MULTIDISCIPLINARY CRITICAL CARE MEDICINE – GETTING THINGS DONE ACROSS SPECIALTIES

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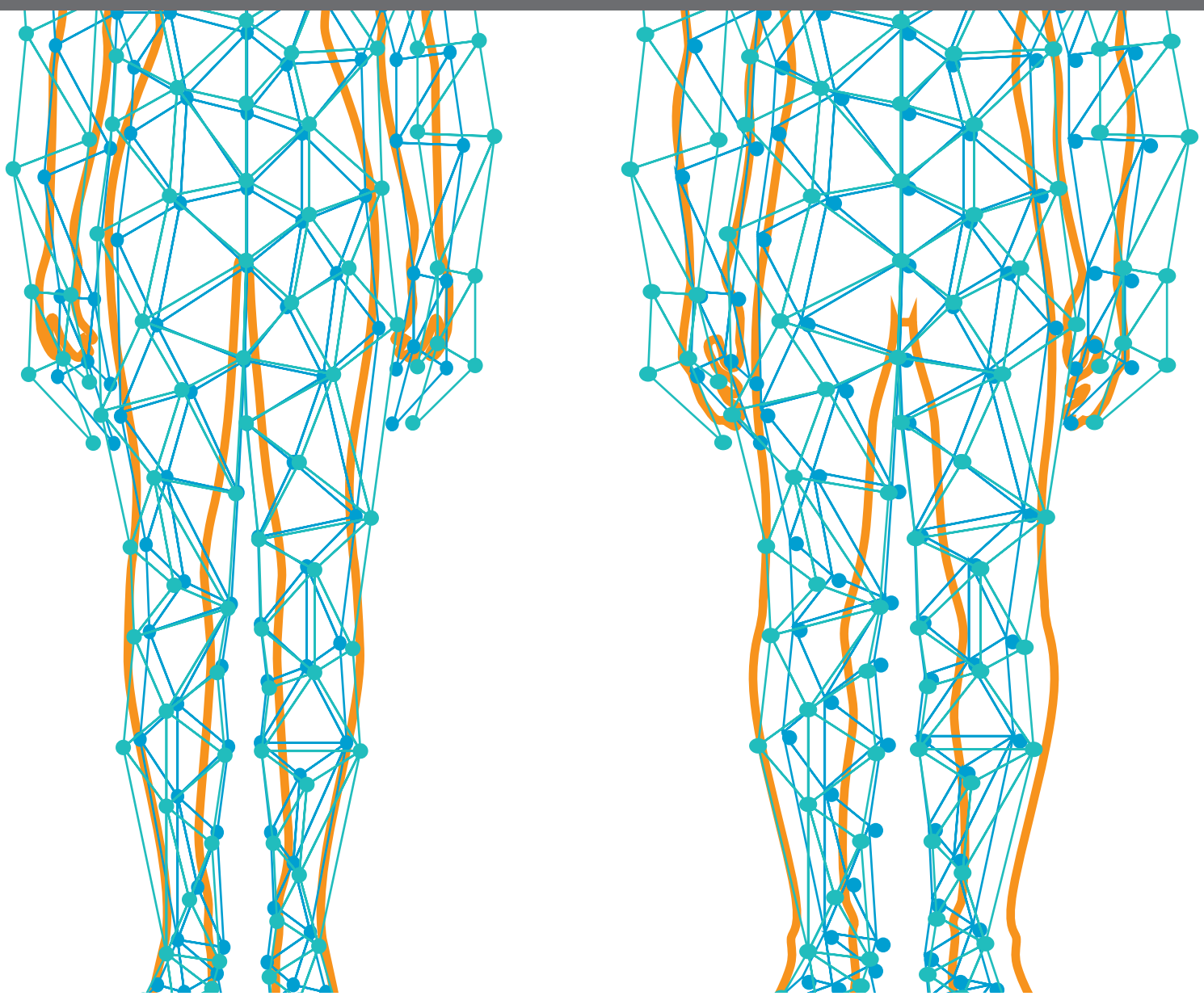

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MULTIDISCIPLINARY CRITICAL CARE MEDICINE – GETTING THINGS DONE ACROSS SPECIALTIES

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Table of Contents

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Editorial: Multidisciplinary critical care medicine – Getting things done across specialties

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Editorial on the Research Topic
Multidisciplinary critical care medicine – Getting things done across specialties

Introduction

Critical Care Medicine is a team sport and requires collaboration not only between different healthcare professionals but also between different specialties. While specialization and sub-specialization are common and needed in modern medicine due to the increasing knowledge and complexity of care, solid knowledge is fundamental for optimal patient care. This becomes most evident in critical care medicine, where patients' lives are at stake, and management decisions are crucial for patient survival. Critical care medicine and its practice differ around the globe. In some countries, anesthesiologists are the leading providers, while in others, there may be dedicated intensivists or chest physicians responsible for the organization of the intensive care unit (ICU). In academic centers, many departments run their ICUs: These may be internists (nephrologists, cardiologists), cardiovascular or abdominal surgeons, neurologists, or anesthesiologists. They all have particular expertise and view on patients and their critical illnesses. With the emerging COVID-19 pandemic and hyperinflammatory syndromes, immunological treatments have gained attractiveness in critical care. In this regard, solid knowledge of new immunological drugs is emerging. With this Research Topic entitled "*Multidisciplinary Critical Care Medicine – Getting Things Done Across Specialties*," we aimed to gather insights from many (sub-) specialties and invited authors from various specialties to contribute their data and opinions. With this editorial, we will give an overview of the topics covered.

The Research Topic has received many submissions, of which 14 were finally accepted for publication. Of these, 10 were original papers dealing with various aspects of critical care medicine, and four were reviews or opinion papers.

External and internal influencing factors

In the first paper, Álvarez and Parada share their opinion on pain as an essential yet under-investigated contributing factor for the development of delirium in critically ill patients. They highlight that currently used delirium assessments, such as the Confusion Assessment Method for the intensive care unit (CAM-ICU) (1), do not incorporate pain. While there are indicators that pain may influence attention, further research is required to corroborate this hypothesis.

The following paper, by Naef et al. investigated methods for measuring sound and noise levels in an ICU. In short, they first provided a framework for measuring sound pressure levels and sound sources of two beds in a four-bedroom with four sound level meters and four different observers. Then, they tested the method's feasibility in a concrete ICU setting. They found that their proposed method over 24 h was applicable with a good or very good interrater reliability in most of the assessed domains. The paper provides a basis for future studies in the same field with a clearly defined methodology.

The third paper assessed the impact of oxygen saturation on mortality in mechanically ventilated patients Here, Li et al. provided data from a retrospective analysis of roughly 25,000 patients in China. They analyzed the impact of different oxygen saturations in obese and non-obese using a multivariable regression model. Specifically, they found that oxygen saturation levels of 99–100% were associated with higher mortality in obese patients, whereas lower values (between 89 and 93%) had an increased mortality in non-obese patients. Thus, different target oxygen saturation levels may be applied depending on body weight.

The fourth paper investigating assessments and other factors in ICU patients reported a one-day point prevalence study of implementing the ABCDEF bundle during the COVID-19 pandemic (Liu et al.). The ABCDEF bundle is an evidence-based guide for the optimization of ICU care considering various aspects (2): (A) represents "Assess, Prevent, and Manage Pain," (B) "Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT)," (C) stands for "Choice of analgesia and sedation," (D) relates to "Delirium: Assess, Prevent, and Manage," (E) "Early mobility and Exercise," and (F) represents the concept of "Family engagement and empowerment." In this paper, Liu et al. investigated the implementation in COVID-19 and non-COVID patients. They found that, at the time of the investigation, implementation of the entire bundle was 0% for non-COVID-19 patients and 1% for COVID-19 patients. The highest implementation rates were reported for the "A" component (64% non-COVID-19, 55% COVID-19 patients), "C" (45 and 61%, respectively), and "D" (39 and 35%, respectively). On the other hand, breathing trials (component "B"), exercise programs (component "E"), and family engagement (component "F") were implemented, ranging from 10 to 30% of patients.

Medications and infusions

The next set of papers dealt with medications or infusions and their influence on outcomes or their clinical applications in ICU patients. The first paper was a retrospective study on adverse reactions to intravenous immunoglobulin (IVIg) infusions by Kato et al.. Their study of roughly 750 patients identified female sex, neuromuscular diseases, and higher cumulative IVIg doses (around 10 g/kg of body weight) as risk factors for adverse reactions. Overall, the incidence of adverse events was low, ranging from 1 to 8% for most risk factors. Exceptions to this were neuromuscular diseases (e.g., chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, myasthenia gravis) with an incidence of about 26% and eosinophilic granulomatosis with polyangiitis with an incidence of almost 19%.

Another study presented by Tseng et al. investigated a long-debated topic in ICU patients, whether lactated ringer's (LR) solution or saline (normal saline, NS) were associated with better or worse outcomes. In their prospective study of 938 patients, the LR group had an overall lower mortality than the NS group (adjusted hazard ratio: 0.59; 95% CI 0.43–0.81). Also, the length of the hospital stay was shorter in the LR group. The differences were more pronounced in patients with chronic pulmonary disease than those with chronic kidney or liver disease. The underlying reasons are not clear yet. However, comorbidities should probably be considered when choosing the type of fluid. A recent systematic review with meta-analysis provided evidence from randomized controlled clinical trials that balanced crystalline solutions may offer mortality benefits in unselected ICU patients (3).

Next, Cao et al. provided a literature review on the use of hemoglobin-based oxygen carrier-201 (HBOC-201), a potential blood substitute that is currently very infrequently used in clinical practice. The authors comprehensively review the available evidence from clinical trials, including surgical and medical conditions. As such, HBOC-201 may have an emerging role as a blood substitute when there is a shortage of blood products. Nevertheless, potential side effects on the cardiovascular system, methemoglobinemia, and liver enzyme abnormalities, among others, must be monitored carefully.

Biomarkers

The only study included in this Research Topic that investigated a potential new biomarker sought to determine the role of sphingosine-1-phosphate (S1P) in cardiac surgery patients (Greiwe et al.). Sphingosine-1-phosphate is known to have a possible beneficial effect on inflammation, and agonists of S1P have been approved for use in multiple sclerosis (MS) or inflammatory bowel disease (4). In addition, S1P is being investigated In rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis (4). In their study, Greiwe et al. provided evidence for S1P as a potential new biomarker during cardiac surgery. They found that serum levels of S1P decreased immediately after surgery and, in patients whose levels failed to reach baseline levels, the ICU stay was prolonged and postoperative inflammation prolonged. A critical limitation of this study was the potential inhibitory of heparin, which may have influenced serum levels during and after surgery. In addition, in a recent small randomized controlled clinical trial, fingolimod, an S1P agonist approved for the treatment of MS, failed to improve overall outcomes in COVID-19 patients but was associated with a lower re-admission rate (5). S1P is an interesting molecule, but its role, whether biomarker or potential drug target in ICU patients, has yet to be determined.

Outcome predictors

A total of six papers described outcome predictors of ICU populations. The first paper by Choon et al. examined the association between completeness of discharge documentation and subsequent follow-up of acute kidney injury (AKI) survivors who required kidney replacement therapy (KRT) treated at the intensive care unit (ICU) in a retrospective cohort study. The development of AKI and the need for KRT were mentioned in 85 and 82% of critical

care discharge letters, respectively. Monitoring kidney function post-discharge was recommended in 51.6% of critical care and 36.3% of hospital discharge summaries. At 3 months, creatinine and urine protein were measured in 88.2 and 11.8% of survivors, respectively. The prevalence of chronic kidney disease stage III or worse increased from 27.2% before hospitalization to 54.9% 1 year after that. These data demonstrate that discharge summaries of patients with AKI who received KRT lacked essential information. Furthermore, renal follow-up was poor in patients with appropriate documentation, suggesting the need for more education and streamlined care pathways. This is especially relevant since failure to record an episode of AKI treated with KRT can have serious implications for patients' future long-term management (6).

The paper by Zhang et al. aimed to explore the clinical features and mortality risk factors of patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) requiring ICU treatment. The authors identified that active vasculitis was the most frequent reason for ICU admission, and the leading cause of death was an infection. Acute Physiology and Chronic Health Evaluation II (APACHE II) at admission and respiratory failure were independent risk factors. At the same time, hemoglobin was an independent protective factor of in-ICU mortality for AAV patients admitted to the ICU. The risk prediction model developed in this study may be a helpful tool for clinicians in the early recognition of high-risk patients in this population to apply appropriate management. Because the inconsistent predictive value of biological markers (including hemoglobin) has previously been described, this multivariate model may improve risk prediction in this patient population (7, 8).

The study conducted by Liou et al. aimed to investigate the outcome differences between bystander cardiopulmonary resuscitation (BCPR) and no-BCPR in patients who received Targeted temperature management (TTM) after cardiac arrest. After undertaking a multiple logistic regression analysis, the authors found that BCPR was a significant positive predictor for in-hospital survival. In conclusion, this study demonstrated that BCPR had a favorable survival and neurological impact on spontaneous circulation (ROSC) return in patients receiving TTM after cardiac arrest. While the survival and neurological benefits of BCPR have already been described, this study expands our current knowledge about the outcome benefits of BCPR in patients receiving TTM (9).

The article by Bansal et al. described the development and validation of a multivariate Re-Intubation Summation Calculation (RISC) score for the prediction of respiratory failure after extubation. Predictors of extubation failure included body mass index <18.5 kg/m^2, a threshold of Glasgow Coma Scale (GCS) of at least 10 points, mean airway pressure at 1 min of spontaneous breathing trial <10 cmH_2O, fluid balance $\geq$1,500 mL 24 h preceding extubation, and total mechanical ventilation for $\geq$5 days. Multivariate logistic regression demonstrated that an increase of 1 in the RISC score significantly increased the odds ratio for extubation failure by 1.6-fold. These variables are available in the electronic medical record. The risk prediction model developed in this study may be helpful for clinicians in identifying patients at risk for extubation failure. Since extubation failure is associated with adverse outcomes, including increased hospital mortality, prolonged hospitalization, and increased requirement for tracheotomy, this topic is of great relevance (10, 11).

In the study by Yin et al., a novel critical illness prediction system combining baseline risk factors with dynamic laboratory tests was evaluated in patients with coronavirus disease 2019 (COVID-19). A baseline nomogram model to predict the risk for critical illness at admission consisted of seven variables: age, sequential organ failure assessment (SOFA) score, neutrophil-to-lymphocyte ratio (NLR), D-dimers, lactate dehydrogenase (LDH), international normalized ratio (INR), and pneumonia are interpreted from computed tomography (CT) images. In addition, a linear mixed model (LMM) predicting the occurrence time of critical illness onset during hospitalization based on the dynamic change of seven variables was identified: SOFA score, NLR, C-reactive protein (CRP), glucose, D-dimers, LDH, and blood urea nitrogen (BUN). During the ongoing COVID-19 pandemic, this predictive system could assist in accurately and dynamically predicting critical illness in patients with COVID-19 for appropriate management. This study confirms our current knowledge about risk predictors for severe COVID-19 (12–14).

In the opinion article by Calmels et al., the authors summarize the current knowledge about motor simulation as a plausible non-invasive, safe, easy to implement, and low-cost complementary adjunct among the healthcare delivery provided during the (post-) ICU recovery process. In summary, multidisciplinary healthcare professionals may consider motor simulation as a practical, relevant, and therapeutic option to maximize a patient's return to autonomy.

Conclusions

In this Research Topic, many research areas from different specialties were covered. While many papers focused on outcome predictors, others investigated the effects of infusions, medications, or analyzed new biomarkers. We are confident that many of the presented articles provide relevant data for critical care specialists across all specialties and settings.

Author contributions

PK and BT conceived the article and co-wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

PK has received honoraria or travel support from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb, Chugai, Galapagos, GlaxoSmithKline, Janssen-Cilag, Lilly, Novartis, and Pfizer, all unrelated to this paper. In addition, PK received research grants from GlaxoSmithKline and Diamed Medizintechnik GmbH, all unrelated to this paper. BT reports honoraria or travel support from Vifor Pharma, unrelated to this paper. In addition, BT received research grants from Vifor Pharma and Evotec SE, all unrelated to this paper.

Publisher's note

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OPINION
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Association of Pain During the Evaluation of Delirium in Intensive Care Unit Patients

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Keywords: pain, intensive care unit, delirium screening, connectome, electroencephalography

INTRODUCTION

The present article aims to discuss how pain can affect cognitive performance, focusing our attention on the evaluation of delirium in critical patients and its relation with pain. To achieve this, we will briefly review (i) neural changes and dynamic adaptation processes between pain and attention; (ii) the effects of acute pain in performance and neural activity of attentional tasks; (iii) the implementation process of delirium's evaluation in hospitalized patients with pain at an intensive care unit. We finally discuss these elements in the light of implementing cognitive assessments processes in pain patients.

PAIN AND ATTENTION

We understand pain as an unpleasant sensory, psychological, and emotional experience emerging from the interaction between an agent and a situation associated with threat and potential physical and/or psychological damage, facilitating behaviors oriented toward protecting from such damage. Pain is generally caused by a noxious stimulus triggering physiological processes called nociception, which is mediated by a series of sensory and contextual events (behavioral, emotional, cognitive, and sociocultural). Thus, pain is a dynamic bodily-effective integrative phenomenon (1). Given its high dimensionality, it could be said that pain demands a high level of cognitive resources, interfering, distracting, and demanding the focusing of attention (2) and thus decreasing the offloading and extending capacities of cognition (3, 4). Depending on the temporality of a painful experience, it can be classified as acute or chronic. Acute pain occurs in the short term and can be resolved within 3 to 6 months, being the response to an injury or specific trauma and acting as a warning system for the body. When tissue damage is involved, this type of pain is self-limited and it is resolved with cicatrization. In some cases, acute pain can turn into chronic pain, which we understand as intermittent or persistent pain experienced during more than 3 months and/or persisting beyond healing time (5). Chronic pain has been observed to affect attention in demanding tasks (6). In healthy individuals, any type of pain causes immediate protective responses, such as safety-seeking behaviors, including escape and avoidance. Attention protects the pursuit of current goals by inhibiting the processing of irrelevant information (6).

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Neural Changes and Dynamic Processes Between Pain and Attention

At a neural processes level, pain has been assessed through functional/structural connectivity (i.e., connectomics) and cognitive electrophysiology using electroencephalography (EEG). Connectomics allows us to understand the connectivity and communication among brain networks, analyzing the nodes and functional and anatomic tracts interconnections through complex-network analysis (7). Relevant to our case is the identification of the salience network, which comprises brain areas such as the anterior insula, medial cingulate cortex, temporoparietal junction and prefrontal cortex. The intrinsic activity or resting-state network composed by posterior cingulate cortex, medial prefrontal cortex, lateral parietal lobe, along with medial temporal lobe areas has also been shown as relevant in the process of pain detection in conjunction with an antinociceptive modulation system that includes the central region of the periaqueductal gray area in the brain stem (7). Thus, when attention is directed toward a painful stimulus, the medial prefrontal cortex exercises causal influences over the primary sensorimotor cortex. In contrast, by removing attention (i.e., distraction), this influence disappears (1). The foregoing suggests dynamism from the information flow's context in pain processing, being an adaptable network with functional connections, neurobiologically constructing the painful experience as a flexible phenomenon (8).

Furthermore, electrophysiological evidence shows that neural oscillatory activity -described in terms of frequency, phase and amplitude- codifies specific activity (9). EEG dynamics allow quantifying the brain's functional integration and segregation processes. Low-frequency oscillations (<30 Hz) can be found at the base of the signal known as event-related potentials (ERP), which are an average of neural activity at time-domain (**Box 1**) (19). ERP studies related to pain, where stimuli are caused by nociceptive laser stimuli, show modulations in the complex known as N2-P2, occurring within the 200–400 ms latency range when the back of the hand is stimulated (20). Other studies have shown that pain stimuli generate above-threshold voltage deflections in the N1-N2 components, in contralateral somatosensory areas or in the posterior insula. Considering neural activity in time and frequency domains, broadband and frequency specific changes in Theta (4–8 Hz), Alpha (8–15 Hz), Beta (15–30 Hz), and Gamma (>30 Hz) oscillations have been identified in the nociceptive processing during the presence of chronic and acute pain (**Box 1**). Furthermore, functional coupling of Theta and Gamma involves nodes in both the salience and default network in chronic pain (21).

Evidence suggests that when cognitive, behavioral, and contextual resources are required, attention can optimize resources toward goal-relevant information (22). Pain -as an inherent prominent stimulus (23)- and nociceptive processing are closely intertwined with attentional processes (8), situating and embedding the dynamic integration of sensory and contextual processes during painful experiences (1).

Pain-Related Neural Dynamics During Attentional Tasks

In a meta-analysis conducted in 2019 (6), eight studies describing the influence of acute pain and attentional changes were found, considering the following subcomponents: (i) *orientation*, five studies evaluated spatial signals, where they found that subjects with pain presented more errors in the identification of non-valid signals; (ii) *awareness*, two studies conducted continuous performance assessments and found that pain diminishes alertness; and (iii) *executive attention*, two studies used Go/No-Go and Stroop paradigms to detect slight changes in response time and performance. Considering this evidence, pain changes both the performance and execution of attentional tasks. Similarly, a recently published quasi-experimental study measured pain-modulated neural activity during attentional tasks (24). Participants performed an executive attention task, in which the subjects had to remember a series of numbers in two conditions: low-cognitive load (i.e., two digits) or high-cognitive load (i.e., six digits). The experimental group reported moderate pain after capsaicin-induced painful stimulation. Neural activity was recorded using EEG. Results show that the experimental group decreased their behavioral accuracy without supra-threshold ERP differences considering cognitive load. In contrast, the control group reported above-threshold ERP differences between low- and high-load cognitive tasks. Authors interpret their results as indicating participants experiencing pain decrease attention to cognitive demands, affecting the use of appropriate strategies to solve the task, allocating similar attentional resources in cognitive tasks with different load. Furthermore, frequency analysis showed that Delta and Theta oscillations exhibit a delay in high-load tasks for the subjects within the experimental group considering cognitive load. This study showed that pain and cognitive load affect both cognition and behavior, interfering in the accuracy of the responses. Furthermore modulating early stages of attention, impeding participants experiencing pain to adjust to task demands both at behavioral and neurophysiological levels. Thus, the experience of acute nociceptive stimulation has significant changes in attention with relevant neurobehavioral consequences.

PAIN AND ATTENTION AT THE INTENSIVE CARE UNIT

Pain is a permanent concern and a common symptom among critically ill adults. Approximately 50-80% of the patients report pain at rest and/or during procedures (25) caused by the process of primary diseases and tissue injury, invasive procedures, endotracheal suction, presence of endotracheal and nasogastric tubes, invasive monitoring catheters, urinary catheters, drainage, insertion and extraction of tubes and catheters, wounds care, immobility and position changing. These medical procedures are described by patients as painful interventions (26–28). It is important to emphasize that patients describe their pain as a significant part of their intensive care unit (ICU) experiences (29), classifying it from moderate to severe (28). Considering

BOX 1 | Neural activity's information description through EEG.

Event-related potentials (ERP).

The ERP have an adequate temporal resolution that allows the measurement of the brain activity relevant to attentional and perceptual tasks (10). The electric responses from the cortex generate voltage fluctuations, which are measured by the EEG. These fluctuations are temporally related to motor or cognitive sensory events. In general, these are generated as a response to peripheral or external stimulations and appear as somatosensory, visual and hearing brain potentials, or as a slow-evolution brain activity observed before voluntary movements or during the anticipation of the conditional stimulation (11).

That is how attentional and pain aspects related to ERP have been found, such as:

- N1 with spatial attention and discrimination tasks, along with pairing processes (12)
- P2 with the sensation-seeking behavior (13)
- N2 with relevant and disparate stimuli identification
- LPP with emotional intensity stimuli (14)
- P300 obtained from parietal and central areas as a response to visual or hearing salient stimuli (15)

Frequency bands

Brain oscillations recorded by EEG have been classified into frequency bands, and through research work, they have been associated with different brain states or functions (16). A brief description of them are listed below:

- Delta waves (up to 4 Hz) are high-amplitude waves that have been associated with deep sleep stages, in awake subjects with cortical plasticity, as a participating oscillation in cognitive processes of event-related potentials, contributing within P3, and also associated with the assessment of stimuli and the decision-making process (17). Detection of pain (6).
- Theta wave (4–8 Hz). On a frontal level, it has a role within attention processing, cognitive control and working memory (18)
- Alpha wave (8–13 Hz) manifests itself spontaneously in adults during the vigil and in a relaxed state, and shows variations during working memory retention. Sensitivity to pain
- Beta wave (13–25 Hz). It has been observed greater activity in the frontal and central areas during the execution of activities, resolution of problems and sustained attention. During spatial discrimination tasks and visual attention, activity in occipital areas has been observed. It detects sensory variations and pain
- Gamma waves (over 25 Hz) are quick oscillations that can be found during conscious perception. It is also related to attentional processes, working memory and long-term memory (14). Pain saliency (8, 16).

that pain is complex and subjective, self-report is still the gold standard for its detection and evaluation. Given that ICU patients are critically ill, intubated, and with different levels of sedation, pain detection is a permanent challenge because communication and self-report opportunities are often limited (27). Furthermore, ICU patients are prone to developing delirium. Delirium is a neuropsychiatric disorder that occurs in an acute and fluctuant manner, affecting attention and other cognitive areas (30). It generates long-term complications [i.e., longer periods of mechanical ventilation (31), hospital stay (32), cognitive and mental health impairment (33, 34), caretakers' overload (35), mortality (36)].

Considering the effects of pain, the implementation of timely monitoring becomes relevant. Thus, several guidelines (37, 38) suggest the use of instruments, the most well-known being (i) Confusion Assessment Method (CAM-ICU) and (ii) Intensive Care Delirium Screening Checklist (ICDSC) (39). These assessment methods are based on brief interviews and simple tests that measure cognitive function focusing on attention (i.e., instruction following, alertness, sustained attention). These instruments take into account the use of sedation scales measuring the state of consciousness in a quantitative manner. Nevertheless, they neglect pain evaluations, which can directly interfere in orientation, awareness, and executive attention.

Finally, ICU patients' condition who are constantly exposed to pain is highly complex due to the challenging non-ecologic physical environment in which they are embedded (i.e., environmental noise, regulation of the sleep-wake cycle, temperature, artificial light, etc.) and their physical/volitional restrictions (i.e., equipment for drug's administration, bladder-bowel control management, respiratory control, etc.) (40) is prone to generate overloaded nociceptive stimulation and experiences. Hence, researchers and practitioners within the ICU environment must ask ourselves, what is the proper form of an ICU delirium evaluation? How can it be properly implemented in this type of patient? and How to interpret the information obtained from such an assessment?. We are ways away to answer these and other questions.

CONCLUDING REMARKS

In the present piece, we briefly reviewed the current evidence showing how pain impacts cognitive functioning, specifically attention. Furthermore, we conceptualize pain as a dynamic and flexible process that generates salience effects linked to specific neurodynamics in large thalamocortical networks related to perception, cognition, and behavior. Laboratory-based evidence can provide us some insights to understanding people's neurobehavioral states when in fragile and high nociceptive demanding situations. These can be thought of as a model for ICU patients, where pain is reported as a frequent complication and where their cognitive skills show an apparent performance deterioration. More specifically, attentional and thought-organization abilities measured with delirium assessments, appear as heavily compromised. Thus, we invite delirium researchers and practitioners to consider pain -in its complexity- as a main factor during delirium evaluations.

Furthermore, since assessing delirium depends on evaluating attentional and thought-related alterations, identifying and understanding the experience of pain can be a key component toward improving our practices. Thus, the main goal of the

present piece is to invite researchers and practitioners to discuss delirium assessment practices and procedures to improve its implementations and interpretation of results, especially in the ICU context which facilitates painful experiences. Hence, understanding the unique coupling parameters and constraints enabling and/or constituting patient states embedded in the ICU, will provide better orientation for assessment, treatment or intervention rationale, and a shared language for interdisciplinary dialogue and research integration.

AUTHOR CONTRIBUTIONS

EÁ wrote the first manuscript draft. EÁ and FP wrote and edited the final manuscript version for publication. All authors contributed to the article and approved the submitted version.

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Discharge Documentation and Follow-Up of Critically Ill Patients With Acute Kidney Injury Treated With Kidney Replacement Therapy: A Retrospective Cohort Study

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Leading organisations recommend follow-up of acute kidney injury (AKI) survivors, as these patients are at risk of long-term complications and increased mortality. Information transfer between specialties and from tertiary to primary care is essential to ensure timely and appropriate follow-up. Our aim was to examine the association between completeness of discharge documentation and subsequent follow-up of AKI survivors who received kidney replacement therapy (KRT) in the Intensive Care Unit (ICU). We retrospectively analysed the data of 433 patients who had KRT for AKI during ICU admission in a tertiary care centre in the UK between June 2017 and May 2018 and identified patients who were discharged from hospital alive. Patients with pre-existing end-stage kidney disease and patients who were transferred from hospitals outside the catchment area were excluded. The primary objective was to assess the completeness of discharge documentation from critical care and hospital; secondary objectives were to determine cardiovascular medications reconciliation after AKI, and to investigate kidney care and outcomes at 1 year. The development of AKI and the need for KRT were mentioned in 85 and 82% of critical care discharge letters, respectively. Monitoring of kidney function post-discharge was recommended in 51.6% of critical care and 36.3% of hospital discharge summaries. Among 35 patients who were prescribed renin-angiotensin-aldosterone system inhibitors before hospitalisation, 15 (42.9%) were not re-started before discharge from hospital. At 3 months, creatinine and urine protein were measured in 88.2 and 11.8% of survivors, respectively. The prevalence of chronic kidney disease stage III or worse increased from 27.2% pre-hospitalisation to 54.9% at

1 year ($p < 0.001$). Our data demonstrate that discharge summaries of patients with AKI who received KRT lacked essential information. Furthermore, even in patients with appropriate documentation, renal follow-up was poor suggesting the need for more education and streamlined care pathways.

Keywords: acute kidney injury, kidney replacement therapies, survival, chronic kidney disease, discharge letter, medication reconciliation, acute dialysis

INTRODUCTION

Acute kidney injury (AKI) is common in the Intensive Care Unit (ICU) affecting more than 50% of critically ill patients (1, 2). Between 10 and 15% of patients with AKI receive kidney replacement therapy (KRT) (3). The development of AKI is associated with serious complications, increased mortality and high health care costs (4–6). Survivors of AKI remain at risk of long-term sequelae, including *de novo* or progressive chronic kidney disease (CKD), end-stage kidney disease (ESKD), cardiovascular events, re-hospitalisation, recurrent AKI, and poorer quality of life, even if renal function initially recovers (7). About 1 in 6 patients with severe AKI become dialysis dependent in the following 2–3 years (8). There is also increasing recognition that an episode of AKI is associated with a deterioration of other chronic illnesses, either directly or as a result of changes to medications (7). Although leading organisations, including the National Institute for Health and Care Excellence (NICE), the Renal Association and the Royal College of General Practitioners (RCGP) recommend nephrology follow-up after an episode of severe AKI, actual follow-up rates range from 8.5 to 41% (3, 9–12). Furthermore, delayed or inadequate follow-up care has been shown to contribute to worse outcomes (12).

A working group of the RCGP United Kingdom (UK) recently published guidance which promotes tailored and timely follow-up care for people who had a hospital admission complicated by AKI. An important component of this recommendation is the safe transition of care between hospital and primary care teams which includes the transfer of relevant information, the importance of accurate discharge documentation, the need for correct coding of the diagnosis of AKI, drug optimisation, and recommendations related to repeat measurement of creatinine and urine protein (13). Repeat measurement of renal function is recommended within 1–12 weeks depending on risk factors and degree of renal recovery after AKI. In addition, it is suggested that high-risk patients are referred for nephrology follow-up, including those with persistent poor kidney recovery and/or glomerular filtration rate (GFR) $\leq$ 30 ml/min/1.73 m^2 during follow-up (14). The need for more education, as well as effective communication between healthcare providers and the patient is also highlighted.

Previous reports from centres in France and the United States (US) concluded that hospital discharge summaries were often inadequate to facilitate appropriate follow-up care (15, 16). In the scarcity of data from the UK (17), we aimed to investigate the process and effectiveness of information transfer for critically ill patients with AKI who received KRT and left hospital alive. In particular, we examined the comprehensiveness of the critical care and hospital discharge summaries with regard to AKI diagnosis, the need for KRT, recommendation for follow-up management, and actual kidney and patient outcomes at 1 year. In addition, we explored whether chronic cardioprotective medications were re-started prior to discharge from hospital.

MATERIALS AND METHODS

Setting

Guy's & St Thomas' NHS Foundation Hospital is a tertiary care centre in the UK with a 64-bed, level 2/3 multi-disciplinary adult critical care unit. The critical care unit has a fully computerised electronic patient record system (ICCA, Philips) where all data are recorded at the time of generation. A pertinent summary discharge document is exported in read-only format when the patient is stepped down from critical care to a general or specialist ward. At time of discharge from hospital, the relevant specialty generates the final discharge summary for the primary care team, i.e., general practitioners (GP).

Study Design and Population

This was a retrospective cohort study. We retrospectively screened the electronic database of all critically ill patients who were admitted to the critical care unit between 1st June 2017 and 31st May 2018. We identified adults ($\geq$16 years old) who had KRT for AKI and left hospital alive. Exclusion criteria were: (a) known ESKD on long-term dialysis or previous renal transplant; and (b) external transfers from ICUs outside the hospital's catchment area. The report was adhered to the STROBE Guideline (18). Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data Collection

Baseline characteristics, comorbidities, chronic medication use, reason for admission, AKI causes, and creatinine values and dialysis status at hospital discharge were collected from the electronic healthcare records. AKI was defined according to the Kidney Diseases: Improving Global Outcomes (KDIGO) Guideline (19). Baseline kidney function was defined as the most recent outpatient non-emergency serum creatinine concentration between 7 and 365 days before admission (19). Estimated glomerular filtration rate (eGFR) was determined using the CKD Epidemiology Collaboration (CKD-EPI) equation (20).

We hand-searched the discharge documents from critical care and the hospital discharge summaries for the documentation of AKI, KRT, and follow-up arrangements, with either these

keywords, coding, or a synonymous descriptor. Two investigators (X.Y.C. and N.L.) independently examined all data, and a third investigator (M.O.) adjudicated any differences. One investigator (N.L.) and a team of critical care pharmacists (led by L.C.) independently explored medications prior to ICU admission and at hospital discharge including renin-angiotensin-aldosterone-system inhibitors (RAASi), diabetes drugs, diuretics, and statins. We also identified the frequency and the results of creatinine and urine protein measurements after hospital discharge by checking existing healthcare records, and the outpatient follow-up rates by nephrologists and/or other medical subspecialties within 12 months of hospital discharge. Laboratory results from local hospitals and primary care services were accessed where possible. Finally, we looked at the kidney and patient outcomes, including dependence on chronic dialysis and survival at 1 year. Information about dialysis dependence was obtained from the United Kingdom Renal Registry (UKRR), a mandatory registry which includes all patients with ESKD in the UK.

Outcomes

The primary outcome was the completeness of the discharge documentation with regard to (1) AKI diagnosis, (2) receipt of KRT, (3) recommendation to monitor renal function, and (4) recommendation to refer for nephrology follow-up. "Completeness" was defined as the inclusion of criteria (1) and (2) and either (3) or (4). Secondary outcomes were proportion of survivors with impaired kidney function (eGFR < 60 ml/min/1.73 m^2), dialysis dependence at 1 year, survival at 1 year, and rate of follow-up in a specialist nephrology clinic. In addition, we explored whether creatinine and urinary protein results (either by urine dipstick, urine albumin:creatinine ratio, or urine protein:creatinine ratio) were available at 3 months and 1 year after ICU discharge. Chronic kidney disease (CKD) was defined as eGFR persistently < 60 ml/min/1.73 m^2 at 3 months after hospitalisation (21). Continuation or discontinuation of relevant medications (RAASi, statins, diuretics, diabetes drugs) was explored as an additional outcome.

Statistical Analysis

Categorical data are presented in numbers and proportions, and continuous data are presented in median (interquartile range, IQR). Comparisons were made using Chi square or Fisher exact test for categorical data and Wilcoxon test for continuous data. Wilcoxon sign rank test was used to assess the difference between eGFR at baseline and 1 year. A $p < 0.05$ was considered statistically significant. Stata 16.1 (StataCorp, Texas, USA) was used for statistical analysis.

RESULTS

Patient Characteristics

Between June 2017 and May 2018, 2,380 patients were admitted to the critical care unit of whom 433 (18.2%) critically ill patients received continuous kidney replacement therapy (CKRT) and/or prolonged intermittent kidney replacement therapy (PIKRT) (**Supplementary Figure 1**). We excluded patients with ESKD ($n = 96$) or a renal transplant ($n = 22$), patients transferred from an ICU in another catchment area ($n = 72$) and patients who died during hospitalisation ($n = 164$). Twelve patients had more than one exclusion criteria.

Ninety-one patients were included in the final analysis of whom 55% were male (**Table 1**). Their median age was 61 (IQR 47–73) years; 52.8% had pre-existing hypertension, and 25.3% had diabetes mellitus. Twenty-seven (29.7%) patients had prior CKD with a median baseline eGFR of 39 (IQR 27–52) ml/min/1.73 m^2, of whom 4 (14.8%) were known to nephrology service prior to admission. The main causes of AKI were sepsis (36.3%) and cardiac-related (20.9%).

Discharge Documentation

The critical care discharge summary included documentation about AKI in 85.7% of all patients; in 82.4% of cases, it was reported that the patient had received KRT; in 51.6% of summaries, further renal function monitoring was recommended, and 47.3% of summaries included a recommendation for nephrology follow-up (**Table 2**; **Supplementary Figure 2**). Overall, only 50 AKI survivors (54.9%) had complete critical care discharge documents.

Hospital discharge summaries included less AKI-related information compared with critical care summaries: AKI was mentioned in only 71.4% documents, "need for KRT" in 61.5%, recommendation for kidney function monitoring in 36.3%, and a recommendation for nephrologist follow-up in only 20.9% cases (**Table 2**). Only 29 (31.9%) hospital discharge documents included complete information. Patients whose critical care discharge summaries fulfilled the "completeness" criteria for documenting an AKI episode were more likely to also fulfil the "completeness" criteria in the hospital discharge summaries when compared to those critical care discharge summaries that failed to meet the "completeness" criteria.

