it is not clear whether these criteria are applicable in other areas at the same altitude or at other elevations, which must be verified by future multicenter clinical trials. 3) As there is no other strong basis for the diagnosis of ARDS at present, mortality was regarded as the main prognostic end point in this study, and in the process of disease progression, a variety of clinical intervention measures are often provided, which may affect the prognosis of patients to a certain extent. 4) In this study, we observed that there was no difference in the setting of PEEP at different severity levels. We collected the patient's first PEEP according to the Berlin definition of PEEP $>$ 5 cmH_2O, but since only the first PEEP was recorded. Due to this uncertainty, we cannot determine whether PEEP has an effect on the improvement in the P/F.

CONCLUSION

For Xining, Qinghai Province, the Berlin Definition plateau criteria can distinguish the severity of ARDS in high-altitude areas, but these results need to be confirmed in a larger sample and in multicenter clinical studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The study was a single-center, retrospective, and observational study. In order to verify the application value of Berlin Definition plateau criteria of ARDS in Xining, Qinghai (altitude:2261m). Because the data would be received in de-identified form (non-human subjects research), the Hospital Institutional Review Board waived the need for informed consent and approved the study.

AUTHOR CONTRIBUTIONS

CP and HQ designed the experiment. ST and XL collected the data. LS and YN analyzed the data. XL wrote the manuscript. CP and GG revised the manuscript. All authors contributed to the article and approved the submitted version.

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Tropisetron Preconditioning Decreases Myocardial Biomarkers in Patients Undergoing Heart Valve Replacement Surgery

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Background: Cardioplegic arrest during the heart valve replacement surgery frequently leads to myocardial damage. Tropisetron (TRP) has been demonstrated to reduce myocardial ischemia-reperfusion injury and inflammation in animals. We examined the efficacy of TRP in lowering myocardial biomarkers in patients undergoing heart valve replacement surgery.

Methods: A total of seventy-five patients, scheduled for elective heart valve replacement surgery, were randomly chosen to receive either 10 ml of normal saline or 10 mg/10 ml of TRP immediately after anesthesia induction. Blood samples for the measurement of cardiac troponin I (cTnI), creatine kinase (CK-MB), lactate dehydrogenase (LDH), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-10 (IL-10) were taken before anesthesia, as well as 4, 12, and 24 h after aortic cross-clamp release to evaluate myocardial injury using two-way ANOVA for repeated measurements. The study was registered at www.chictr.org.cn (number, ChiCTR-1800018681).

Results: Treatment with TRP decreased the increment of cTnI (Fgroup = 4.911, p = 0.030; Ftime = 55.356, p = 0.001; Fgroup × time = 5.340, p = 0.002) at 12 and 24 h; of CK-MB (Fgroup = 6.552, p = 0.013; Ftime = 49.276, p = 0.001; Fgroup × time = 7.627, p = 0.003) at 4, 12, and 24 h; of TNF-α (Fgroup = 4.153, p = 0.046; Ftime = 28.244, p = 0.002; Fgroup × time = 4.692, p = 0.006) at 4 and 12 h; and of LDH (Fgroup = 4.275, p = 0.043; Ftime = 63.225, p = 0.001; Fgroup × time = 2.501, p = 0.083) at 24 h after the release of the aortic cross-clamp. It increased IL-10 (Fgroup = 5.958, p = 0.018; Ftime = 31.226, p = 0.002; Fgroup × time = 1.464, p = 0.236) at 12 h after the release of the aortic cross-clamp. Multiple linear regression analysis showed that cardiopulmonary bypass (CPB) time was a risk factor, and that TRP treatment was a protective factor for postoperative cTNI change (β = 4.449, 95% CI [0.97–7.92], p = 0.013 for CPB time; and β = −381, 95% CI [−613.4 to −148.5], p = 0.002 for TRP treatment).

Conclusions: Tropisetron had cardioprotective and anti-inflammatory effects in patients undergoing heart valve replacement surgery with cardioplegic arrest. The addition of TRP and reduction of CPB time should be considered for myocardial protection in heart valve replacement surgery.

Clinical Trial Registration: [www.chictr.org.cn/index.aspx], identifier [ChiCTR1800018681].

Keywords: tropisetron, heart surgery, myocardial injury, α7 nACh receptor, inflammation

INTRODUCTION

Myocardial injury is one of the major factors for perioperative complications and mortality. During the heart surgery, ascending aorta cross-clamp and cardiac arrest result in myocardial ischemic damage (1). After cross-clamp release and subsequent oxygenated blood reperfusion, free oxygen radicals are released, which causes further myocardial injury. Importantly, ischemia-reperfusion (IR) injury and cardiopulmonary bypass (CPB) lead to a proinflammatory response and the release of various inflammatory cytokines such as interleukins, complement, histamine, serotonin, and other proinflammatory cytokines (2). Inflammation causes myocardial cell and vascular endothelial cell injury and ultrastructure damage, mitochondrial structure disorder, calcium overload and electrophysiological change, and even severe arrhythmia and death (3). Therefore, seeking effective measures to prevent perioperative inflammation is critical for perioperative myocardial protection and Prevention of Heart Injury-Related Complications.