Patients with poor kidney function or ongoing need for dialysis at time of hospital discharge were more likely to have complete documentation and nephrology follow-up. There was no statistically significant difference in assessment of serum creatinine and proteinuria during the follow-up period between patients with complete and incomplete discharge documents: serum creatinine was measured in 96.6 vs. 87.1% of patients ($p = 0.26$), and proteinuria was determined in 27.6 vs. 19.4% of patients ($p = 0.38$), respectively (**Table 3**). There was no difference in mortality at 1 year between patients with and without complete discharge documentation (**Table 3**). Multivariate logistic regression analysis showed that complete discharge documentation was associated with nephrology follow-up when adjusted for baseline CKD status, creatinine at discharge and completeness of critical care discharge documentation [odds ratio (OR) 7.14 (95% confidence interval 1.36–37.40), $p = 0.02$] (**Supplementary Table 1**).

Medication Reconciliation

The proportions of patients who received RAASi, anti-diabetic drugs, diuretics, and statins prior to admission and at hospital discharge are shown in **Supplementary Table 2**. In patients taking RAASi ($n = 35$) and/or statin ($n = 37$) before admission, the medications at hospital discharge

TABLE 1 | Baseline characteristics.

Variable	Value
Age (years)	61 (IQR 47–73), range 16–90
Men (%)	50 (55)
Ethnicity (%)	
- White	68 (74.7)
- Black	14 (15.4)
- Other	9 (9.9)
Diabetes (%)	23 (25.3)
Comorbidities	
Chronic kidney disease (%)*	
Stage 1 or 2	2 (2.2)
Stage 3	17 (18.7)
Stage 4	6 (6.6)
Stage 5	2 (2.2)
Hypertension (%)	48 (52.8)
Coronary artery disease (%)	15 (16.5)
Active malignancy (%)	14 (15.4)
Atrial fibrillation (%)	13 (14.3)
Congestive heart failure (%)	21 (23.1)
Chronic liver disease (%)	5 (5.5)
Chronic lung disease (%)	9 (9.9)
Medication use before critical care admission (%)	
- RAAS inhibitors	35 (38.5)
- Diuretics	25 (27.5)
- Statin	37 (40.7)
- NSAIDs	8 (8.8)
Baseline creatinine (μmol/l)	91 (IQR 73–117), range 46–316
Baseline eGFR (ml/min/1.73 m^2)	75 (IQR 52–79), range 13–120
Admission type (%)	
- Elective surgery	10 (11.0)
- Emergency surgery	13 (14.3)
- Medical	68 (74.7)
Aetiology of AKI (%)	
- Sepsis	33 (36.3)
- Post-operative setting	17 (18.7)
- Cardiac related cause	19 (20.9)
- Liver related cause	1 (1.1)
- Hypoperfusion	7 (7.7)
- Obstructive uropathy	3 (3.3)
- Primary renal disease	11 (12.1)

eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; NSAIDs, non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone-system; IQR, interquartile range.

***CKD staging:** Stage 1, signs of kidney disease and eGFR ≥ 90 ml/min/1.73 m^2, Stage 2, eGFR 60–89 ml/min/1.73 m^2, Stage 3, eGFR 30–59 ml/min/1.73 m^2, Stage 4, eGFR 15–29 ml/min/1.73 m^2, Stage 5, eGFR < 15 ml/min/1.73 m^2 or dialysis.*

included RAASi in only 20 (57.1%) and statins in 14 (37.8%) of cases. In addition, 12.5 and 1.9% of patients were newly started on RAASi and statin medications during their hospital stay.

Post-discharge Follow-Up

Only 22 (24%) patients were reviewed in a nephrology clinic within 12 months of discharge. Those who received nephrology follow-up were characterised by worse renal function or being dialysis dependent ($n = 7$) at time of discharge from hospital. They were also more likely to have proteinuria measurement within the following 12 months (40.9 vs. 15.9%, $p = 0.01$) (**Table 4**). Seventy-six were followed-up by other medical specialties. Overall, in dialysis-independent survivors, creatinine results were available in 88.2 and 71.8% at 3 and 12 months, respectively. Correlation between eGFR at hospital discharge and eGFR at 3 and 12 months was poor [$r^2 = 0.62$ ($p < 0.001$) and 0.55 ($p < 0.001$), respectively]. Quantitative assessment of proteinuria was performed in only 11.8% of patients at 3 months and in 21.1% at 12 months (**Table 5**).

One-Year Outcomes

The overall 1-year post-ICU discharge survival rate was 82%. Of those who underwent repeat assessment of renal function during the 12-month period after discharge from hospital, a large proportion (∼50%) had significant ongoing renal problems that warranted specialist review/input. Of the 7 patients who were still dialysis dependent at hospital discharge, 3 recovered sufficient kidney function within 12 months to be independent of dialysis, 2 died, and 2 developed ESKD and remained chronically dialysis dependent. Three additional patients became newly dependent on dialysis within 12 months of hospital discharge (**Supplementary Figure 1**).

In the remaining cohort of patients who were not dialysis-dependent at 1 year and had creatinine results available ($n = 71$), 54.9% had an eGFR < 60 ml/min/1.73 m^2 consistent with CKD stage 3 or worse compared with 27.2% prior to hospitalisation ($p < 0.001$). In 57.2% of patients with CKD stage 3 or worse at 1 year, there was no evidence of pre-existing CKD. Median eGFR declined significantly from 75 (IQR 52–79) at baseline to 55 (IQR 38–74) ml/min/1.73 m^2 at 1 year ($p = 0.0003$) (**Table 5**).

DISCUSSION

Our study has revealed significant gaps in AKI aftercare in a UK tertiary care setting. In patients who had KRT for AKI and survived, important information relating to AKI, KRT receipt, and follow-up recommendations after hospitalisation was missing in 45% of critical care discharge summaries and almost 79% of hospital discharge letters. Cardioprotective medications which were discontinued during stay in hospital were not re-started before hospital discharge in 40–60% of patients. Despite classifying as high-risk patients, proteinuria was infrequently monitored following discharge from hospital, and only 24% were reviewed by a nephrologist. These findings call for more education and training but also indicate an urgent need for improvement in the systematic information transfer between critical care, hospital teams and primary care providers.

The importance of the above is underscored by the growing evidence that the burden of severe AKI extends beyond the duration of hospitalisation (4). Whilst the majority of our cohort of AKI survivors were liberated from KRT before discharge from

TABLE 2 | Discharge documentation.

	Record of AKI	Record of KRT	Recommendation to monitor renal function	Recommendation to refer for nephrology follow-up	"Complete" discharge summary[a]
Critical care discharge summary	78 (85.7%)	75 (82.4%)	47 (51.6%)	43 (47.3%)	50 (54.9%)
Hospital discharge summary	65 (71.4%)	56 (61.5%)	33 (36.3%)	19 (20.9%)	29 (31.8%)

AKI, acute kidney injury; KRT, kidney replacement therapy.

[a] *The completeness of the discharge documentation including (1) AKI diagnosis AND (2) Receipt of KRT AND either (3) Recommendation to monitor renal function or (4) Recommendation to refer for nephrology follow-up.*

TABLE 3 | Characteristics and outcomes by completeness of discharge documentation.

Discharge summary	Critical Care discharge summary			Hospital discharge summary		
	Incomplete ($n = 41$)	Complete ($n = 50$)	*P*-value	Incomplete ($n = 62$)	Complete ($n = 29$)	*P*-value
Baseline						
Age (years)	61 (48, 71)	61 (47, 75)	0.48	63 (47, 71)	57 (48, 75)	0.60
Male gender (%)	23 (46)	27 (54)	0.84	33 (66)	17 (34)	0.63
Diabetes (%)	8 (34.8)	15 (65.2)	0.25	16 (69.6)	7 (30.4)	0.86
Chronic kidney disease (%)	9 (33.3)	18 (66.7)	0.14	15 (55.6)	12 (44.4)	0.09
Hypertension (%)	19 (39.6)	29 (60.4)	0.27	31 (64.6)	17 (35.4)	0.44
Coronary artery disease (%)	5 (33.3)	10 (66.7)	0.40	7 (46.7)	8 (53.3)	0.051
Active malignancy (%)	7 (50)	7 (50)	0.69	11 (78.6)	3 (21.4)	0.54
Atrial fibrillation (%)	6 (46.2)	7 (53.9)	0.93	7 (53.9)	6 (46.2)	0.23
Congestive heart failure (%)	9 (42.9)	12 (57.1)	0.82	14 (66.7)	7 (33.3)	0.89
Chronic liver disease (%)	3 (60)	2 (40)	0.65	4 (80)	1 (20)	1.00
Chronic lung disease (%)	5 (55.6)	4 (44.4)	0.73	7 (77.8)	2 (22.2)	0.71
Baseline creatinine (μmol/l)	89 (72, 105)	91 (74, 132)	0.16	90 (72, 108)	98 (74, 123)	0.32
Baseline eGFR (ml/min/1.73 m^2)	75 (62, 85)	75 (46, 75)	0.09	75 (62, 79)	66 (49, 75)	0.23
Admission diagnosis (%)						
- Surgical	15 (65.2)	8 (34.8)	0.03	16 (69.6)	7 (30.4)	0.86
- Medical	26 (38.2)	42 (61.8)		46 (67.7)	22 (32.4)	
Creatinine at discharge* (μmol/l)	82 (60, 125)	155 (95, 302)	<0.001	86 (64, 155)	205 (118, 328)	0.0003
eGFR at discharge*	78 (43, 118)	36 (17, 67)	<0.001	67 (33, 107)	24 (13, 46)	0.0002
Dialysis dependence at discharge (%)	0	7 (14)	0.02	1 (1.6)	6 (20.7)	0.004
Outcomes						
Nephrology follow-up (%)	1 (2.4)	21 (42.0)	<0.001	5 (8.1)	17 (58.6)	<0.001
Creatinine measurement (%)	36 (87.8)	46 (92)	0.73	54 (87.1)	28 (96.6)	0.26
Proteinuria measurement (%)	9 (21.95)	11 (22)	1.00	12 (19.4)	8 (27.6)	0.38
Mortality (%)	7 (17.1)	8 (16)	0.89	11 (17.7)	4 (13.8)	0.64

eGFR, estimated glomerular filtration rate.

**In non-dialysis dependent patients.*

hospital, the 1-year mortality was 18% (22). Importantly, in those who survived, in the first year alone, 31% developed *de-novo* CKD and 8% progressed to dialysis dependent ESKD. This further emphasises the urgent need to optimise the aftercare of this high-risk group (23–25) albeit there being ongoing debate and controversy what constitutes optimal aftercare (26–29). Similar to reports in the literature, we found that the proportion of patients who had a nephrology review and/or assessment of creatinine and quantitative proteinuria was low even though 30% of the patients had pre-existing CKD (3, 9, 30). Although multiple factors may play a role, our data suggest that opportunities for improved care are missed, including early recognition of CKD, appropriate initiation of nephroprotective interventions, and timely nephrology referral, all of which are known to prevent CKD progression and reduce the risk of emergency initiation of dialysis and premature death (7, 31).

An accurate written discharge hand-over is a cornerstone of information transfer between healthcare providers and is essential to facilitate continuity of care (32). Although the discharge document is a formal factual report, it is most often produced by a junior member of the medical team who may have had variable input into the patient's care. The

TABLE 4 | Characteristics and outcomes by nephrology vs. no-nephrology follow-up in following 12 months after hospital discharge.

	Not seen by nephrologist ($n = 69$)	Seen by nephrologist ($n = 22$)	*P*-value
Baseline CKD (%)	17 (24.6)	10 (45.5)	0.06
Known to nephrologists prior to admission (%)	2 (13.3)	2 (20.0)	1.00
Creatinine at hospital discharge (μmol/L)	95 (68–146)	334 (232–458)	<0.001
eGFR at hospital discharge (ml/min/1.73 m^2)	63 (36–98)	17 (12.5–26)	<0.001
KRT at hospital discharge (%)	0	7 (31.8)	<0.001
Outcomes			
Creatinine measurement (%)	60 (87)	22 (100)	0.11
Proteinuria measurement (%)	11 (15.9)	9 (40.9)	0.01

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy.

TABLE 5 | Outcomes.

	Discharge from hospital	3 months	*P*-value[#]	1 year	*P*-value[##]
Death (*n*)	–	1	–	15	–
Survivors (*n*)	91	90	–	76	–
Need for dialysis (*n*)	7	5	–	5	–
Cr measurement performed[a] (%)	84/84 (100)	75/85 (88.2)	–	51/71 (71.8)	–
Cr value (μmol/l), median (IQR)	117 (72–206)	118 (78–162)	0.11	100 (77–141)	0.04
eGFR (ml/min/1.73 m^2), median (IQR)	53.5 (24.5–86.5)	55 (36–72)	0.53	55 (38–74)	0.15
eGFR < 60 ml/min/1.73 m^2 (%)	46/84 (54.8)	39/75 (52)	<0.001	28[b] / 51 (54.9)	<0.001
Proteinuria measurement[a] (%)	No data	10/85 (11.8)	No data	15/71 (21.1)	No data

Cr, creatinine; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a] *In non-dialysis dependent survivors.*
[b] *Of 28 patients, 12 (42.9%) had pre-existing CKD, and 16 (57.1%) developed new CKD.*
[#] *3 months vs. at discharge.*
[##] *1 year vs. at discharge.*

reasons for incomplete discharge documentation are likely to be multifactorial, including lack of awareness of the long-term complications of AKI but also a false sense of security in cases where serum creatinine is relatively low (e.g., in patients with muscle wasting) and eGFR is overestimated as also shown by the poor correlation between GFR at discharge and subsequent measurement in our study (3, 33). Of equal importance to the clinical information that a discharge document holds is its use for coding and reimbursement purposes. Failure to record an episode of AKI treated with KRT can have serious implications and affect patients' future or long-term management (34).

Our data suggest that if the discharge document includes a recommendation to arrange a referral to nephrology services, there is a greater likelihood this is acted upon by primary care and a greater chance of subsequent monitoring of kidney function and proteinuria measurement. Unfortunately, the low referral and follow-up rates in our study are similar to other reports in the literature. A previous study reported that whilst 91% of nephrologists agreed that patients who received dialysis for AKI should be followed up (35), nephrology follow-up rates ranged from 6 to 19% in AKI survivors to only 21–50% in those who had acute dialysis within 1 year after hospitalisation (9, 12, 35–39). Nephrology follow-up was found to be associated with reduced mortality (12, 40). The reasons for low referral rates in our study are unclear and need to be further explored.

Medication reconciliation after AKI can be challenging (41). Several observational studies have suggested that RAASi administration after renal recovery may halt CKD progression and reduce long-term mortality, but more confirmatory studies are needed (42–46). The role of statins after AKI remains unclear, too (47). Statin use was associated with reduced 2-year mortality but had no effects on cardiovascular outcomes or CKD progression (48). Our data show that 40–60% of patients who were taking RAASi's and statins pre-hospitalisation were not re-started on these medications before discharge from hospital. A proportion of these discontinuations may have been for valid clinical reasons relating to the evolution of the patient's condition, but it is possible that some were oversights where the medicine was stopped but inadvertently not re-started, and future work should explore this in more depth. As many of these medicines have pleiotropic effects, the impact on control of other conditions including hypertension, diabetes, and cardiovascular disease is unknown.

Our data highlight the gaps in practise and probable lack of awareness about the long-term prognosis of AKI survivors. Given the large number of staff, often junior, and in rotating roles, individual education and training is unlikely to be the best effector of change. Moreover, it is likely that institutions need to develop standardised approaches to recognition, documentation and subsequent management of this patient group, with in-built quality metrics to ensure ongoing improvement in routine patient care, similar to other areas in clinical medicine (17, 49). Incorporation of a structured framework into the discharge document has been recommended (11, 17). In addition to detailing past events, it should include a recommendation for nephrotoxin avoidance, weight and blood pressure monitoring advice, cardiovascular medication management, and sick day rules (28). An automatic AKI follow-up clinic was found to increase the proportion of patients seen by nephrologists and triggered interventions (37). In addition, post ICU recovery clinic may have a role in supporting the GP in the first 3 months after hospital discharge with focused practise on AKI recovery. For example, at our hospital, the post-ICU clinic letter routinely includes information about AKI diagnosis and staging, number of days treated with KRT, and recommendations for general renal management. Once established, iterative quality improvement methodologies should then be employed to confirm impact on patient-centred outcomes allowing robust upscaling and dissemination. Until more evidence is available from ongoing studies (50), the current recommendations by the RCGP should apply to the follow-up management of AKI survivors.

We acknowledge several limitations to our study. First, this was a retrospective observational study with a small sample size and 1-year follow up period. We were unable to show any associations between completeness of discharge documentation and development of relevant patient-centred outcomes, including progression of CKD, risk of mortality, quality of life, need for re-hospitalisation and cardiovascular events. Second, our data represents a single-centre population in the context of the UK healthcare setting and the findings may not be generalisable. However, these results should trigger local audits and reviews in other centres given the consistency of our findings with the existing literature. Third, we focussed on patients with AKI who received KRT since the risk of serious kidney and non-kidney outcomes is highest in this cohort. We are unable to comment on patients with less severe AKI. Fourth, we report a high prevalence of CKD at 1 year but acknowledge that creatinine and urine protein results were not available for all patients. Fifth, it was not possible to explore the exact reasons for incomplete or absent AKI documentation in the discharge summary. Sixth, we compared medications pre- and post-hospitalisation but did not investigate whether the dosages were appropriate when the medication was re-started. Finally, future projects are needed to investigate whether completeness of discharge summaries correlates with patient-centred short- and long-term outcomes. Further studies should also identify which patient subgroups are at highest risk of accelerated deterioration in renal function, thus allowing healthcare providers to prioritise them and to avoid unnecessary interventions in low-risk patients.

This is the first published report describing gaps in the aftercare of ICU patients with severe AKI in a UK hospital, whilst also confirming existing concerns that patients who had KRT for AKI and survived are at high risk of long-term complications. Our study identifies that there is substantial scope for better aftercare, particularly in relation to the information transfer from critical care to non-critical care services and primary care providers, and in monitoring of renal function. We believe that this is likely best achieved through a standardised, iterative, multi-disciplinary quality-improvement approach to advance the care delivered to this important patient group. This will need to be investigated in a future project.

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

Ethical approval was not provided for this study on human participants because the project had institutional approval (GSTT/10207). The need for Ethics review and individual informed consent was waived as this was a retrospective analysis of data collected prospectively for routine clinical care, and there was no breach of privacy or anonymity (UK National Research Ethics Service). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XYC contributed with data collection and writing the first draught of the manuscript. NL contributed to data collection, statistical analysis, and revision of the paper. LC oversaw medication conciliation and revision of the paper. AJ, AS, HV, NB, and RL interpreted the data and revised the paper. MO originated, supervised the project, and revised the paper. All authors approved the final draught.

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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.2021.710228/full#supplementary-material

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A Retrospective Observational Study of Adverse Reactions Associated With Intravenous Immunoglobulin Infusion

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Background: Although intravenous immunoglobulin (IVIG) therapy is generally safe and well tolerated, adverse reactions (ARs) do occur. The majority of these ARs are mild and transient. Risk factors for ARs associate with IVIG infusions are not well established. This study investigated possible risk factors influencing the occurrence of IVIG-associated ARs.

Study Design and Methods: This was a retrospective observational analysis of data accumulated over 5 years, including patient demographics, clinical condition, IVIG dosing regimens, number of IVIG infusions, and any ARs.

Results: ARs were associated with IVIG in 4.9% of patients and 2.5% of infusions. By univariate analyses, ARs correlated with female sex, adult age, high dose IVIG, and autoimmune disease. Multivariate logistic regression identified three statistically significant of risk factors: on a per-patient basis, being female ($p=0.0018$), having neuromuscular disease ($p=0.0002$), and receiving higher doses of IVIG per patient body weight ($p<0.001$), on a per-infusion basis, being female ($p < 0.001$), being adolescents to middle age ($p < 0.001$), and having neuromuscular disease ($p < 0.001$).

Conclusion: Neuromuscular disease emerged as one of the significant factors for ARs to IVIG.

Keywords: immunoglobulin, adverse reactions, risk factors, autoimmune diseases, neuromuscular diseases

INTRODUCTION

Intravenous immunoglobulin is widely used to treat primary and secondary immunodeficiencies, and to modulate the course of autoimmune and inflammatory conditions, such as idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, eosinophilic granulomatosis with polyangiitis (EGPA), as well as various neuromuscular and dermatologic diseases (1–5). Although intravenous

immunoglobulin is generally safe and well tolerated, adverse reactions (ARs) do occur. The majority of these ARs are mild and transient (6). More severe ARs, such as deep venous thrombosis, renal failure, aseptic meningitis, and hepatitis, are rarely reported. Advanced patient age, preexisting renal failure, and diabetes are associated with higher rates of IVIG infusion-related complications (7). Vascular disease and other causes of increased serum viscosity are associated with an increased risk of thromboembolism with IVIG treatment (8). However, there are limited data about ARs drawn from broad patient cohorts, so there may be risk factors not yet shown to have statistical significance. In the present study, we investigated possible risk factors influencing the occurrence of IVIG-associated ARs, with the ultimate aim of improving the comfort and safety of the patients received IVIG.

PATIENTS AND METHODS

Study Design

We conducted a single-hospital retrospective chart review at Aichi Medical University in Japan. This study was approved by the ethics committee of Aichi Medical University, which is guided by local policy, national law, and the World Medical Association Declaration of Helsinki. We analyzed infusion protocols of all patients who received intravenous immunoglobulin (IVIG) between 1 May 2014 and 31 December 2018. Patients included in the study were diagnosed with primary immunodeficiency, hypogammaglobulinemia, antibiotic resistant sepsis, Kawasaki disease, idiopathic thrombocytopenic purpura (ITP), chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barre syndrome (GBS), myasthenia gravis (MG), pemphigus, polymyositis/dermatomyositis (PM/DM), eosinophilic granulomatosis with polyangiitis (EGPA), and other diseases for which IVIG is recognized as a treatment in Japan.

All patients received IVIG according to the infusion protocol of the manufacturer's guidelines for IVIG. The course was considered to be the prescribed treatment regimen (i.e., the total dose infused over the number of infusion days) and varied between patients. IVIG was infused continuously at the rate recommended by the manufacturer's guidelines. Infusions were started slowly (about 0.01 mL/kg body weight/minute) and were increased to the maximum prescribed rate (less than 0.06 mL/kg body weight/minute) over 1 hour.

To aggregate data from both physicians' and nurses' notes, prescriptions, medication administration charts, and any other documents comprising a patient's medical record, a uniform data collection sheet was structured in accordance with the study design and objectives. Required information included: patient demographics (age, gender, and weight), indication for IVIG administration, clinical condition of patients (including vital signs), dosing regimen, the number of infusions, AR signs and symptoms, and information gained during follow-up examinations. Any reaction that occurred during an infusion and diagnosed by a physician was considered an immediate infusion-related AR. Signs and symptoms defined by the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT) are based on documents issued by the International Society of Blood Transfusion (ISBT) Working Party for Haemovigilance (9).

Reactions occurring during IVIG infusion were classified as mild, moderate, or severe. Mild reactions were those that caused only minimal discomfort and were tolerated by the subject without treatment or interruption of infusion. Moderate reactions were those that caused moderate discomfort not tolerated by the subject, for which the infusion was interrupted. Severe reactions were those that interrupted the infusion, produced sequelae, and required prolonged treatment.

Statistical Analysis

Descriptive analyses compared baseline characteristics of patients receiving IVIG, including demographics and other potential AR risk factors, using the chi-square test for categorical variables and the Wilcoxon test for continuous variables. Crude incidence rates for ARs were estimated overall and by age, gender, disease for which IVIG was indicated and dose of IVIG. To verify any associations between the occurrence of ARs and possible risk factors (age, gender, diagnostic indication, dose of IVIG), while considering the possible influence of multiple infusions to a particular patient, logistic regressions were adjusted to consider patient characteristics [age: < 60 years *vs.* ≥ 60 years, gender: male *vs.* female, diagnostic indication: neuromuscular disease *vs.* other autoimmune diseases, dose of IVIG: < 7.0 g/kg BW *vs.* ≥ 7.0 g/kg BW (cumulative dose per patient) or < 0.45 g/kg BW *vs.* ≥ 0.45 g/kg BW (does per infusion)] as a random effect. In these regressions, the AR was the dependent variable and each factor was posited as an explanatory variable. Logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of AR occurrence for each factor. In all analyses, conducted using SPSS (SPSS software package version 23.0, IBM, Tokyo, Japan), a significance threshold of <0.05 was used.

RESULTS

Patient Demographics

During this study, 748 patients received IVIG (**Table 1**), of whom 389 were male and 359 patients were female. Their mean age was 41.7 (range 0-99) years. Just over half (377) had autoimmune diseases, including neuromuscular diseases (n = 71), dermatologic diseases (n = 58), ITP (n = 61), EGPA (n = 16), and Kawasaki disease (n = 171). The neuromuscular diseases included CIDP (n = 27), GBS (n = 20), and MG (n = 24). The 58 dermatologic diagnoses included pemphigus (n = 24) and PM/DM (n = 34). Other patients had hypogammaglobulinemia (n = 64), sepsis (n = 296), and various other conditions (n = 11).

During this study, a total of 4070 infusions were administered, of which 1658 were for males and 2412 were for females. Just over half (2856) were autoimmune diseases, including neuromuscular diseases (n=1038), dermatologic diseases (n=1102), ITP (n=341), EGPA (n=153), and Kawasaki disease (n=222). Other infusions

TABLE 1 | Patients demographics.

	Patients	Infusions
Numbers	748	4070
Male	389	1658
Female	359	2412
Mean age (years) (range)	41.7 (0-99)	
Indications for receiving IVIG (n)		
Autoimmune	377	2856
Neuromuscular	71	1038
CIDP	27	495
GBS	20	425
MG	24	118
Dermatologic	58	1102
Pemphigus	24	835
PM/DM	34	217
ITP	61	341
EGPA	16	153
Kawasaki disease	171	222
Hypogammaglobulinaemia	64	288
Sepsis	296	904
Others	11	22

CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barre syndrome; MG, myasthenia gravis; PM/DM, polymyositis/dermatomyositis; ITP, idiopathic thrombocytopenic purpura; EGPA, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

were for hypogammaglobulinemia (n=288), sepsis (n=904), and various other conditions (n=22).

Average doses of IVIG per patient body weight varied by diagnosis: 3.7 g/kg for autoimmune diseases, 0.6 g/kg for hypogammaglobulinemia, 0.4 g/kg for sepsis, and 1.2 g/kg for other conditions in aggregate. Thus, the average dose of IVIG for autoimmune diseases was highest by a substantial margin. The mean daily dose per body weight of IVIG varied by diagnosis: 0.45 g/kg for neuromuscular diseases, 0.42 g/kg for dermatologic diseases, 0.49 g/kg for ITP, 0.39 g/kg for EGPA, 1.55 g/kg for Kawasaki disease, 0.15 g/kg for hypogammaglobulinemia, 0.15 g/kg for sepsis, and 0.61 g/kg for other conditions. Thus, the daily dose of IVIG for autoimmune diseases was highest by a substantial margin. Furthermore, the mean course dose per body weight of IVIG for autoimmune diseases (1.76 g/kg) was higher than those for non-autoimmune diseases (0.25 g/kg) excepting other conditions (0.98 g/kg). Thus, patients with non-autoimmune diseases including hypogammaglobulinemia and sepsis received low-dose IVIG (less than 0.7 g/kg body weight per course). In contrast, patients with autoimmune diseases and other conditions received high-dose IVIG (more than 0.7 g/kg body weight per course).

As for the gender distribution of patients with autoimmune diseases, the male-to-female ratio for neuromuscular diseases (male/female: 1.09) was higher than that for non-neuromuscular diseases (male/female: 0.78). However, there was no significant difference in these ratios (p = 0.186) (**Table 2**). Furthermore, among neuromuscular diseases, the male-to-female ratios for CIDP, GBS, and MG were 1.25, 1.22, and 0.85, respectively (p = 0.601). In contrast, on the infusions, the male-to-female ratio for neuromuscular diseases (male/female: 0.95) was significantly higher than that for no-neuromuscular diseases (male/female: 0.33) (p < 0.001).

TABLE 2 | Patients demographics on gender in autoimmune diseases.

	Patient basis (n=377)		Infusion basis (n=2856)	
	Gender ratio (male/female)	***P* value**	**Gender ratio (male/female)**	***P* value**
Neuromuscular	1.09	0.186*	0.95	<0.001*
CIDP	1.25		1.35	
GBS	1.22		1.36	
MG	0.85	0.601†	0.57	<0.001†
Non-neuromuscular	0.78		0.33	
Dermatologic	0.53		0.21	
ITP	0.56		0.41	
EGPA	0.45		0.53	
Kawasaki disease	1.04		1.04	

**p values refer to gender ratio between neuromuscular and non-neuromuscular diseases.*
†p values refer to gender ratio among neuromuscular diseases (CIDP/GBS/MG).

Adverse Reactions

Of 360 patients received low-dose IVIG (less than 0.7 g/kg body weight per course), 3 (0.8%) experienced ARs. As shown in **Table 3**, the incidence of ARs was not different between males (0.9%) and females (1.3%). Furthermore, the incidence of ARs for patients age under 15 years was not significantly higher than for patient age 15 years and over (p = 0.245). On a per infusion basis, 5/1,192 infusions of IVIG (0.4%) administered were associated with ARs. The average doses (g) of IVIG per body weight (kg) for patients and infusions with ARs (1.4 g/kg and 0.19 g/kg, respectively) were not significantly higher than for patients and infusion without ARs (0.4 g/kg and 0.16 g/kg, respectively) (p = 0.395 and 0.564, respectively).

Among patients received high-dose IVIG (more than 0.7 g/kg body weight per course), ARs were recorded in 8.5% of patients and in 3.4% of infusions (**Table 4**). The incidence of ARs per patient was significantly higher for females (12.3%) *vs.* males (4.0%) (p = 0.003). The mean ages of patients with and without ARs were 52.8 and 28.4 years, respectively. Furthermore, the incidence of ARs for patients age 15 years and over was significantly higher than for patients age under 15 years (p < 0.001). Thus, among patients who received IVIG, ARs were more likely to occur in adults than in children. The average doses (g) of IVIG per body weight (kg) for patients with ARs (10.9 g/kg body weight) were significantly higher than for patients without ARs (3.0 g/kg body weight) (p = 0.003).

The incidence of ARs per infusion was significantly higher for females (4.4%) *vs.* males (1.4%) (p < 0.001). Similarly to the results on a per-patient basis, the incidence of ARs for patients age 15 years and over was significantly higher than for patients age under 15 years (p = 0.003). However, contrary to the results on a per-patient basis, the average doses (g) of IVIG per body weight (kg) for infusions without ARs (0.65 g/kg body weight) were significantly higher than for infusions with ARs (0.48 g/kg body weight) (p = 0.004).

Of 377 patients with autoimmune diseases, 33 (8.8%) experienced ARs. In contrast, just 1 of 64 patients (1.6%) with hypogammaglobulinemia, 3 of 296 patients (1.0%) with sepsis, and 0 of 11 patients with other diseases experienced ARs.

TABLE 3 | Factor-specific incidences of adverse reactions to low-dose IVIG*.

	Patient basis (n=360)			Infusion basis (n=1192)		
	Adverse reaction			Adverse reaction		
	No	Yes	*p* value	No	Yes	*p* value
Gender, n (%)						
Male	211 (99.1)	2 (0.9)		680 (99.6)	3 (0.4)	
Female	145 (98.7)	2 (1.3)	1.00	507 (99.6)	2 (0.4)	1.00
Age, n (%)						
< 15 years	69 (97.2)	2 (2.8)		181 (97.2)	3 (1.6)	
≥ 15 years	287 (99.3)	2 (0.7)	0.245	1006 (99.3)	2 (0.2)	0.025
IVIG doses (average, g/kg BW)	0.4†	1.4†	0.395	0.16	0.19	0.564
Indication, n (%)						
Hypogammaglobulinaemia	63 (98.4)	1 (1.6)		286 (99.4)	2 (0.6)	
Sepsis	293 (99.0)	3 (1.0)		901 (99.7)	3 (0.3)	

**The low-dose IVIG is less than 0.7 g/kg body weight per course.*
†The values indicate the cumulative doses from multiple treatment of IVIG on one patient.
BW, body weight of patient.

TABLE 4 | Factor-specific incidences of adverse reactions to high-dose IVIG*.

		Patient basis (n=388)			Infusion basis (n=2888)		
		Adverse reaction			Adverse reaction		
		No	Yes	*p* value	No	Yes	*p* value
Gender, n (%)							
Male		169 (96.0)	7 (4.0)		961 (98.6)	14 (1.4)	
Female		186 (87.7)	26 (12.3)	0.003	1820 (95.6)	83 (4.4)	< 0.001
Age, n (%)							
< 15 years		196 (99.0)	2 (1.0)		314 (99.4)	2 (0.6)	
≥ 15 years		159 (83.7)	31 (16.3)	< 0.001	2467 (96.3)	95 (3.7)	0.003
IVIG doses (average, g/kg BW)		3.0†	10.9†	0.003	0.65	0.48	0.004
Indication, n (%)							
Autoimmune		344 (91.2)	33 (8.8)		2759 (96.6)	97 (3.4)	
	Neuromuscular	52 (73.2)	19 (26.8)		973 (93.7)	65 (6.3)	
	Dermatologic	51 (87.9)	7 (12.1)		1078 (97.8)	24 (2.2)	
	ITP	59 (96.7)	2 (3.3)		339 (99.4)	2 (0.6)	
	EGPA	13 (81.2)	3 (18.8)		149 (97.4)	4 (2.6)	
	Kawasaki disease	169 (98.8)	2 (1.2)		220 (99.1)	2 (0.9)	
Others		11 (100.0)	0 (0.0)		22 (100.0)	0 (0.0)	

**The high-dose IVIG is more than 0.7 g/kg body weight per course.*
†The values indicate the cumulative doses from multiple treatment of IVIG on one patient.
BW, body weight of patient.

Furthermore, of 2856 infusions with autoimmune diseases, 97 (3.4%) experienced ARs. In contrast, 2 of 288 infusions (0.7%) with hypogammaglobulinemia, 3 of 904 infusions (0.3%) with sepsis, and 0 of 22 infusions with other diseases experienced ARs. Thus, the incidence of ARs to IVIG for autoimmune diseases was higher than on non-autoimmune diseases. Overall, gender, age, IVIG dose, and indication (diagnosis) were found to be associated with AR incidence.

Therefore, logistic regression was used to identify characteristics associated with ARs in the subgroups with high incidence of ARs by univariate analyses (age ≥ 15 years and autoimmune diseases). Of 184 patients and 2548 infusions in this subgroup, 31 patients (16.8%) and 95 infusions (3.7%) experienced ARs. 19 of 67 patients (28.4%) and 65 of 1014 infusions (6.4%) with neuromuscular disease experienced ARs. In contrast, 12 of 117 patients (10.3%) and 30 of 1534 infusions (2.0%) with non-neuromuscular diseases experienced ARs. The incidences of ARs per patient and per infusion were higher for females (25/108 patients: 23.1% and 82/1714 infusions: 6.5%, respectively) *vs.* males (6/76 patients: 7.9% and 13/834 infusions: 3.8%). The incidence of ARs for patients age between 15 and 59 years (20/89 patients: 22.5%) was significantly higher than for patients age 60 years and over (11/95 patients: 11.6%). Similarly, on a per-infusion basis, the incidence of ARs for patient age between 15 and 59 years (79/1392 infusions: 5.7%) was significantly higher than for patients age 60 years and over (16/1156 patients: 1.4%). The incidence of ARs for patients received a total dose of IVIG above 7.0 g/kg bodyweight (15/29: 51.7%) was higher than that for patients received less than 7 g/kg bodyweight (16/155: 10.3%). In contrast, the incidence of ARs on less than 0.45 g/kg

bodyweight per infusion (77/1961: 3.9%) was higher than that on above 0.45 g/kg bodyweight per infusion (18/587: 3.1%). As shown **Table 5**, on a per-patient basis, significant univariate risk factors for ARs to IVIG included gender (male/female) (odds ratio [OR], 0.285; 95% CI, 0.111-0.733), neuromuscular disease (OR, 3.464; 95% CI, 1.557-7.703), and dose of IVIG per body weight (OR, 9.308; 95% CI, 3.809-22.744), while age was not significant (p = 0.0521). Furthermore, multivariate logistic regression of risk factors for ARs to IVIG identified being female (p = 0.0018), having neuromuscular disease (p = 0.0002), and receiving higher doses of IVIG per body weight (p < 0.001) as significant risk factors. On the other hand, there was no correlation between neuromuscular disease and dose of IVIG per patient bodyweight as risk factors for ARs by Spearman's rank correlation coefficient. On a per-infusion basis, significant univariate risk factors for Ars to IVIG included gender (male/female) (odds ratio [OR], 95% CI), neuromuscular disease (OR, 3.434; 95% CI, 2.211-5.333), and age (OR, 0.233; 95% CI, 0.136-0.402), while dose of IVIG per body weight per infusion was not significant (p = 0.336). Furthermore, multivariate logistic regression of risk factors for ARs to IVIG identified being female (p < 0.001), having neuromuscular disease (p < 0.001), and adolescents to middle age (age < 60 years) (p < 0.001) as significant risk factors.

The most commonly documented ARs were fever (54.1%) and headache (51.4%), followed by flu-like symptoms (16.2%) and rash (10.8%) on a per-patient basis (**Table 6**). The most commonly documented ARs were fever (47.1%) and headache (42.2%), followed by flu-like symptoms (8.8%) and rash (3.9%) on a per-infusion basis. Also, the distribution of ARs among patients with autoimmune diseases was almost the same as among all patients. Among patients with neuromuscular diseases, the most commonly documented ARs were headache (per patient: 73.7%, per infusion: 49.2%) and fever (per patient: 57.9%, per infusion: 46.2%). However, among patients without neuromuscular diseases, the most documented ARs was fever (per patient: 42.9%, per infusion: 43.8%).

DISCUSSION

We retrospectively analyzed ARs to IVIG with uniform data collection forms and consistent methodology to aggregate 5 years of data from multiple departments. The incidence of ARs was

TABLE 5 | Logistic regression analyses of risk factors for adverse reaction to IVIG therapy.

	Univariate			Multivariate		
	Odds	**95%CI**	**P value**	**Odds**	**95%CI**	**P value**
Patient basis (n = 184)						
Male/Female	0.285	0.111-0.733	0.0092	0.156	0.049-0.501	0.0018
Age ≥ 60 years	0.452	0.203-1.007	0.0521	0.542	0.21-1.396	0.2043
Neuromuscular disease	3.464	1.557-7.703	0.0023	6.914	2.485-19.237	0.0002
Dose ≥ 7.0 g/kg BW*	9.308	3.809-22.744	<0.001	12.259	4.28-35.108	<0.001
Infusion basis (n = 2548)						
Male/Female	0.315	0.175-0.569	<0.001	0.178	0.097-0.328	<0.001
Age ≥ 60 years	0.233	0.136-0.402	<0.001	0.235	0.134-0.414	<0.001
Neuromuscular disease	3.434	2.211-5.333	<0.001	4.635	2.92-7.356	<0.001
Dose ≥ 0.45 g/kg BW	0.774	0.459-1.304	0.336	1.045	0.598-1.821	0.878

**The values indicate the cumulative doses from multiple treatment of IVIG on one patient.*
BW, body weight of patient.

TABLE 6 | Clinical presentations of IVIG-related adverse reactions.

ARs	**All patients**		**Autoimmune diseases**					
			All		**Neuromuscular diseases**		**Other#**	
	Patients n = 37	**Infusions n = 102**	**Patients n = 33**	**Infusions n = 97**	**Patients n = 19**	**Infusions n = 65**	**Patients n = 14**	**Infusions n = 32**
Headache	19 (51.4)	43 (42.2)	19 (57.6)	43 (44.3)	14 (73.7)	32 (49.2)	5 (35.7)	11 (34.4)
Fever	20 (54.1)	48 (47.1)	17 (51.6)	44 (45.4)	11 (57.9)	30 (46.2)	6 (42.9)	14 (43.8)
Flu-like symptoms	6 (16.2)	9 (8.8)	5 (15.2)	8 (8.2)	3 (15.8)	5 (7.7)	2 (14.3)	3 (9.4)
Hypertension	1 (2.7)	1 (1.0)	1 (3.0)	1 (1.0)			1 (7.1)	1 (3.1)
Dyspnea	1 (2.7)	1 (1.0)	1 (3.0)	1 (1.0)	1 (5.3)	1 (1.5)		
Chest pain	2 (5.4)	2 (2.0)	2 (6.1)	2 (2.1)	2 (10.5)	2 (3.1)		
Rash	4 (10.8)	4 (3.9)	3 (9.1)	3 (3.1)			3 (21.4)	3 (9.4)

ARs, adverse reactions. All table values are n (%).
#Other of autoimmune diseases are those without neuromuscular manifestations.

4.9% of all patients treated with IVIG, among whom univariate analyses showed AR risk factors to be female sex, adult age, higher doses of IVIG, and autoimmune disease. Furthermore, when multivariate logistic regression analyses for AR risk factors were applied to high risk subgroups, being female ($p = 0.0018$), having neuromuscular disease ($p = 0.0002$), and receiving higher doses of IVIG per patient body weight ($p < 0.001$) were significant risk factors. On the other hand, the incidence of ARs was 2.5% of all infusions administered IVIG, among which univariate analyses showed AR risk factors to be female sex, adult age, and autoimmune disease. Furthermore, when multivariate logistic regression analyses for AR risk factors were applied to high risk subgroups, being female ($p < 0.001$), having neuromuscular disease ($p < 0.001$), and being adolescents to middle age ($p < 0.001$) were significant risk factors.

IVIG has been widely used for a variety of conditions, including primary and secondary immunodeficiency diseases, autoimmune diseases (including ITP, CIDP, Guillain-Barre syndrome, PM/MD, Kawasaki disease, etc.), and sepsis. Although a large number of clinical trials have demonstrated that IVIG is generally safe and well tolerated, various ARs do occur. The reported incidence of ARs varies widely, from 1% to more than 50% of patients, depending on the study (10–14). ARs are rare among immunodeficient patients when receiving the same dose as previously well tolerated at regular intervals. Struff et al. (15) reported that among 1705 immunodeficient patients at 72 centers, given 15,548 infusions of the same product, only 10 patients (0.6%) ever had an AR, with their per-infusion rate an order of magnitude lower, at 0.064%. On the other hand, the highest rates of ARs occur among non-immunodeficient and non-septic patients with autoimmune diseases receiving high doses IVIG, e.g., 1 to 2 g/kg. Donofrio et al. (16) reported that 18% of infusions and 55% of 113 patients with chronic inflammatory polyneuropathy developed ARs to IVIG. Indeed, in this study, although the incidences of ARs among those with non-autoimmune diseases, such as hypogammaglobulinemia and sepsis, were low (1.6% and 1.0%, respectively), the incidences of ARs among those with autoimmune diseases was high (8.8%). In addition, the IVIG doses for patients with autoimmune diseases were higher than for those with non-autoimmune diseases. Furthermore, the present and previous studies (14, 17) have reported that the mean course doses per bodyweight (g/kg) for patients with ARs (1.9 g/kg) were significantly higher than for patients without ARs (1.1 g/kg) ($p < 0.001$) (data not shown). The mean course dose per bodyweight of IVIG for autoimmune diseases (1.76 g/kg) was higher than those for non-autoimmune diseases (0.25 g/kg) excepting other conditions (0.98 g/kg). We speculate that these different incidences of ARs between the non-autoimmune diseases cohort (including immunodeficiency, sepsis, etc.) and the autoimmune diseases cohort might be due to different IVIG infusion doses.

The previous study (18) has reported that the higher infusion rates were strongly associated with ARs. In addition, reducing the infusion rate after the occurrence of ARs may improve symptoms of ARs (19). In this study, ARs can be avoided by beginning the infusion slowly and gradually increasing the rate. In contrast, the previous study (20) reported that the infusion rate was significantly slower in patients with ARs after IVIG infusion. Thus, we speculate that the infusion rates were not associated with ARs, because the infusion rates were not significantly different among patients received IVIG due to manufacturer's guidelines in our study.

Our data show that ARs were more likely to occur in adults (6.9%) than in children (1.5%), in contrast to a previous study that showed no such difference (19). However, the patient cohort in that previous study consisted only of those with primary immunodeficiency diseases and did not include anyone with autoimmune diseases. Our study patients included those with immunodeficiency diseases, sepsis, and autoimmune diseases. Furthermore, although the age was not reflected in the incidence of ARs in the low-dose IVIG cohort (including immunodeficiency and sepsis), ARs were more likely to occur in adults (16.3% on a per-patient basis, 3.7% on a per-infusion basis) than in children (1.0% on a per-patient basis, 0.6% on a per-infusion basis) in high-dose IVIG cohort (including autoimmune diseases) (**Table 4**). Thus, the influence of the age on ARs among those with autoimmune diseases need further investigation.

Our study quantified risk factors for the occurrence of ARs with IVIG therapy among those with a high incidence of ARs, i.e., age ≥ 15 years and autoimmune diseases. By multivariate logistic regression analyses on a per-patient basis, female gender, neuromuscular diseases, and higher doses of IVIG per patient bodyweight emerged as risk factors for ARs, while younger age (less than 60 years old) was not (**Table 5**). In contrast, on a per-infusion basis, multivariate logistic regression of risk factors for ARs to IVIG identified adolescents to middle age (age < 60 years) ($p < 0.001$) as significant risk factors. Waheed et al. (12) reported that multivariate analyses identified the following risk factors for ARs on a per-infusion: younger age. Thus, the age as risk factors for ARs was reflected on a per-infusion basis rather than on a per-patient basis. In particular, the likelihood of ARs to IVIG correlated with having neuromuscular diseases (odds: 6.914) among patients with any autoimmune disease. In fact, in that subgroup, the incidence of ARs for neuromuscular diseases was 28.4% (data not shown), consistent with other studies (12, 14, 21) that have reported ARs in more than 20% of patients with neuromuscular diseases. Wietek et al. (22) analyzed data from 112 patients with ITP receiving IVIG, in which there were five cases with at least one AR. In addition, ARs to IVIG were experienced by up to 10% of patients with dermatologic diseases (1). A possible reason for higher incidence of ARs with neuromuscular diseases is that the total doses of IVIG for patients with neuromuscular diseases might be higher than those with non-neuromuscular diseases. The previous study reported that ARs occurred more often during treatment in the group that received a high total dose, suggesting that this side effect was dose-dependent (14). We showed that the average total dose per patient with ARs was significantly higher than among those without ARs. Furthermore, by multivariate logistic regression, total dose per patient emerged as a risk factor for ARs (odds: 12.259). In addition, by multivariate logistic regression on a per-

infusion basis, dose per infusion was not emerged as a risk factor for ARs (odds: 1.045). However, there was no correlation between neuromuscular disease and total dose of IVIG per patient in risk factors of ARs to IVIG by Spearman's rank correlation coefficient. Indeed, there is no difference in total average dose per patient between those with neuromuscular diseases and those with dermatologic diseases (data not shown). Also, the female sex was one of AR risk factors among patients with autoimmune diseases. However, when the gender distributions were investigated in this study, neuromuscular diseases were found to be male-significant compared to non-neuromuscular diseases both on the patient basis and the infusion basis (**Table 2**). Therefore, the hypothesis that there was higher rate of ARs to IVIG among patients with neuromuscular diseases based on total dose of IVIG and gender distributions is not supported by our results. While the reason for this is unclear, this implicates neuromuscular disease as a risk factor for ARs to IVIG.

The most common immediate ARs are headache, fever, flu-like symptoms (23), chest pain, and rash. These usually are mild and occur within an hour of starting an infusion and disappear within 6 hours. Particularly, headaches are a common complaint during or shortly after IVIG infusions. Headaches are common with high dose IVIG therapy, typically used in autoimmune diseases. In this study, headaches occurred in 57.6% of patients with autoimmune diseases. In particular, most ARs in patients with neuromuscular diseases were headache (73.7%), whereas headache in patients with other autoimmune diseases were observed only 35.7%. Bertorini et al. (14) reported that the proportion of headaches among all ARs in patients with neuromuscular diseases was higher than in patients with non-neuromuscular autoimmune diseases. The mechanism of IVIG-induced headache is unclear, but patients with neuromuscular diseases frequently have headaches in conjunction with IVIG therapy.

The previous study (24) has reported that headache could be prevented by changing from IVIG treatment to subcutaneous immunoglobulin (SCIG) treatment. However, patients with frequent ARs were autoimmune diseases that treated high-dose IVIG in this study. It is a small amount when patients treated by SCIG. Therefore, it is possible that patients with autoimmune diseases will be given frequently SCIG.

We conclude that having neuromuscular disease, being female, and receiving higher doses of IVIG are all risk factors for infusion-related ARs. Related to this, we found no correlation between neuromuscular disease and the total dose of IVIG per patient in the risk of ARs. In particular, the majority of ARs in patients with neuromuscular diseases are headaches. Although having neuromuscular disease emerged as a factor contributing to ARs, a limitation of our study is that it is a retrospective analysis. Despite this limitation the study provides insight into risks for ARs in patients receiving IVIG. In the future, more elaborate analyses of data collected from individual patients may allow recommendations to emerge that improve the safety and comfort of IVIG therapy.

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 the Aichi Medical University (Approval No. 2021-043). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HK and MH: design and concept of study, data analysis, drafting and revision of manuscript. WO: data analysis, drafting and revision of manuscript. TY, ST, AKo, SG, AKa, RN, TM, KI, TA, MO, and TN: data collection, drafting and revision of manuscript. All authors contributed to the article and approved the submitted version.

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Dynamics of Vascular Protective and Immune Supportive Sphingosine-1-Phosphate During Cardiac Surgery

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Introduction: Sphingosine-1-phosphate (S1P) is a signaling lipid and crucial in vascular protection and immune response. S1P mediated processes involve regulation of the endothelial barrier, blood pressure and S1P is the only known inducer of lymphocyte migration. Low levels of circulatory S1P correlate with severe systemic inflammatory syndromes such as sepsis and shock states, which are associated with endothelial barrier breakdown and immunosuppression. We investigated whether S1P levels are affected by sterile inflammation induced by cardiac surgery.

Materials and Methods: In this prospective observational study we included 46 cardiac surgery patients, with cardiopulmonary bypass (CPB, n=31) and without CPB (off-pump, n=15). Serum-S1P, S1P-sources and carriers, von-Willebrand factor (vWF), C-reactive protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6) were measured at baseline, post-surgery and at day 1 (POD 1) and day 4 (POD 4) after surgical stimulus.

Results: Median S1P levels at baseline were 0.77 nmol/mL (IQR 0.61-0.99) and dropped significantly post-surgery. S1P was lowest post-surgery with median levels of 0.37 nmol/mL (IQR 0.31-0.47) after CPB and 0.46 nmol/mL (IQR 0.36-0.51) after off-pump procedures (P<0.001). The decrease of S1P was independent of surgical technique and observed in all individuals. In patients, in which S1P levels did not recover to preoperative baseline ICU stay was longer and postoperative inflammation was more severe. S1P levels are associated with its sources and carriers and vWF, as a more specific endothelial injury marker, in different phases of the postoperative course.

Determination of S1P levels during surgery suggested that also the anticoagulative effect of heparin might influence systemic S1P.

Discussion: In summary, serum-S1P levels are disrupted by major cardiac surgery. Low S1P levels post-surgery may play a role as a new marker for severity of cardiac surgery induced inflammation. Due to well-known protective effects of S1P, low S1P levels may further contribute to the observed prolonged ICU stay and worse clinical status. Moreover, we cannot exclude a potential inhibitory effect on circulating S1P levels by heparin anticoagulation during surgery, which would be a new pro-inflammatory pleiotropic effect of high dose heparin in patients undergoing cardiac surgery.

Keywords: sphingosine-1-phosphate, systemic inflammation, sepsis, cardiac surgery, heparin, SIRS

INTRODUCTION

Cardiac surgery is still associated with a high early perioperative in-hospital mortality (1, 2). Surgery related mortality has partially been attributed to the surgery induced acute inflammatory response. In this context, cardiopulmonary bypass (CPB) induces severe inflammation and is associated with higher risk of organ failure such as acute kidney injury (AKI), which increases the risk of not surviving the hospital stay by 2-fold (3–5). Although techniques such as off-pump procedures may reduce postoperative mortality, the acute inflammatory response after cardiac surgery remains challenging due to the massive cardiovascular stress after surgery (6). Mechanisms of surgery induced inflammation and other causes of systemic inflammation are very similar. For example, the clinical presentation of sepsis patients compared to patients with severe postoperative inflammation after cardiac surgery is indistinguishable and hemodynamic instability, volume deficiency and lactate acidosis are leading symptoms (7, 8). Hallmarks are hypotension caused by vasoplegia, edema formation caused by endothelial barrier disruption and uncontrolled cytokine secretion with an increased vulnerability for secondary infections. All of these processes are potentially regulated by the vascular protective G-protein coupled signalling lipid sphingosine-1-phosphate (S1P) (9). S1P supports crucial functions relevant in inflammation and in the control of hyperinflammatory states: I) Regulation of the endothelial cell (EC) barrier: S1P is fundamental for EC barrier stabilization by regulating the EC cytoskeleton (10, 11). *In-vivo* models have demonstrated a robust stabilizing effects of S1P preventing lung edema and microvascular permeability induced by toxins (endotoxin, lipopolysaccharide) or high-volume ventilation (12, 13). II) Recruitment of lymphocytes and host response: S1P is the only known inducer of lymphocyte migration from lymphatic organs into peripheral blood. Mice with depleted S1P levels are lymphopenic (14–16). This effect of S1P on the immunity is induced by FTY-720 (Fingolimod), which is a standard of care in Multiple sclerosis. Moreover, S1P agonists are effectful inhibitors of viral induced inflammation in mice infected with influenza (17). Finally, S1P signaling may depend on its main carrier, high-density lipoprotein (HDL) or albumin (18).

There is growing evidence that S1P levels are low in patients with sepsis induced systemic inflammation and that low S1P levels correlate with a higher mortality and morbidity (19–22). Moreover, decreased S1P levels are predictive of hyperinflammatory shock with similar precision as the sequential organ failure assessment (SOFA) (20). Manipulating S1P-controlled processes by S1P substitution or S1P-receptor activation are discussed as therapeutic options to attenuate the systemic inflammatory response. These effects are within the range of expectancy due to the well-known activities of S1P on endothelial integrity, the immune response and as a pro-survival factor (20, 23–25). Considering the observations in human systemic inflammation and current experimental data, we aimed to investigate S1P in patients undergoing cardiac surgery induced inflammation.

MATERIALS AND METHODS

Study Design and Subjects

Forty-six adult patients (age >18 years) scheduled for elective major cardiac surgery, with or without CPB, at the University Heart and Vascular Center at the University Medical Center Hamburg-Eppendorf, Germany, were enrolled in the study after written informed consent was obtained. Non-inclusion criteria was a preexisting infection or the suspicion thereof based on laboratory results. Treatment of patients was entirely left to the discretion of the caring surgeon, anesthesiologist and intensive care provider. After insertion of an arterial radial catheter by the caring anesthesiologist prior to anesthesia induction, the first blood samples (7,5 ml volume) were drawn to define a preoperative baseline. Blood samples were repeatedly drawn after surgery, before transfer of the patient to the intensive care unit (ICU), on the first postoperative day (POD1) and on the fourth postoperative day (POD4). In six patients, additional serum blood samples were drawn at skin incision, before CPB and every 30 minutes during CPB. Laboratory tests included S1P concentrations in blood, potential sources of S1P (red blood cells (RBC), platelets), coagulation tests (partial thromboplastin time (PTT), international normalized ratio (INR), inflammatory markers (interleukin-6 (IL-6), procalcitonin (PCT), c-reactive protein (CRP)), von-Willebrand factor antigen (vWF : AG),

fibrinogen), potential S1P carriers (high-density lipoprotein (HDL), low-density lipoprotein (LDL), albumin), bilirubin and creatinine. Except for S1P, all other laboratory measurements were performed with routine patients' diagnostic tests with appropriate quality controls and clinical standards (Institute of Clinical Chemistry and Laboratory Medicine at the University Medical Center Hamburg-Eppendorf). In addition to basic patient characteristics and performed surgical procedure we documented the following clinical parameters during the perioperative phase: duration of ECC and aortal cross-clamping time, overall time of surgery, fluid balance, dosage of vasoactive drugs, perioperative administration of blood products, length of ICU stay and the Sequential Organ Failure Assessment (SOFA) score on POD1.

Serum Preparation and S1P Measurements

Blood serum was obtained by coagulation for at least 60 min, cleared by centrifugation and immediately frozen and stored at −80°C until further use. According to the manufacturer's protocol we used serum tubes filled with kaolin or silicate coated beads to guarantee a full coagulation within the expected time of at least 60 min (S-monovette™, Sarstedt, Nümbrecht, Germany). S1P measurements were performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) as previously described (26). Briefly, after the addition of internal standard (1 nmol/mL S1P-d7, Avanti Polar Lipids, Alabaster, AL, USA), 20 µL-aliquots of serum were de-proteinated by the addition of 180 µL acetonitrile/water (80/20, vol/vol). Extracts were cleared by centrifugation and subjected to reverse-phase chromatography on a Zorbax SB-C8 column (2.1 × 50 mm; Agilent Technologies, Santa Clara, CA, USA) at a flow rate of 0.35 mL/min. S1P was eluted by a binary gradient over six minutes (methanol/acetonitrile/0.1% formic acid, 2.5/2.5/95, vol/vol/vol to methanol/acetonitrile/0.1% formic acid, 30/30/40, vol/vol/vol) and quantified by LC-MS/MS (Varian L1200 MS/MS, Agilent Technologies, Waldbronn, Germany) in the multiple reaction mode. Four level calibration curves and two levels of quality controls (QCs) were included. Imprecision of the method was determined to 8% and 9% for QC-low and QC-high samples, respectively (26).

Statistical Analysis

The primary variable was S1P concentration in nanomoles (nmol) per milliliter (mL). Differences between groups were tested for significance by using non-parametric tests: Mann–Whitney U test for two groups and Kruskal-Wallis analysis of variance (ANOVA) for more than two groups. Data are presented as median with interquartile range and *in-vitro* experiments as mean with standard error of the mean. Correlations and multivariate regression analysis were performed either by the Spearmans' rank correlation test and multivariate regression analysis using SPSS (version 21; IBM Corporation, Armonk, NY, USA). In addition, a Kaplan-Meier curve was generated for subgroup analysis. For all tests, a P-value of less than 0.05 was considered significant. Statistical analyses were performed by using SPSS or GraphPad Prism (version 8.4.2, GraphPad, La Jolla, CA, USA) with guidance from members of the Department of Medical Biometry and Epidemiology at the University Hospital Hamburg-Eppendorf.

RESULTS

Circulatory S1P Levels Decrease, Whereas Inflammatory Markers Increase After Surgery

We included 46 patients admitted for elective cardiac surgery. Thirty-one (67.4%) patients underwent on-pump procedures for coronary artery bypass surgery (n=17), valve replacement/reconstruction (n=13) or a combination of coronary artery bypass surgery and valve replacement (n=1). Fifteen patients (32.6%) underwent off-pump procedures (off-pump coronary artery bypass surgery). All patients were admitted to hospital because of coronary heart disease (CHD) and received the preoperative standard of care for CHD. The chart in **Figure 1** summarizes the included patient groups. We compared S1P levels and five inflammatory markers to investigate whether levels were altered in relation to pre-surgery levels and **Table 1** is showing basic patient characteristics. S1P was the only laboratory characteristic, which significantly decreased compared to pre-surgery baseline levels (**Figure 2**). The lowest S1P concentrations were found post-surgery when patients were transferred to the intensive care unit (ICU). All other markers showed a contrary trend with significant peak levels either directly post-surgery (leucocytes), on postoperative day (POD) 1 (procalcitonin/PCT, interleukin-6/IL6), or POD4 (von-Willebrand-factor:AG/vWF : AG, C-reactive protein/CRP, **Figure 2**).

Cardiac Surgery Disrupts Serum-S1P Levels Irrespective of the Use of CPB

In order to investigate the influence of CPB on S1P kinetics we defined two groups (**Figure 1**): patients operated with support of CPB (referred to as on-pump), and patients operated without CPB (referred to as off-pump group). Basic patient characteristics and baseline inflammatory markers were compared between the two groups (**Table 1**). We found the same S1P kinetics in both groups with significant lowest levels observed post-surgery (**Figure 3**). S1P levels dropped by 58% in the on-pump and 31% in the off-pump group (**Figure 3**). Regardless of baseline levels being high or low, patients reached their individual nadir post-surgery with lowest S1P levels of 0.37 nmol/mL in the on-pump group and 0.46 nmol/mL in the off-pump group (**Figure 3**). However, the difference between these two levels was not significant. Taken together, the lowest S1P levels post-surgery were independent of the use of CPB.

Changes of Serum-S1P Levels Are Associated With S1P Sources and Carriers

To identify potential parameters that define the U-shaped course of S1P levels during treatment, a multivariate regression analysis was performed for three perioperative phases: intraoperative, early recovery (POD 1) and late recovery (POD 4). We included S1P sources, red blood cells (RBC) and platelets, S1P carriers,

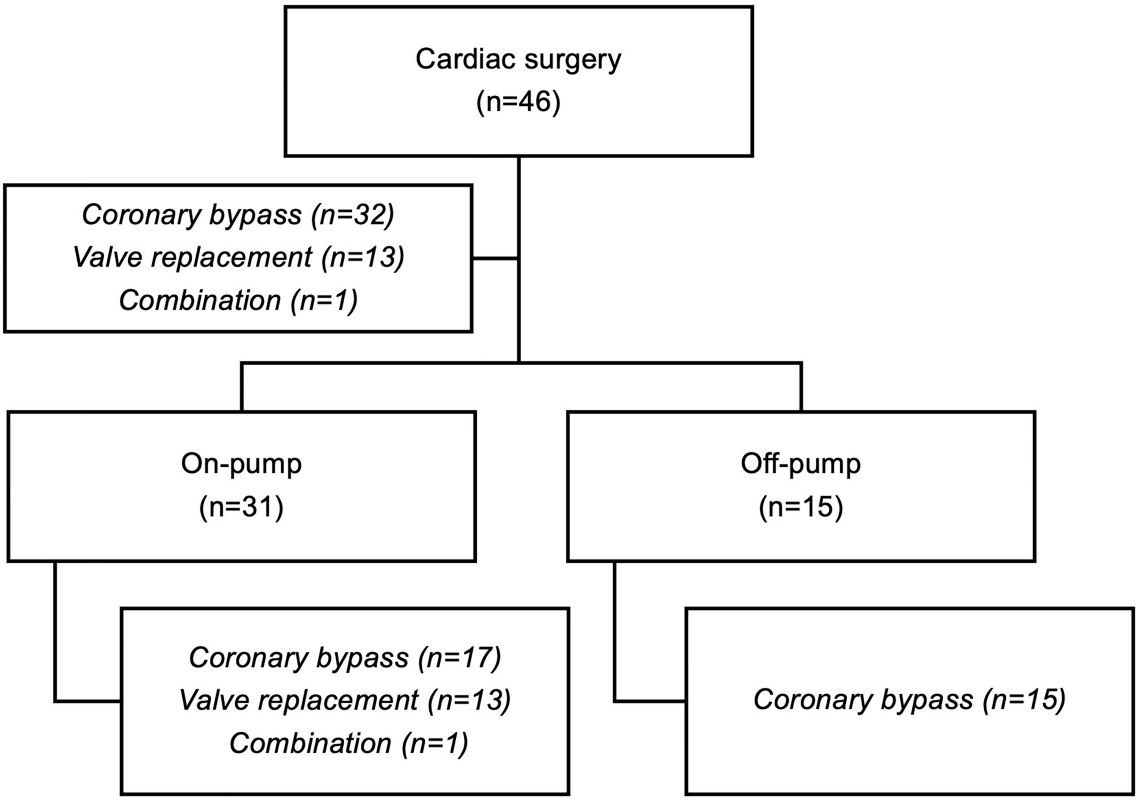

FIGURE 1 | Flow-chart of the included study participants.

serum albumin, high-density lipoprotein (HDL) and a marker for endothelial cell injury, vWF : AG. Intraoperative loss of S1P was associated with RBC and platelets depletion, whereas the increase of S1P levels on POD 1 and POD 4 was dependent on albumin, HDL and vWF : AG activity (**Table 2**). Next, we investigated whether postsurgical S1P levels were predictive for patient outcome. Patients were divided into two groups: S1P levels increasing to reach individual pre-surgery levels, and S1P levels remaining low. Both groups were compared using the sequential organ failure assessment (SOFA) score on POD1, fluid

TABLE 1 | Baseline patient's characteristics.

Parameter	All patients	On-pump	Off-pump	P-value
Number of patients, n	46	31	15	N/A
Age, y	70 (62-75)	68 (57-74)	72 (67-75)	ns
Male/Female, n/n	34/12	21/10	13/2	<0.05
S1P, nmol/mL	0.77 (0.61-0.99)	0.85 (0.66-1.03)	0.67 (0.54-0.76)	<0.05
S1P source and vWF : AG				
Erythrocytes, 10^6/µL	4.25 (3.79-4.53)	4.27 (3.99-4.52)	4.07 (3.48-4.67)	ns
Platelets, 10^3/µL	234 (195-263)	237 (198-300)	200 (181-248)	ns
vWF : AG, %	174 (137-201)	162 (126-195)	193 (155-253)	<0.05
S1P carriers				
HDL, mg/dL	43.0 (36.-57.0)	44.5 (33.5-59.0)	43.0 (38.5-51.5)	ns
Albumin, g/L	34.0 (31.0-36.0)	34.0 (32.0-36.0)	33.0 (30.0-35.5)	ns
Inflammatory marker				
Leucocytes, 10^3/µL	5.8 (4.9-6.5)	5.9 (4.9-6.6)	5.6 (4.8-6.3)	ns
IL-6, ng/L	4.3 (2.7-6.5)	4.4 (2.2-6.1)	4.3 (3.1-9.6)	ns
CRP, mg/L[#]	5 (5-8)	5 (5-7)	5 (5-10)	ns
PCT, ng/mL	0.04 (0.04-0.06)	0.04 (0.04-0.06)	0.04 (0.035-0.055)	ns

Data are presented as median and interquartile range (IQR); CRP, C-reactive protein; vWF, AG, von Willebrand-Factor antigen; IL-6, Interleukin-6; PCT, Procalcitonin; N/A, not applicable; ns, not significant; [#]Detection limit 5 mg/dL.

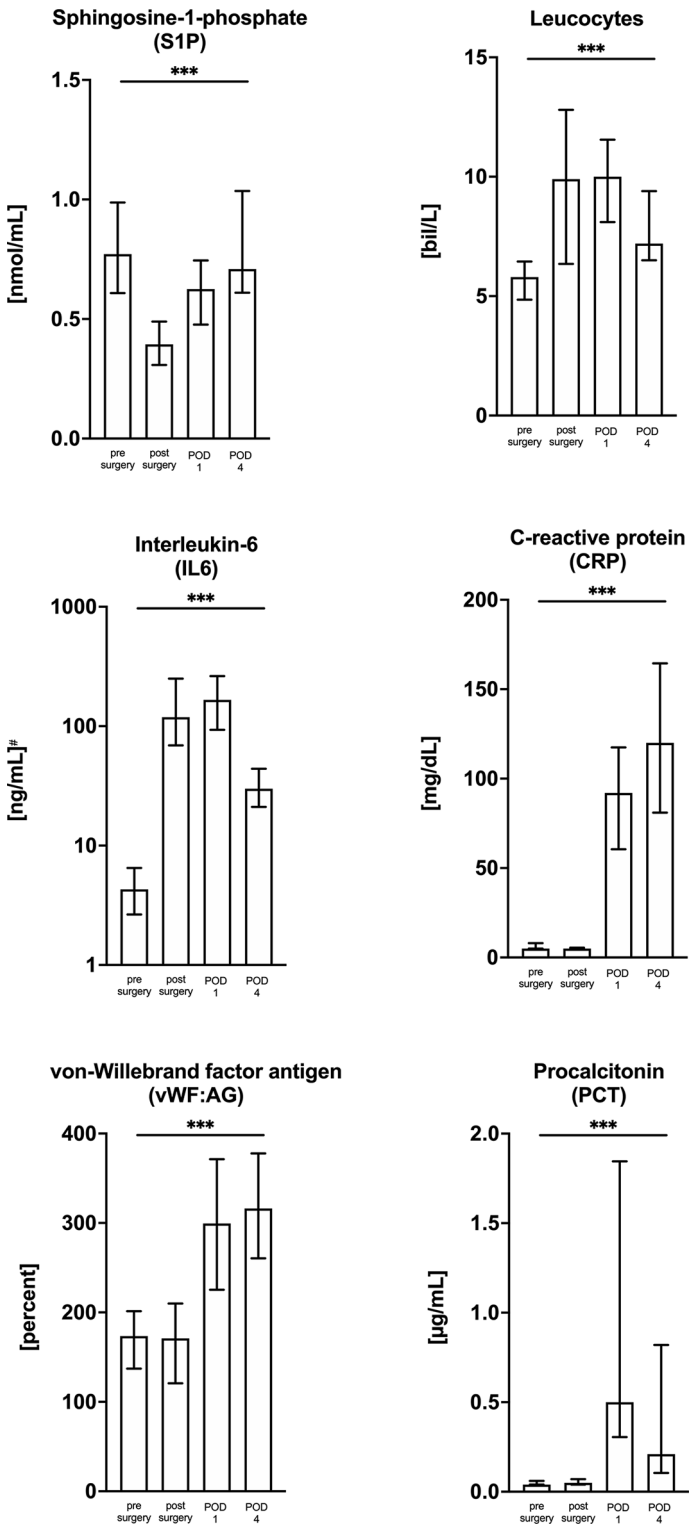

FIGURE 2 | Kinetic of S1P levels and other inflammatory markers in cardiac surgery patients from pre-surgery levels (baseline) up to day four after surgery. All markers were measured in 46 patients admitted to hospital for cardiac surgery. Among all measured parameters only S1P decreased after surgical intervention. The unity and scale have been adjusted for each marker and data are presented as median with interquartile range (IQR). The statistic is showing the ANOVA Kruskal-Wallis test for trend analysis. ****p < 0.001*. POD, postoperative day.

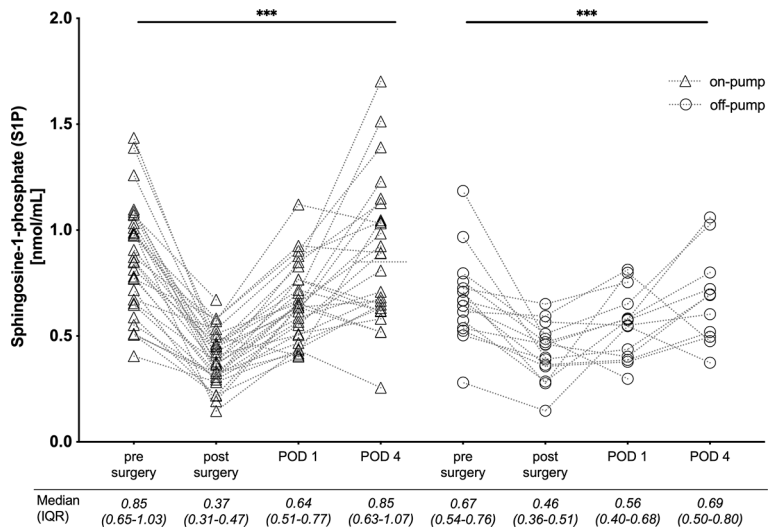

FIGURE 3 | Comparison of S1P levels in 46 cardiac surgery patients operated with cardiopulmonary bypass (on-pump) and without (off-pump). Individual serum-S1P levels are plotted at four time points: pre-surgery, post-surgery with admission to intensive care unit, on day one (POD 1) and four (POD 4) after surgery. The median and interquartile range (25^{th} to 75^{th} percentile) of measured serum-S1P are listed below. The trend for serum S1P was significant for both groups and lowest S1P levels were reached post-surgery. Median post-surgery levels were not different when comparing on- versus off-pump patients. The statistic within the graph is showing ANOVA Kruskal-Wallis test for trend analysis for the complete observational period. ****p < 0.001*. POD, postoperative day; IQR, interquartile range.

balance within the first 24 hours after surgery and length of ICU stay. Patients with a full recovery of S1P levels presented with a lower SOFA score ($p<0.05$), had a reduced volume uptake (not significant) and stayed significantly shorter on ICU ($p<0.05$) (**Figure 4** and **Table 3**).

Serum-S1P Levels Drop Before the Start of CPB

To further define the time window in which S1P concentrations drop during treatment, S1P levels were measured every 30 min in 6 patients during CPB. In all cases, a significant drop of S1P levels was observed immediately before the start of CPB, which is in coincidence with the application of heparin (**Figure 5**).

DISCUSSION

This report analyses S1P levels in cardiac surgery induced inflammation. Our main findings are that S1P levels are disrupted by heart surgery, changes of S1P levels inversely correlate with acute phase markers for inflammation, and the influence of CPB on S1P levels seems negligible compared to off-pump procedures. Cardiac surgery is an extremely strong inflammatory stimulus induced by tissue trauma, contact activation of the blood with non-endothelial surfaces, coagulation activation, endotoxemia and ischaemia-reperfusion injury (5, 27). This provokes an immediate acute-phase response, which is characterized by alterations of cytokines levels and acute-phase proteins (28, 29). Clinically, the resulting systemic inflammatory response is associated with severe intra- and postoperative complications as myocardial, respiratory and acute kidney injury (AKI), neurological impairment, bleeding and in its most severe form multiorgan failure (27). A recently published systematic review, including data of more than 14,000 patients, analysed which markers were useful in determining the magnitude of surgery induced injury (30). For example, the authors found that peak CRP was 36-times higher in patients after cardiac surgery compared to pre-surgery and that high concentrations of IL-6 and

TABLE 2 | Multivariate regression analysis with sphingosine-1-phosphate (S1P) as dependent variable for different perioperative phases.

Parameter	Intraoperative Regression-coefficient (CI 95%)*	P-value	POD 1 Regression-coefficient (CI 95%)*	P-value	POD 4 Regression-coefficient (CI 95%)*	P-value
Erythrocytes, 10^6/µL	+0.307 (0.009 - 0.284)	<0.05	+0.073 (-0.149 - 0.212)	ns	-0.013 (-0.165 - 0.152)	ns
Platelets, 10^3/µL	+0.404 (0.001 - 0.003)	<0.01	+0.121 (0.001 - 0.002)	ns	+0.271 (-0.001 - 0.002)	ns
vWF : AG, %	-0.134 (0.001 - 0.001)	ns	+0.195 (-0.001 - 0.001)	ns	-0.523 (0.003 - 0.001)	<0.01
HDL, mg/dL	+0.017 (-0.009 - 0.009)	ns	-0.068 (-0.011 - 0.008)	ns	-0.404 (-0.023 - 0.001)	<0.05
Albumin, g/L	+0.106 (-0.016 - 0.026)	ns	+0.345 (0.001 - 0.027)	<0.05	+0.521 (0.006 - 0.064)	<0.05
Model-$R^{2\#}$	*0.46*	*N/A*	*0.24*	*N/A*	*0.50*	*N/A*

*Multivariate linear regression with S1P as dependent variable and S1P sources and carriers has been performed to predict S1P during the intraoperative phase, on day one (POD 1) and four (POD 4) after surgery. *Standardized regression coefficient (standard beta) is shown together with confidence interval (95% CI). #R-square of the model is shown to demonstrate goodness-of-fit. vWF, AG, von Willebrand-Factor antigen; HDL, high-density lipoprotein; N/A, not applicable; ns, not significant.*

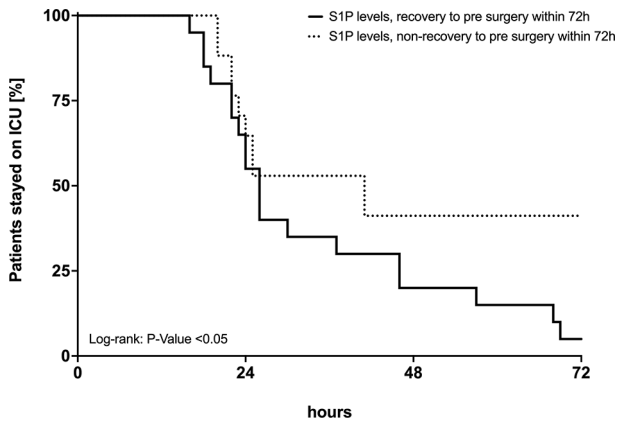

FIGURE 4 | Length of ICU stay in two patient groups. Patients in which sphingosine-1-phosphate (S1P) levels recovered and patients in which S1P levels did not recover to pre-surgery levels. The x-axis shows ICU stay in hours, the y-axis the percentage of patients remaining on ICU for further observation and treatment. Differences between the two groups were tested by Log-rank-test for comparison of survival curves.