Recent reviews have reported that 5-HT3 receptor antagonists have anti-inflammatory actions and are effective for treating neurologic and psychiatric disorders (4, 5). Tropisetron (TRP) is a frequently used drug for treating clinical nausea and vomiting by inhibition of 5-HT3 receptors. Moreover, serotonin, induced by surgery and CPB, activates 5-HT3 receptors and induces an inflammatory response, which aggravates myocardial injury after IR (6). Surprisingly, TRP has also been reported as a partial agonist of alpha7 nicotine acetylcholine (α7 n Ach) receptor. In addition, the activation of α7 n Ach receptor suppresses inflammation through the "cholinergic anti-inflammatory pathway" (7). Recently, studies on animals have demonstrated that TRP is cardioprotective due to its anti-inflammatory effect (8, 9). Thus, we designed this study to examine the cardioprotective effect of TRP in a clinical setting. We determined the efficacy of TRP in lowering perioperative cardiac biomarkers and inflammatory response in patients undergoing heart valve replacement surgery with cardioplegic arrest.

Abbreviations: α7 n Ach, Alpha7 nicotinic acetylcholine; 5-HT, 5-hydroxytryptamine; BP, blood pressure; CPB, cardiopulmonary bypass; CK-MB, creatine kinase isoenzyme; cTNI, cardiac troponin I;C VP, central venous pressure; HR, heart rate,; IL-1β, interleukin-1β; IL-10, interleukin-10; LVEF, left ventricular ejection fraction; LDH, lactate dehydrogenase; MAP, mean arterial pressure; MAPK, mitogen-activated protein kinase; TNF-α, tumor necrosis factor-α; TRP, tropisetron.

MATERIALS AND METHODS

The study was carried out in accordance with the Declaration of Helsinki (October 2000) outlined by the World Medical Association. The research protocol was approved by the institutional ethics committee of Taihe Hospital, Shiyan, China. After obtaining informed written consents from all subjects, a total of 75 patients aged 30–75 years, with an ASA physical status from 2 to 3, who were scheduled for mitral and/or aortic valve replacement, were scrutinized in this study. Exclusion criteria were as follows: patients with an LVEF <45%; any coronary artery disease with >70% stenosis; acute heart failure; myocardial infarction less than 4 weeks ago or angina within the previous week; uncontrolled hypertension; any brain, renal, pulmonary, or hepatic disease; any serious allergy to trial medications; any contraindication to midazolam, fentanyl, rocuronium, TRP, and propofol; and any administration of serotonin reuptake inhibitors in the previous 4 weeks.

Before the experiment, a biostatistician generated randomized numbers and allocated patients into two groups: group C, receiving 10 ml of normal saline; or group TRP receiving 10 mg/10 ml of TRP. After the admission to an operating room, a right internal jugular vein cannula and a radial arterial cannula were placed for hemodynamic monitoring under local anesthesia. Then, biostatistician prepared the drug according to the number sequence. An anesthesia assistant took the drug from the biostatistician and injected it using a pump within 20 min after anesthesia induction. For anesthesia induction, we used imidazoline (0.04 mg/kg), etomidate (0.2 mg/kg), and rocuronium (0.15 mg/kg), followed by sufentanil (1 μg/kg) administration. Then, 3 min later, endotracheal intubation was performed by an experienced anesthetist. Anesthesia in all of the patients was maintained with continuous infusions of propofol (50–150 μg/kg/min) and sevoflurane (1%). A total dose of sufentanil 5 μg/kg was used for analgesia during the surgery.

All of the patients were monitored with a standard 5-lead electrocardiograph. During the anesthesia, the mean arterial pressure was maintained within 20% from its baseline value and above 60 mm Hg, which was achieved either by infusion of 20 μg phenylephrine or by 20 μg nitroglycerin each time to increase or decrease the radial arterial pressure, respectively. If HR was above 90 or below 45 beats per min, 20 mg esmolol and 0.3 mg atropine were injected, and these treatments were repeated if necessary. After the release of the aortic cross-clamp, inotropic support with dopamine was considered if mean arterial pressure (MAP) was less than 60 mm Hg. In addition, nitroglycerin was