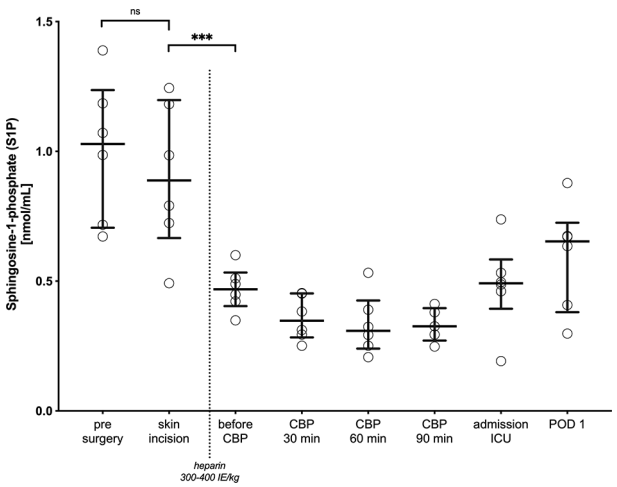

FIGURE 5 | Intraoperative kinetic of S1P levels. Blood was drawn and analyzed every 30 minutes when cardiopulmonary bypass (CPB) had started, post-surgery, when patients were admitted to the intensive care unit (ICU), and 24h after surgery. Dots are individual serum-S1P concentrations and bars represent median levels together with interquartile range (IQR). A non-parametric paired t-test was performed to compare serum-S1P levels pre-surgery with levels before CPB at skin incision, before and after administration of intravenous unfractionated heparin (300-400 IE/kg) to reach the necessary anticoagulatory effect for CPB. While serum-S1P levels were not different before CPB starts, the most drastic drop was observed after administration of heparin. ns, not significant, $***p < 0.001$. CBP, Cardio pulmonary bypass; ICU, intensive care unit; POD, postoperative day; ns, not significant.

CRP were closely associated with the degree of surgical injury (30). PCT is another well-described marker, but rather suitable for postoperative infectious complications after cardiac surgery (31). Elevated levels of IL-6, CRP, leucocytes and PCT indicate a substantial inflammatory reaction during and after surgery in our cohort. Inflammation in cardiac surgery is often attributed to CPB and there is a still on-going scientific debate on whether operative strategies avoiding CPB may be superior. In our study there was no significant difference in the measured parameters of inflammatory response in both patient groups with and without CPB. Additionally, we did not observe a relevant difference in S1P levels between the two groups and S1P levels are altered in all patients regardless of the use of CPB. In contrast to the clinically established inflammatory markers IL-6, CRP or leukocyte counts, S1P may better indicate a disturbed immune response together with endothelial cell injury. Our data suggests that there is a reliable and prompt S1P drop after the surgical stimulus. The time from the surgical stimulus until the significant S1P drop is very short. Therefore, we believe that, due to the important role of circulating S1P in stabilizing endothelial integrity and immune response, S1P may function as a potential marker of endothelial injury during and after cardiac surgery, which might be predictive for recovery.

A hallmark of systemic inflammation is the damage to the endothelial cell layer and recovery of endothelial cell function determines the outcome. This is most relevant in systemic reactions induced by bacterial pathogens such as in sepsis (32). Cardiac surgery induces a sepsis-like syndrome associated with a high degree of endothelial cell dysfunction. Recent studies report drastically increased postoperative levels of endothelial markers in blood such as vascular endothelial cadherin and endocan, which correlate with the severity of endothelial cell injury after cardiac surgery (33, 34). Von-Willebrand factor regulates adhesion of immune cells to injured endothelium and has been previously studied in cardiac patients (35). In contrast to components released by injured endothelial cells, S1P is a signalling molecule regulating endothelial cell structure *via* specific G-protein coupled receptors (36). The endothelium is an important source of circulatory S1P and maintains cell function in an auto-protective manner (37). Cardiac surgery may interrupt this balance and injured endothelial cells may produce less S1P, which further promotes endothelial

TABLE 3 | Comparison of outcome parameters.

Parameter	Full recovery of S1P	No recovery of S1P	P-value
Number of patients, n	23	20	N/A
SOFA	3 (2-3)	4 (3-4)	<0.05
ICU stay, h	24 (19-41)	41 (23-69)	<0.05
Balance, 24h post-surgery	700 (50-1800)	850 (550-1775)	ns

The study group was divided into two subgroups depending on whether serum S1P levels after surgery reached pre-surgery levels (full recovery of S1P) or not (no recovery of S1P). Data are presented as median, interquartile range (IQR); Groups were compared using non-parametric Mann-Whitney-U test. N/A, not applicable; ns, not significant.

dysfunction and barrier breakdown. An analogue mechanism has been discussed by other researchers for chronic endothelial dysfunction in atherosclerosis (38). Furthermore, circulating S1P levels are not only determined by endothelial cells. Hematopoietic cells, erythrocytes and platelets are a rich source for S1P as well and all contribute to plasma-S1P levels (15). Cardiac surgery induces haemolysis; bleeding complications are common and high platelet turnover and microthrombi are frequent. This could be reason for the observed acute changes in S1P concentration during surgery when hematopoietic S1P sources are compromised. Circulating S1P further depends on its carrier proteins HDL and albumin, which contribute to S1P related effects (39). During recovery after surgical trauma healing mechanisms, such as increased production of anti-inflammatory proteins as HDL or albumin, may be involved in restoring S1P homeostasis and explain our observation.

Another function of S1P is its protective role in hyperinflammatory states. Experimental studies have been performed in various models. For instance, in mice infected with H1N1 influenza, administration of S1P receptor 1 agonists attenuate the cytokine release by pulmonary endothelial cells (17). Another well-studied role for S1P is the regulation of lymphocyte egress from lymphatic organs into the blood (14). It is possible, due to the lack of the immunoregulative function of S1P in the perioperative phase following cardiac surgery, that patients are vulnerable for infectious postoperative complications. Even though it is a comparably small cohort with a short observational period of only 4 days, we have found that patients with S1P levels not recovering to preoperative levels stayed longer on the ICU and had a higher SOFA score on POD1.

S1P levels dropped in every individual. The analysis of S1P kinetics revealed the most relevant decrease before the onset of CPB and before equivalent off-pump-procedures, respectively. The decrease in S1P coincided with invasive surgical measures as sternotomy, luxation of the heart and cannulation for CPB and the administration of unfractionated heparin in a high dose to prepare for upcoming CPB or off-pump procedure. According to the standard institutional protocol, on- and off-pump patients receive an initial i.v. bolus of 300-400 IE/kg heparin and one possibility is that S1P levels are influenced by heparin. Yatomi et al. measured 60% lower S1P levels in non-coagulated blood (191 ± 79 vs. 484 ± 82 pmol/mL) (40). Thus, it is possible that heparin is causing the drop of S1P. The release of S1P by thrombin-activated platelets into the circulation has previously been described (41, 42). In trauma, tissue factor (TF) is exposed and initiates the coagulation cascade. Binding of activated factor (F) VII to TF allows the binding of FX and its conversion to FXa, which than stimulates thrombin generation (43). Consequently, targeting FXa, *via* heparin, may attenuate platelet activation and subsequently cause S1P levels to drop. The role of platelet aggregation inhibitors in S1P release by platelets has recently been investigated in pre-clinical studies. The release of S1P induced by activation of thrombin receptor (PAR-1) is inhibited by aspirin *in-vitro* and *ex-vivo* (44). Moreover, FXa induces the expression of S1P producing kinases and subsequently increases S1P formation (45). Taken together, FXa inhibitors, such as heparin, may decrease circulating S1P levels, which has been lately included in a US patent description (US20170296549A1). Mechanistically, this could be an effect of inhibited thrombin activation of platelets, which is a main source for circulating S1P. Reduced S1P levels in open heart surgery might be affected by injured endothelial cells, reduced hematopoietic sources and carriers or by iatrogenic inhibition of the coagulation system. Interestingly, this is the first report showing that high dose anticoagulation with heparin may influence S1P levels in patients undergoing cardiac surgery. We cannot exclude that this hypothetical pleiotropic effect of heparin might have a larger effect on vascular- and immunomodulatory S1P than we expected. A S1P/heparin interaction on the immune response has been described and therefore cannot be excluded also under high-dose heparin treatment during cardiac surgery (46).

Limitations of this study are that it was carried out at a single center and involved a relatively small number of patients. The results are strictly observational and therefore, the identity of underlying mechanisms remains speculative. Nevertheless, due to the reliable drop of S1P in all patients, we believe that our observations warrant follow-up studies. For instance, confirmatory studies are needed to evaluate a possible relationship of high dose heparin with the drop of S1P levels. The observed drop of S1P is robust, however, we do not know if the observed lower S1P levels will have a functional significance on S1P signalling. Follow-up interventional studies should address the potential of S1P or S1P mimics to benefit patients undergoing cardiac surgery.

CONCLUSION

In conclusion, in this prospective observational study we report a severe drop in circulatory S1P in patients undergoing cardiac surgery independent of the use of CBP. S1P concentrations might be negatively affected by endothelial injury, loss of S1P sources or other intraoperative events such as anticoagulation by heparin. It is an intriguing possibility to utilize measurements of circulatory S1P to predict the severity of surgery-induced inflammation, ICU length of stay and general clinical outcome. Moreover, our observations encourage future interventional studies to investigate the therapeutical potential of S1P or S1P mimics in cardiac surgery.

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 - Aerztekammer Hamburg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study conception and design: GG and MW. Acquisition of data: GG, EM, HS, AP, AN, ES, and MW. Analysis and interpretation of data: GG, EM, KA, ES, GD, BT, and MW. Drafting manuscript: GG, ES, KA, GD, and MW. Critical revision: GG, AN, SK, HR, CZ, ES, GD, BT, and MW. All authors contributed to the article and approved the submitted version.

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Predictors of Mortality in Critically Ill Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: Patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) may require intensive care unit (ICU) admission due to different reasons, and the in-ICU mortality is high among AAV patients. The aim of this study was to explore the clinical features and risk factors of mortality of patients with AAV in the ICU.

Methods: A retrospective study was conducted based on 83 AAV patients admitted to the ICU in a tertiary medical institution in China. Data on clinical characteristics, laboratory tests, treatment in ICU and outcomes were collected. The data were analyzed using univariate and multivariate logistic regression analysis to explore the variables that were independently related to mortality. Kaplan–Meier method was used to assess the long-term survival.

Results: Among the 83 patients, 41 (49.4%) were female. The mean age of patients was 66 ± 13 years. Forty-four patients deceased, with the in-ICU mortality of 53%. The most common cause for ICU admission was active vasculitis (40/83, 48.2%). The main cause of death was infection (27/44, 61.4%) followed by active vasculitis (15/44, 34.1%). A multivariate analysis revealed that the Acute Physiology and Chronic Health Evaluation II (APACHE II) at ICU admission (*OR* = 1.333, 95% *CI*: 1.031–1.722) and respiratory failure (*OR* = 620.452, 95% *CI*: 11.495–33490.306) were independent risk factors of in-ICU death. However, hemoglobin (*OR* = 0.919, 95% *CI*: 0.849–0.995) was an independent protective factor. The nomogram established in this study was practical in predicting the risk of in-ICU mortality for AAV patients. Moreover, for 39 patients survived to the ICU stay, the cumulative survival rates at 0.5, 1, and 5 years were 58.3%, 54.2%, and 33.9%, respectively, and the median survival time was 14 months.

Conclusion: In our study, active vasculitis was the most frequent reason for ICU admission, and the main cause of death was infection. APACHE II and respiratory failure

were independent risk factors while hemoglobin was an independent protective factor of in-ICU mortality for AAV patients admitted to the ICU. The risk prediction model developed in this study may be a useful tool for clinicians in early recognition of high-risk patients and applying appropriate management.

Keywords: antineutrophil cytoplasmic antibody-associated vasculitis, intensive care unit, mortality, predictors, Acute Physiology and Chronic Health Evaluation II, nomogram

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic necrotizing vasculitis that predominantly affects small vessels and is associated with the presence of ANCAs in serum (1, 2). AAV comprises three entities, including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) (3). Early diagnosis of AAV combined with administration of immunotherapies such as glucocorticoids, immunosuppressive drugs and rituximab have significantly improved the survival rate of AAV patients (4, 5). However, some AAV patients may require intensive care unit (ICU) admission due to life-threatening manifestations at the time of diagnosis, disease flare-up or severe complications due to immunosuppressive therapies (6–8). AAV is one of the most frequent systemic rheumatic diseases (SRD) in the ICU (9, 10) with high mortality ranging from 15.5% to 58.8% (8, 11, 12). According to researches, the in-ICU mortality is higher among AAV patients compared with other SRD patients (13).

The number of studies on the clinical features and ICU outcome of AAV patients is limited. Previous studies have reported that infection and life-threatening manifestations of active vasculitis are the main reasons for ICU admission of AAV patients (8, 11). The prediction of patients' outcome is clinically important, especially for patients in the ICU. Different methods for measuring disease severity in ICU patients have been developed, including Acute Physiology and Chronic Health Evaluation II (APACHE II) (14), Sequential Organ Failure Assessment (SOFA) (15) and Simplified Acute Physiologic Score II (SAPS II) (16). These disease severity scores are computed at the time of admission to ICU and have been reported to be associated with ICU outcome of AAV patients in some studies (8, 11). However, the value of specific vasculitis score like Birmingham vasculitis activity score system (BVAS) on patients' outcome in the ICU is yet to be shown (6, 17). To date, few studies have investigated the relationship between clinical features and risk of mortality in the ICU for AAV patients. Most of the studies are small-sized and lack data about Asians. Therefore, further research in this area is needed.

To identify the predictors of in-ICU mortality for AAV patients in the Chinese population, we conducted a single-center, retrospective study. In the study, data about clinical characteristics, laboratory tests and treatment in ICU were collected. Our results revealed that active vasculitis was the most common reason for ICU admission and a novel model combined respiratory failure, hemoglobin and APACHE II is a good predictor of in-ICU mortality for AAV patients.

Abbreviations: AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiologic Score II; BVAS, Birmingham vasculitis activity score system; ESRD, end-stage renal disease; GFR, glomerular filtration rate; DAH, diffuse alveolar hemorrhage; ILD, interstitial lung disease; ENT, ear, nose and throat; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SRD, systemic rheumatoid disease; DCA, decision curve analysis; ROC, receiver operating characteristic.

MATERIALS AND METHODS

Patients and Study Design

In this retrospective study, patients with AAV admitted to the ICU of the First Affiliated Hospital of Zhengzhou University from May 2011 to May 2021 were identified. All patients fulfilled the 2012 revised International Chapel Hill Consensus Conference definitions for the AAV (3) or the American College of Rheumatology criteria for Wegener's granulomatosis and Churg-Strauss syndrome (18, 19). Exclusion criteria included patients with drug-induced AAV, patients who were less than 18 years or those with other SRDs such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathy and antiphospholipid syndrome. Consequently, among 975 patients diagnosed with AAV, we selected 83 patients who were admitted to the ICU during the study period (**Figure 1**). For patients admitted to the ICU more than once, only the first admission was considered. In this study, the primary outcome for AAV patients hospitalized in the ICU was in-ICU death. Patients who were discharged from ICU against medical advice and ended up deceased within 1 week were also considered to have undergone in-ICU death. Besides, long-term outcomes were also recorded of the patients survived to the first ICU stay. Our study complied with the Declaration of Helsinki and was approved by the Ethical Committee of the First Affiliated Hospital of Zhengzhou University (**No. 2021-KY-0610**).

Clinical Data and Laboratory Examinations

In this study, we collected patients' data, including age, gender, medical history of chronic comorbidities (20), classification of AAV, reasons for ICU admission, length of stay in ICU, clinical features and organ involvement, treatment at the moment of ICU admission and during ICU hospitalization as well as patients' outcome. To assess AAV disease activity and severity, APACHE II (14) and BVAS (21) were calculated within the first 24 h of

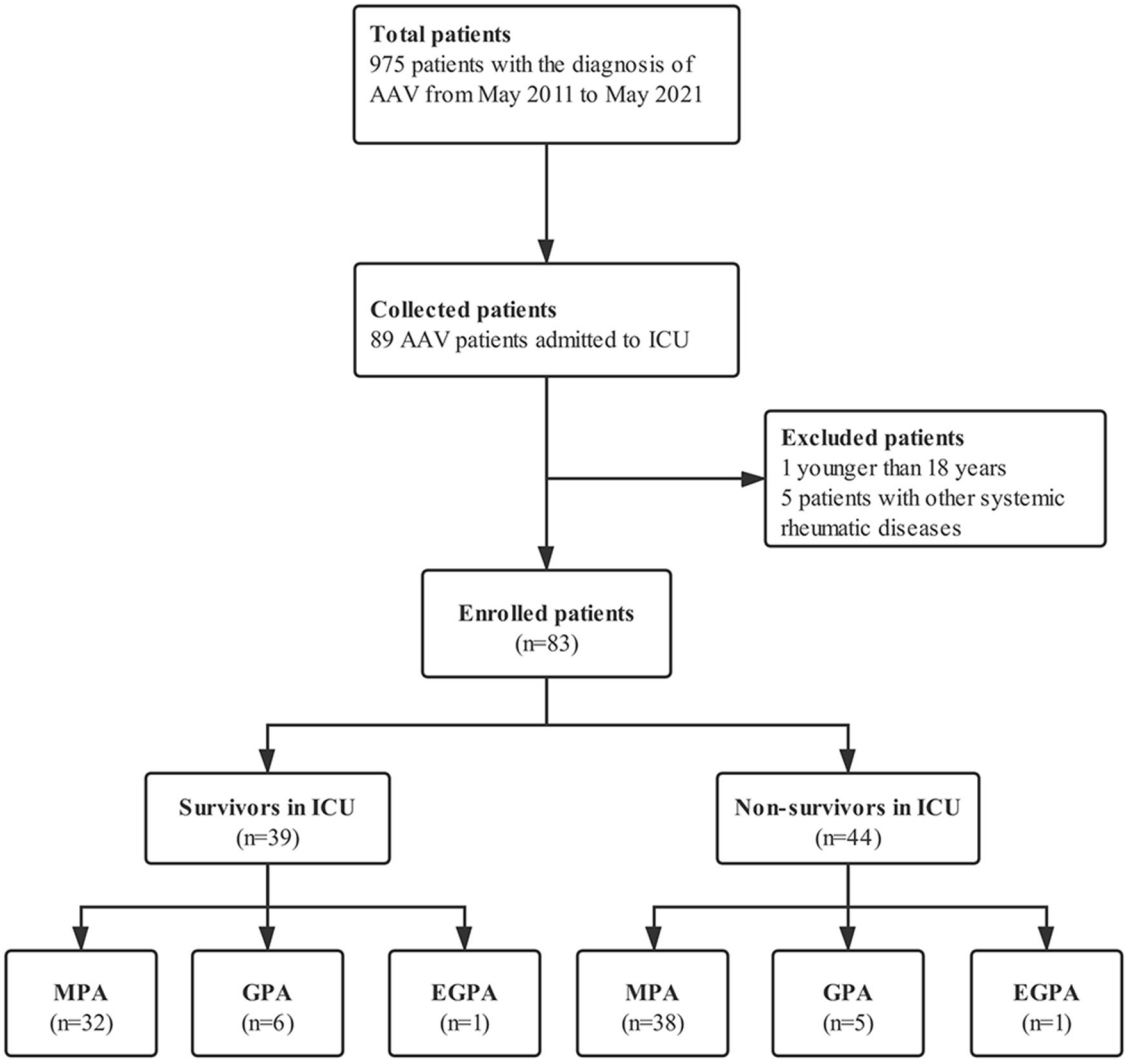

FIGURE 1 | Flow chart of the study design.

ICU admission. APACHE II is determined by total points from three sections, including age, chronic health status, and 12 acute physiologic variables. It is computed using the most deranged physiologic variables during the patient's initial 24 h in ICU, with a total score between 0 and 71 points (14). BVAS is computed by points from 10 systems (one general, eight tissue-specific and one open), with a maximum score for each system (21). Different laboratory tests were performed for ICU patients including routine blood analysis, liver function test, kidney function test, ANCA, arterial blood gas analysis and inflammatory indexes like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin analysis.

Definition of Terms

The causes for admission to the ICU were classified as active vasculitis, infection and other causes not attributed to infection or active vasculitis. Active vasculitis was diagnosed when new, persistent, or worsening clinical symptoms attributed to AAV and not related to prior organ damage were detected (22). Infection was defined by suspected clinical signs of infection accompanied with sufficient laboratory and imaging findings or microbiological results. Respiratory failure was diagnosed if oxygenation index (PaO_2/FiO_2) was <300 mmHg (23) or patient was in need of mechanical ventilation. Diffuse alveolar hemorrhage (DAH) was defined as the presence of hemoptysis, rapid decrease in hemoglobin and alveolar infiltrates on chest imaging or hemorrhagic bronchoalveolar lavage fluid accompanied with hemosiderin-laden macrophages (24). Interstitial lung disease (ILD) was defined according to British Thoracic Society guidelines, excluding the causes of infection, medication and pulmonary edema (25). Pulmonary arterial hypertension was diagnosed if the tricuspid regurgitation jet velocity was more than 2.8 m/s or systolic pulmonary artery pressure was more than 35 mmHg determined by

echocardiography or confirmed by right heart catheterization (26, 27). Renal insufficiency was diagnosed by the presence of glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2, rapidly rising plasma creatinine or oliguria (urine volume <30 mL/h or 400 mL/day) (28). Glomerulonephritis was defined if proteinuria was >0.5 grams per 24 h accompanied with hematuria or confirmed renal biopsy. End-stage renal disease (ESRD), was defined as GFR <15 ml/min per 1.73 m^2, in need of regular course of long-term renal-replacement therapy or kidney transplantation (28, 29). Cardiovascular diseases included acute myocardial infarction, arrhythmia, and the class IV cardiac function according to the New York Heart Association functional classification system (30). Shock was defined as systolic blood pressure <90 mmHg and/or diastolic blood pressure <60 mmHg with signs of organ hypoperfusion (31). Other manifestations of active vasculitis were defined according to BVAS (21).

Statistical Analysis

Data were reported as means with standard deviation or median with inter-quartile range (Q1–Q3) for continuous variables and as frequencies or percentages for categorical data. Differences between survivors and non-survivors were explored using independent-samples *t*-tests or Mann–Whitney *U* test for continuous variables and Chi-square test or Fisher's exact test for categorical data. Univariate and multivariate logistic regression analysis was performed to explore the variables that were independently related to mortality. Laboratory tests, disease assessment scores and clinical features were treated as independent variables. In-ICU death was used as dependent variable. A nomogram was constructed based on the results of multivariate logistic regression analysis to predict the risk of in-ICU death. Besides, calibration curves, decision curve analysis (DCA) and receiver operating characteristic (ROC) curves were plotted to determine the reliability of our nomogram. Kaplan–Meier method was used to assess the long-term survival. A two-tailed *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software (Version 25.0), GraphPad Prism (Version 8.0.2) and R software (Version 3.6.1).

RESULTS

Patients' Characteristics and Disease Severity Scoring

The characteristics of the patients and disease severity data are detailed in **Table 1**. Among the 83 patients admitted to the ICU, 41 (49.4%) were female and the mean age of all the patients was 66 ± 13 years. The type of AAV was established for all 83 patients, with MPA in 70 patients (84.3%), GPA in 11 patients (13.3%) and EGPA in 2 patients (2.4%). The groups between non-survivors and survivors were similar regarding gender, age, medical history and classification of AAV. Forty-eight patients (57.8%) were newly diagnosed with AAV. The median duration between AAV diagnosis and ICU admission in the remaining 35 patients was 12 (3–44) months. Thirty-nine patients (47%) were receiving glucocorticoids while therapies showed no statistical difference between groups at the moment of ICU admission. Disease severity assessed by APACHE II score at ICU admission was significantly higher in non-survivors' group [20.00 (15.00–25.75)] than that in survivors' group [12.00 (9.00–14.00)]. Disease activity assessed by BVAS score at ICU admission was also higher for non-survivors (25.16 ± 8.69) than that for survivors (15.67 ± 9.44).

TABLE 1 | Demographic and clinical data of 83 AAV patients admitted to ICU.

Parameters	Total (*n* = 83)	Survivors (*n* = 39)	Non-survivors (*n* = 44)	*P*-value
Age (years, mean ± SD)	66 ± 13	65 ± 12	66 ± 13	0.886
Female gender (*n*, %)	41 (49.4)	20 (51.3)	21 (47.7)	0.746
Medical history (*n*, %)				
Diabetes	13 (15.7)	8 (20.5)	5 (11.4)	0.252
Hypertension	33 (39.8)	17 (43.6)	16 (36.4)	0.502
Coronary heart disease	14 (17.3)	6 (15.4)	8 (18.2)	0.734
Cerebrovascular disease	16 (19.3)	7 (17.9)	9 (20.5)	0.773
Malignancy	2 (2.4)	1 (2.6)	1 (2.3)	1.000
Classification of AAV (*n*, %)				0.859
MPA	70 (84.3)	32 (82.1)	38 (86.4)	
GPA	11 (13.3)	6 (15.4)	5 (11.4)	
EGPA	2 (2.4)	1 (2.6)	1 (2.3)	
Newly diagnosed as AAV (*n*, %)	48 (57.8)	22 (56.4)	26 (59.1)	0.805
Course of AAV (month), M (Q1–Q3)	12.00 (3.00–44.00)	10.50 (2.00–37.75)	18.00 (3.50–51.00)	0.366
Treatment at the moment of ICU admission				
Glucocorticoids	39 (47.0)	16 (41.0)	23 (52.3)	0.306
Cyclophosphamide	7 (8.4)	1 (2.6)	6 (13.6)	0.157
Mycophenolate mofetil	3 (3.6)	1 (2.6)	2 (4.5)	1.000
Azathioprine	1 (1.2)	0 (0)	1 (2.3)	1.000
Plasma exchange	2 (2.4)	1 (2.6)	1 (2.3)	1.000
Hemodialysis	12 (14.5)	6 (15.4)	6 (13.6)	0.821
Length of stay in ICU (day), M (Q1–Q3)	5 (2–10)	5 (2–11)	5 (3–8)	0.953
Disease and severity assessment scores				
APACHE II, M (Q1–Q3)	15.00 (11.00–21.00)	12.00 (9.00–14.00)	20.00 (15.00–25.75)	**<0.001**
BVAS (mean ± SD)	20.70 ± 10.18	15.67 ± 9.44	25.16 ± 8.69	**<0.001**

Values highlighted in bold represent statistically significant P values (P < 0.05).
AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; BVAS, Birmingham vasculitis active scoring system.

Causes of ICU Admission for AAV Patients

The causes of admission to the ICU for the 83 patients are displayed in **Table 2**. The most common reason for ICU admission was active vasculitis, accounting for 48.2% of the AAV patients. Active vasculitis cases included 17 with acute

TABLE 2 | Causes of ICU admission of 83 AAV patients.

Causes of ICU admission	Number of patients
Active vasculitis (*n*, %)	40 (48.2)
Pulmonary-renal syndrome	9
Diffuse alveolar hemorrhage	8
Acute renal insufficiency	17
Stroke	5
Subglottic stenosis	1
Infection (*n*, %)	35 (42.2)
Pneumonia	29
Sepsis	5
Urinary tract infection	1
Other reasons (*n*, %)	8 (9.6)
Cancer cachexia	1
Pericardial tamponade	1
Acute heart failure	1
Exacerbation of dilated cardiomyopathy	1
Mediastinal emphysema	1
AE-COPD	1
Coma after cardiopulmonary resuscitation	1
Postoperative complication of anterior chamber paracentesis	1

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; AE-COPD, acute exacerbation of chronic obstructive pulmonary disease.

renal insufficiency, eight with diffuse alveolar hemorrhage, nine with pulmonary-renal syndrome, five with stroke and one with subglottic stenosis. For the 35 patients (42.2%) admitted to the ICU mainly due to infection, the most common cause was pneumonia. In addition, eight patients (9.6%) were admitted for other reasons, including pericardial tamponade, acute heart failure, mediastinal emphysema, etc.

Clinical Features and Laboratory Tests of Non-survivors and Survivors

Data for clinical features of the 83 patients in the ICU are provided in **Table 3**. Nineteen patients (22.9%) had DAH while 25 patients (30.1%) had ILD, though no significant difference was showed between non-survivors and survivors. Notably more non-survivors suffered from respiratory failure (95.5% vs. 23.1%) and pulmonary arterial hypertension (27.3% vs. 2.6%) than survivors. We further analyzed pulmonary involvement between cytoplasmic or proteinase-3-ANCA (c/PR3-ANCA)-positive and perinuclear or myeloperoxidase-ANCA (p/MPO-ANCA)-positive patients (**Supplementary Table 1**). In the total of 83 patients, 73 (88.0%) had a positive ANCA during the ICU admission. DAH was more frequent in c/PR3-ANCA-positive patients (50.0%) than p/MPO-ANCA-positive patients (22.2%). However, ILD was more common in p/MPO-ANCA-positive patients (31.7%) than c/PR3-ANCA-positive patients (10.0%), though no statistical significances were shown between the two groups regarding DAH and ILD. Besides, the groups of c/PR3-ANCA-positive and p/MPO-ANCA-positive patients were similar in terms of pulmonary arterial hypertension, pulmonary nodules, pulmonary infiltrates, pleural effusions, pulmonary embolism and respiratory failure.

Renal insufficiency occurred in 59 patients (71.1%) while 38 patients (45.8%) had glomerulonephritis (**Table 3**). However,

TABLE 3 | Clinical features of 83 AAV patients in ICU.

Characteristics (n, %)	Total (*n* = 83)	Survivors (*n* = 39)	Non-survivors (*n* = 44)	*P*-value
Fever	48 (57.8)	20 (51.3)	28 (63.6)	0.255
Respiratory system				
Cough	31 (37.3)	14 (35.9)	17 (38.6)	0.797
Hemoptysis	11 (13.3)	4 (10.3)	7 (15.9)	0.448
Diffuse alveolar hemorrhage	19 (22.9)	7 (17.9)	12 (27.3)	0.313
Interstitial lung disease	25 (30.1)	10 (25.6)	15 (34.1)	0.402
Pleural effusions	48 (57.8)	22 (56.4)	26 (59.1)	0.805
Pulmonary embolism	3 (3.6)	1 (2.6)	2 (4.5)	1.000
Pulmonary arterial hypertension	13 (15.7)	1 (2.6)	12 (27.3)	**0.002**
Respiratory failure	51 (61.4)	9 (23.1)	42 (95.5)	**<0.001**
Renal disease				
Renal insufficiency	59 (71.1)	24 (61.5)	35 (79.5)	0.071
Glomerulonephritis	38 (45.8)	14 (35.9)	24 (54.5)	0.089
Cardiovascular disease				
Heart failure	53 (63.9)	22 (56.4)	31 (70.5)	0.184
Acute myocardial infarction	5 (6.0)	1 (2.6)	4 (9.1)	0.432
Arrhythmia	3 (3.6)	1 (2.6)	2 (4.5)	1.000
Digestive system				
Gastrointestinal bleeding	10 (12.0)	4 (10.3)	6 (13.6)	0.893
Bowel obstruction	2 (2.4)	1 (2.6)	1 (2.3)	1.000
Hypoalbuminemia	45 (54.2)	21 (53.8)	24 (54.5)	0.949
Liver dysfunction	10 (12.0)	2 (5.1)	8 (18.2)	0.137
Neuropsychiatric disease				
Stroke	14 (16.9)	2 (5.1)	12 (27.3)	**0.007**
Others [a]	3 (3.6)	0 (0)	3 (6.8)	0.284
ENT involvement	9 (10.8)	3 (7.7)	6 (13.6)	0.606
Hematologic involvement				
Leukopenia	4 (4.8)	2 (5.1)	2 (4.5)	1.000
Anemia	69 (83.1)	29 (74.4)	40 (90.9)	**0.044**
Thrombocytopenia	11 (13.3)	6 (15.4)	5 (11.4)	0.590
MAS	1 (1.2)	0 (0)	1 (2.3)	1.000
TTP	1 (1.2)	0 (0)	1 (2.3)	1.000
Infection				
Pneumonia	72 (86.7)	30 (76.9)	42 (95.5)	**0.013**
Urinary tract infection	3 (3.6)	0 (0)	3 (6.8)	0.284
Sepsis	9 (10.8)	2 (5.1)	7 (15.9)	0.221
Shock	27 (32.5)	2 (5.1)	25 (56.8)	**<0.001**

Values highlighted in bold represent statistically significant P values (P < 0.05).
[a]Other neuropsychiatric disease including one patient with seizure, one with uremic encephalopathy and one with lower-extremity numbness.
AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; ENT, Ear, Nose, and Throat; MAS, macrophage activation syndrome; TTP, thrombotic thrombocytopenic purpura.

there were no significant differences between non-survivors and survivors in terms of renal involvement. More non-survivors suffered from stroke (27.3% vs. 5.1%) and anemia (90.9% vs 74.4%) than survivors. Besides, shock was more frequent in non-survivors (56.8%) than survivors (5.1%). Pneumonia was reported in 72 patients (86.7%), with a significantly higher proportion in non-survivors (95.5% vs. 76.9%). The most common pathogens identified by culture of sputum or bronchoalveolar lavage fluid were *Acinetobacter baumannii* (12, 16.7%), followed by *Candida albicans* (10, 13.9%), *Klebsiella pneumonia* (8, 11.1%), *Aspergillus* (7, 9.7%), virus (7, 9.7%), *Pseudomonas aeruginosa* (5, 6.9%) and *Pneumocystis carinii* (5, 6.9%). However, 20 patients suffered from mixed infections while 30 were infected with unknown infectious agents. Urinary tract infection was detected in three patients (3.6%). Urine cultures of the patients revealed that they were separately infected with *Klebsiella pneumonia*, *Enterococcus faecalis* and *Candida tropicalis*. Sepsis was detected in nine patients (10.8%), with *Klebsiella pneumonia* (2, 22.2%) and *Staphylococcus aureus* (2, 22.2%) being the dominant causal bacteria.

The laboratory data collected during the ICU admission for non-survivors and survivors are presented in **Supplementary Table 2**. Non-survivors had lower level of hemoglobin (78.62 ± 21.83 g/L) than survivors (91.80 ± 27.94 g/L). Moreover, blood urea nitrogen, cardiac troponin I and procalcitonin were significantly higher for non-survivors than that for survivors. Most patients (75.9%) with AAV admitted to the ICU had positive p-ANCA while only 12.0% of the patients had positive c-ANCA. There was no statistical difference between non-survivors' and survivors' groups in the ANCA subtypes.

Treatment Strategies for Non-survivors and Survivors

Strategies for management of the 83 AAV patients during admission in ICU are provided in **Table 4**. Thirty-two patients (72.7%) in non-survivors and 28 patients (71.8%) in survivors' group received glucocorticoids. Cyclophosphamide was administered intravenously to one patient in the survivors' group and orally to another patient in the non-survivors' group. Our results indicated that there were more patients from the non-survivors' group (56.8%) in need of catecholamines to maintain normal blood pressure than from the survivors' group (7.7%). In total, 43 patients (51.8%) required mechanical ventilation during the ICU, among whom 32 patients (38.6%) received endotracheal intubation. A significantly higher proportion of non-survivors needed mechanical ventilation and endotracheal intubation than survivors ($P < 0.001$). Plasma exchange was performed in 11 patients (13.3%) and hemodialysis was performed in 33 patients (39.8%), with no statistical difference between non-survivors' and survivors' groups.

TABLE 4 | Treatment for 83 AAV patients in ICU.

Treatment	Total ($n = 83$)	Survivors ($n = 39$)	Non-survivors ($n = 44$)	*P*-value
Glucocorticoids	60 (72.3)	28 (71.8)	32 (72.7)	0.925
Pulsed methylprednisolone	12 (14.5)	3 (7.7)	9 (20.5)	0.099
Oral cyclophosphamide	1 (1.2)	0 (0)	1 (2.3)	1.000
Intravenous cyclophosphamide	1 (1.2)	1 (2.6)	0 (0)	0.952
IVIG	26 (31.3)	10 (25.6)	16 (36.4)	0.293
Catecholamines	28 (33.7)	3 (7.7)	25 (56.8)	**<0.001**
Antibiotics	80 (96.4)	38 (97.4)	42 (95.5)	1.000
Plasma exchange	11 (13.3)	4 (10.3)	7 (15.9)	0.448
Hemodialysis	33 (39.8)	15 (38.5)	18 (40.9)	0.820
Mechanical ventilation	43 (51.8)	8 (20.5)	35 (79.5)	**<0.001**
Endotracheal intubation	32 (38.6)	5 (12.8)	27 (61.4)	**<0.001**
Tracheotomy	3 (3.6)	1 (2.6)	2 (4.5)	1.000

Values highlighted in bold represent statistically significant P values ($P < 0.05$).
AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; IVIG, intravenous immunoglobulin.

Mortality and Predictors of In-ICU Mortality for AAV Patients

In total 44 patients deceased in ICU, representing a mortality rate of 53%. The main cause of death was infection (27/44, 61.4%) followed by active vasculitis (15/44, 34.1%). The remaining two patients deceased of other reasons. One was suffering from cachexia due to advanced esophageal cancer while the other deceased of respiratory arrest due to cerebral hernia. When further analyzing the association between in-ICU death and respiratory failure, 36 patients (81.8%) died of respiratory failure with the causes of active vasculitis (13/36, 36.1%) or pulmonary infection (23/36, 63.9%). However, 18 patients (18/36, 50.0%) actually deceased of respiratory failure accompanied with renal failure or heart failure. Mortality rates among MPA (54.3%), GPA (45.5%) and EGPA (50%) were similar with no statistical difference. Mortality rates were comparable ($P = 0.056$) among different causes of ICU admission, including active vasculitis (52.5%), infection (54.3%) and other reasons (50.0%).

To identify the possible factors influencing the risk of in-ICU death for AAV patients, univariate and multivariate logistic regression analysis was performed (**Table 5**). Univariate logistic regression analysis found that APACHE II, BVAS, hemoglobin, pneumonia, pulmonary arterial hypertension, stroke, respiratory failure and shock were significantly associated with in-ICU death. The multivariate logistic regression analysis of the eight independent variables indicated that APACHE II ($OR = 1.333$, 95% CI: 1.031–1.722, $P = 0.028$) and respiratory failure ($OR = 620.452$, 95% CI: 11.495–33490.306, $P = 0.002$) were associated with in-ICU mortality. However, hemoglobin ($OR = 0.919$, 95% CI: 0.849–0.995, $P = 0.037$) was adversely associated with in-ICU mortality of AAV patients. The cut-off value of APACHE II was 14.5 determined by the ROC curve, with sensitivity of 79.5% and specificity of 79.5%. Besides, APACHE II more than 14.5 was significantly associated with in-ICU mortality ($OR = 12.963$, 95% CI: 4.560–36.849, $P < 0.001$).

TABLE 5 | Risk factors of in-ICU mortality for AAV patients.

	Univariate logistic analysis		Multivariate logistic analysis	
	***OR*(95% *CI*)**	***P*-value**	***OR*(95% *CI*)**	***P*-value**
APACHE II	1.311 (1.161–1.479)	**<0.001**	1.333 (1.031–1.722)	**0.028**
BVAS	1.129 (1.061–1.202)	**<0.001**	0.823 (0.663–1.020)	0.076
Hemoglobin	0.979 (0.961–0.997)	**0.023**	0.919 (0.849–0.995)	**0.037**
AST	1.010 (0.993–1.027)	0.257	-	-
TBil	1.060 (0.984–1.142)	0.122	-	-
BUN	1.018 (0.989–1.047)	0.238	-	-
CNI	8.931 (0.386–206.485)	0.172	-	-
PCT	1.013 (0.976–1.051)	0.502	-	-
BGA-pH	0.041 (0.001–2.221)	0.117	-	-
Anemia	3.448 (0.984–12.086)	0.053	-	-
Pneumonia	6.300 (1.269–31.273)	**0.024**	241.791 (0.393–148,792.713)	0.094
Renal insufficiency	2.431 (0.916–6.451)	0.075	-	-
Glomerulonephritis	2.143 (0.886–5.183)	0.091	-	-
PAH	14.250 (1.756–115.613)	**0.013**	7.486 (0.128-436.908)	0.332
Stroke	6.937 (1.443–33.344)	**0.016**	18.511 (0.349–980.626)	0.150
Respiratory failure	70.000 (14.102–347.479)	**<0.001**	620.452 (11.495–33490.306)	**0.002**
Shock	24.342 (5.204–113.870)	**<0.001**	22.365 (0.965–518.384)	0.053

Values highlighted in bold represent statistically significant P values (P < 0.05).
AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; BVAS, Birmingham vasculitis active scoring system; AST: aspartate aminotransferase; TBil: total bilirubin; BUN, blood urea nitrogen; CNI, cardiac troponin I; PCT, procalcitonin; BGA-pH, blood gas analysis-power of hydrogen; PAH, pulmonary arterial hypertension.

TABLE 6 | Characteristics of 19 AAV patients with diffuse alveolar hemorrhage.

Characteristics	Total (*n* = 19)	Survivors (*n* = 7)	Non-survivors (*n* = 12)	*P*-value
Demographics				
Age (years, mean ± SD)	63 ± 13	61 ± 13	64 ± 14	0.702
Female gender (n, %)	11 (57.9)	3 (42.9)	8 (66.7)	0.377
Classification of AAV (*n*, %)				0.305
MPA	14 (73.7)	4 (57.1)	10 (83.3)	
GPA	5 (26.3)	3 (42.9)	2 (16.7)	
EGPA	0 (0)	-	-	
Autoantibodies (*n*, %)				0.305
c/PR3-ANCA	5 (26.3)	3 (42.9)	2 (16.7)	
p/MPO-ANCA	14 (73.7)	4 (57.1)	10 (83.3)	
Newly diagnosed as AAV (*n*, %)	15 (78.9)	5 (71.4)	10 (83.3)	0.603
Length of stay in ICU (day), M (Q1-Q3)	6 (2–11)	6 (2–11)	6 (2-8)	0.670
Clinical manifestations (*n*, %)				
Hemoptysis	9 (47.4)	4 (57.1)	5 (41.7)	0.650
Cough	10 (52.6)	3 (42.9)	7 (58.3)	0.650
Respiratory failure	14 (73.7)	3 (42.9)	11 (91.7)	**0.038**
Renal insufficiency	14 (73.7)	4 (57.1)	10 (83.3)	0.305
Heart failure	15 (78.9)	5 (71.4)	10 (83.3)	0.603
Shock	6 (31.6)	0 (0)	6 (50.0)	**0.044**
Anemia	18 (94.7)	6 (85.7)	12 (100)	0.368
Infection	18 (94.7)	6 (85.7)	12 (100)	0.368
Disease and severity assessment scores				
APACHE II, M (Q1–Q3)	15 (11–18)	10 (9–14)	16 (14-26)	**0.008**
BVAS, M (Q1–Q3)	24 (21-30)	20 (15-26)	25 (23-32)	0.127
In-ICU management				
Mechanical ventilation	11 (57.9)	2 (28.6)	9 (75.0)	0.074
Endotracheal intubation	7 (36.8)	1 (14.3)	6 (50.0)	0.173
Plasma exchange	4 (21.1)	2 (28.6)	2 (16.7)	0.603
Hemodialysis	8 (42.1)	3 (42.9)	5 (41.7)	1.000
Catecholamines	7 (36.8)	0 (0)	7 (58.3)	**0.017**
Glucocorticoids	14 (73.7)	6 (85.7)	8 (66.7)	0.603
Pulsed methylprednisolone	6 (31.6)	2 (28.6)	4 (33.3)	1.000
Cyclophosphamide	0 (0)	-	-	-
IVIG	6 (31.6)	4 (47.1)	2 (16.7)	0.129

Values highlighted in bold represent statistically significant P values (P < 0.05).
AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; c/PR3-ANCA, cytoplasmic or proteinase-3 antineutrophil cytoplasmic antibody; p/MPO-ANCA: perinuclear or myeloperoxidase antineutrophil cytoplasmic antibody; APACHE II, Acute Physiology and Chronic Health Evaluation II; BVAS, Birmingham vasculitis active scoring system, IVIG, intravenous immunoglobulin.

Characteristics of AAV Patients With Diffuse Alveolar Hemorrhage

As one of common causes for ICU admission and respiratory failure, further analysis of patients with DAH was presented (**Table 6**). In total, 19 patients (22.9%) suffered from DAH in our study, among whom 12 (63.2%) died in the ICU. Eleven patients (57.9%) were female, with a mean age of 63 ± 13 years of all the patients. All of the patients complicated with DAH were ANCA positive (p/MPO-ANCA positive: 73.7%, and c/PR3-ANCA positive: 26.3%). The groups between non-survivors and survivors were similar regarding gender, age, classification of AAV and ANCA types. Most of the patients (78.9%) were newly diagnosed with AAV, with DAH occurring as the first manifestation. Hemoptysis was presented in 47.4% and cough was presented in 52.6%. Fourteen patients (73.7%) suffered from respiratory failure and 14 (73.7%) were accompanied with renal insufficiency. More non-survivors suffered from respiratory failure (91.7% vs. 42.9%) and shock (50.0% vs. 0%) than survivors. The median of APACHE II score at ICU admission

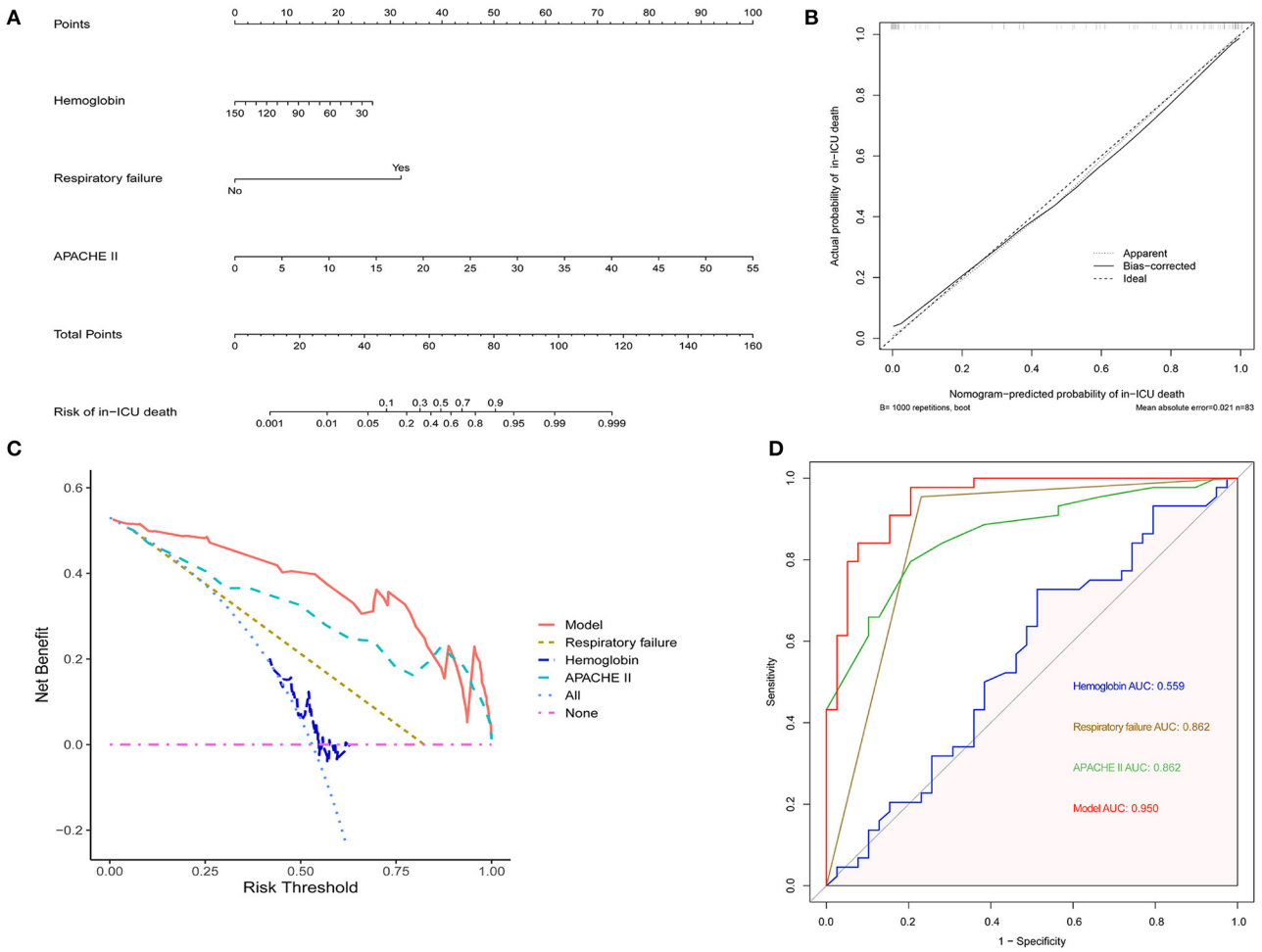

FIGURE 2 | The establishment of nomogram to predict in-ICU mortality of AAV patients. **(A)** The nomogram for predicting in-ICU mortality of AAV patients. **(B)** Calibration curve of the nomogram. **(C)** DCA of the nomogram. **(D)** ROC curves comparing the nomogram with APACHE II, hemoglobin and respiratory failure. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; DCA, decision curve analysis; ROC, receiver operating characteristic; AUC, area under curve.

was higher in non-survivors' group [16 (14–26)] than that in survivors' group [10 (9–14)], whereas the median of BVAS scores were comparable between the two groups.

Among 11 patients (57.9%) who required mechanical ventilation, endotracheal intubation was performed in 7 (36.8%). Four patients (21.1%) were treated with plasma exchange and 8 (42.1%) with hemodialysis, while no statistical difference was detected between non-survivors' and survivors' groups. A significantly higher proportion of non-survivors (58.3%) needed catecholamines than survivors (0%). Fourteen patients (73.7%) were administered with glucocorticoids, among whom 6 (31.6%) received pulsed methylprednisolone. All of the 12 non-survivors deceased of respiratory failure, mainly due to active vasculitis or infection complications. Among the remaining seven survivors, one patient suffered from DAH relapse 2 months after admission to the ICU.

Establishment of a Nomogram for Predicting the Risk of In-ICU Mortality for AAV Patients

To further evaluate the in-ICU death risk of AAV patients, a nomogram was developed based on independent factors of in-ICU mortality by multivariate logistic regression analysis (**Figure 2A**). The calibration curve of the established nomogram for the prediction of in-ICU death risk of AAV patients demonstrated good agreement in this cohort (**Figure 2B**). The results of DCA showed that the established nomogram had a good net benefit and a wide range of threshold probability (**Figure 2C**). The comparison of different ROC indicated that the established nomogram had a better predictive value (**Figure 2D**). Therefore, the nomogram we established has a significant clinical use.

Long-Term Outcome of AAV Patients

Given the relatively high in-ICU mortality in our study, we further explored the long-term outcome of 39 patients that survived to the first ICU stay (**Figure 3**). Twelve patients (30.8%) deceased within 3 months after admission to the ICU. Kaplan–Meier analysis showed that the cumulative survival rates of 39 patients at 0.5, 1, and 5 years were 58.3%, 54.2%, and 33.9%, respectively (**Figure 3A**), and the median survival time was 14 months. The renal survival rates at 0.5, 1, and 5 years were 100%, 74.6%, and 56.8%, respectively (**Figure 3B**). During the follow-up period, 20 patients died, with the overall mortality of 51.3%. ESRD occurred in seven patients (36.8%) among the remaining 19 survivors, with one patients survived with a transplanted kidney and the others received long-term renal-replacement therapy.

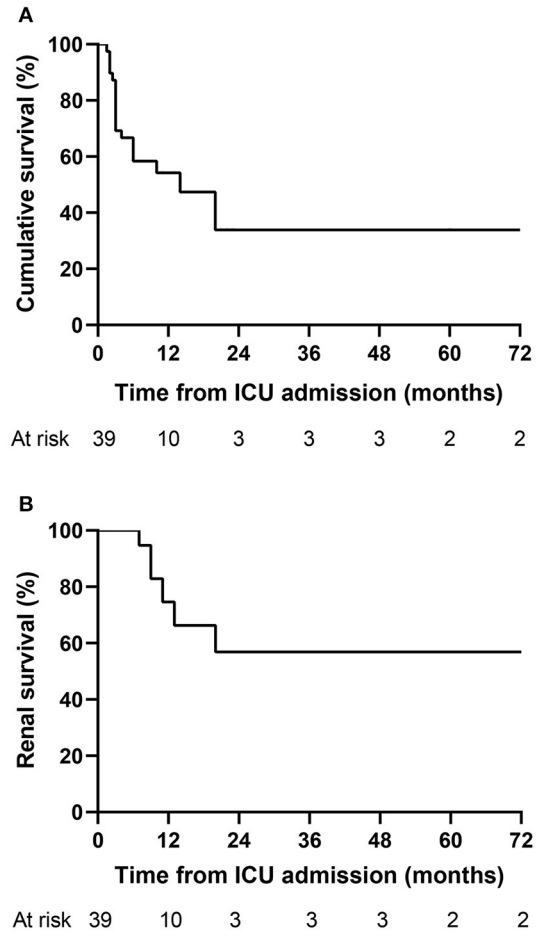

FIGURE 3 | Kaplan–Meier curves for the long-term outcome of AAV patients. **(A)** Cumulative survival of 39 patients that survived to the first ICU stay. **(B)** Renal survival of 39 patients that survived to the first ICU stay. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ICU, intensive care unit.

DISCUSSION

AAV is one of common systemic rheumatic diseases (SRD) requiring ICU admission (9, 32) and represents a challenge in the ICU. Despite the improvement of therapeutic strategies, the in-ICU mortality of AAV is still high, ranging from 15.5% to 58.8% (8, 11, 12). Several studies have focused on the outcome of AAV patients in the ICU (6, 8, 11, 17, 33). However, most of them are small-sized and data for the Asian populations are lacking. Here, we conducted a single-center, retrospective study in a tertiary medical institution of China, to analyze the clinical features of AAV patients admitted to the ICU and explore the risk factors of in-ICU mortality. A nomogram was established using the identified risk factors to predict the risk of in-ICU mortality of AAV patients.

In this study, active vasculitis was identified as the leading cause of ICU admission. Active vasculitis mainly included diseases such as acute renal insufficiency, diffuse alveolar hemorrhage and pulmonary-renal syndrome. A multicenter retrospective study showed that the main reason of AAV patients admitted to the ICU was respiratory failure due to massive hemoptysis (11). Frausova et al. (6) illustrated in their study that the most frequent cause of ICU admission was active vasculitis with pulmonary-renal syndrome. The manifestations of AAV are various, including non-specific clinical symptoms like weight loss, malaise, arthralgia and myalgia (2), while some patients may manifest with severe or life-threatening diseases thereby requiring ICU admission. Therefore, AAV should be considered as a possible diagnosis if a patient admitted to the ICU has unexplained severe systemic manifestations, mainly pulmonary or renal failure.

Infection was reported in the majority of our patients during the ICU, with pneumonia being the most common diagnosis. Since AAV patients are usually treated with high doses of glucocorticoids accompanied with immunosuppressive therapies, opportunistic infections, such as *Pneumocystis carinii*, *Aspergillus* and *Cytomegalovirus* are frequently observed (7). In addition, invasive operations like endotracheal intubation, central venous catheterization may lead to nosocomial infections (6, 34). In this study, the most common infectious pathogens were *Acinetobacter baumannii*, *Candida albicans*, *Klebsiella pneumonia* and *Aspergillus*, mainly belonging to Gram-negative bacteria and Fungi. Some studies illustrated that Gram-negative bacteria were the most frequent pathogens (8, 11). Other studies did not show a significant predominance of pathogens (34, 35) probably due to small sample size and insufficient data. Therefore, there is a need to test for more infectious pathogens in AAV patients admitted the ICU.

For AAV patients, the most commonly and severely affected systems are the respiratory and renal systems. Main presentations of pulmonary involvement may be various among different AAV categories (36–38). The study of Hruskova et al. demonstrated that severe DAH was more frequent in c/PR3-ANCA than p/MPO-ANCA-positive patients (67.9% vs. 32.1%) (39). The prevalence of DAH was comparable between the groups of PR3-AAV and MPO-AAV in the Rituximab in ANCA-associated Vasculitis (RAVE) trial (40). Although 73.7% of patients with DAH was p/MPO-ANCA-positive in our study, more c/PR3-ANCA-positive patients suffered from DAH when we further

analyzed in different types of ANCAs. However, some studies reported that DAH was more frequent in MPA or p/MPO-ANCA-positive patients compared to GPA (37, 41). ILD was reported to be more common in MPA or p/MPO-ANCA-positive patients (42, 43). Our study revealed a higher prevalence of ILD in p/MPO-ANCA-positive patients, though failing to present a statistical significance. However, more researches regarding heterogeneity of pulmonary presentations are needed in the future. In our study, the majority of patients suffered from renal insufficiency. However, no significant difference was found between in-ICU non-survivors and survivors in renal insufficiency possibly because of timely renal replacement therapy performed for most of the patients during the ICU. Previous studies demonstrated that renal involvement was associated with worse long-term prognosis of AAV patients (41, 44), highlighting the importance of earlier diagnosis and prompt therapy.

The in-ICU mortality of our study group was 53%, which was comparable with the study results of Biscetti et al. (17) and Befort et al. (34). However, other studies have reported results of ICU mortality rates that are inconsistent with ours (6, 11, 45). The major reasons may be the heterogeneity of the included population and different follow-up durations. Similar to the results of our study, infection was the most frequent reason of in-ICU death in previous studies (6, 34). Besides, ICU mortality was higher in AAV patients admitted for infectious complication than for exacerbation of rheumatic diseases (46), though which was not significant in our study. As reported by Flossmann et al., infection was one of main causes of death within (48%) and after (20%) the first year (5). Therefore, it is necessary for clinicians to test sputum, blood, urine and catheters in order to identify and treat infections timely.

Identification of the predictors of in-ICU mortality of AAV patients is vital. We identified eight factors related to in-ICU mortality by univariate logistic analysis. However, when incorporating all of them in the multivariate logistic analysis, only APACHE II and respiratory failure were associated with an increased risk of in-ICU mortality while hemoglobin was an independent protective factor. Today, administration with glucocorticoids accompanied with cyclophosphamide or rituximab is still highly recommended for remission induction in AAV patients (22). However, immunosuppressive drugs are not routinely prescribed for severe vasculitis in ICU, possibly due to less awareness of the underlying disease or the worry of severe side effects concerning the immunosuppressant, including infections, bone marrow suppression and hemorrhagic cystitis (47, 48). In our study, only two patients received cyclophosphamide during ICU admission. Most of the patients suffered from infection at the moment of or during ICU admission, so physicians in ICU always considered prudently and were hesitant to prescribe immunosuppressive agents, such as cyclophosphamide. Mechanical ventilation, endotracheal intubation and administration of catecholamine were considered as necessary therapeutic measures in this study. Therefore, these therapies were not included in logistic regression analysis. The APACHE II is a simple and accurate assessment system of the severity of disease in critically ill patients (14). Several studies reported a higher APACHE II score for non-survivors of AAV patients (6, 11, 35). This indicated that APACHE II could be used to predict the outcome of AAV patients admitted to the ICU.

Respiratory failure, probably resulting from diffuse alveolar hemorrhage or pulmonary fibrosis accompanied with severe pneumonia, was another independent risk factor of in-ICU death. In a study that focused on the outcome of rheumatology patients with acute respiratory failure, the in-ICU mortality rate was high (59.8%), and vasculitis was associated with increased mortality (49). Ozdemir et al. showed in their study that 5 (25.0%) patients died of respiratory failure, with massive hemoptysis (four patients) and resistant pulmonary edema (one patient) (11). Demiselle et al. reported that in-ICU death of five patients (33.0%) was attributed to multiple organ failure likely due to sepsis (12). As respiratory failure was one of independent risk factors in our study, it was also a vital cause of in-ICU death among the non-survivors. Patients with DAH had a higher mortality (63.2%) compared with the overall mortality (53.0%) of all the patients in our study. All of them deceased of respiratory failure, further highlighting the importance of vigilance and prompt therapy to it. Arterial blood gas analysis is a convenient and direct way to monitor the saturation and pressure of oxygen. It can also be used to compute the oxygenation index (PaO_2/FiO_2). So arterial blood gas analysis may be helpful for clinicians to monitor if the AAV patients are suffering from respiratory failure and try to remove the pathogenic factors in time.

In this study, hemoglobin was an independent protective factor from ICU mortality. Most of the patients in our cohort suffered from anemia. Chronic anemia may result from renal involvement. Additionally, a higher proportion of non-survivors had diffuse alveolar hemorrhage and sepsis which might lead to reduced hemoglobin in a short duration. Ge et al. illustrated that a lower hemoglobin level (<90 g/L) was significantly associated with a greater risk for poor renal survival in patients with MPO-ANCA-associated glomerulonephritis (50). Flossmann et al. revealed that lower hemoglobin was one of significant negative prognostic factors for AAV patients' long-term survival (5). However, whether hemoglobin is associated with higher in-ICU mortality need to be further studied. The BVAS comprises ten systems and is used to assess disease activity of AAV (21). In this study, BVAS was not associated with mortality risk in multivariate analysis. However, Biscetti et al. (17) found that BVAS>10 in ICU might be a practical tool to predict in-ICU mortality. Befort et al. (34) reported that BVAS score (OR = 1.16, 95% CI: 1.01–1.34) was predictive of mortality in the ICU. However, more research is needed to establish whether BVAS can be used to predict the outcome of AAV patients in the ICU.

This study has several limitations which can form the basis for further research. Firstly, this is a single-center, retrospective study. Therefore, information bias maybe exists. As a consequence, our results as well as the established nomogram need to be interpreted cautiously. Secondly, due to the relatively high in-ICU mortality in our study, a relatively small number of patients were remained during the follow-up. Therefore, predictive factors of long-term prognosis for critically ill AAV patients should be further explored in a larger cohort. The results

in our study should be confirmed by multi-center and prospective clinical research studies in the future.

CONCLUSION

In this study, active vasculitis was identified as the most common reason for ICU admission. The in-ICU mortality of AAV patients was 53%. The main cause of in-ICU death was infection. APACHE II and respiratory failure were independent risk factors while hemoglobin was an independent protective factor of in-ICU deaths for AAV patients admitted to the ICU. Finally, a simple model for predicting in-ICU mortality of AAV patients was established for clinical application.

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 Ethical Committee of the First Affiliated Hospital of Zhengzhou University. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

SL, YZ, and JG conceived and participated in the design of the study. YZ, PZ, XD, and LZ collected the clinical data of patients. YZ, PZ, XS, and NG analyzed the data. SL, LZ, and XS performed the conceptualization. The manuscript was written by YZ and JG. All authors 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.2021.762004/full#supplementary-material

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Implementation of the ABCDEF Bundle for Critically Ill ICU Patients During the COVID-19 Pandemic: A Multi-National 1-Day Point Prevalence Study

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Background: Data regarding delivery of evidence-based care to critically ill patients in Intensive Care Units (ICU) during the COVID-19 pandemic is crucial but lacking. This study aimed to evaluate the implementation rate of the ABCDEF bundle, which is a collection of six evidence-based ICU care initiatives which are strongly recommended to be incorporated into clinical practice, and ICU diaries for patients with and without COVID-19 infections in ICUs, and to analyze the impact of COVID-19 on implementation of each element of the bundle and independent associated factors.

Methods: A world-wide 1-day point prevalence study investigated the delivery of the ABCDEF bundle and ICU diary to patients without or with COVID-19 infections on 27 January 2021 *via* an online questionnaire. Multivariable logistic regression analysis with adjustment for patient demographics evaluated the impact of COVID-19 and identified factors in ICU administrative structures and policies independently associated with delivery.

Results: From 54 countries and 135 ICUs, 1,229 patients were eligible, and 607 (49%) had COVID-19 infections. Implementation rates were: entire bundle (without COVID-19: 0% and with COVID-19: 1%), Element A (regular pain assessment: 64 and 55%), Element B (both spontaneous awakening and breathing trials: 17 and 10%), Element C (regular sedation assessment: 45 and 61%), Element D (regular delirium assessment: 39 and 35%), Element E (exercise: 22 and 25%), Element F (family engagement/empowerment: 16 and 30%), and ICU diary (17 and 21%). The presence of COVID-19 was not associated with failure to implement individual elements. Independently associated factors for each element in common between the two groups included presence of a specific written protocol, application of a target/goal, and tele-ICU management. A lower income status country and a 3:1 nurse-patient ratio were significantly associated with non-implementation of elements A, C, and D, while a lower income status country was also associated with implementation of element F.

Conclusions: Regardless of COVID-19 infection status, implementation rates for the ABCDEF bundle, for each element individually and an ICU diary were extremely low for patients without and with COVID-19 infections during the pandemic. Strategies to facilitate implementation of and adherence to the complete ABCDEF bundle should be optimized and addressed based on unit-specific barriers and facilitators.

Keywords: ABCDEF bundle, COVID-19, ICU diary, ICU liberation bundle, pandemic (COVID-19)

INTRODUCTION

For patients in the intensive care unit (ICU), evidence-based treatment such as the ABCDEF bundle (1–4) and ICU diary (5), should be established as part of routine clinical practice because they are strongly linked not only to short-term outcomes of ICU patients (6, 7) but also their long-term function and quality of life (QOL) (8). Recent studies confirmed that the beneficial effects of the ABCDEF bundle are maximized when provided as a combination of elements or as the entire bundle (9, 10).

However, drastic changes in practice related to the COVID-19 pandemic, including unbalanced resources, overwhelmed facility capacity, and strict infectious regulations, occurred world-wide and prevented ICU staff from performing evidence-based approaches to patient care in ICUs (11). Our recent survey demonstrated low implementation rates of each element and the entire ABCDEDF bundle and other supportive ICU care for patients with COVID-19 infections in the ICU (12). We could not assess the total impact of COVID-19 in the ICU because of a lack of data on patients without COVID-19 infections. To overcome low implementation rates which result in poor outcomes of ICU patients (13), a number of studies proposed efficient ways associated with the ICU administrative structure and environment to promote evidence-based ICU care before the pandemic (14–16). Nonetheless, clinical data on promoting factors and barriers during the pandemic are lacking and these factors could vary when treating patients without or with COVID-19 infections because the policy of less physical contact in a short time while wearing protective personal equipment was generally enforced only for patients with COVID-19 infections. Moreover, low- and middle-income countries are more vulnerable to these resource-dependent changes (17).

Therefore, we conducted a 1-day point prevalence study, to investigate the implementation rate of evidence-based ICU care for both patients without and with COVID-19 infections and the impact of COVID-19 infections on implementation on a world-wide scale to capture the current clinical practice situation. We sought to identify ICU-related factors associated with implementation in the ICU.

MATERIALS AND METHODS

Study Design and Settings

This was an international 1-day point prevalence study conducted on 27 January 2021, with approval by the ethics committee of the Saiseikai Utsunomiya Hospital (2020-69) and pre-registration in UMIN (ID: 000040405). The study design and construction followed the STROBE cross-sectional guidelines.

The study committee recruited participants from January 8 to 26 by disseminating an invitation letter to members of the Indian Society of Critical Care Medicine, the Korean Society of Critical Care Medicine, and other local or national networks in collaboration with regional/national coordinators (**Appendix 1**). The invitation letter included a brief introduction of this study, a specific link to the web site explaining the study details (https://form.jsea2005.org/isiic-II-study/), ethical considerations, and the URL for registration created by Google Forms (Google Inc.). According to the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan (18), ethical approval at each participating institution was waived because of the anonymous nature of this study which will not collect specific

data that could identify ICUs or individual patients. All ICUs which agreed to the study policies could register and there were no exclusion criteria. The name of one representative for each participating ICU, the name of the hospital, and its country were registered to confirm the reliability of data sources (**Appendix 1**).

Study Process

The study committee requested all registered representatives to provide background data for their hospitals and ICUs *via* a Google Form starting 20 January 2021, before the survey date. The questionnaire used to obtain background data (e.g., number of hospital beds, ICU beds, COVID-19 specific ICU beds, nurse-to-patient ratio) is shown in **Appendix 2** (18 questions, 3 min). The income level was classified according to the World Bank Country Classification (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups) according to the country where the participating ICUs are located, which was obtained as the background data. Each representative received a different Facility Registration Number automatically soon after the completion of the questionnaire. On the survey date, 27 January 2021, the URL for the survey of evidence-based and supportive ICU care (21 questions, 3–5 min, Google Form) were sent to all registered representatives. All representatives were asked to input the institution-specific Facility Registration Number at the first question, and only those who had it could continue to complete the survey (**Appendix 3**). The questions in the survey were pre-reviewed by the study co-authors and pre-tested by collaborative physicians and nurses listed in the acknowledgment. The URL for the survey was open from January 27 to 30.

Data Collection

In the survey, patient demographics, such as age, gender, Body Mass Index (BMI), and ICU length of stay as of the survey date, use of medical devices, continuous use of neuromuscular blockade, vasoactive, analgesia, and sedation agents, prone positioning and its duration, the presence of a target/goal of each ICU care modality given to ICU patients on the survey date, and the implementation of each element of the ABCDEF bundle, ICU diary provided on the survey data were collected. The operational definitions of each element of the ABCDEF bundle and ICU diary (**Table 1**) were provided to respondents at the appropriate place in the survey. The representatives completed one questionnaire for each patient, except for patients who were terminally ill and receiving palliative care. For example, if there were three ICU patients in the ICU, the representative needed to complete the questionnaire for the survey of evidence-based and supportive ICU care three times. Data obtained from the survey were anonymous both for patients and institutions, the data of evidence-based and supportive ICU care was linked to data of the background data for their hospitals and ICUs by the facility-specific Facility Registration Number.

All the data were stored online (Google Drive, Google Inc.) and managed or exported by the authorized person out of the authors (**Appendix 1**).

TABLE 1 | Operational definitions of evidence-based and supportive ICU care.

Elements of the ABCDEF bundle	Operational definition
Element A[a,b]	Regular standardized **PAIN** assessment using valid and reliable pain assessment scales six times or more per day. The pain assessment scales include Numerical Rating Scale (NRS), Critical-care Pain Observation Tool (CPOT), Behavioral Pain Scale (BPS), and others.
Element B[a,b]	Both **SPONTANEOUS AWAKENING TRIALS** and **SPONTANEOUS BREATHING TRIALS**. The spontaneous awakening trial is cessation of sedatives and narcotics or similar protocols to evaluate consciousness. The spontaneous breathing trial is to turn the respiratory rate to zero with eight or less of pressure support ventilation or similar local protocol to evaluate whether the patient meets the requirements for extubation.
Element C[a,b]	Regular standardized **SEDATION** assessment using valid and reliable sedation assessment scales (※4) six times or more per day. The sedation assessment scales include Richmond Agitation- Sedation Scale (RASS), Sedation-Agitation Scale (SAS), Ramsay Sedation Scale, and others.
Element D[a,b]	Regular standardized **DELIRIUM** assessment using valid and reliable delirium monitoring tools (※5) two times or more per day. The delirium assessment tools include Confusion Assessment Method for ICU (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), and others.
Element E[a,b,c]	**MOBILITY** activities that were out of bed or higher. It is equal to a score of 4 or higher according to the Intensive Care Unit Mobility Scale[c] (i.e., dangling at edge of bed, standing at side of bed, walking to bedside chair, marching in place, walking in room or hall.).
Element F[a,b]	**FAMILY ENGAGEMENT AND EMPOWERMENT** that a family member/significant other of this patient is educated regarding the ABCDEF bundle and/or participates in at least one of the following: rounds; conference; plan of care; or ABCDEF bundle related care, e.g., re-orientation, calming talks etc. This element could be conducted in person or online.
Other ICU care	
ICU diary[d]	An **ICU DIARY** is a patient journal, written by staff and families for several purposes, and includes daily entries about what happened.

ICU intensive care unit. These definitions are based on the following references.
[a] *Pun et al. (13).*
[b] *Liu et al. (12).*
[c] *Hodgson et al. (19). IMS, 0: Nothing (lying in bed, passive exercise), 1: sitting in bed, exercises in bed; 2: passively moved to chair (no standing); 3: sitting over edge of bed; 4: standing; 5: transferring bed to chair; 6: marching in place (at bedside); 7: walking with assistance of two or more people; 8: walking with assistance of one person; 9: walking independently with a gait aid; 10: walking independently without a gait aid.*
[d] *Nydahl and Deffner (5).*

Outcomes

The primary outcome was the implementation rate of the entire ABCDEF bundle. Secondary outcomes were the implementation rates for each element of the ABCDEF bundle, including element A (regular pain assessment), element B [both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)], element C (regular sedation assessment), element D (regular delirium assessment), element E (early mobility and exercise), and element F (family engagement and empowerment), and an ICU diary.

The implementation of element E during mechanical ventilation, the implementation of element F performed online, and visitation policies for family members were also described. Independent factors associated with successful implementation of each element of the ABCDEF bundle were evaluated by multivariable logistic regression analysis.

Statistical Analysis

Non-normally distributed continuous data were reported as medians with interquartile range (IQR). Categorical data were described as numbers or percentages. Comparisons of patient demographics, implementation of the ABCDEF bundle, and the ICU diary between the groups of patients with out and with COVID-19 infections were made with the Mann-Whitney *U*-test for non-normally distributed continuous data and the chi-squared test and Fisher's exact test for categorical data appropriately. There was no missing data.

In multivariable logistic regression analysis with adjustment for patient demographics, the association between the implementation of each element of the ABCDEF bundle and the presence of COVID-19 infection or ICU administrative structures was investigated. Patient demographics included length of ICU stay, age, gender, body mass index, use of mechanical ventilation, extracorporeal membrane oxygenation including veno-venous and veno-arterial, renal replacement therapy, and left ventricular unloading device, continuous use of neuromuscular blockade, vasoactive drugs, analgesia agents and sedation agents, and prone positioning. The following variables were changed to factors and used in the multivariable logistic regression analysis: number of hospital beds, nurse-to-patient ratio, frequency of multidisciplinary rounds, number of visiting hours for a family, type of hospital and ICU, primary responsibility to make decisions to implement the ABCDEF bundle, age, body mass index, income level. As a sub-analysis, associated independent factors among ICU administrative structures for each group (non-COVID-19 and COVID-19) were evaluated through the stepwise method with Akaike information criterion and with adjustments of the same variables of patients demographics described above. The stepwise method was used to focus on significant factors. In the sub-analysis, the variables that the number of patients allocated to the category is too few ($\leq$5 patients) to create a suitable model were excluded from multivariable logistic regression analysis.

The calculated sample size with 95% power and a two-sided alpha of 0.05 was 508 patients under the assumption of the implementation rate of the entire ABCDEF bundle for patients without and with COVID-19 infections (8 and 1%, respectively) based on previous surveys (12, 13). All statistical analyses were carried out using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (20) and R (R Project, Vienna, Austria). The *p*-value was reported as two-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Background of Hospitals and ICUs

Of 283 registered ICUs, 135 ICUs completed the survey (response rate 48%) (**Figures 1**, **2**). Respondents included 78% physicians.

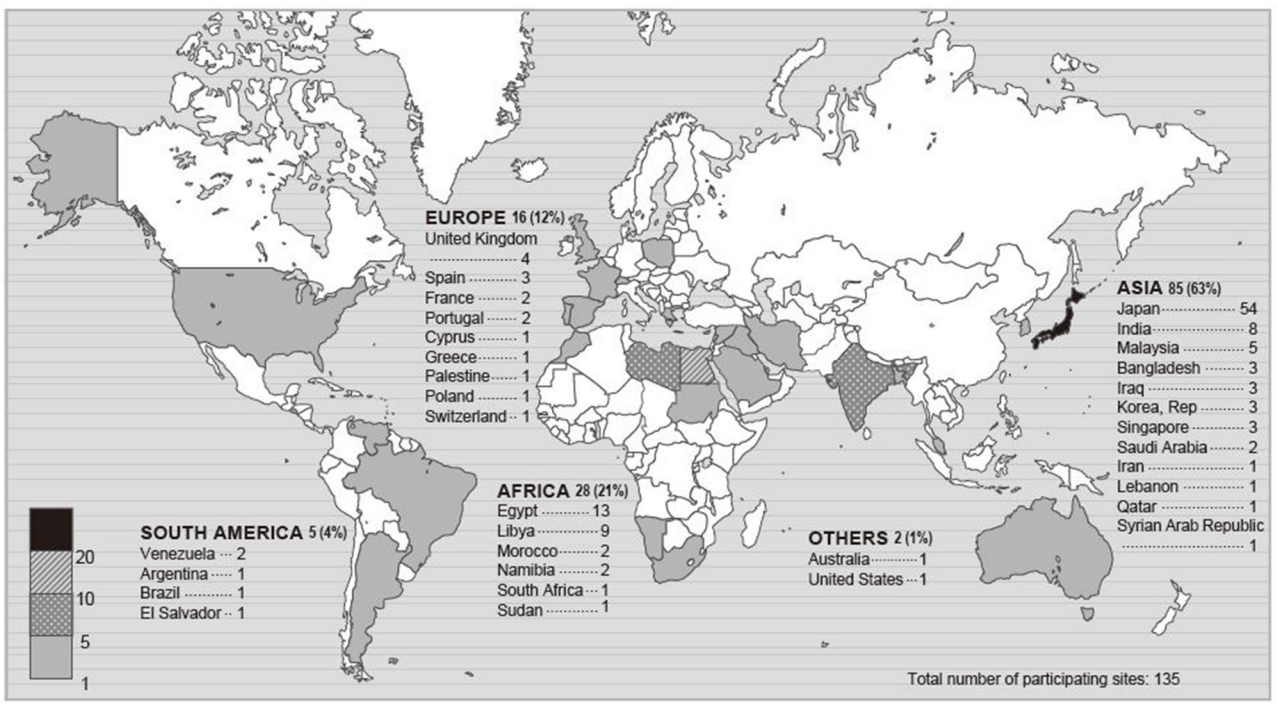

FIGURE 1 | Map of participating sites. The numbers in this figure indicate the number of participating ICUs in each country or a percentage. Percentage indicates the proportion of the total participating ICUs.