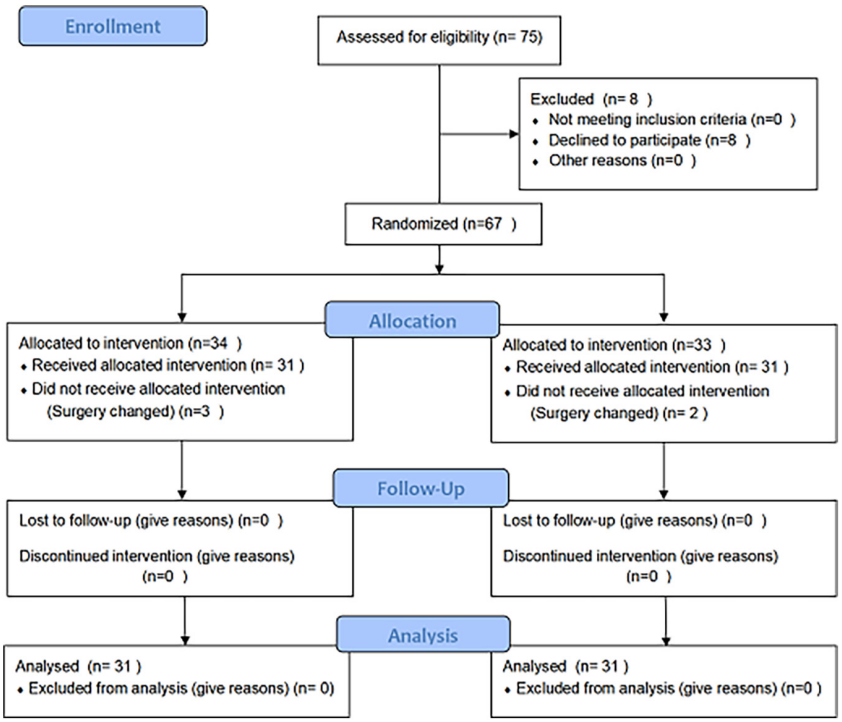

FIGURE 1 | Trial flowchart.

infused continuously, and the infusion rate (0.1–10 μg/kg/min) changed depending on the central venous pressure (CVP) and MAP. CVP, MAP, and HR were recorded at end-expiration. The hemodynamic data at one time point were averaged from three repeated measurements with 2-min intervals while the patient was in a relatively stable hemodynamic condition.

The durations of CPB, operation, aortic occlusion, and intensive care unit (ICU) and postoperative hospitalization stay were recorded. Serial blood samples for the calculation of myocardial injury and inflammatory cytokines were taken before anesthesia and 4, 12, and 24 h after the release of the aortic clamp. The samples were quickly cooled down to 4°C and centrifuged at 4,000 rpm at 4°C for 5 min using cryogenic centrifuge (5840R, Eppendorf, Hamburg, Germany); then, the plasma samples were stored at −80°C for assay with ultralow-temperature freezer (TSE240V, Thermo Fisher Scientific, Waltham, MA, United States). cTnI, CK-MB, LDH, TNF-a, IL-1β, and IL-10 were measured using an ELISA kit in accordance with the instructions (RayBiotech, GA, United States for cTnI and CK-MB; Neobioscience Ltd., Shenzhen, China for TNF-a, IL-1β, and IL-10; Nanjing Jiancheng Bioengineering Institute, Nanjing, China for LDH). ELISA readings were done in line with the manufacturer's procedures and read with an instrument (Multiskan FC, Thermo Fisher Scientific, Waltham, MA, United States). Abnormal levels of cTnI and CK-MB were defined as levels over 0.5 ng/ml and 0.6 ng/ml, respectively.

The sample size calculation used cTNI content with the formula: $n1 = n2 = 2[(\mu\alpha + \mu\beta) \times \sigma/\delta]^2 + \mu\alpha^2/4$, based on a two-sided alpha error of 0.05 and power of 80%. From our preliminary data, the cTNI content was 538 ± 382 and 337 ± 133 pg/ml in the control and treatment groups, respectively (n = 12 per group), and n = 27 per group was required in each group in the experiment. Considering that 15–20% of patients were expected to possibly drop out from the experiment, we scrutinized 75 patients in total to evaluate the effect of TRP.

Categorical data were expressed by their number and analyzed using the chi-square or Fisher's exact test. Quantitative data were expressed as means ± standard deviation (SD). Comparisons of quantitative data between the groups were done using the two-tailed Student's t-test. Comparisons of biomarkers and hemodynamic data recorded over time between the groups were analyzed using two-way ANOVA for repeated measurements. If an overall significant difference between the groups was found, Bonferroni *post-hoc* tests were conducted. The statistical analyses were done using the GraphPad Prism software (GraphPad Prism 5.0, version 2.0; GraphPad Software Inc., San Diego, CA, United States 5.0). The study was registered at www.chictr.org.cn with the number ChiCTR-1800018681.

RESULTS

Patients' Baseline Characteristics and Perioperative Hemodynamics

Out of a total of 75 patients who were scrutinized, eight patients refused to participate in the experiment. A number of three and two patients in the control and TRP group, respectively,

were excluded due to changes in the surgery according to the assessment of the surgeon during the surgery. Ultimately, 62 patients met the criteria and were included in our study, and all of the surgeries were successfully conducted by the same surgical team. Two patients died in the control group (7 and 19 days after surgery) because of heart failure (**Figure 1**).

Patients' characteristics in the two groups were comparable in terms of sex, preexisting medical conditions, and comorbidities ($p > 0.05$, *t*-test or chi-square test, **Table 1**). The anesthesia and surgery time, as well as the duration of hospital stay, were not different between the groups ($p > 0.05$, *t*-test, **Table 2**). The duration of ICU stay in the TRP group was shorter than that in the control group ($p < 0.05$, *t*-test, **Table 2**). The HR, MAP, and CVP were not different before the surgery or 12 and 24 h after surgery between the TRP and the control groups ($p > 0.05$, two-way ANOVA for repeated measurements, **Table 3**).