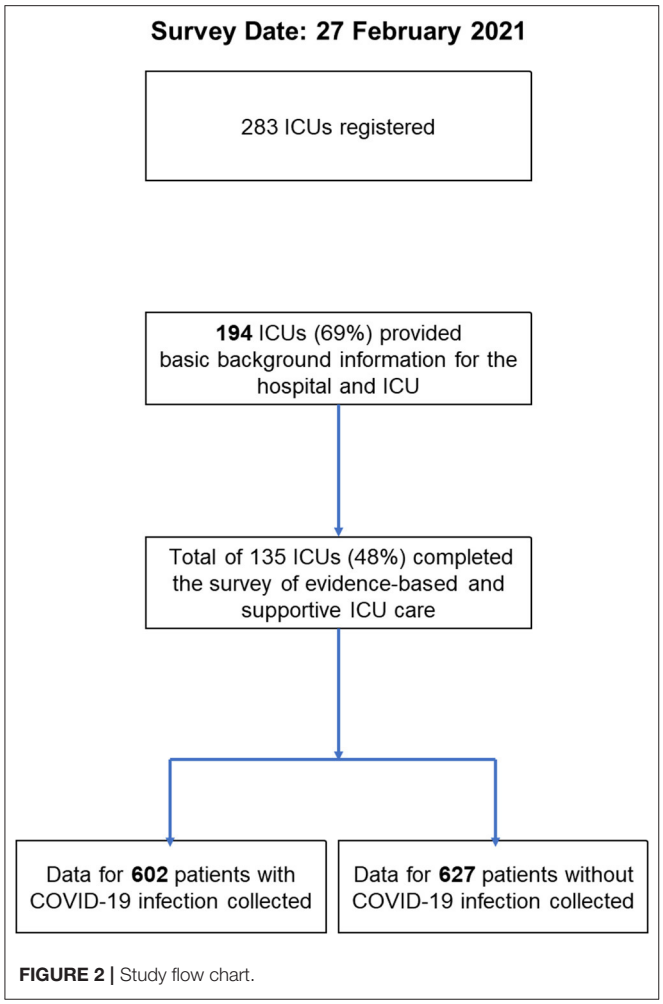

FIGURE 2 | Study flow chart.

The most common size of participating hospitals was 800 beds or more, with a median of 14 ICU beds and 4 beds allocated for patients with COVID-19 infections (**Table 2**). The nurse: patient ratio was 1:2 in 53% of ICUs. Multidisciplinary rounds were conducted significantly less frequently for patients with COVID-19 infections ($p = 0.004$). Compared to before the pandemic, family visiting hours to patients both without and with COVID-19 infection were reduced (<0.001 and $p = 0.004$, respectively), and more stringent restrictions imposed on families of patients with COVID-19 infections ($p < 0.001$). A specific protocol for each element of the ABCDEF bundle was in place in <50% of ICUs except for a protocol for pain management (51%).

The details of the types of hospitals and ICUs participating, professionals dedicated to the ICU, and the personnel with primary responsibility for implementing the ABCDEF bundle are shown in **Supplementary Table 1**.

Patient Demographics

There were significant differences in the demographics of the two groups for ICU length of stay, age, BMI, gender, use of mechanical ventilation (49 vs. 66%) and left-ventricular

TABLE 2 | Background, administrative structure, and policies of participating hospitals and ICUs.

Characteristic	Participating ICUs (n = 135)
Number of hospital beds (beds), *n* (%)	
x < 200	21 (16%)
200 ≤ x < 400	19 (14%)
400 ≤ x < 600	27 (20%)
600 ≤ x < 800	26 (19%)
x ≥ 800	42 (31%)
Total number of ICU beds (beds), median [IRQ]	14 [10–25]
ICU beds exclusively for patients with COVID-19 infection (beds), median [IRQ][a]	4 [2–10]
Number of participating ICUs where tele-medicine is available	6 (4%)
Nurse-to-patient ratio, *n* (%):	
1	41 (30%)
2	72 (53%)
x ≥ 3	21 (16%)
Number of participating ICUs which belong to the following income level, *n* (%)[b]	
Low and lower middle-income countries	30 (22%)
Upper middle-income countries	26 (19%)
High income countries	79 (59%)
The frequency of multidisciplinary rounds for patients **WITH** COVID-19 in the ICU, *n* (%)	
Not applicable	35 (26%)
Daily	78 (58%)
Other frequency (at least once a week or a month)	22 (16%)
The frequency of multidisciplinary rounds for patients **WITHOUT** COVID-19 in the ICU, *n* (%)	
Not applicable	14 (10%)
Daily	91 (67%)
Other frequency (at least once a week or a month)	28 (21%)
Number of visiting hours in the ICU for a family per day **BEFORE** the COVID-19 pandemic (hours), *n* (%)	
No visiting hours available	9 (7%)
0< x <6	87 (64%)
6 ≤ x ≤ 24	39 (29%)
Number of visiting hours to a patient **WITHOUT** COVID-19 infection per day in the ICU **AFTER** the COVID-19 pandemic (hours), *n* (%)	
No visiting hours available	66 (49%)
0< x <6	64 (47%)
6 ≤ x ≤ 24	5 (4%)
Number of visiting hours to a patient **WITH** COVID-19 infection per day in the ICU **AFTER** the COVID-19 pandemic (hours), *n* (%)	
No visiting hours available	106 (79%)
0< x <6	26 (19%)
6 ≤ x ≤ 24	3 (2%)
Presence of a specific written protocol for each element of the ABCDEF bundle, *n* (%)	
Element A: Pain management	69 (51%)
Element B: Spontaneous Awakening Trial (SAT) management	47 (35%)
Element B: Spontaneous breathing trial (SBT) management	64 (47%)

(Continued)

TABLE 2 | Continued

Characteristic	Participating ICUs (n = 135)
Element C: Sedation management	66 (49%)
Element D; Delirium management	54 (40%)
Element E: Early mobility and exercise	61 (45%)
Element F: Family engagement and empowerment	13 (10%)
No written protocol associated with the ABCDEF bundle	18 (13%)

Data in table are presented as number (%) or median [Interquartile range]. ICU, intensive care unit; IQR, interquartile range.

[a]*Among 135 participating ICUs, 106 (79%) ICUs accommodated the ICU beds exclusively allocated for patients with COVID-19 infection.*

[b]*The income level was classified according to the World Bank Country and Lending Group. Available online at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed 4 March in 2021).*

unloading device, continuous use of neuromuscular blockade, analgesia and sedation agents, prone positioning, and its duration (**Table 3**). The two groups were not significantly different regarding the use of extracorporeal membrane oxygenation and renal replacement therapy and continuous use of vasoactive drugs (**Table 3**). The target/goal for pain control was less frequently applied to patients with COVID-19 infections and more sedation was given to them, while no difference was seen for early mobilization and rehabilitation.

Implementation of Evidence-Based ICU Care

The implementation of the entire ABCDEF bundle, including elements A, B, C, D, E, and F which targets patients undergoing mechanical ventilation and continuous sedation, was rarely performed for patients both without and with COVID-19 infections (without COVID-19: 0% vs. with COVID-19: 1%, $p = 0.53$) (**Table 4**). The rate was similar if one element of the six was excluded (2 vs. 3%, $p = 0.59$). Given elements A, C, D, E, and F which target all ICU patients, the implementation rate of all of these elements was low (1 vs. 3%. $P = 0.07$), even when one of the five was excluded (5 vs. 7%, $p = 0.08$).

Element A (64 vs. 55%), element B (17 vs. 10%), SAT (21 vs. 14%), and SBT (29vs. 16%) were implemented significantly less often for patients with COVID-19 infection, while element C (45 vs. 61%), element F (16 vs. 30%) and the online conduct of element F (4 vs. 21%), were performed significantly more frequently for patients with COVID-19 infections. There was no significant difference in the implementation of element D (39 vs. 35%), element E (22 vs. 25%), even while patients were undergoing mechanical ventilation (6 vs. 6%), and the ICU diary (17 vs. 21%). In-person visits were significantly less frequently allowed but online visits using electronic devices were more often used for the families of patients with COVID-19 infection.

Independent Factors Associated With Implementation of the ABCDEF Bundle

In multivariable regression analysis adjusted for baseline conditions, the presence of COVID-19 infection was not associated with non-implementation of individual elements of the bundle, but was significantly associated with implementation of elements D, E, and F (**Figure 3**).

Among ICU administrative structural elements, specific factors associated with implementation were identified for each element of the bundle. Element A: presence of a written protocol and a target/goal, management as a tele-ICU, the presence of dedicated intensivists, and responsibility by a multidisciplinary team. Element B (SAT): presence of a written protocol, management as a tele-ICU, and responsibility by a multidisciplinary team and intensivists. Element B (SBT): management as a tele-ICU, responsibility by a multidisciplinary team, intensivists, and nurses, and being in an upper-middle-income country. Element C: presence of a written protocol and a target/goal, management as a tele-ICU, and presence of dedicated intensivists. Element D: management as a tele-ICU, performing multidisciplinary rounds daily and at least once a week or month, presence of dedicated respiratory therapists, and responsibility by nurses. Element E: presence of a target/goal and visiting hours ($0 < x < 6$ h). Element F: management as a tele-ICU, visiting hours ($0 < x \leq 24$ h), presence of dedicated Intensivists, respiratory therapist, and nutritionist, and being in an upper-middle-income country.

In the sub-analysis, a variety of different independent factors were identified for patients without and with COVID-19 infections (**Figure 4**). The presence of a specific written protocol, application of a target/goal, and tele-ICU management were associated with implementation of elements of the bundle in both groups. For patients without and with COVID-19 infections, a 1:1 nurse-patient ratio and daily multidisciplinary round were not significant independent factors, and being in lower- and lower-middle-income countries and a 3:1 nurse-patient ratio were significantly associated with a lower rate of implementation of elements C and D for both groups and element A for those without COVID-19 infections.

DISCUSSION

This world-wide 1-day prevalence study demonstrates that implementation of the entire ABCDEF bundle, or its individual elements and an ICU diary for patients without and with COVID-19 infections is extremely low even though the implementation rate of specific individual elements of the ABCDEF bundle was different for the two groups. The presence of COVID-19 infection was not a factor preventing implementation. A variety of ICU-related factors were identified as independently associated facilitators or barriers for the implementation of the ABCDEF bundle, and these were different for each element, comparing patients without and with COVID-19 infections.

Implementation of the ABCDEF bundle is much lower in this study compared with that reported by a survey before

TABLE 3 | Comparison of demographics of patients without and with COVID-19 infections.

Variable	Patients without COVID-19 infection (n = 627)	Patients with COVID-19 infection (n = 602)	*P*-value
ICU length of stay (days), median [IQR]	5 [2–10]	9 [2–10]	<0.001
Age (years), *n* (%)			<0.001
x < 50	190 (30%)	107 (18%)	
50 ≤ x <60	90 (13%)	132 (22%)	
60 ≤ x <70	120 (19%)	193 (32%)	
x ≥ 70	227 (36%)	170 (28%)	
Gender (male), *n* (%)	391 (62%)	425 (70%)	0.003
Body mass index (kg/m^2), *n* (%)			<0.001
x < 18.5	84 (13%)	10 (2%)	
18.5 ≤ x <25	310 (49%)	150 (25%)	
25 ≤ x <30	155 (25%)	218 (36%)	
x ≥ 30	78 (12%)	224 (37%)	
Use of medical devices, *n* (%)			
Mechanical ventilation	306 (49%)	395 (66%)	<0.001
Extracorporeal membrane oxygenation[a]	18 (3%)	30 (5%)	0.076
Renal replacement therapy	66 (11%)	56 (9%)	0.505
Left ventricular unloading device (Impella®, IABP)	10 (2%)	1 (0%)	0.012
Patients receiving continuous use of neuromuscular blockade, *n* (%)	19 (3%)	159 (26%)	<0.001
Patients receiving continuous use of vasoactive drugs, *n* (%)	208 (33%)	186 (31%)	0.427
Patients receiving continuous use of analgesia agents, *n* (%)	291 (46%)	358 (59%)	<0.001
Patients receiving continuous use of sedation agents, *n* (%)	233 (37%)	356 (59%)	<0.001
Patients receiving prone positioning, *n* (%)	17 (3%)	209 (34%)	<0.001
Scheduled total number of hours of prone positioning (hours), *n* (%)			<0.001
0 hours (no performing)	191 (30%)	333 (55%)	
0 < x < 6	11 (2%)	58 (10%)	
6 ≤ x < 12	2 (0%)	38 (6%)	
12 ≤ x < 18	4 (1%)	57 (9%)	
18 ≤ x ≤ 24	0 (0%)	56 (9%)	
Not candidate (i.e., because of no respiratory failure)	419 (67%)	60 (10%)	
Presence of a target or goal applied to ICU patients on the survey date, *n* (%)			
Pain	255 (41%)	201 (33%)	0.009
Sedation	280 (45%)	393 (65%)	<0.001
Mobilization/Rehabilitation	296 (47%)	261 (43%)	0.187

Data in table are presented as median [Interquartile range] or number (%). ICU, intensive care unit; IQR, interquartile range; IABP, intra-aortic balloon pump.
[a]Among the 18 patients received extracorporeal membrane oxygenation WITHOUT COVID-19 infection 9 were Veno-Venous extracorporeal membrane oxygenation and 9 were Veno-Arterial extracorporeal membrane oxygenation. Among the 30 patients received extracorporeal membrane oxygenation WITH COVID-19 infection, 29 were Veno-Venous extracorporeal membrane oxygenation and 9 were Veno-Arterial extracorporeal membrane oxygenation.

the pandemic (13, 21), but similar to a survey conducted in the early stages of the COVID-19 pandemic on 3 June and 1 July 2020 (12) (**Table 5**). These results suggest that COVID-19 affects the care of not only patients with COVID-19 infections but also patients without COVID-19 infections and this effect may have been present since the beginning of the pandemic. Numerous studies strongly show that each element of the ABCDEF bundle or an ICU diary itself has a beneficial effect on patient outcomes (7, 22–26), while low and incomplete implementation can result in adverse outcomes including increased time of ventilatory support, longer ICU and hospital lengths of stay, increased incidence of delirium, functional disability, and increased medical costs and mortality (13, 27). Efficient ways to incorporate evidence-based ICU care into clinical practice during the pandemic are urgently needed. To note, the studies included in **Table 5** had various methods to collect data, hence the simple comparison might lead to the misleading. Further and continuous international surveys with same methodology are necessary to follow the implementation rate of the ABCDEF bundle in future. In addition, studies to investigate the effects of the ABCDEF bundle and other evidence-based ICU care are expected.

Differences in the implementation of elements of the ABCDEF bundle might be caused by differences in underlying

TABLE 4 | Comparison of implementation of evidence-based and supportive ICU care.

Variables	Total ICU patients (*n* = 1,229)	The patients without COVID-19 infection (*n* = 627)	The patients with COVID-19 infection (*n* = 602)	*P*-value
Primary outcomes: implementation of an entire or a synchronized form of the ABCDEF bundle				
Performing an entire of the ABCDEF bundle, *n* (%)[a]	2 (0%)	0 (0%)	2 (1%)	0.241
Performing any combinations of five of six elements: A, B, C, D, E, and F, *n* (%)[a]	15 (3%)	4 (2%)	11 (3%)	0.070
Performing an entire of the ABCDEF bundle except B, *n* (%)[b]	25 (2%)	8 (1%)	17 (3%)	0.068
Performing any combinations of four of five elements: A, C, D, E, and F, *n* (%)[b]	76 (6%)	31 (5%)	45 (7%)	0.075
Secondary outcomes: implementation of each element in the ABCDEF bundle				
Element **A**, *n* (%)	731 (59%)	400 (64%)	331 (55%)	0.002
Element **B:** both SAT and SBT[a]	67 (12%)	33 (17%)	34 (10%)	0.030
SAT under continuous sedation, *n* (%)[c]	98 (17%)	49 (21%)	49 (14%)	0.024
SBT during mechanical ventilation, *n* (%)[d]	154 (22%)	90 (29%)	64 (16%)	<0.001
Element **C**, *n* (%)	650 (53%)	283 (45%)	367 (61%)	<0.001
Element **D**, *n* (%)	452 (37%)	244 (39%)	208 (35%)	0.124
Element **E**, *n* (%)	175 (14%)	77 (12%)	98 (16%)	0.050
Element **E** during mechanical ventilation, *n* (%)[d]	44 (6%)	19 (6%)	25 (6%)	1
Element **F**, *n* (%)	279 (23%)	98 (16%)	181 (30%)	<0.001
Element **F** which was conducted *via* online, *n* (%)	150 (12%)	26 (4%)	124 (21%)	<0.001
Visiting arrangement for a family to meet patients in the ICU, *n* (%)				
Meeting not allowed	630 (51%)	297 (47%)	333 (55%)	0.006
In person	307 (25%)	251 (40%)	56 (9%)	<0.001
Visiting through the glass outside the room	36 (3%)	12 (2%)	24 (4%)	0.040
Using electronic device (using a monitor such as phone/video)	269 (24%)	75 (12%)	194 (32%)	<0.001
Implementation of other evidence-based and supportive ICU cares				
ICU Diary, *n* (%)	234 (19%)	106 (17%)	128 (21%)	0.059

Data in table are presented as number (%) or median [Interquartile range]. ICU, intensive care unit; SAT, spontaneous awakening trials; SBT, spontaneous breathing trials; IQR, interquartile range.

[a]The targeted ICU patients are those who receive continuous sedation and mechanical ventilation at the same time. A total number of those patients are 539, including 340 patients with COVID-19 infection and 199 patients without COVID-19 infection. Percentages were calculated by dividing by these numbers of sedated and ventilated patients.

[b]The targeted ICU patients are all ICU patients on the survey date.

[c]The targeted ICU patients are those who receive continuous sedation. A total number of those patients are 589, including 356 patients with COVID-19 infection and 233 patients without COVID-19 infection. Percentages were calculated by dividing by these numbers of sedated patients.

[d]The targeted ICU patients are those who receive mechanical ventilation. A total number of those patients are 701, including 395 patients with COVID-19 infection and 306 patients without COVID-19 infection. Percentages were calculated by dividing by these numbers of ventilated patients.

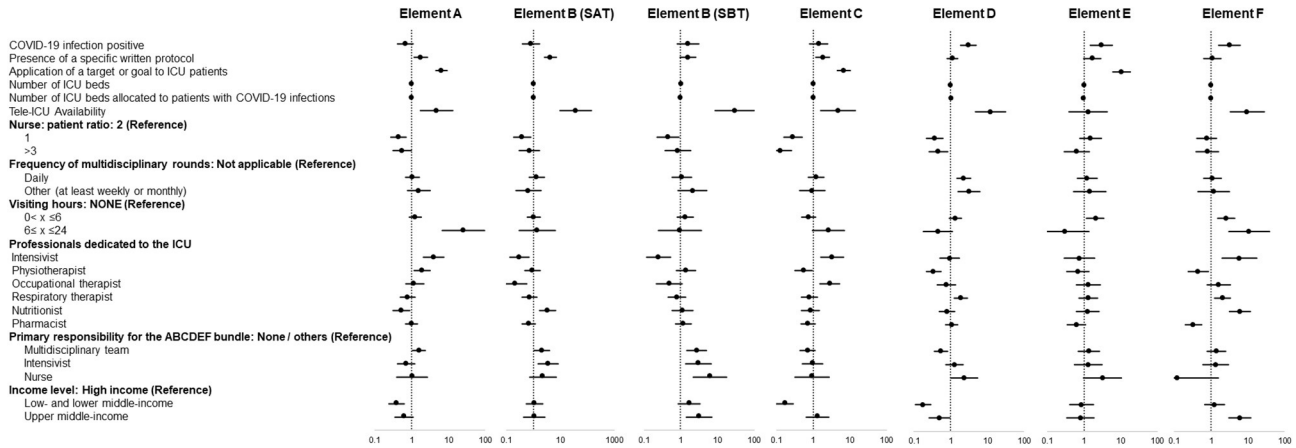

FIGURE 3 | Independent factors associated with implementation of each element of the ABCDEF bundle. Data in figure are shown as adjusted odds ratio with 95% confidential interval.

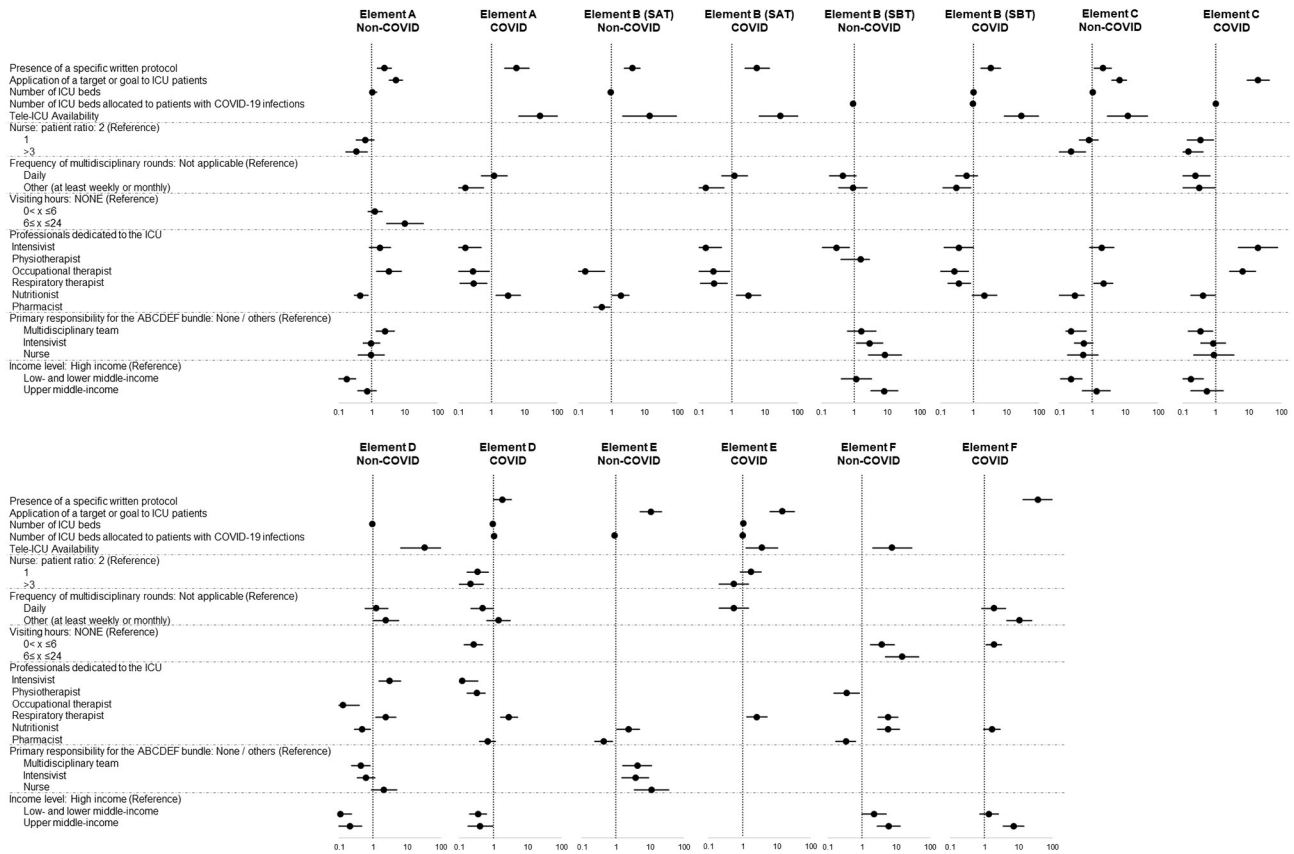

FIGURE 4 | Differences in associated independent factors in patients without and with COVID-19 infections. Data in figure are shown as adjusted odds ratio with 95% confidential interval. The blank lines in the figure are the variables which are excluded from the multivariable logistic regression analysis because the number of patients allocated to the category is too small (≤5 patients) to create the suitable model or the variables which are removed through the stepwise method with Akaike information criterion.

diseases and ICU length of stay between the two groups. Patients with COVID-19 infections, admitted to the ICU because of severe respiratory failure (28), need longer mechanical ventilation treatment with more sedation and require more intense sedation monitoring compared to patients without COVID-19 infections who have a variety of reasons for admission to the ICU but result in a shorter ICU length of stay. This might lead to more frequent implementation of element C for patients with COVID-19 infections. However, the deeply sedated state could result in non-implementation of element A as seen in patients with COVID-19 infections because few pain assessment tools can be used in heavily sedated patients. The strong respiratory drive and effort associated with COVID-19 infections could be a factor contributing to progression of lung injury (29–31) and could prevent conduct of SAT and SBT for patients with COVID-19 infection, to avoid further exacerbation of the lung injury. However, element F of the ABCDEF bundle was more frequently performed for patients with COVID-19 infections, especially using electronic devices (using a monitor such as phone/video). COVID-19 brought technological expansion in the fields of remote and tele-practice which have been applied to the COVID-19 situation (32). However, it might result in overlooking patients without COVID-19 infections who received less online benefits as shown in this survey, and also need involvement of their families. In the context of an increasing trend for implementation of element E (33, 34), COVID-19 brought it to a previous level, but into more resource-unbalanced and time-restricted settings. As the guideline suggests, it is important to note that evidence-based ICU care, such as the ABCDEF bundle and ICU diary, should be incorporated into clinical practice for all ICU patients regardless of their underlying diseases or the ICU length of stay (1–4, 16, 35).

After adjusting for the backgrounds of hospitals and ICUs and the baseline condition of patients, the presence of COVID-19 infection was not a barrier to the implementation of each element of the ABCDEF bundle. For elements D, E, and F, the presence of COVID-19 was significantly associated with their implementation. The warnings of high risk for and high incidence of delirium in the early stage of the pandemic may be a factor (36) or the use of online systems in patients with COVID-19 infections (32) might contribute to these results. In addition, this could be a strong message that the impact of the COVID-19 pandemic broadly affected patients without and with COVID-19

TABLE 5 | Implementation of the ABCDEF bundle compared with previous studies before and after the COVID-19 pandemic.

Element of the ABCDEF bundle	This study		Reference[a]	Reference[b]	Reference[c]
Before or after the pandemic	After the COVID-19 pandemic			Before the COVID-19 pandemic	
Survey date	27th January in 2021		3rd June and 1st July in 2020	January 2015–March 2017	March–September in 2016
Survey settings	International		International	National (USA)	International
Target ICU patients	WITHOUT COVID-19 infection	WITH COVID-19 infection	WITH COVID-19 infection	WITHOUT COVID-19 infection	
Number of enrolled patients	(*n* = 627)	(*n* = 602)	(*n* = 262)	(*n* = 15,226)	(*n* = 1,521)
An entire of the ABCDED bundle	(0%)	(1%)	(1%)	(8%)	
Element A, *n* (%)	(64%)	(55%)	(45%)	(77%)	(83%)
Element B (both SAT and SBT)	(17%)	(10%)			
Spontaneous awakening trial, *n* (%)	(21%)	(14%)	(28%)	(34%)	(66%)
Spontaneous breathing trial, *n* (%)	(29%)	(16%)	(28%)	(36%)	(67%)
Element C, *n* (%)	(45%)	(61%)	(52%)	(59%)	(89%)
Element D, *n* (%)	(39%)	(35%)	(39%)	(56%)	(70%)
Element E, *n* (%)	(12%)	(16%)	(35%)	(29%)	
Element F, *n* (%)	(16%)	(30%)	(16%)	(63%)	(67%)

Data presented as number (%). SAT, spontaneous awakening trial; SBT, spontaneous breathing trial.
[a]*Liu et al. (12).*
[b]*Pun et al. (13).*
[c]*Morandi et al. (21).*

infections and special considerations are necessary to improve the quality of ICU care for both types of patients.

This study demonstrates the diversity of independent factors associated with the implementation of each element of the ABCDEF bundle in addition to variations comparing non-COVID-19 and COVID-19 settings. These results particularly show that a promising strategy to introduce or implement a specific element of the bundle in an ICU could vary and should be designed depending on the context and local situation in which it will be implemented. For many elements in the ABCDEF bundle, regardless of COVID-19 status, a specific protocol and presence of a target/goal for ICU care were consistently identified as facilitating independent factors. However, this study also showed the low frequency to equip the specific protocol in each ICU, or 50% or less, which could be considered as one of the major barriers to be managed regardless of the presence of COVID-19. As many studies successfully showed a pivotal role for implementation or introduction of ICU care, this simple, but not time- or resource-consuming approach could be a key stimulus and should be routine in the ICU to facilitate efficient implementation of evidence-based approaches to ICU care (12, 16, 37, 38). Tele-medicine, which is getting public interest and recommended in several elements such as elements E (39) and F (37, 40), could be also an alternative to promote implementation instead of strict regulations regarding infection control or family visits. This is a relatively novel field of intensive care. Therefore, the impact of tele-medicine on implementation of evidence-based ICU care and its effect on outcomes should be investigated in a large prospective cohort study or randomized controlled study. The professionals dedicated to the ICU and the individual with primary responsibility could be decided by a policy maker in the hospital or ICU director based on what is to be achieved (41–44). The income level, used as a resource barometer, might show that less resources prevent implementation of evidence-based approaches (17, 37, 45). Relatively resource-intense care, such as a 1:1 nurse-patient ratio and daily multidisciplinary rounds, were not independently associated with implementation of the ABCDEF bundle, consistent with a previous report (12). ICUs in lower income countries performed more element F in this survey. These countries might apply relatively flexible visiting hours, which was also detected as a facilitating factor for element F, for a family rather than being in a high-income country.

This study has several acknowledged limitations. First, the limited number of patients and participating countries (Japan accounts for 40%) could lead to selection bias and limit generalizability to other ICUs and countries. These numbers might not be enough for the multivariable analysis with a number of covariates. Although the survey date captured a peak in the wave in Japan (46), the status of the pandemic in each area could affect the results. In addition, some COVID-19 hotspots, such as the USA, Brazil, and Russia, were under-represented. Second, the nature of a point prevalence study does not define a causal relationship and reflects the overwhelming situation at participating sites. This point prevalence study took place entirely on 1 day. Third, potential confounding factors associated with implementation, such as disease-related factors, were not investigated. Finally, an odds ratio with a relatively broad confidence interval may indicate an unstable model created by multivariate analysis. For example, Tele-ICU availability and Visiting hours might not be suitable to be incorporated

into the multivariable analysis. Interpreting the results into the clinical world needs cautions regarding these statistical aspects. Further investigation and observations are necessary to validate these results.

CONCLUSIONS

Though having a COVID-19 infection was not associated with a failure to implement evidence-based ICU care, the implementation rates for the entire ABCDEF bundle, each of its elements and the ICU diary for patients without and with COVID-19 infections, were various, but extremely low on the whole regardless of the presence of COVID-19 infection. Since the impact of the COVID-19 pandemic on evidence-based ICU care varies depending on the conditions in each ICU, strategies to facilitate the implementation of each element of the ABCDEF bundle must be tailored to each institution.

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 the Saiseikai Utsunomiya Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KL, KN, HK, PN, EE, SK, KT, SI, and ON: study conception and design. KL, KN, HK, PN, EE, SK, and KT: statistical analysis or interpretation of data and drafting the manuscript. KN, HK, ME, PN, EE, SK, KT, MG, BL, CC, JB, SI, AL, and ON: critical review and revision of the manuscript for important intellectual insight. PN, EE, SK, KT, SI, AL, and ON: study supervision. KL, KN, HK, ME, PN, EE, SK, MG, BL, CC, JB, SI, and ON: recruitment the participating ICUs in overseas countries. KN confirmed that all authors meet authorship criteria according to ICMJE. All authors drafted the manuscript for important intellectual content, contributed to revision of the final version of the manuscript, approved the final version submitted, and agreed 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.

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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.2021.735860/full#supplementary-material

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REVIEW
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New Applications of HBOC-201: A 25-Year Review of the Literature

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If not cured promptly, tissue ischemia and hypoxia can cause serious consequences or even threaten the life of the patient. Hemoglobin-based oxygen carrier-201 (HBOC-201), bovine hemoglobin polymerized by glutaraldehyde and stored in a modified Ringer's lactic acid solution, has been investigated as a blood substitute for clinical use. HBOC-201 was approved in South Africa in 2001 to treat patients with low hemoglobin (Hb) levels when red blood cells (RBCs) are contraindicated, rejected, or unavailable. By promoting oxygen diffusion and convective oxygen delivery, HBOC-201 may act as a direct oxygen donor and increase oxygen transfer between RBCs and between RBCs and tissues. Therefore, HBOC-201 is gradually finding applications in treating various ischemic and hypoxic diseases including traumatic hemorrhagic shock, hemolysis, myocardial infarction, cardiopulmonary bypass, perioperative period, organ transplantation, etc. However, side effects such as vasoconstriction and elevated methemoglobin caused by HBOC-201 are major concerns in clinical applications because Hbs are not encapsulated by cell membranes. This study summarizes preclinical and clinical studies of HBOC-201 applied in various clinical scenarios, outlines the relevant mechanisms, highlights potential side effects and solutions, and discusses the application prospects. Randomized trials with large samples need to be further studied to better validate the efficacy, safety, and tolerability of HBOC-201 to the extent where patient-specific treatment strategies would be developed for various clinical scenarios to improve clinical outcomes.

Keywords: HBOC-201, red blood cell, oxygen-carrying capacities, oxygen bridge, clinical settings

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INTRODUCTION

Tissue ischemia and hypoxia cause increased anaerobic metabolism, ion imbalance, mitochondrial uncoupling, activation of endothelial cells and various cell death programs, and pro-inflammatory immune responses (1, 2). Timely resolution of ischemia and hypoxia in cells, tissues, and organs is beneficial in restoring the cellular demand for energy metabolism and oxygen. In clinical practices, the increase of red blood cells (RBCs) and hemoglobin (Hb) in the blood is promoted mainly by the use of erythropoiesis-stimulating agents (ESAs) (3), intravenous iron (4), vitamin B12 (5),

and folic acid (6) to improve tissue oxygenation. In the case of life-threatening diseases requiring blood transfusion, allogeneic blood transfusion is the most common and closest physiological option to improve the blood volume, Hb, and hypoxia of the patient. However, blood has some potential disadvantages including immune phenomena, blood infection, cross-matching, and scarcity. Therefore, the search for ideal blood substitutes to provide oxygen to ischemic and hypoxic tissues and organs to maintain normal cellular energy metabolism is an ongoing quest.

Hemoglobin-based oxygen carrier-201 (HBOC-201) [hemoglobin glutamer-250 (bovine); Hemopure, HbO_2 Therapeutics LLC, Souderton PA 18964, USA] is a solution of purified, glutaraldehyde-polymerized, stroma-free, bovine Hb (7). HBOC-201 has been on the market in South Africa since 2001 and is approved for surgical patients with acute anemia (8). However, in 2008, the meta-analysis of cell-free hemoglobin-based blood substitutes and risk of myocardial infarction (MI) and death by Natanson et al. and related editorials have caused widespread controversy over the safety of clinical patients using HBOC-21 (9–12). The meta-analysis included 13 randomized controlled trials and concluded that the use of HBOCs was associated with a significantly increased risk of death and MI based on analysis of available data (9). The Food and Drug Administration (FDA), hence, suspended all the HBOC trials in the United States. However, related editorials suggested that the conclusions of this meta-study based on mixed studies at different levels must be treated with caution (10–12). They argued that the imminent risk of death due to low Hb outweighs the risk of HBOCs, so indiscriminately requiring suspension of all the HBOC trials could be fatal to these patients. The appeal submitted by the company that produces HBOC-201 to the Drug Control Board was finally successful in 2010 and the company officially resumed the registration. HBOC-201 is an investigational product that is currently only available through Expanded Access (EA). The EA program has been conducted in the United States since 2014, primarily in patients who have refused blood transfusions due to their religious beliefs (13). It is also currently approved for veterinary use in the United States and the European Union (14). HBOC-201 serves as a temporary oxygen bridge to improve local and systemic oxygenation and as a substitute for effective resuscitation fluids and RBCs in emergencies (15, 16). HBOC-201 can be used in various ischemic and hypoxic clinical scenarios such as traumatic hemorrhagic shock, hemolysis, MI, cardiopulmonary bypass, perioperative period, and organ transplantation. Compared with various resuscitation fluids, HBOC-201 is fluid as a volume expander and retains the ability to bind and release oxygen. When RBCs are not available, HBOC-201 can also replace RBCs as an oxygen bridge to improve tissue oxygenation *in vivo* until enough RBCs are produced to meet the needs of life. The main adverse effects currently reported with HBOC-201 include vasoconstriction, MI, and increased methemoglobin, which can be managed with close clinical monitoring and appropriate therapeutic measures (17, 18).

The purpose of this study is to summarize the properties of HBOC-201, the application of HBOC-201-related preclinical and clinical studies in various clinical scenarios, adverse events (AEs) and corresponding solutions, and prospects for its application. In this study, all the HBOC-201-related preclinical studies and clinical studies searched in Pubmed were included. From the selected studies, we further extracted information on HBOC-201-related clinical trials (**Table 1**) and case reports (**Table 2**). By reviewing the relevant preclinical and clinical studies of HBOC-201, clinical decision-makers are familiar with the characteristics and indications of HBOC-201 that could benefit patients in emergencies.

PROPERTIES OF HBOC-201

Hemoglobin-based oxygen carrier-201 is derived from bovine RBCs. Free Hbs are then purified by chromatography and cross-linked with glutaraldehyde to increase its stability and molecular size. Unlike human RBCs, HBOC-201 has no cell membrane, no blood type, no cross-matching requirement, no risks of viral infection, a long-term storage capability, timely availability, and other characteristics (**Table 3**). The molecular structure of HBOC-201 is similar to that of human Hb and the molecular diameter of HBOC-201 (8 nm) is much smaller than the RBC diameter (7,000 nm), which can pass through narrow blood vessels where RBCs cannot pass and penetrate the subendothelial space (41). Since HBOC-201 has a lower oxygen affinity than human Hb, it increases the rate of oxygen uptake. As the Hb dissociation curve shifts to the right, the release of oxygen to the tissue is promoted (42). HBOC-201 use chloride instead of 2,3-diphosphoglycerate (2,3-DPG) as on-loading and off-loading of oxygen (43). HBOC-201 has lower concentrations of organic phosphates, which leads to facilitated oxygen unloading in ischemic tissue (the acid Bohr effect) and increase Hb binding of carbon dioxide in the deoxygenated state (the Haldane effect) (44). The physiological effect of 1 g of bovine Hb in HBOC-201 is equivalent to 3 g of human Hb. Analysis of oxygen binding and release properties of Hb by Gregory et al. showed that HBOC-201 could theoretically deliver more oxygen to tissues than RBCs under physiological conditions (16). The results of Thomas et al. also suggested that an increase in extracellular Hb concentration increased oxygen transport efficiency for both the uptake and release (42). The plasma clearance rate of HBOC-201 follows first-order pharmacokinetics, regardless of whether it is a single dose or multiple doses, which intravascular half-life is 19 h (45). The metabolism of HBOC-201 in men and women seems to be similar and metabolized by the mononuclear phagocyte system (MPS) to bilirubin. Ashenden et al. reported that after healthy male subjects were infused with HBOC-201, the blood oxygen-carrying capacity was improved (46). HBOC-201 has been shown to be effective in increasing oxygen extraction and delivery to peripheral and central organs and improving tissue oxygenation in studies related to isovolumetric hemodilution (47–51). Although HBOC-201 can induce the production of immunoglobulin G (IgG) antibodies in humans, it will not lyse RBCs and its efficacy is not affected by specific IgG antibodies (52). Immunoglobulin E (IgE) anti-HBOC-201 was not detected in the serum samples of patients who received repeated HBOC-201 treatment (53). Therefore, repeated

TABLE 1 | Summary of clinical trials of hemoglobin-based oxygen carrier-201 (HBOC-201).

References	Blinding, study type	Clinical scenario	Dose of HBOC-201	Patients population	Outcome	Physiologic effects	Author conclusion
Mackenzie et al. (13)	Unblinded, multicenter study	Life-threatening anemia	Loading dose (2–4 units); 1–2 units infusion every 19–20 h, or continuous infusion	HBOC-201 ($n = 54$)	Early use of HBOC-201 can improve the survival chance of patients with acute bleeding and hemolysis. HBOC-201 did not cause serious adverse events.	Hypertension (SBP = 160 mmHg), increased liver enzymes and methemoglobin	Early use of HBOC-201 can increase the survival chance of patients with acute bleeding and hemolysis. If the duration and degree of low hemoglobin before HBOC-201 treatment is minimized, the patient is more likely to survive.
Mackenzie et al. (15)	N	Acute anemia, untreatable anemia, when no blood is available, when blood cannot be given	N	HBOC-201 ($n = 1,701$)	When hemoglobin is <5 g/dL, early use of HBOC-201 can improve the patient's chance of survival. HBOC-201 transfusion avoidance of 96% for 24 h, 70% for 1 week. More non-serious events occurred in the HBOC-201 group. Age, history of heart disease, and Hb deficiency are predictors of cardiac ischemic events.	Increased blood pressure, oliguria, gastro-intestinal symptoms, yellow skin and scleral discoloration, decreased pulse oximetry measurements and transient increased in methemoglobin, hepatic and pancreatic enzymes.	HBOC-201 transfusion was well-tolerated. When blood is not available or cannot be provided, HBOC-201 should be considered, and can maintain O_2 delivery. Infusion of HBOC-201 can save blood transfusion has been proven in Phase 3 clinical trials.
Serruys et al. (19)	Randomized 3-arm (1:1:1), double-blind, placebo-controlled, dose-finding pilot (phase II)	Unstable angina or NSTE ACS and had a severe stenosis in at least one coronary artery eligible for PCI	15 or 30 g	15 g HBOC-201 ($n = 15$); 30 g HBOC-201 ($n = 15$); non-oxygen carrier colloid ($n = 15$)	HBOC-201 produced an increase in SBP, pulmonary capillary wedge pressure and calculated SVR and a concomitant decrease in CO. The proportion of patients with adverse events did not differ significantly between the two groups.	Increased blood pressure, transient increased in liver transaminases and/or pancreatic enzymes, increased methaemoglobin andcell-free plasma hemoglobin	HBOC-201 had no effect on resting and hyperaemic coronary blood flow. No compromise in the coronary blood flow or LVSWI was observed despite HBOC-201's known vasoactive effects.
Meliga et al. (20)	single-center, phase II, placebo controlled, crossover, single-blind	coronary balloon occlusion	11–12 g/dl at 48 ml/min up to 3 min	N=5	EF, CO, and dP/dTMIN decreased significantly and the EDP and time constant of relaxation increased significantly during dry occlusions in the HBOC-201 group. HBOC-201 failed to alter conduit coronary artery tone	Increased blood pressure	Intracoronary infusion of oxygenated HBOC-201 is capable of preserving left ventricular function, likely through maintenance of myocardial oxygenation. HBOC-201 can effectively preserve myocardial mechanical and electrical properties in the face of total coronary occlusion.
Sprung et al. (21)	Randomized, single-blinded, multicenter study	surgery	0.6, 0.9, 1.2, 1.5, 2.0, or 2.5 g/kg of body weight	HBOC-201 ($n = 42$); Lactated Ringer's ($n = 26$)	HBOC-201 didn't reduce the use of blood during the entire hospitalization.	Serum transaminases, transient skin discoloration, increased methemoglobin	HBOC-201 was generally well-tolerated. A single dose of HBOC-201 did not reduce the intraoperative allogeneic blood requirements.

(Continued)

TABLE 1 | Continued

References	Blinding, study type	Clinical scenario	Dose of HBOC-201	Patients population	Outcome	Physiologic effects	Author conclusion
Levy et al. (22)	Randomized, double-blind efficacy trial	Cardiac surgery	Initial dose (60 g in 500 mL); two subsequent dose (30 g in 250 mL); extra demand replenishes RBC	HBOC-201 ($n = 50$); RBC ($n = 48$)	HBOC-201 eliminated the need for red blood cell transfusions in 34% of patients. Oxygen extraction was greater in the HBOC group. Hematocrit values were transiently lower in the HBOC group.	Hypertension	HBOC-201 may be an initial alternative to RBC transfusions for patients with moderate anemia after cardiac surgery.
Jahr et al. (23)	Randomized, single-blind, parallel-group multicenter study	Elective orthopedic surgery	Loading dose (65 g); up to an additional 260 g; extra demand replenishes PRBC	HBOC-201 ($n = 35$); PRBC ($n = 33$)	HBOC-201 eliminated the need for red blood cell transfusions in 59.4% of patients; Adverse events and serious adverse events have a higher incidence in HBOC-201.	Troponin, hypertension	Patients <80 years old with moderate clinical need may safely avoid transfusion when treated with up to 10 units of HBOC-201; Adverse events may be related to patient age, volume overload, undertreatment and was isolated to patients that could not be managed by HBOC-201 alone.
Van et al. (24)	Randomized, single-blind, multicenter study	Non-cardiac surgery	Initial dose [2 units (60 g Hb)];up to 7 units	HBOC-201 up to 7 units ($n = 83$); RBCs ($n = 77$)	HBOC-201 eliminated the need for red blood cell transfusions in 43% of patients. There were no significant differences in mortality and the incidence of serious adverse events.	Hypertension, fever, transient jaundice	The ability of HBOC-201 to restore total Hb was less than RBCs. The short-term effect of HBOC-201 transfusion on HCT was similar to that of plasma volume expanders, and on Hb it is similar to that of whole blood. In addition, the relatively short (19–24 h) half-life of HBOC-201 required constant re-dosing to maintain total Hb levels.
LaMuraglia et al. (25)	Randomized, single-blinded, multicenter study	Aortic surgery	Initial dose 60 g; three more doses (30 g each) within 96 h; extra demand replenishes RBC	HBOC-201 ($n = 48$); RBC ($n = 24$)	HBOC-201 eliminated the need for red blood cell transfusions in 27% of patients.	Hypertension, increased in serum urea nitrogen concentration	HBOC-201 transfusion was well-tolerated and did not influence morbidity or mortality rates. HBOC-201 may provide a temporary oxygen transport bridge until endogenous RBC can recover adequate oxygen-carrying capacity, especially when RBC are not immediately available but surgery is urgently required.
Kasper et al. (26)	Unblinded, randomized study	Elective abdominal aottic surgery	6.9 ml/kg or 9.2 mL/kg (HBOC-20113.4 +- 0.7 g/dL)	HBOC-201 ($n = 12$); 6% hydroxyethyl starch (HES) ($n = 12$)	HBOC-201 (0.9 and 1.2 g/kg hemoglobin) increased perioperative vascular resistance and reduce cardiac output.	Increased vascular resistance [systemic (SVRI) and pulmonary vascular resistance (PVRI)];decreased cardiac output	Bovine hemoglobin in a dose range of 55–97 g hemoglobin increases vascular resistance and reduces cardiac output in patients undergoing anesthesia. However, HBOC-201 has no obvious advantages in hemodynamics and oxygen transport compared with hydroxyethyl starch. It may be that the advantage of increased oxygen-carrying capacity is offset by increased vascular resistance and decreased cardiac output.

(Continued)

TABLE 1 | Continued

References	Blinding, study type	Clinical scenario	Dose of HBOC-201	Patients population	Outcome	Physiologic effects	Author conclusion
Dubé et al. (16)	Randomized, single blind, multi-center, phase III clinical trial	Elective orthopedic surgery	loading dose (2-unit);10 units received in total	HBOC-201 ($n = 121$); PRBCs ($n = 115$)	Hemoglobin deficit in patients treated with HBOC-201 was more common than in the PRBC control group and emerged as a predictor of SAEs in a logistics model. The subjects randomly assigned to HBOC-201 had more severe anemia, which may be the cause of more SAE in the HBOC group.	myocardial infarction; cardiotoxic	HBOC can serve as a bridge to meet the oxygen-carrying needs of patients with severe anemia until RBC is available or patients can establish a safe hematocrit. However, according to the principle of relative efficacy, this clinical trial had shown that blood or PRBCs are generally preferred treatment for severe anemia when available and acceptable to the patient.
Pearce et al. (27)	N	Surgery	N	HBOC-201 ($n = 806$); Control ($n = 661$)	The research supports that the application of HBOC-201 can be extended to the treatment and management of trauma and ischemia. Severely injured patients may urgently need early blood transfusion, especially when blood is scarce or unavailable. The oxygen delivery of HBOC201 can lifesaving in the pre-hospital environment.	anemia, tachycardia, abdominal pain, diarrhea, dysphagia, nausea, vomiting, pyrexia, jaundice, lipase increases, oliguria, and hypertension	HBOC-201 was well-tolerated in various doses and regimens, as well as in various clinical, particularly perioperative. As the dose is increased for a long time, it is proved that HBOC-201 may provide a temporary oxygen transport bridge until endogenous RBC mass can restore adequate oxygen-carrying capacity, especially when RBCs are not immediately available but surgery is urgently required.
van et al. (28)	Controlled trials	Liver transplantation	N	DHOPE-COR-NMP ($n = 16$);successfully transplanted ($n = 11$)	During NMP, all livers cleared lactic acid and produced sufficient bile volume. However, five livers was excluded from transplantation due to bile pH <7.45. 69% of discarded human livers meeting all criteria were successfully transplanted, with 100% patient and graft survival at 3 and 6 months.	N	In summary, this prospective clinical trial proved the safety and feasibility of combining sequential DHOPE-COR-NMP and HBOC-201 to transplant human high-risk liver transplantation. The pretransplant resuscitation and viability assessment of these discarded livers resulted in a 20% increase in the number of deceased donor liver transplants in author's center.
de Vries et al. (17)	N	Liver transplantation	N	DHOPE-COR-NMP ($n = 7$); successfully transplanted ($n = 5$)	DHOPE-COR-NMP using an HBOC-based perfusion fluid protected livers against ischemia-reperfusion injury and performed hepatobiliary viability assessment before transplantation. The graft survival rate at 3 months after transplantation was 100%.	Increased methemoglobin	The use of a novel sequential DHOPE-COR-NMP using an novel HBOC-201-based perfusate eliminated the need to change the perfusate at different temperature stages and offered a novel method of liver machine perfusion for combined resuscitation and viability testing of discarded livers before transplantation. HBOC-201 appeared to be a safe alternative for RBC as oxygen carrier in DHOPE-COR-NMP.

N, not reported; SBP, systolic blood pressure; CO, cardiac output; LVSWI, left ventricular stroke work index; EF, ejection fraction; dP/dTMIN, minimal rate of LV pressure change; EDP, end-diastolic pressure; RBC, red blood cell; PRBC, packed red blood cell; Hb, hemoglobin; GI, gastrointestinal; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; FFP, fresh frozen plasma; HOPE, hypothermic oxygenated perfusion; COR, controlled oxygenated rewarming; NMP, normothermic machine perfusion; UW, University of Wisconsin.

TABLE 2 | Summary of cases report of HBOC-201.

References	Study Type	Clinical scenario	Patients population	Dose	Outcome	Adverse event	Author conclusion
Marinaro et al. (29)	Case report	Traumatic brain injury	Jehovah's Witness	Initial dose (4 units); 2 units for 2 days	Died	Hypertensive event (systolic to 280 mmHg)	HBOC-201 rapidly corrected cerebral venous, central venous oxygen saturation and profound anemia.
Mullon et al. (30)	Case report	Severe autoimmune hemolytic anemia	Acute hemolysis	The first unit 0.25 g per minute; Subsequent units 0.50 g per minute; a total of 11 units	Discharged	Average mean arterial pressure was 104.7 mm Hg, pulmonary arterial systolic and diastolic pressures increased slightly	HBOC-201 may support oxygen delivery in patients with severe autoimmune hemolytic anemia.
Gannon et al. (31)	Case report	Gastrointestinal hemorrhage	Jehovah's Witness	7 units	Died	N	HBOC-201 can adequately serve as initial therapy to maintain tissue oxygen delivery while waiting the maximal effect of recombinant erythropoietin on bone marrow RBC production.
Pachinburava et al. (32)	Case report	Severe Autoimmune Hemolytic Anemia	Due to the presence of allogeneic antibodies and autoantibodies, it extremely difficult to find blood for patients.	2 units	Discharged	Increased methemoglobin	HBOC-201 successfully assisted blood transfusion therapy.
Epperla et al. (33)	Case report	Warm autoimmune hemolytic anemia	Jehovah's Witness	27 units	Discharged	Hypertension, increased methemoglobin, achalasia	Clinicians' early recognition of the patient's needs and familiarity with its characteristics are essential for safe and timely use.
Gomez et al. (34)	Case report	Kidney-pancreas transplant	Jehovah's Witness	12 units	Discharged	Hypertension, increased methemoglobin, pulse oximetry desaturation.	HBOC-201 can be used as a life-saving measure for patients with severe anemia who refuse blood transfusion, and it should be regarded as a bridging alternative until the patient's hematocrit has returned to a safe level.
Davis et al. (35)	Case report series	Severe sickle cell crisis	Jehovah's Witnesses or compatible RBCs were not available	Two patients received more than 20 units; the other received 27 units	All discharged	Myocardial injury, stroke, achalasia, hypertension, increased methemoglobin	HBOC-201 can provide an oxygen bridge in SCC, until Hb levels are restored to meet metabolic demands.
Epstein et al. (36)	Case report	Sickle cell anemia	Hyperhaemolysis syndrome	One unit	Discharged	Bilirubin to 8.2 mg/dL and ALT to 218 U/L (might laboratory effect)	Multi-drug regimens including bortezomib and HBOC-201 have been successfully used in an extreme condition of HHS.
Unnikrishnan et al. (37)	Case report	Sickle cell disease	Anti-N and anti-Doaimmunoglobulin G alloantibody-mediated delayed hemolytic transfusion reaction with hyperhaemolysis	19 units	Discharged	Hypertension, increased methemoglobin and liver enzymes	HBOC-201 can be a lifesaving alternative in this hyperhemolysis. This study also further supported the use of eculizumab in severe DHTR.

(Continued)

TABLE 2 | Continued

References	Study Type	Clinical scenario	Patients population	Dose	Outcome	Adverse event	Author conclusion
Zumberg et al. (38)	Case report series	Severe anemia	Life threatening anemia	At least 10 units of HBOC-201 (n = 10)	All discharged	Increased methemoglobin, gastrointestinal symptoms, hypertension	For patients with severe anemia who cannot be infused with RBC, long-term use of HBOC-201 is a feasible and safe oxygen bridge.
Donahue et al. (39)	Case report	Acute lymphoblastic leukemia	Refused allogeneic blood transfusions	15 units	Discharged	Increased methemoglobin	When blood transfusion is not an option, HBOC-201 can be used as a life-saving intervention for patients with severe anemia.
Agrawal et al. (40)	Case report	Relapsed secondary acute myeloid leukemia	Jehovah's Witness	1,230 g (41 units)	Died	Renal toxicity	The homogeneous extraction of oxygen by the brain in the presence of and perhaps from HBOC-201 was demonstrated.

N: not reported.

TABLE 3 | Overview of the characteristics of HBOC-201 and human red blood cells.

Characteristics	HBOC-201	Human red blood cells
Hemoglobin	Bovine-derived, glutaraldehyde polymerized	Human-derived
Average molecular weight	250 KDa	64 KDa
Molecular diameter	8 nm	7,000 nm
PH	7.6–7.9	7.35–7.45
Ion concentration	Na^+: 145–160 mmol/L, Cl^-: 105–120 mmol/L, K^+: 3.5–5.5 mmol/L,Ca^{2+}: 0.5–1.5 mmol/L	Na^+: 135–150 mmol/L, Cl^-: 96–106 mmol/L, K^+: 13.5–5.5 mmol/L, Ca^{2+}: 2.25–2.75 mmol/L
Osmolarity	290–310 mOsm/L	280–310 mOsm/L
Hemoglobin concentration	13 g/dL	11–16 g/dL
Oxygen bound per gram of hemoglobin	1.36 ml	1.34 ml
Methemoglobin concentration	<5%	<2%
P50	43 mmHg	27 mmHg
Viscosity (37°C)	1.3 centipoise	4 centipoise
Temperature range of application	4–37°C	37°C
Half life	19–24 h	120 days
Shelf life	3 years	3 weeks

infusions of HBOC-201 appear to be safe for patients and do not increase the risk of type 1 hypersensitivity.

TRAUMA AND HEMORRHAGIC SHOCK

After trauma, HS can lead to insufficient perfusion of vital organs, cell hypoxia, and organ dysfunction. HBOC-201 can provide sufficient oxygen, reduce the risk of disease transmission, and longer shelf-life. Its effect on neutrophil activation and immune function is similar to other resuscitation fluids, suggesting that it may be safe as a resuscitation fluid in patients with HS (54, 55). Compared with various resuscitation fluids, HBOC-201 can restore tissue oxygenation, maintain blood pressure, reduce the need for blood transfusion in the hospital, reverse anaerobic metabolism, and even improve survival rate (56–59). Even for low-volume resuscitation, HBOC-201 still can improve intracranial pressure and brain oxygen (60–62), improve hemodynamics (63), avoid blood transfusions (64), and improve survival rate (65). Although some preclinical studies have elevated aspartate aminotransferase in the early stage of HBOC-201 infusion, they tend to be normal afterward (63). Incidentally, the usage of HBOC-201 during HS resuscitation, combined with physiological parameters and hypotension to guide fluid volume, will reduce the risk of hyperinfusion and increase the potential benefits. The low-volume strategy for HS resuscitation can maximize the beneficial effects of HBOC-201, while minimizing any potentially harmful effects.

Trauma, bleeding, and fluid resuscitation will cause the consumption and dilution of coagulation factors, adversely affecting the coagulation of trauma patients. Arnaud et al. in a preclinical study showed that transfusion of HBOC-201 successfully resuscitated and avoided blood transfusion in animals, but it caused dilutional coagulopathy (lower hematocrit, platelets, and fibrinogen) (66). HBOC-201 combined with other coagulation substances such as freeze-dried plasma (FDP) (67) or recombinant coagulation factor VIIa (rfVIIa) that had little effect on functional coagulation indicators and had no significant survival benefit (68). However, in the combination of a bleeding model with the Folts model, due to the interaction of many factors such as platelet count, hematocrit, and platelet aggregation, HBOC-201 can reduce thrombosis (69).

In a porcine model with controlled bleeding (40%) and soft-tissue injury, infusion of HBOC-201 not only improved tissue perfusion, stabilized hemodynamics, reduced fluid requirements, and mortality (70), but also increased strong ion difference (SID) and electrochemistry to promote alkalosis (71), which might be beneficial for therapy in high lactate conditions. In the more severe porcine model with rectus abdominus crush (64), the benefit from HBOC-201 might become more pronounced. In a porcine model of uncontrollable bleeding caused by liver injury, HBOC-201 stabilized tissue oxygenation, stabilized hemodynamic and metabolic parameters, and improved survival (59, 66, 72–74). Although Gurney et al. reported that HBOC-201 increased systemic and pulmonary artery pressure (59) and Johnson et al. found that aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, and mild renal papillary damage in the HBOC-201 group were higher than those of 6% hetastarch (HEX) (74) and these AEs were mild. In the abovementioned severe HS porcine model, selective aortic arch perfusion (SAAP) and HBOC-201 not only quickly restored survival of cardiovascular function after cardiac arrest (75), but also effectively induced return of spontaneous circulation (ROSC) and provided the critical oxygenation and perfusion support necessary for successful resuscitation (76, 77).

Compared with other resuscitation fluids, HBOC-201 can improve the mean arterial pressure (MAP), cerebral perfusion pressure (CPP), brain tissue oxygen tension [PbtO(2)] and reduce the secondary damage, and the need for blood transfusion in the traumatic brain injury (TBI) model (78–80). In preclinical studies of TBI, infusion of HBOC-201 not only rapidly restored the self-regulatory mechanisms of cardiovascular system, but also improved cerebral blood flow (CBF), CPP, PbtO(2), and cerebral vasoreactivity to hypercapnia (CVH) (78, 81–83). However, the decrease in nitric oxide (NO) caused by infusion of HBOC-201 may cause constriction of the cerebral vasculature. Cerebral metabolic demand for oxygen is critical in the case of TBI and oxygen supply is increased to minimize ongoing neuronal damage and, thus, reduce morbidity and mortality, so cerebral vasoconstriction may have a devastating effect on patients. Since HBOC-201 causes slight vasoreactivity and has the ability to carry and release oxygen efficiently, it may further improve CBF, CPP, and PbtO(2). In the porcine multiple injury model of TBI bleeding and aortic tear injury, the fluid resuscitation of HBOC-201 is not better than that of Lactated Ringer's (LR) solution (82). The possible reason is that in the case of high-pressure aortic injury, the boosting effect of HBOC-201 may lead to increased bleeding and it may also be related to the severity of shock at the beginning of resuscitation. Therefore, when considering the resuscitation strategy, it is necessary to consider the different injuries of high-pressure blood vessels and low-pressure solid organs and the different severity of shock. In future studies of traumatic HS, how to balance the benefits of HBOC-201 infusion with the potential side effects and how to personalize emergency treatment assistance to patients need to be thoroughly investigated in further studies. Jonathan et al. first used HBOC-201 in a patient with severe TBI, a Jehovah's witness who refused a blood transfusion (29). The patient was transfused with 6 units of HBOC-201 (180 g) and non-invasive cerebral oximetric devices were used to monitor the brain tissue oxygen saturation of the patient. The results of this study showed that not only brain tissue oxygen saturation, central venous oxygen saturation, and hemodynamic variables increase significantly after HBOC-201 administration, but total Hb increased from 3.2 to more than 7 g/dl. The patient developed severe hypertension 12 h after the last HBOC-201 injection, followed by massive cerebral edema and death. The possible cause was massive reperfusion injury from delayed repayment of cerebral oxygen debt in a severely ischemic brain, but it cannot yet be excluded that HBOC-201 itself directly caused massive edema and brain herniation. There is no doubt that HBOC-201 rapidly corrected cerebral venous and central venous oxygen saturation, but further applications in patients with TBI and controlled research need to be explored in the future.

ANEMIA

Hemoglobin-based oxygen carrier-201 has been allowed by the FDA for use under the expanded access in Jehovah's Witnesses patients who require blood transfusion. HBOC-201 has no cell membrane and lacks cell surface antigens, making HBOC-201 an ideal substitute for blood to save lives when blood is unavailable or blood transfusion is refused for patients with severe autoimmune hemolytic anemia (30, 32, 33, 36, 37). Epperla et al. demonstrated that early recognition of patient needs and familiarity with the characteristics of HBOC-201 by clinicians are essential for the safe and timely use of HBOC-201 to save the lives of the patients (33). Davis et al. reported three cases of critically ill patients with sickle cell disease with multiorgan failure who refused RBCs or were not able to use RBCs and whose lives were ultimately saved by the administration of HBOC-201 therapy (35). This study demonstrated that HBOC-201 could provide an oxygen bridge in treating patients with sickle cell crisis (SCC) until Hb levels restored to meet metabolic demands. A Jehovah's Witness patient with acute lymphoblastic leukemia (ALL) developed severe anemia (Hb as low as 3.1 g/dl) during chemotherapy. During the infusion of HBOC-201, Hb of the patient remained between 3.6 and 5.3 g/dl without any ischemia or organ dysfunction (39). Gomez et al. reported for the first time that kidney–pancreas double solid organ transplant recipients whose Hb dropped to a critical level

(2 g/dl) and Hb increased to 6.8 g/dl after infusion of HBOC-201 (34). Gannon et al. demonstrated that a combination of HBOC-201 and high-dose recombinant human erythropoietin (rHuEpo) for life-threatening anemia (Hb, 3.5 g/dl) improved survival of the patient and a significant increase in Hb to 7.6 g/dl (31). This study demonstrated that HBOC-201 can provide adequate tissue oxygen supply until marrow RBC recovery and HBOC-201 combined with high-dose rHuEpo also increase hematocrit and survival in patients with severe symptomatic anemia. Therefore, HBOC-201 is a viable and safe oxygen bridge for patients who cannot infuse RBCs or for whom RBCs are not feasible, hence saving the life of the patient in a life-threatening situation. Furthermore, the existing data supported that although HBOC-201 can cause common side effects such as methemoglobin, gastrointestinal symptoms, and hypertension when the cumulative dose reaches 10 units, it is generally a feasible and safe "oxygen bridge" (13). This study showed that early use of HBOC-201 increased the chances of survival in patients with acute bleeding and hemolysis. Zumberg et al. reported on the treatment of 10 patients with life-threatening anemia and poor prognosis with at least 10 units of HBOC-201 and all of them survived and discharged without long-term complications (38). The results of these cases supported that long-term and high-dose administration of HBOC-201 is a feasible and safe treatment modality for early and proactive correction of life-threatening severe anemia until adequate intrinsic Hb is restored, in cases where blood transfusion is not an option. Agrawal et al. reported on a Jehovah's Witness who presented with chemotherapy-induced anemia following a relapse of secondary acute myeloid leukemia, documenting the highest dose and longest duration of experience with HBOC-201 treatment to date (40). Over a period of 18 days, the patient was infused with 1,230 g of HBOC-201. This study revealed by PET scan that the bilaterally similar and homogeneous extraction of oxygen in the presence of soluble HBOC-201 by the brain tissue. However, nephrotoxicity of HBOC-201 during the infusion of the patient cannot be excluded and, therefore, HBOC-201 may not be useful as the sole oxygenating component of anemia treatment during myelosuppressive therapy. These studies support the safety and feasibility of HBOC-201 in patients with anemia, but the consequences of AEs that occur to patients are worthy of attention. Future randomized, multicenter, and large sample size clinical trials are needed to obtain further high-quality evidence to validate the efficacy, safety, and tolerability of HBOC-201.

MYOCARDIAL INFARCTION

Since the diameter of HBOC-201 is smaller than that of RBCs, it is easily transported through plasma to places where RBCs cannot reach. Therefore, its characteristic of carrying and releasing oxygen makes HBOC-201 more beneficial than whole blood in emergencies. Infusion of HBOC-201 30 min before myocardial ischemia, the infarct size/area at risk (Inf/AAR) was significantly reduced (84). George et al. also reported a similar study that infusion of HBOC-201 after 15 min after ischemia can also significantly reduce Inf/AAR and improve myocardial survival (85). Bloodless reperfusion is a promising strategy that restores oxygen delivery and delays the re-exposure of ischemic myocardium to blood cells, plasma proteins, and other blood-borne inflammatory substances. Intracoronary preoxygenated HBOC-201 can reduce changes in infarct size and stroke volume, improve aerobic metabolism, systolic shortening (SS), and stroke volume in swine during coronary artery occlusion (CAO) in a dose- and temperature-dependent manner (86). Preoxygenated HBOC-201 can match the oxygen delivery of blood in almost equal amounts. The study by Garciá-Ruiz et al. found that the preoxygenated HBOC-201 solution did not lead to increase in infarct size (IS) or deterioration of long-term ventricular function, but it is still feasible and safe (87). The infarct size in the MI model is larger than other studies, mainly due to the use of intravenous anesthetics to avoid the known infarct-limiting effects of inhaled gas anesthetics. With the introduction of percutaneous coronary intervention (PCI), the morbidity, mortality, and disability rates of acute coronary syndromes (ACSs) have been greatly reduced, but the selection of the best drug to limit myocardial injury occurs during ischemia and early reperfusion remains challenging. Since HBOCs have the ability to deliver oxygen, they have been considered for the treatment of ACS. In a randomized, double-blind study, Serruys et al. made the first attempt to introduce HBOC-201 in ACS treatment, examining the safety and tolerability of HBOC up to 230 ml in low-to-moderate risk cardiac patients scheduled for elective PCI (19). The results showed that although intravenous HBOC-201 had side effects such as cell-free plasma Hb and increased blood pressure, no impaired coronary blood flow or left ventricular stroke work index (LVSWI) was observed in patients, nor did it affect the autoregulation of coronary blood flow. In a single-center, phase II, placebo-controlled, crossover, single-blind study, intracoronary infusion of preoxygenated HBOC-201 in five patients undergoing elective PCI improved myocardial "oxygenation" and maintained left ventricular function during brief coronary occlusion (20). This study demonstrates that HBOC-201 can be effective as an oxygen bridge to preserve myocardial mechanical and electrical properties in the face of total coronary occlusion, prolonging the "golden" time period in patients with PCI and improving myocardial oxygenation in patients with MI. More complex patient populations, including ST-elevation MI (STEMI), can benefit from oxygenated HBOC-201 in the future that remains to be further explored. Moreover, higher quality evidence is needed to further collect and validate the efficacy, safety, and tolerability of HBOC-201 in patients with MI.

CARDIOPULMONARY BYPASS

Cerebral ischemia may occur during extracorporeal circulation, especially at low flow. Neuronal death due to cerebral ischemia can cause a series of irreversible complications. Jeffrey et al. first verified that in a porcine model of normothermic low-flow cardiopulmonary bypass (CPB), compared with donor whole-blood priming, adding HBOC-201 to the pump-priming solution during CPB seems to improve cerebral oxygenation

by minimizing overall end-organ ischemia (88). Cerebral oxygenation was maintained in the HBOC-201 group, even during the decrease in blood flow. Although myocardial impairment and elevated troponin levels following HBOC-201 treatment need to be further evaluated before clinical application, this study supported the possible benefits provided by HBOC-201 during CPB. Extracorporeal membrane oxygenation (ECMO) is an accepted treatment for resuscitating critically ill neonates and children with high predicted mortality. Since the blood volume of children is so small relative to the initiation volume of the ECMO circuit, an extracorporeal circuit containing a large volume of blood is required to initiate the ECMO circuit. The donor RBCs in ECMO circuits carry the risk of viral infection, immune response, and blood from multiple donors. Given these concerns, the use of an effective blood substitute during ECMO would be beneficial for the management of ECMO in child patients. In models of ECMO of piglets with healthy or acute respiratory distress syndrome (ARDS), the results of Gregory et al. and Henderson et al. demonstrated that although the hematocrit of the HBOC-201 group was significantly lower than the blood group and the blood pressure and methemoglobin concentration in the HBOC-201 group were slightly increased, HBOC-201-primed ECMO was well-tolerated, maintained hemodynamic stability, and provided good oxygen delivery (89, 90). HBOC-201-primed ECMO appears to be very promising and feasible. HBOC-201 not only has a long half-life, but also eliminates the risk of infection of the patient, immune response, and exposure to multiple donors. However, the initial dosing, the circuit transfusion support, the potential concerns with respect to methemoglobin and vasoconstriction, and the impact on platelet and coagulation factor depletion still warrant further investigation.

PERIOPERATIVE PERIOD

Perioperative preoperative sampling, surgery-related blood loss, and hemodilution result in acute postoperative anemia, which can lead to a reduction in oxygen-carrying capacity. In addition, some emergency surgeries do not have sufficient time and physiologic reserves to donate autologous blood in advance; therefore, many patients require allogeneic RBC transfusions during the perioperative period to maintain cellular energy metabolic needs. During the 1970's and 1980's, many concerns began to be expressed about the safety of blood transfusions. However, a large number of clinical studies have shown that patients after HBOC-201 infusion had good tolerance in different dosing regimens and various clinical conditions, especially in the perioperative period (15, 21, 27, 53). In addition, the improvement of hemodynamics after administration of HBOC-201 may be attributed to its highly colloidal intravascular expansion properties. Although HBOC-201 cannot significantly increase and maintain THb, it can meet the oxygen-carrying needs of patients with severe anemia until RBC is available or patients can establish a safe hematocrit (16). Moreover, in some studies, HBOC-201 can eliminate the need for any allogeneic RBC transfusion for some patients during the perioperative period (22–24). However, insufficient treatment, effective treatment delay, and volume overload were the reasons why the incidence of AE and serious AE (SAE) in the HBOC-201 group was significantly higher than that in PRBC (23).

A multicenter, randomized clinical study showed that HBOC-201 reduced the intraoperative requirements for allogeneic blood transfusion during aortic reconstructive surgery, but led to an increased requirement for allogeneic transfusion later during the hospitalization and ultimately did not reduce the need for allogeneic blood (25). This study indicated that HBOC-201 might be most effective in eliminating need of the patient for emergency transfusions without reducing the total RBC transfusion requirement. In addition, this study discovered that HBOC-201 was associated with a transient increase in systemic blood pressure, but this slight systemic blood pressure increase produced by HBOC-201 may be an advantage for patients with vascular disease who often require temporary blood pressure support. In a study of elective abdominal aortic surgery (26), HBOC-201 provided no significant benefit to hydroxyethyl starch (HES) because the advantage of increased oxygen-carrying capacity was offset by increased vascular resistance and reduced cardiac output. In a limited safety analysis, it can be shown that HBOC-201 is acceptable in the stable trauma, hypotension, and younger age population, especially when safe blood transfusions are not available quickly (91). Overall, in cases where patients require emergency surgery or safe blood transfusions are not rapidly available, HBOC-201 provides a temporary oxygen transport bridge until endogenous RBC mass can be restored to adequate oxygen-carrying capacity or allogeneic transfusion is available.

ORGAN TRANSPLANTATION

For dynamic preservation of isolated organs, the earliest clinical series used is hypothermic machine perfusion (HMP) without oxygenation; however, recent studies have shown that solid organ damage can be mitigated by providing oxygen dissolved in the perfusate (92–94). Subsequent clinical applications for MP employed a single roller pump device utilizing RBCs-based perfusate under normothermic conditions, but it also has several potential drawbacks including the fact that RBCs are a relatively scarce human blood product that may induce immune reactions or cause infections, RBC hemolysis, and logistical difficulties associated with using cross-matched blood (95, 96).

Hemoglobin-based oxygen carrier-201 is a polymerized bovine with low immunogenicity and similar oxygen-carrying capacity to human Hb at normothermic temperatures (21). Compared with cold static preservation (CSP) or blood perfused, the subnormothermic MP (SNMP)/HBOC-201 system significantly improved graft function and provided effective oxygenation to the tissue (97, 98). Laing et al. presented the first experience using HBOC-201 in discarded high-risk human livers of normothermic MP (NMP) (99). The vascular blood flow parameters and lactate clearance rate of the liver perfused with HBOC-201 and RBCs were similar and the HBOC group could extract more oxygen. Compared with RBCs +

fresh frozen plasma (FFP) perfused livers, livers perfused with HBOC-201-based perfusion solution had significantly higher hepatic ATP content, cumulative bile production, and portal and arterial flows (100). HBOC-201 was first used in the study of discarded human kidneys NMP, which was similar to PRBC with respect to vascular flow, oxygen consumption, and reconstitution of tissue ATP (101). HBOC-201-*ex-vivo* normothermic limb perfusion (EVNLP) is identical to RBC-EVNLP, retaining muscle contractility and mitochondrial structure (102). The above study showed that HBOC-201 can be used as an alternative oxygen carrier to RBC in livers, kidneys, and isolated limbs NMP. However, White et al. found that RBC + Plasma can minimize injury and provide superior preservation of myocardial function during *ex vivo* heart perfusion (EVHP) compared with HBOC-201-based perfusion solution (100). The reason may be that the experimental conditions of this study promoted the spontaneous oxidation and the production of reactive oxygen species (ROS) of HBOC-201 and the methemoglobin gradually increased.

Red blood cell cannot be used during HMP because the stiffness of the erythrocyte lipid membranes increases and hemolysis occurs at low temperatures, thus prompting the need for an alternative oxygen carrier, especially when combined with hypothermia and NMP (17). Mahboub et al. reported better renal function recovery in a rat donation after circulatory death (DCD) kidney model after rewarming with HBOC-201 compared to rewarming without an oxygen carrier (103). Although continuous cold-to-warm (HBOC-201) protocol is similar to an interrupted hypothermic oxygenated perfusion (HOPE) [University of Wisconsin (UW) solution] + NMP (HBOC-201) protocol in terms of increasing ATP synthesis and reducing tissue expression of oxidative tissue damage markers, the use of a single perfusate eliminated unnecessary ischemia time required for perfusate exchange (103). HBOC-201-based perfusate was used in two clinical studies of the dual hypothermic oxygenated machine perfusion (DHOPE)-controlled oxygenated rewarming (COR)-NMP trial. After being assessed, most livers that met all the criteria were transplanted (17, 28). Totto B et al. increased the number of transplantable livers by 20% by using a combination of sequences DHOPE-COR-NMP and HBOC-201 to resuscitate and evaluate high-risk donor livers (28). Livers of suboptimal quality that are not repaired and functionally assessed post-transplant will increase the risk of primary non-function and early allograft dysfunction in patients. Combining HBOC-201 with the MP platform is feasible and provides novel and safe perfusion protocols for expanding the transplanted organ pool.