Routine blood tests showed that white blood cell (WBC), neutrophil (NE), and platelet (PLT) counts were not different between the control and the TRP groups. However, CRP was lower in the TRP group than in the control group 24 h after the cross-clamp release ($p < 0.05$, *t*-test, **Table 4**). None of the patients were diagnosed with acute myocardial infarction, stroke, hepatic, or renal failure during the hospital stay. Postoperative complications, which include ventricular arrhythmia, perioperative myocardial infarction, cerebrovascular accidents, abnormal coagulation function, infection, stroke, hospital death, and endocarditis, were not different between the control and TRP groups ($p > 0.05$, chi-square test, **Table 5**).

Changes in the Biomarkers of Myocardial Injury

Myocardial injury biomarkers (cTnI, CK-MB, and LDH) were measured, and the results showed that cTnI, CK-MB, and LDH (**Figures 2A–C**) were not different between the groups before anesthesia. Their values increased at 4 h after the aortic clamp release, with CK-MB and LDH peaking at 4 h and cTnI peaking at 12 h, compared to the baseline values ($p < 0.05$, two-way ANOVA for repeated measurements followed by Bonferroni *post-hoc* tests; **Figures 2A–C**). In addition, the administration of TRP after anesthesia decreased the levels of cTnI at 12 and 24 h; of CK-MB at 4, 12, and 24 h; and of LDH at 24 h after the aortic clamp release.

Changes in Inflammatory Cytokines

The cytokine contents of IL-10, TNF-α, and IL-1β in the serum were not different between the groups before anesthesia and were increased after the aortic clamp release when compared to the baseline values. The addition of TRP after anesthesia increased the level of IL-10 at 12 h and decreased the level of TNF-α at 4 and 12 h after the aortic clamp release ($p < 0.05$, two-way ANOVA for repeated measurements followed by Bonferroni *post-hoc* tests, **Figures 2D–F**), whereas it did not affect IL-1β content.

TABLE 1 | Patients baseline characteristics.

Characteristic	Control group ($n = 31$)	TRP group ($n = 31$)	*P*-value
Age (years)	50.5 ± 11.4	48.7 ± 10.8	0.517
Sex ratio (M/W)	21/10	17/14	0.297
Height (cm)	165.5 ± 6.3	163.8 ± 6.6	0.330
Weight (kg)	61.0 ± 10.8	61.2 ± 11.6	0.648
BMI (kg/m^2)	22.2 ± 2.9	22.6 ± 2.9	0.522
EF (%)	59.7 ± 5.9	56.8 ± 6.6	0.072
LEVDd (mm)	51.7 ± 9.2	49.8 ± 8.9	0.418
LAD (mm)	47.5 ± 12.9	45.8 ± 10.7	0.593
Cardiac function (NYHA)			
II, n (%)	7 (22.6)	9 (29.0)	0.562
III, n (%)	24 (77.4)	22 (71.0)	0.562
Type of surgery, n (%)			
Mitral valve replacement	13 (41.9)	15 (48.4)	0.610
Aortic valve replacement	12 (38.7)	10 (32.3)	0.596
Joint valve replacement	6 (19.4)	6 (19.4)	–
Hypertension, n (%)	6 (19.4)	10 (32.3)	0.246
Coronary artery disease, n (%)	6 (19.4)	5 (16.1)	0.740
Rheumatic heart disease, n (%)	25 (80.6)	29 (93.5)	0.256

Results are expressed as mean ± SD.
M/W, men/women; BMI, body mass index; EF, ejection fraction; LEVDd, left ventricular end-diastolic dimension; LAD, left atrial diameter; NYHA, New York Heart Association.

TABLE 2 | Patients' perioperative variables.

Variables	Control group ($n = 31$)	TRP group ($n = 31$)	*P*-value
CPB time (min)	104.3 ± 27.7	109.2 ± 39.2	0.566
Aortic cross-clamp time (min)	71.8 ± 32.0	68.2 ± 31.1	0.659
Operation time (min)	251.9 ± 55.0	251.5 ± 68.5	0.976
Duration of ventilation (h)	35.8 ± 45.6	29.8 ± 34.5	0.559
Length of ICU stay (h)	85.8 ± 68.8	52.1 ± 40.1*	0.022
Postoperative hospital stay (days)	19.7 ± 7.8	18.97 ± 6.0	0.690

Results are expressed as mean ± SD.
**P < 0.05 compared with the control group.*
SD, standard deviation; CPB, cardiopulmonary bypass; ICU, Intensive care unit.

Correlation and Multivariate Regression Analysis of Potential Risk Factors for Myocardial Injury

Linear correlation analysis was conducted to explore the potential association of cTNI with age, gender, BMI, CPB time, WBC, NE, PLT, CRP, EF, LVEDD, LAD, and TRP treatment (**Table 6**). The results showed that cTNI correlated with CPB time, CRP level, and TRP treatment (r = 0.268, $p = 0.035$ for CPB time; r = 0.024, $p = 0.06$ for CRP; r = −0.357, $p = 0.004$ for TRP treatment). Then, CPB time, CRP level, and TRP treatment were included in the multivariate regression analysis. The results showed that CPB time was a risk factor, whereas TRP treatment was a protective factor for postoperative cTNI change (β = 4.449, 95% CI [0.97–7.92], $p = 0.013$ for CPB time, and β = −381, 95% CI [−613.4 to −148.5], $p = 0.002$ for TRP treatment).

TABLE 3 | Patients' perioperative hemodynamic data.

Time	Heart rate		MAP		CVP	
	Control group	TRP group	Control group	TRP group	Control group	TRP group
T0	86.5 ± 24.4	84.8 ± 15.1	89.9 ± 14.0	90.3 ± 8.9	7.3 ± 2.2	7.4 ± 2.1
T1	95.2 ± 18.8	91.5 ± 14.0	77.1 ± 9.5	77.5 ± 5.7	7.9 ± 1.9	7.5 ± 1.9
T2	99.8 ± 13.7	96.7 ± 13.2	77.9 ± 10.8	78.4 ± 9.2	7.7 ± 2.5	7.6 ± 2.4
T3	97.8 ± 7.4	98.6 ± 10.8	79.0 ± 8.0	81.35 ± 7.3	8.2 ± 2.0	8.1 ± 2.3
T4	98.2 ± 9.8	100.0 ± 7.7	80.4 ± 11.4	82.3 ± 10.8	10.5 ± 2.4	8.9 ± 2.5
T5	99.4 ± 8.4	98.7 ± 10.1	80.95 ± 7.1	83.4 ± 13.4	10.3 ± 2.3	9.4 ± 2.7

Results are expressed as mean ± SD.
SD, standard deviation; MAP, mean arterial pressure; CVP, central venous pressure.

DISCUSSION

The results of this study suggested that TRP provides superior myocardial protection over normal saline in patients undergoing heart valve replacement surgery. The conclusions were verified by lower concentrations of cTnI, CK-MB, and LDH in the TRP group after surgery.

In our experiment, the surgery of heart valve replacement involved aortic cross-clamp, cardiac arrest, and reperfusion. Since IR frequently contributes to myocardial injury and biochemical marker elevation, we chose patients scheduled for valvular replacement surgery as our target population to evaluate the cardioprotective effects of TRP. In this study, we measured myocardial injury, which includes cTnI, CK-MB, and LDH. Furthermore, cTnI is a conventional myocardial contractile protein, which can be detected in the blood 3–6 h after the cessation of regional coronary blood flow. It is a reliable marker for evaluating myocardial damage and is more sensitive and specific than other serum enzymes. The study has recommended cTnI for the early diagnosis of acute coronary syndromes, and cTnI also has a good prognostic value (10). Creatine kinase (CK) has three cytoplasmic isozymes in three kinds of tissues, which include CK-MB (heart), CK-MM (muscle), and CK-BB (brain). After the onset of coronary syndrome, the concentration of CK-MB begins to increase within approximately 4–6 h, peak after 17 h (±1 h), with a half-life of 11 h (±1 h) in plasma (11). In clinical medicine, CK-MB plays an essential role as a biomarker in the diagnosis and the assessment of myocardial infarction in combination with cTnI. LDH is a traditional enzyme that catalyzes the pyruvic acid to lactic acid. In the setting of myocardial damage, LDH is released into serum; it has been verified for the assessment of myocardial injury, as it correlates well with the degree of injury (12). These markers increase and peak immediately after the myocardial injury. Since the first 24 h is the most critical for the development of myocardial accident, these three biochemical markers were chosen and tested before anesthesia, as well as at 4, 12, and 24 h after the cross-clamp release, to evaluate myocardial injury.

Our results showed that the levels of cTnI, CK-MB, and LDH were increased after the release of the aortic cross-clamp, but TRP decreased those increments, which suggests a cardioprotective effect of TRP. A previous study has demonstrated the cardioprotective effects of TRP both *in vivo* and *in vitro*. Doxorubicin has a life-threatening cardiotoxic effect in animals. However, a prior intraperitoneal injection of TRP has been shown to improve heart contractility and electrocardiographic changes in addition to decreasing the mortality rate induced by doxorubicin in animal experiments. In addition, TRP robustly counteracted the increment in serum biomarkers and alleviated the histopathological changes compared with the control group (8). Trauma-hemorrhage shock results in excessive production of proinflammatory mediators, such as cytokines and chemokines. Multiple organ failure or dysfunction secondary to a systemic inflammatory response is a major cause of mortality and morbidity. Nevertheless, the administration of TRP significantly improves multiple organ dysfunction, cardiac function, and

TABLE 4 | Routine blood tests before and 24 h after heart surgery.

Time		Control group (n = 31)	TRP group (n = 31)	P-value
Before	WBC	6.4 ± 1.9	6.9 ± 2.6	0.407
	NE	4.1 ± 1.5	4.8 ± 2.8	0.249
	PLT	199.9 ± 51.9	185.5 ± 47.3	0.257
98QJ	CRP	1.7 ± 2.1	1.8 ± 1.8	0.742
After	WBC	16.3 ± 4.1	16.3 ± 4.8	0.964
	NE	14.4 ± 4.2	15.0 ± 4.6	0.647
	PLT	136.4 ± 42.1	134.2 ± 36.6	0.828
	CRP	149.8 ± 70.8	120.8 ± 33.7*	0.043

Results are expressed as mean ± SD.
**P < 0.05 compared with the control group.*
SD, standard deviation; WBC, white blood cell; NE, neutrophil; PLT, platelet; CRP, C-reactive protein.

TABLE 5 | Postoperative complications.

Complications	Control group (n = 31)	TRP group (n = 31)	P-value
Ventricular arrhythmia, n (%)	7 (22.6)	5 (16.1)	0.520
Perioperative MI, n (%)	0	0	–
Cerebrovascular accidents, n (%)	0	0	–
Abnormal coagulation function, n (%)	4 (12.9)	2 (6.5)	0.668
pulmonary Infection, n (%)	6 (19.4)	4 (12.9)	0.490
Shock, n (%)	1 (3.2)	0	1.000
Endocarditis, n (%)	0	0	–
Hospital death, n (%)	2 (6.5)	0	0.472

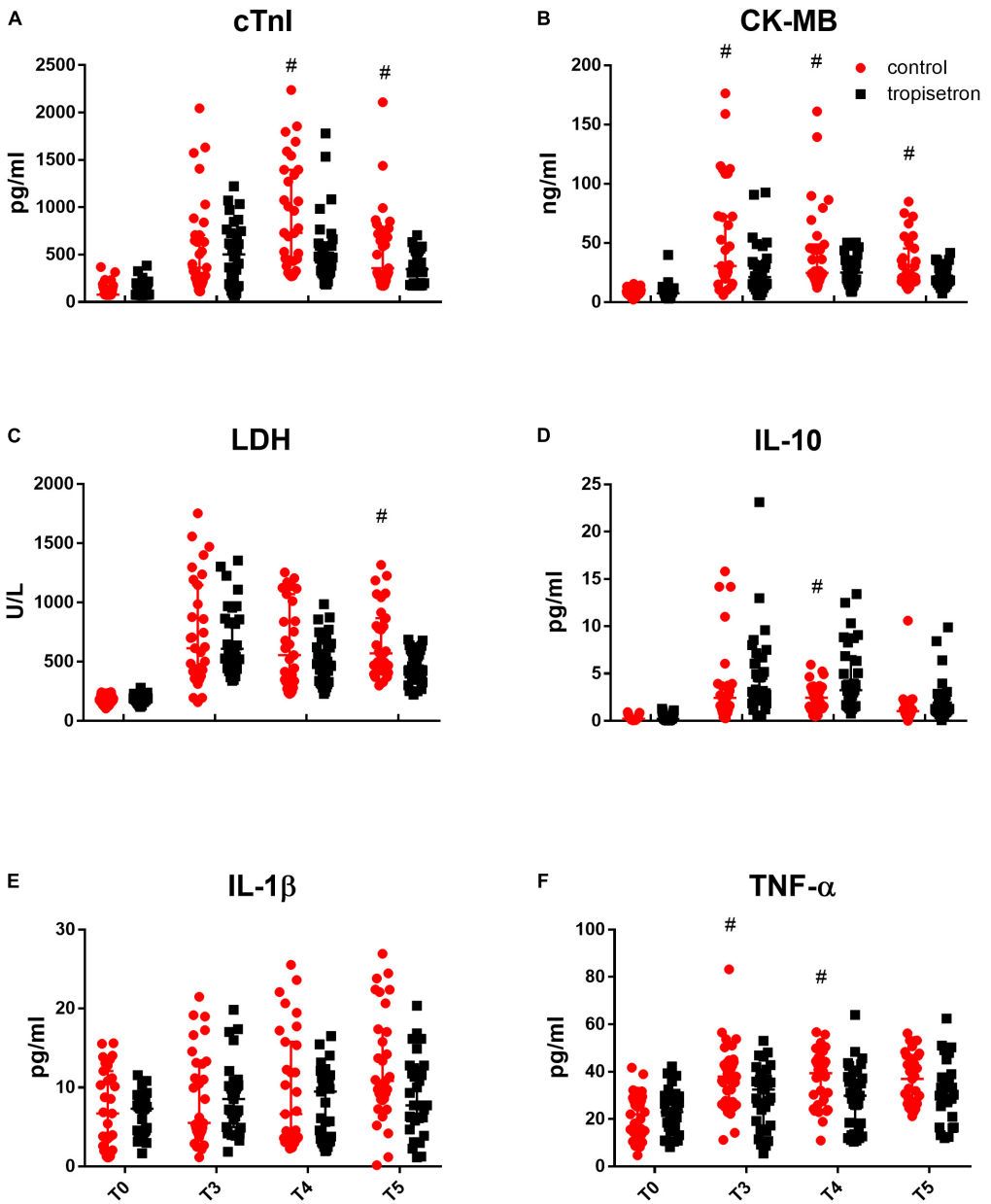

FIGURE 2 | Effect of TRP on perioperative myocardial biomarkers and inflammatory cytokines. Myocardial injury biomarkers, which include **(A)** cTnI, **(B)** CK-MB, and **(C)** LDH, increased after the release of aortic cross-clamp, while TRP treatment decreased that effect ($p < 0.05$, two-way ANOVA for repeated measurements followed by Bonferroni *post-hoc* tests). Inflammatory cytokines, such as **(D)** IL-10, **(E)** IL-1β, and **(F)** TNF-α, were increased, while TRP treatment increased IL-10 and decreased TNF-α levels compared with the control group after the release of the aortic cross-clamp ($p < 0.05$, two-way ANOVA for repeated measurements followed by Bonferroni *post-hoc* tests). $^{\#}P < 0.05$ compared with the control group.

survival (9). The mechanisms may involve the prevention of inflammation and apoptosis of cardiac cells in rats subjected to hemorrhage shock. Furthermore, an *in vitro* study has shown that TRP may have protective effects against high glucose-induced cardiomyocyte hypertrophy. The mechanism responsible for this beneficial effect seems to be, at least in part, due to a blockade of calcineurin–nuclear factor of an activated T-cell signaling pathway (13). Generally, consistent with the previous preclinical studies, our clinical outcomes suggested that TRP had a cardioprotective effect after CPB.

Such a cardioprotective effect may be attributed to the activation of α7 n Ach receptors and the inhibition of 5-HT3 receptors. Recently, α7 n Ach receptor activation has been demonstrated to present cardioprotective effects. According to this report, activating α7 n Ach receptors at the initiator stage of reperfusion reduces myocardial infarct size by inhibiting

TABLE 6 | Correlation and multivariate regression analysis of potential risk factors for cTnI 12 h after surgery.

Independent variable	Correlation analysis		Multivariate linearity Regression analysis		
	r	p	β	95%CI	p
Age	−0.097	0.455			
Gender	0.103	0.424			
BMI	−0.059	0.647			
CPB time	0.268	0.035	4.449	0.97–7.92	0.013
WBC	−0.123	0.342			
NE	−0.061	0.637			
PLT	−0.062	0.634			
CRP	−0.024	0.060	−52.183	−112.18 to 7.82	0.087
EF	0.034	0.791			
LEVDd	0.135	0.294			
LAD	−0.172	0.181			
Treatment	−0.357	0.004	−380.998	−613.4 to −148.5	0.002

BMI, Body mass index; CPB, cardiopulmonary bypass; WBC, white blood cell; NE, neutrophil; PLT, platelet; CRP, C-reactive protein; LEVDd, left ventricular end-diastolic dimension; LAD, left atrial diameter.

Beclin-1 and cascading of signaling pathways against IR injury (14). In addition, high-sensitivity CRP increased IL-6 level, p38MAPK expression, and monocyte activation, which contribute to coronary artery spasm, whereas the overexpression of the monocytic α7 n Ach receptor decreases oxidative stress and inflammation-associated coronary artery spasm (15). Inflammation is a major cause of myocardial IR injury, while vagal nerve stimulation presents an anti-inflammatory effect and reduces the infarct size through α7 n Ach receptor activation (16, 17). Importantly, Nrf2 is a transcriptional factor and has a pivotal role in redox signaling; TRP activates Nrf2 *via* α7 n AChR, which results in apoptosis inhibition (18). Also, TRP exerts notable anti-inflammatory effects through peroxisome proliferator-activated receptor gamma, another crucial transcriptional factor that regulates anti-inflammatory signaling (19). Generally, TRP presents anti-inflammatory effects by the activation of α7 nAch receptors. Unlike other anti-inflammatory medications, α7 n Ach receptor activation is a part of the inner "cholinergic anti-inflammatory pathway"; thus, it has minimum side effects. However, the downstream mechanisms of α7 n Ach receptor activation are still very complex and poorly understood.

In addition, 5-HT3 receptor inhibition may contribute to TRP-induced myocardial protection. Surgery, trauma, CPB surgery, and cardiac arrest increase the release of serotonin and activation of 5-HT3 receptors. 5-HT3 receptor activation mediates platelet activation and thrombosis after cardiac ischemic damage, and inhibition of 5-HT3 receptors prevents platelet activation and thrombosis and reduces ischemic damage after valve replacement surgery (20). Moreover, serotonin activates cardiac sympathetic afferents through the stimulation of 5-HT3 receptors, which results in elevated plasma levels of norepinephrine and cardiac dysfunction. Inhibition of 5-HT3 receptors reduces the elevated plasma level of norepinephrine in mice, prevents cardiac hypertrophy, and restores desensitization of cardiac β-adrenergic receptors in aortic banding-treated rats (21). Sepsis is a severe infection that aggravates myocardial structural changes because of proinflammatory cytokines; however, the addition of a 5-HT3 receptor antagonist significantly inhibits the cytokines' overexpression and myocardial injury in sepsis (22). 5-HT3 receptor agonists cause a rapid depolarization of the membrane potential, which results in the opening of cation channels and Ca^{2+} inflow, while the blockade of 5-HT3 receptors diminishes intracellular Ca^{2+} overload and decreases reactive oxygen species and glutamate excitotoxicity (23). Thus, 5-HT3 receptor activation-related inflammation suppression is another critical factor for the cardioprotective effect of TRP. The effects are mainly mediated by platelets inhibition, sympathetic afferent suppression, and cation channels blockade.

Inflammation is an independent risk factor for the development of myocardial injury after cardiac stunning (24). In our study, we choose IL-10, TNF-α, and IL-1β as the inflammatory biomarkers for evaluating the anti-inflammatory effects of TRP. Our results showed that TRP decreased the increment of TNF-α postoperatively. TNF-α has been demonstrated to participate in myocardial IR by promoting leukocyte infiltration of the myocardium, while TNF-α knockout mice have decreased arrhythmia and improved cardiac function during reperfusion (25). TNF-α also induces long-term cardiac contractile dysfunction, hypertrophy, fibrosis, and cell death (26). The expression of chemokines and adhesion molecules and the infiltration of leukocytes were significantly reduced in TNF-α knockout mice. IL-1β is critically involved in the postinfarction inflammatory reaction, and it mediates adverse dilative remodeling (27). In contrast, IL-1β inhibition improves adverse cardiac remodeling after acute myocardial infarction, which includes left ventricle end-systolic volume index, change in CRP levels, and proinflammatory response (28). However, our results did not show a significant difference in IL-1β levels between the two groups. IL-10 has been demonstrated to improve cardiac remodeling after myocardial infarction by stimulating M2 macrophage polarization and fibroblast activation (29). The mechanism for the cardioprotective effect of IL-10 may involve the IL-10–STAT3–galectin-3 axis (30). In our experiment, IL-10 was increased and TNF-α was decreased after TRP treatment, which suggests that the cardioprotective effects of TRP may be attributed to the overexpression of IL-10 and suppression of TNF-α expression.

In addition to the activation of α7 n Ach receptors and the inhibition of 5-HT3 receptors, TRP may confer cardioprotective effect through other mechanisms. MAPK is an acute proinflammatory protein; it is activated after injury and mediates the proinflammatory response. TRP has been demonstrated to reverse lipopolysaccharide-induced TNF-α and IL-1β expression *via* inhibition of p38 MAPK activation in the

monocyte (31). Activation of the 5-HT3 receptor allows Ca^{2+} entry, which results in Ca^{2+} overload and aggravates cardiac injury (6). TRP has also been shown to block cation channels, which include cardiac potassium and sodium currents and exhibit mixed class III and class I antiarrhythmic properties in ventricular myocytes after ischemia (32, 33). These effects result in reduced myocardial oxygen consumption and myocardial protection. In addition to the cardiovascular effect, TRP presents immunoregulatory effects in stroke (34) and autoimmune diseases, which includes multiple sclerosis and experimental autoimmune encephalomyelitis (34). TRP decreases the size of infarct volume and inflammatory cytokine release induced by an autologous clot into the middle cerebral artery. TRP also decreases TNF-α, COX-2, iNOS, NF-KappaB, active caspase 3, cytochrome c release, and calcineurin phosphatase activity induced by Aβ neurotoxicity in the hippocampus (35). Importantly, it has been shown that TRP is a potent inhibitor of calcineurin, a canonical enzyme that regulates immune responses (36). Thus, in our study, the cardioprotective effect of TRP may be attributed to multiple anti-inflammatory pathways.

Furthermore, we used several anesthetics, including sufentanil (37) and propofol (38), which have been shown to provide myocardial protective effects. Since it was mandatory procedure to use these anesthetics, this study minimized the bias using the same dosage which was calculated according to the patients' body weight. In both of the groups, sufentanil 5 μg/kg was used for each patient. Propofol 50–150 μg/kg/min was used continuously in both groups during the surgery. The effects of sufentanil and propofol were equal between the two groups perioperatively. Thus, the TRP-related decrease in myocardial biomarkers could not be attributed to sufentanil and propofol.

Our results showed that the baseline characteristics, which include age, gender, weight, LVEF, and preoperative medications, were all comparable between the two groups, which excluded the baseline imbalance. The surgery and anesthesia time and perioperative HR, BP, and CVP were not different between the groups. In addition, all of the surgeries were performed by the same surgery and anesthesia groups, which minimized the bias between the two groups. The cross-clamp time in the TRP group was less than that in the control group, which may have compromised the conclusions. There are several limitations to this study. It was a small population clinical trial, so the results are not suitable for assessing the long-term survival rate and the incidence of adverse outcomes, which includes myocardial infarction, stroke, and death. Furthermore, the anesthesia depth was not measured; however, we used the same anesthesia regime for all patients to minimize the bias.

In conclusion, our study showed that TRP preconditioning reduced myocardial biochemical markers and proinflammatory responses in patients undergoing heart valve replacement surgery with cardioplegic arrest. TRP preconditioning is a safe and effective approach for myocardial protection in patients with cardiovascular disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of Taihe Hospital, Shiyan, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DY, XG, and YZ performed the experiment. XG, QL, and MZ designed the experiment. All authors contributed to the article and approved the submitted version.

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