ADVERSE EVENTS AND RESOLUTIONS

Hemoglobin-based oxygen carrier-201 was originally developed for use as a blood substitute. Based on the characteristics of HBOC-201, it can increase convective oxygen delivery by increasing the oxygen-carrying capacity of blood and promote the release and diffusive transport of oxygen in the microcirculation, thereby promoting tissue oxygenation. Thus, the application of HBOC-201 can also be extended to various ischemic and hypoxic diseases such as traumatic HS, anemia, surgical settings, MI, CPB, and organ transplantation. The efficacy, safety, and tolerability of HBOC-201 in various clinical scenarios have been shown to be promising in published preclinical and clinical studies. The efficacy, safety, and tolerability of HBOC-201 in various clinical scenarios are promising in published preclinical and clinical studies. Unlike natural Hb, the Hb molecules in HBOC-201 have been chemically altered to minimize such toxicity theoretically. However, several AEs occurring during the application of HBOC-201 require widespread attention, with vasoconstriction and increased blood pressure being of great concern and the highest incidence of AEs. The high affinity of HBOC-201 for NO and the lower shear stress lead to a decrease in circulating NO, which may result in systemic vasoconstriction, decreased blood flow, increased pro-inflammatory mediators and vasoconstrictor factors, and platelet inactivation, ultimately leading to increased MI and mortality in patients (104). The vasoconstriction caused by HBOC-201 may also be attributed to increased release of endothelin (105), stimulation of α-adrenergic receptors (106), and delivery of high oxygen concentrations. HBOC-201-induced vasoconstriction and blood pressure can be modulated by reducing the dose, changing the solvent, and adding a vasodilator. In a porcine model of HS, HBOC-201 suspended in the hypertonic saline (HTS) solution significantly decreased systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), increased mean pulmonary artery pressure (MPAP) and cardiac output (107), and reduced the high inflammatory response (108). Inhaling NO before intravenous infusion of HBOC-201 can prevent systemic vasoconstriction without causing methemoglobin (18). Sodium nitrite ($NaNO_2$) also temporarily reduced systemic and pulmonary blood pressure increase from HBOC-201 in a dose-dependent manner (109). Three vasodilators, sodium nitroprusside (SNP), sodium nitrite and nitroglycerin, can all attenuate HBOC-mediated vasoconstriction, with nitroglycerin being the least reactive with HBOC-201 in methemoglobin formation (110). SNP can effectively and safely reduce HBOC-201-related systemic, but not pulmonary vasoactivity (111). Therefore, among the three nitrovasodilators, nitroglycerin seems to be the most promising drug for reducing hypertension caused by HBOCs.

Increased methemoglobin is another common side effect of HBOC-201 application. Unlike RBCs, HBOC-201 lacks the nicotinamide adenine dinucleotide (NADH)-dependent enzyme (methemoglobin reductase). Excessive methemoglobin will lead to a decrease in the ability to release oxygen, which will reduce the amount of oxygen delivered to the tissues. Iron ions mediate the oxidative damage of endothelial cells, leading to increased microvascular permeability. Methemoglobin concentrations below 10% do not significantly alter the mode of oxygen delivery to organs (112). Juraj et al. found that the percentage of methemoglobin was delayed to increase after HBOC-201 infusion, so the methemoglobin load was not caused by HBOC-201 infusion, but was gradually generated by oxidation of plasma Hb. Therefore, close monitoring of the changes in methemoglobin in patients and timely management are beneficial to minimize the damage caused by high concentrations of methemoglobin. The methemoglobinemia resulting from

HBOC-201 infusion in the patient in the case report by Athira et al. responded well to vitamin C and showed no major toxicity secondary to HBOC-201 (37). In addition, Colin et al. showed that the increase in methemoglobin was independent of the dose of HBOC-201 and did not affect patient survival and that patients responded to injectable methylene blue infusions (13). The percentage of methemoglobin can be corrected or reduced by adding additional HBOC-201, glutathione, or vitamin C to the perfusion fluid during the perfusion of isolated organs (17). Since vitamin C affects the pH and osmolarity of the perfusate, addition to the perfusate to reduce methemoglobin is not recommended.

In addition to the two common AEs mentioned above, AEs recorded with HBOC-201 include plasma volume expansion, gastrointestinal discomfort, blood urea nitrogen values, liver and pancreatic enzyme dysregulation, yellow skin, and sclera discoloration, etc. The use of diuretics may improve plasma volume expansion in patients and anticholinergics may treat gastrointestinal discomfort. The increase in blood urea nitrogen may be due to the high protein load associated with the infusion of HBOC-201. A transient increase in hepatic transaminase and pancreatic enzyme concentrations is not usually associated with hepatic or pancreatic dysfunction (19). This may be due to an increase in metabolic load after absorption, distribution, metabolism, and excretion of HBOC-201 involving the hepatopancreatic system (19), resulting in upregulation of enzyme activity or it may be due to very slight damage to hepatocytes and pancreatic cells during the catabolism of HBOC-201. The mechanisms of elevated hepatic and pancreatic enzymes and the clinical significance need to be explored more specifically and in detail in future clinical studies. The skin discoloration and serum discoloration caused by HBOC-201 will not cause problems in pulse oximetry monitoring. The above-mentioned AEs are transient, but close observation and documentation of HBOC-201 in the clinical setting are still required to allow clinical decision-makers to respond promptly with active intervention.

CONCLUSION

Various clinical scenarios of ischemia and hypoxia need to be corrected in time to reduce the sequelae and mortality of patients. HBOC-201 has many potential advantages including being easily available, not affected by storage, and the ability to transport oxygen more efficiently than Hb in RBCs, which is currently a more desirable oxygen carrier. A large amount of evidence shows that HBOC-201 can be used as a temporary oxygen bridge, not only can improve the oxygenation of tissues and organs in emergency situations until the RBCs *in vivo* recover enough oxygen-carrying capacity, but also can provide oxygen to ischemic and hypoxic tissues or/and organs to mitigate ischemia-reperfusion injury. Based on the safety considerations of HBOC-201, clinicians would pay attention to monitoring and recording AEs related to cardiovascular, methemoglobin, clinically relevant liver enzymes and pancreatic enzymes, kidney, gastrointestinal disorders, skin and sclera color, etc. Due to different clinical scenarios, the application of HBOC-201 dosage and protocols would be further explored in the future and individualized treatment of patients will be carried out to maximize potential benefits and minimize adverse consequences. In addition, multicenter randomized clinical trials with large sample sizes would be implemented to obtain high-quality evidence to further verify the efficacy, safety, and tolerability of HBOC-201.

AUTHOR CONTRIBUTIONS

MC, DZ, and XH conceived the idea, coordinated the staff involved in this study, and wrote the first draft. YZ, HHe, RY, and LP revised manuscript critically for important intellectual content. HHu, YR, QQ, XY, TY, and LM were involved in the data collection and checked the data. DZ and XH were responsible for final edits and general revisions. All the authors have read and approved the final version of the manuscript.

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Impact of Comorbidities on Beneficial Effect of Lactated Ringers vs. Saline in Sepsis Patients

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Background: Lactated Ringers reduced mortality more than saline in sepsis patients but increased mortality more than saline in traumatic brain injury patients.

Method: This prospective cohort study was conducted in a medical intensive care unit (ICU) in central Taiwan. We applied standard sepsis evaluation protocol and identified heart, lung, liver, kidney, and endocrine comorbidities. We also evaluated resuscitation response with central venous pressure, central venous oxygen saturation, and serum lactate level simultaneously. Propensity-score matching and Cox regression were used to estimate mortality. The competing risk model compared the lengths of hospital stays with the subdistribution hazard ratio (SHR).

Results: Overall, 938 patients were included in the analysis. The lactated Ringers group had a lower mortality rate (adjusted hazard ratio, 0.59; 95% CI 0.43-0.81) and shorter lengths of hospital stay (SHR, 1.39; 95% C.I. 1.15-1.67) than the saline group; the differences were greater in patients with chronic pulmonary disease and small and non-significant in those with chronic kidney disease, moderate to severe liver disease and cerebral vascular disease. The resuscitation efficacy was the same between fluid types, but serum lactate levels were significantly higher in the lactated Ringers group than in the saline group (0.12 mg/dl/h; 95% C.I.: 0.03, 0.21), especially in chronic liver disease patients. Compared to the saline group, the lactated Ringers group achieved target glucose level earlier in both diabetes and non-diabetes patients.

Conclusion: Lactate Ringer's solution provides greater benefits to patients with chronic pulmonary disease than to those with chronic kidney disease, or with moderate to severe liver disease. Comorbidities are important in choosing resuscitation fluid types.

Keywords: fluid therapy, intensive care, resuscitation, saline, lactated Ringers

INTRODUCTION

The fourth edition of the Surviving Sepsis Campaign suggests using either balanced crystalloids or saline for fluid resuscitation in sepsis patients (1). Recently, a large, pragmatic randomized trial found that critically ill adult patients receiving balanced crystalloids had lower rates of the composite outcome of death and renal adverse events than those receiving saline (2). Our latest network meta-analysis also found a lower risk of mortality in sepsis patients treated with balanced crystalloids than in those treated with saline (3). In contrast, balanced crystalloids increased mortality in traumatic brain injury patients (3). Therefore, both the fluid types and patient condition need to be considered when choosing an optimal fluid treatment.

Saline and balanced crystalloids, such as lactated Ringers, have different fluid osmolalities (saline: isotonic, 308 mOsm/kg; lactated Ringers: hypotonic, 273 mOsm/kg) and contain different electrolyte composites and lactate metabolites, resulting in varying risks for ineffective increases in central venous pressure, hyperkalemia, acidosis or glucose instability, especially in sepsis patients with cormobidities (4). Saline solution contains no potassium or other chemical compounds, while lactated Ringers solution contains 4 mmol/L potassium and 28 mmol/L sodium lactate. The excessive potassium in lactated Ringers may specifically lead to hyperkalemia in chronic kidney disease patients (5). Seventy percent of serum lactate undergoes gluconeogenesis, which can potentially lead to an increase in blood glucose levels and instability, and these effects might be more significant in diabetes patients (6, 7). Thirty percent of serum lactate undergoes oxidation in the liver, producing HCO_3^-, which helps limit acidosis during sepsis. However, lactate metabolism is impaired in chronic liver disease patients, and thus, the acidosis prevention effect of lactated Ringers in chronic liver disease patients is questionable (8, 9).

This study aimed to investigate differences in mortality and lengths of stay in the intensive care unit (ICU) and hospital in sepsis patients treated with lactated Ringers or saline. Subgroup analyses of sepsis patients with different comorbidities, including chronic pulmonary disease, chronic kidney disease, chronic liver disease and diabetes, were also performed. The differences in trends of central venous pressure, central venous oxygen saturation, and the serum lactate level between fluid types were also investigated to compare their resuscitation efficacy. During and after the resuscitation periods, we compared the trends of serum potassium in patients with and without chronic kidney disease, the trends of blood glucose levels in diabetes and non-diabetes patients, and the trends of serum lactate in patients with and without chronic liver disease.

Abbreviations: SHR, subdistribution hazard ratio; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; HbA1c, Hemoglobin A1c; CoV, coefficient of variation; MAGE, mean amplitude of glycemic excursion.

METHODS

Study Population and Care Protocols

This study was conducted at medical ICU of a tertiary-care referral hospital with 1,514 beds in central Taiwan. For sepsis patients who met the criteria (10), we implemented bundled care and included them in this study. The sepsis bundles include (1) guided fluid resuscitation considering lactate clearance, mixed venous oxygen saturation, and urine volume; (2) early empiric antibiotic prescription rules, (3) glucose control protocols, (4) protective ventilator settings, (5) c-reactive protein, procalcitonin, B-type natriuretic peptide, HbA1C, and albumin levels before fluid resuscitation, and (6) lactate and mixed venous oxygenation levels, which are checked every 6 h for every sepsis patient in the first 24 h. Among the bundles, the glucose target was 140∼180 mg/dl. An insulin sliding scale was applied for glucose levels higher than 180 mg/dl. The frequency of the one-touch glucose examination was every 4 h if the blood glucose level was lower than 180 mg/dl or every 2 h if the blood glucose level was higher than 180 mg/dl.

Databases of the sepsis management registry and electronic medical records which were collected prospectively were used for retrospective analysis. The protocol was approved by the Institutional Review Board of the Veteran General Hospital Taichung (IRB no. CF16017A). According to their resuscitation fluid profiles in the first 24 h, patients were divided into two groups: the saline group, who received mainly saline for resuscitation and <500 ml of lactated Ringers, and the lactated Ringers group, who received more than 500 ml of lactated Ringers in the first 24 h. In the sensitivity analysis, we further separated patients into three groups: the saline only, saline predominant (more saline in the total fluid amount) and lactated Ringers predominant groups (more lactated Ringers in the total fluid amount). Definitions of comorbidities, including chronic kidney disease, diabetes, mild or moderate to severe liver disease, congestive heart failure, and cerebral vascular disease, followed those of the Charlson Comorbidity Index (11) (**Supplementary Table 1**). We also recorded blood transfusion volumes, including red blood cells and fresh frozen plasma, and hemodialysis events for every patient.

Statistical Methods for Mortality and Lengths of Stay in the ICU and Hospital

The differences in patient characteristics between two fluid type groups were compared by using Pearson's chi-squared test for categorical variables and Student's *t*-test for continuous variables. As our cohort was not randomly assigned to the two fluid type groups, we used propensity-score matching by fluid type to control for potential confounding factors and selection bias (12), thereby optimizing comparability between the saline group and lactated Ringers group (13). We entered the APACHE score, age and HbA1c level into the logistic regression analysis to compute propensity scores for each participant. The propensity score represented the probability of a patient with sepsis being assigned to the lactated Ringers group. Based on the propensity score, patients who received lactated Ringers were matched with two patients who received saline, and then we created propensity

score-matched sets for the Cox proportional hazard model to estimate the hazard ratio of 90-day mortality. In addition, we also performed a logistic regression analysis to compare 90-day mortality between the saline group and lactated Ringers group (14). Finally, we used the competing risk model to estimate the subdistribution hazard ratios (SHRs) for the lengths of ICU and hospital stays (15, 16). We considered death a competing risk, and discharge from the ICU or hospital was the event of interest. We hypothesized that resuscitation fluid with fewer complications would lead to a shorter length of ICU stay and earlier discharge. We also compared the lengths of ICU stay and hospital stay between patients with and without comorbidities.

Statistical Method for Repeated Measured Data

Mixed-effect linear models were used to analyze changes in the following clinical variables during and after the resuscitation period: central venous pressure, central venous oxygen saturation, serum bicarbonate, serum lactate, creatinine, urine output, serum potassium and blood glucose. Interaction terms between fluid types and changes in those clinical variables were included to investigate whether patients receiving these two fluids showed different trends. All statistical tests were performed with Stata version 14.0 (StataCorp, Texas, USA).

Statistical Method for Glycemic Variability

We used the mean amplitude of glycemic excursions (MAGE) (17) and coefficient of variation (CoV) (18) to assess glycemic variability. The MAGE represents the mean blood glucose value exceeding the standard deviation from the 24-h mean blood glucose level, and CoV represents the ratio of the standard deviation to the mean glucose level. A high blood glucose index and low blood glucose index represent the risks of hyperglycemia and hypoglycemia, respectively (19). The glucose index was derived from a logarithmic transformation of the blood glucose scale that assigned maximum risk to blood glucose of 20 and 600 ml/dl and zero risk to 112.5 mg/dl (20). The above glycemic parameters were calculated using EasyGV software (21).

RESULTS

Baseline Patient Characteristics

We assessed 1,141 cases for eligibility and included 938 sepsis patients for analysis (**Figure 1**). The saline group and lactated Ringers group included 636 and 302 patients, with male percentages of 76.1 and 73.8%, mean ages of 71.9 and 70.7, and mean Acute Physiology and Chronic Health Evaluation (APACHE) scores of 26.0 ± 6.9 and 29.0 ± 6.4, respectively (**Table 1**). The total fluid resuscitation volume on day 1 was not significantly different between the saline and lactated Ringers groups (4,591 vs. 4,959 ml, $p = 0.157$). The results of laboratory tests, including HbA1c, procalcitonin, c-reactive protein, B-type natriuretic peptide and albumin, before fluid resuscitation were not significantly different between the two groups (**Table 1**).

Mortality and Lengths of ICU and Hospital Stays

Overall Kaplan-Maier curve for 90-day mortality between saline and lactated Ringers was shown in **Figure 2**. The propensity score distributions between the saline group and lactated Ringers group were similar after matching (**Supplementary Table 2**). In the propensity-score matched Cox regression analysis, the lactated Ringers group had a lower risk of mortality than the saline group (adjusted hazard ratio, 0.59; 95% CI 0.43-0.81). In the logistic regression analysis for 90-day mortality, the lactated Ringers group also had lower odds of mortality than the saline group (adjusted odds ratio, 0.68; 95% CI 0.51-0.92). In the competing risk regression analysis for length of ICU stay, patients resuscitated with lactated Ringers were discharged from the ICU (SHR, 1.41; 95% CI 1.17-1.71) and hospital (SHR, 1.39; 95% C.I. 1.15-1.67) earlier than those resuscitated with saline. We

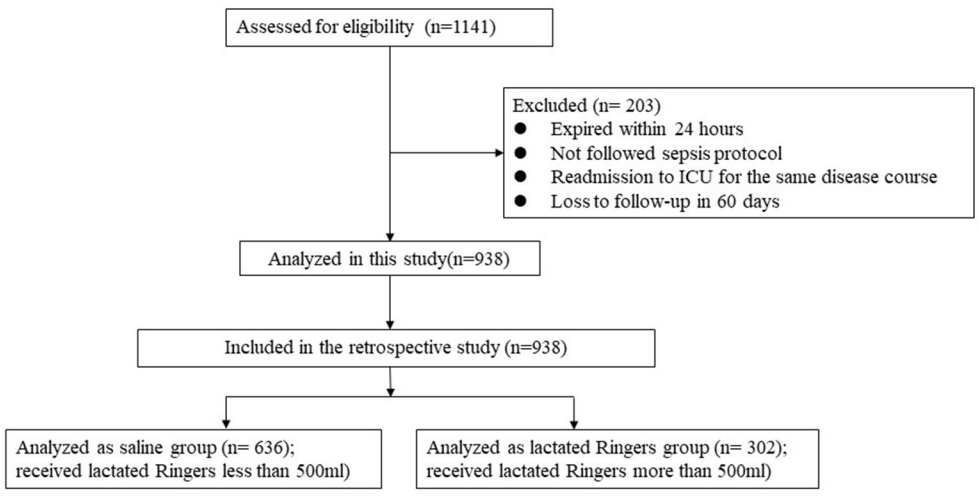

FIGURE 1 | STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) flow chart of study participants.

TABLE 1 | Patient's characteristics according to types of fluid resuscitation.

	Saline group	Lactated Ringer's group	*P*-value
No. of case	636	302	
Gender, *n* (%)			
Male	484 (76.1)	223 (73.8)	0.466
Female	152 (23.8)	79 (26.2)	
Age, mean (SD)	71.9 (15.8)	70.7 (15.3)	0.277
Body mass index, mean (SD)	23.2 (4.4)	23.0 (4.6)	0.613
APACHE II score, mean (SD)	26.0 (6.9)	29.0 (6.4)	<0.001
Total fluid resuscitation in day 1, mean (SD)	4,591 (3,778)	4,959 (3,602)	0.157
Saline fluid amount in day 1, mean (SD)	4,587 (3,776)	1,787 (2,362)	<0.001
Lactated Ringer's fluid amount in day 1, mean (SD)	3.9 (44.2)	3,172 (2442)	<0.001
Comorbidity			
Coronary artery disease, *n* (%)	68 (10.7)	26 (8.6)	0.353
Congestive heart failure, *n* (%)	156 (24.5)	68 (22.5)	0.513
Cerebral vascular disease, *n* (%)	214 (33.6)	83 (31.0)	0.413
Chronic pulmonary disease, *n* (%)	318 (50)	141 (46.7)	0.364
Chronic kidney disease, *n* (%)	45 (7.1)	33 (10.9)	0.057
Chronic liver disease, *n* (%)	29 (4.6)	15 (5.0)	0.869
Diabetes, *n* (%)	316 (49.7)	135 (44.7)	0.162
Laboratory exam before resuscitation			
HbA1C (%), mean (SD)	6.3 (1.4)	6.5 (1.5)	0.186
Procalcitonin (ng/ml), mean (SD)	18.7 (31.0)	18.8 (31.3)	0.979
c-reactive protein (mg/dl), mean (SD)	15.7 (11.7)	14.5 (11.3)	0.162
B-type natriuretic peptide (pg/ml), mean (SD)	8,911 (10,659)	8,385 (10,859)	0.562
Albumin (g/dl), mean (SD)	2.6 (0.7)	2.7 (0.6)	0.013

SD, Standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation.

divided patients into three subgroups according to the saline fluid amount they received. The results showed that both the lactated Ringers predominant group (SHR, 1.49; 95% CI 1.18-1.88) and saline predominant group (SHR, 1.32; 95% CI 1.02-1.71) had significantly shorter ICU stays than the saline group (**Table 2**). Regarding the subgroup analyses stratified by comorbidities (**Table 3**), the use of lactated Ringers, compared to the use of saline, significantly reduced the length of stay in the ICU in patients with chronic pulmonary disease (SHR, 1.80; 95% CI 1.37, 2.36), without chronic kidney disease (SHR, 1.48; 95% CI 1.21, 1.80), without moderate to severe liver disease (SHR, 1.44; 95% CI 1.19, 1.75), and without cerebral vascular disease (SHR, 1.54; 95% CI 1.22, 1.95). No significant differences were found between the two types of fluids in patients without chronic pulmonary disease (SHR, 1.17; 95% CI 0.89, 1.53), with chronic kidney disease (SHR, 077; 95% CI 0.35, 1.70), with moderate to severe liver disease (SHR, 1.01; 95% CI 0.32, 3.17), and with cerebral vascular disease (SHR, 1.27; 95% CI 0.92, 1.76).

Relationships Between Fluid Types and Clinical Variables Associated With Resuscitation

Central venous pressure trends consistently increased in the first 24 h (0.19 mmHg/h; 95% C.I.: 0.15, 0.55) in both the saline group and lactated Ringers group, and the trends were not significantly different between the two groups (0.04 mmHg/h; 95% C.I.: −0.02, 0.11) (**Figure 3A**). Central venous oxygen saturation trends were also not significantly different between the two groups (0.52%/h, 95% C.I.: −1.2, 1.19) (**Figure 3B**). Serum bicarbonate progressively decreased in the saline group (−0.58 mmol/L/h; 95% C.I.: −0.73, −0.42) but increased significantly in the lactated Ringers group (0.85 mmol/L/h; 95% C.I.: 0.64, 1.06) (**Figure 3C**). The serum lactate levels decreased in the first few hours in both groups; it continued to decrease for 72 h in the saline group (−0.35 mg/dl/h; 95% C.I.: −0.41, −0.30) but remained abnormally high in the lactated Ringers group from 12 to 72 h (0.12 mg/dl/h; 95% C.I.: 0.03, 0.21) (**Figure 3D**). For the first 7 days, serum creatinine and urine output trends were not significantly different between the saline group and lactated Ringers group (**Figures 3E,F**).

Relationships Between Fluid Types and Serum Potassium and Blood Glucose

Serum potassium levels were higher than normal on admission to the ICU and gradually decreased in the first 72 h in the saline subgroup without chronic kidney disease (−0.02 mmol/L/h; 95% CI: −0.02, −0.01) but remained in the normal upper limit in the saline subgroup with chronic kidney disease (−0.01 mmol/L/h; 95% CI: −0.02, 0.01). The serum potassium trends between the saline group and lactated Ringers group were not significantly different in patients with or without chronic kidney disease (**Figure 4A**). Blood glucose in the first 24 h consistently remained higher than normal in the saline group in both diabetes (0.15 mg/dl/h; 95% CI: −0.28, 0.31) and non-diabetes patients (0.28; 95% CI: 0.06, 0.51); in the lactated Ringers group, the blood glucose level approached the target level in both patients with diabetes (−1.25 mg/dl/h; 95% CI: −1.78, −0.71) and patients without diabetes (−0.83 mg/dl/h; 95% CI: −1.21, −0.44) (**Figure 4B**). In patients receiving lactated Ringers, the serum lactate level was significantly higher in patients with moderate to severe liver disease than in patients without liver disease ($p = 0.045$) (**Figure 4C**).

Relationships Between Fluid Types and Glycemic Variability (MAGE, CoV)

Compared to the saline group, the lactated Ringers group had a significantly lower glucose CoV (−1.78%, 95% CI: −3.34, −0.23) and a lower MAGE (−0.51%, 95% CI: −0.89, −0.13). The high blood glucose index was significantly lower in the lactated Ringers group than in the saline group (−3.17, 95% CI: −4.40, −1.95), but the low blood glucose index was not significantly different (0.03, 95% CI: −0.66, 0.71) (**Table 4**).

The proportions of patients requiring hemodialysis in the first 7 days were 27.4% in the saline group and 28.5% in the lactated Ringers group. The red blood cell transfusion volumes in the first

7 days were 443.4 ml (95% CI: 405.79, 480.99) in the saline group and 427.98 ml (95% CI: 370.75, 485.21) in the lactated Ringers group. The fresh frozen plasma transfusion volume in the first 7 days was significantly higher in the saline group (0.55 units, 95% CI: 0.45, 0.64) than in the lactated Ringers group (0.36 units, 95% CI: 0.22, 0.50) (**Supplementary Table 3**).

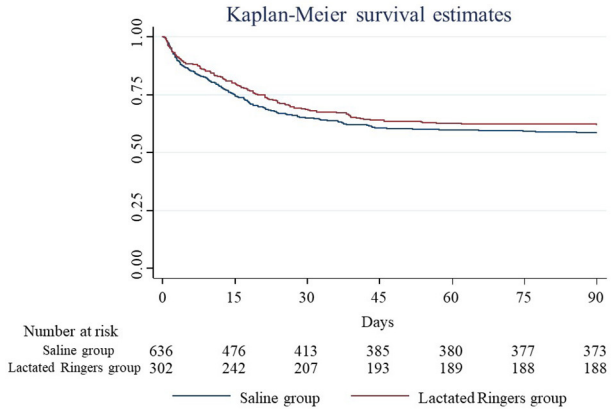

FIGURE 2 | Kaplan-Maier curve for 90-day mortality.

DISCUSSION

This prospective cohort study found that using lactated Ringers solution for resuscitation in sepsis patients decreased mortality and shortened the lengths of ICU and hospital stays compared with using saline, especially in patients with chronic pulmonary disease, without chronic kidney disease, without moderate to severe liver disease and without cerebral vascular disease. The trends for central venous pressure and oxygen saturation during the resuscitation period were similar between the saline group and lactated Ringers group, but the serum lactate level after resuscitation was significantly higher in the lactated Ringers group, especially in the chronic liver disease subgroup. The serum potassium level increased in the first few hours but recovered

TABLE 2 | Mortality analysis and competing risk analysis for length of stay in intensive care unit and hospital.

Propensity score matching cox regression analysis for 90-days mortality			
Outcome	**Comparison**	**Adjusted hazard ratio**	***P*-value**
90 days mortality	Lactated Ringer's group vs. saline group	0.59 (0.43-0.81)	<0.001
Logistic regression analysis for 90-days mortality			
Outcome	**Comparison**	**Adjusted odd ratio**	***P*-value**
90 days mortality	Lactated Ringer's group vs. saline group	0.68 (0.51, 0.92)	0.013
	APACHE	1.09 (1.07, 1.12)	<0.001
Logistic regression analysis for 90-days mortality with three saline exposure level			
Outcome	**Comparison**	**Adjusted odd ratio**	***P*-value**
90 days mortality	Saline predominant vs. saline only group	0.74 (0.50, 1.11)	0.142
	Lactated Ringer's predominant vs. saline only group	0.64 (0.44, 0.93)	0.019
	APACHE	1.09 (1.07, 1.12)	<0.001
Competing risk analysis for ICU and hospital stay			
Outcome	**Comparison**	**SHR (95% C.I.)**	***P*-value**
Length of ICU day	Lactated Ringer's group vs. saline group	1.41 (1.17, 1.71)	<0.001
	15.9 (13.7∼16.1) vs. 17.8 (16.6∼19.7)		
	APACHE	0.95 (0.93, 0.96)	<0.001
Length of hospital day	Lactated Ringer's group vs. saline group	1.39 (1.15, 1.67)	<0.001
	26.0 (23.2∼28.0) vs. 29.7 (27.9∼32.2)		
	APACHE	0.95 (0.93, 0.96)	<0.001
Competing risk analysis for ICU and hospital stay with three saline exposure level			
Outcome	**Comparison**	**SHR (95% C.I.)**	***P*-value**
Length of ICU day	Lactated Ringer's predominant vs. saline only group	1.49 (1.18, 1.88)	0.001
	15.3 (13.4∼16.3) vs. 17.8 (16.6∼19.7)		
	Saline predominant vs saline only group	1.32 (1.02, 1.71)	0.034
	15.0 (12.5∼16.9) vs. 17.8 (16.6∼19.7)		
	APACHE	0.95 (0.93, 0.96)	<0.001
Length of hospital day	Lactated Ringer's predominant vs. saline only group	1.44 (1.14, 1.81)	0.002
	24.5 (22.0∼28.0) vs. 29.7 (27.9∼32.2)		
	Saline predominant vs. saline only group	1.32 (1.01, 1.71)	0.037
	27.0 (23.5∼29.7 vs. 29.7 (27.9∼32.2)		
	APACHE	0.95 (0.93, 0.96)	<0.001

SHR, subdistribution hazard ratio.

TABLE 3 | Competing risk analysis for length of stay in intensive care unit and hospital in different comorbidities.

Comorbidities	No. of cases	Length of ICU day		Length of hospital day	
		SHR* (95% C.I.)	*P*-value	SHR* (95% C.I.)	*P*-value
Chronic pulmonary disease (CPD)					
No CPD	467	1.17 (0.89, 1.53)	0.258	1.13 (0.87, 1.48)	0.356
With CPD	447	1.80 (1.37, 2.36)	<0.001	1.78 (1.36, 2.34)	<0.001
Chronic kidney disease (CKD)					
No CKD	838	1.48 (1.21, 1.80)	<0.001	1.44 (1.18, 1.75)	<0.001
With CKD	76	0.77 (0.35, 1.70)	0.525	0.82 (0.36, 1.85)	0.635
Acute kidney injury or CKD					
No AKI or CKD	373	1.35 (1.04, 1.76)	0.026	1.34 (1.02, 1.75)	0.032
With AKI or CKD	528	1.28 (0.96, 1.70)	0.094	1.25 (0.94, 1.66)	0.125
Mild liver disease (LD)					
No liver disease	676	1.38 (1.11, 1.72)	0.004	1.36 (1.09, 1.69)	0.006
With mild liver disease	238	1.49 (1.02, 2.18)	0.039	1.42 (0.97, 2.06)	0.068
Moderate to severe LD					
No liver disease	873	1.44 (1.19, 1.75)	<0.001	1.41 (1.16, 1.71)	<0.001
With moderate to severe LD	41	1.01 (0.32, 3.17)	0.984	1.01 (0.33, 3.40)	0.924
Cerebral vascular disease (CVD)					
No CVD	615	1.54 (1.22, 1.95)	<0.001	1.52 (1.20, 1.93)	0.001
With CVD	299	1.27 (0.92, 1.76)	0.148	1.24 (0.90, 1.71)	0.183
Congestive heart failure (CHF)					
No CHF	696	1.39 (1.11, 1.72)	0.003	1.36 (1.09, 1.68)	0.006
With CHF	218	1.54 (1.05, 2.27)	0.028	1.55 (1.05, 2.28)	0.026
Diabetes mellitus					
No diabetes mellitus	472	1.41 (1.09, 1.81)	0.008	1.43 (1.10, 1.84)	0.007
With diabetes mellitus	442	1.43 (1.07, 1.91)	0.015	1.34 (1.01, 1.77)	0.041
Rheumatology disease (RD)					
No RD	838	1.32 (1.08, 1.61)	0.006	1.30 (1.07, 1.59)	0.009
With RD	76	2.71 (1.34, 5.51)	0.006	2.35 (1.26, 4.38)	0.007
Malignancy					
No Malignancy	505	1.47 (1.16, 1.87)	0.002	1.46 (1.14, 1.85)	0.002
With Malignancy	409	1.33 (0.98, 1.80)	0.071	1.27 (0.94, 1.71)	0.122

**SHR, Subdistribution hazard ratio; lactated Ringer's group compared to saline group (reference group).*

more slowly in patients with chronic kidney disease regardless of fluid type. Blood glucose reached the target level faster and the glycemic variability was lower in the lactated Ringers group, which may suggest that lactated Ringers helps stabilize blood glucose levels during and after resuscitation.

Our analysis further confirmed that sepsis patients treated with saline had increased mortality compared to those treated with lactated Ringers (2). Evidence has also suggested that saline prolongs the ICU stay and hospital stay due to the increased risk of hyperchloremia acidosis, endothelial glycocalyx damage-related interstitial edema, renal vessel constriction-related kidney injury, and the need for blood product transfusion (22). However, the reduced risk of acidosis and shortened length of ICU stay associated with the use of lactated Ringers were observed in only sepsis patients without chronic kidney disease and without chronic liver disease. This implies that intact kidney and liver functions play important roles in the efficacy of lactated Ringers in inducing acidosis prevention effects. On the other hand, the use of lactated Ringers shortened the ICU length of stay in sepsis patients with chronic pulmonary disease but not in those without; this phenomenon seems to suggest that the acidosis prevention effect of lactated Ringers is especially important for patients with chronic pulmonary disease who often and easily develop respiratory acidosis.

The difference in osmolality did not seem to affect resuscitation efficacy, as the trends of central venous pressure and central venous oxygen saturation were not significantly different between the two fluid groups. However, the lactate levels during and after resuscitation were higher in the lactated Ringers group. This indicates that lactated Ringers may increase the serum lactate level during the resuscitation period. Thus, we cannot use the decreasing trend of serum lactate as a surrogate for perfusion restoration and resuscitation efficacy, especially in patients who receive lactated Ringers as the main resuscitation fluid (23).

The risk of hyperkalemia in patients who receive lactated Ringers, especially those with chronic kidney disease, is a concern. Our analysis found that the serum potassium level increased in the first few hours, and the time to return to normal was not different between the saline and lactated Ringers groups. However, the rate of recovery was slower in

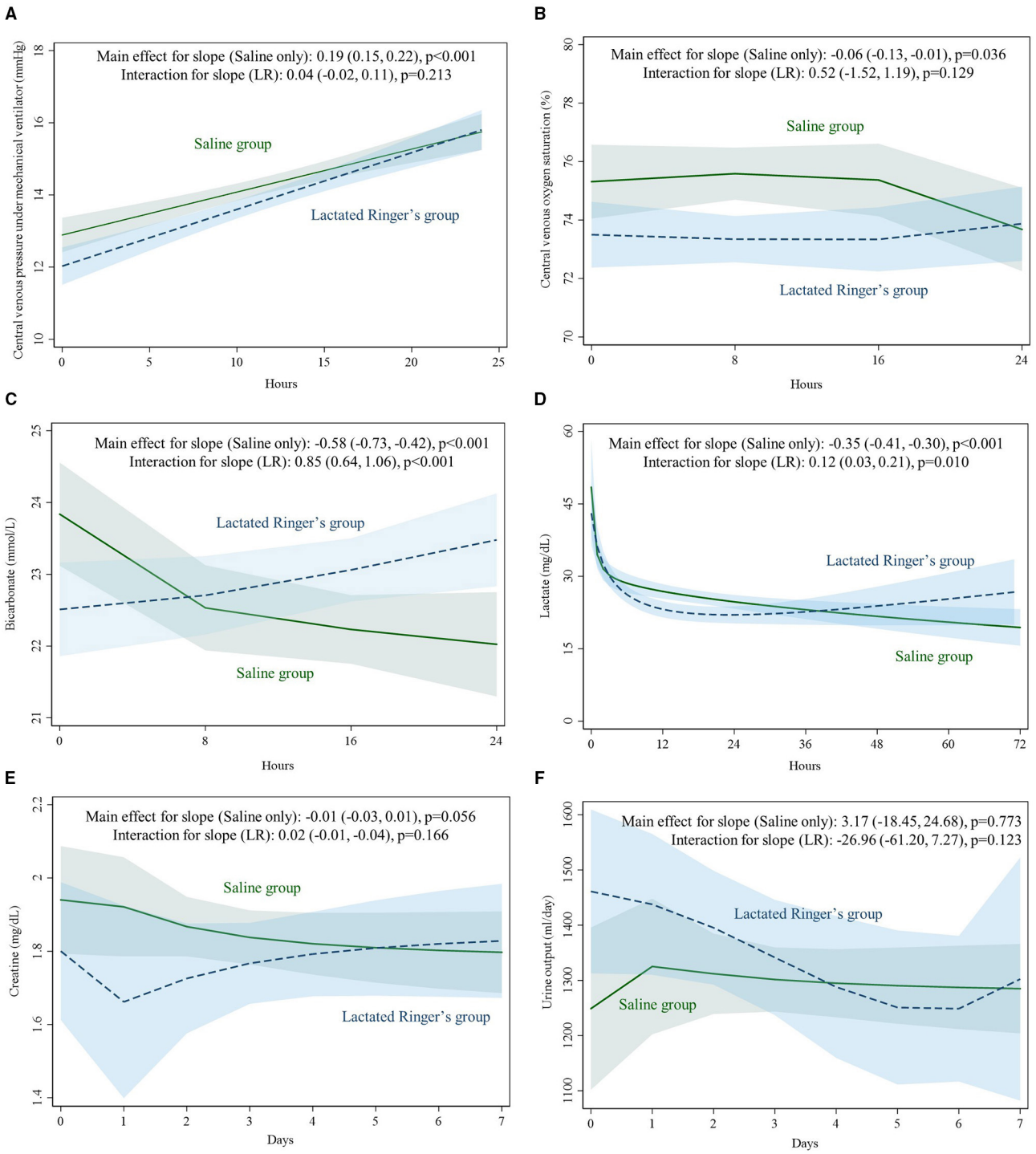

FIGURE 3 | (A–F) Trends for central venous pressure, central venous oxygen saturation, serum bicarbonate, lactate, creatinine changes and urine output among fluid types and diabetes status. LR, lactated Ringer's.

chronic kidney disease patients. Another study found that the hyperkalemia risk was lower in chronic kidney disease patients among patients who received lactated Ringers (24). This implies that the acid-base effects of saline are more important for serum potassium homeostasis than those induced by the small amount of potassium in lactated Ringers fluid.

Lactated Ringers solution delays glycemic recovery in diabetic ketoacidosis, but acidosis recovery is faster with the administration of lactated Ringers solution (7). Our study found that in the lactated Ringers group, the initially high glucose level decreased to the target glucose level faster than that in the saline group. Lactated Ringers also decreased glycemic variability and

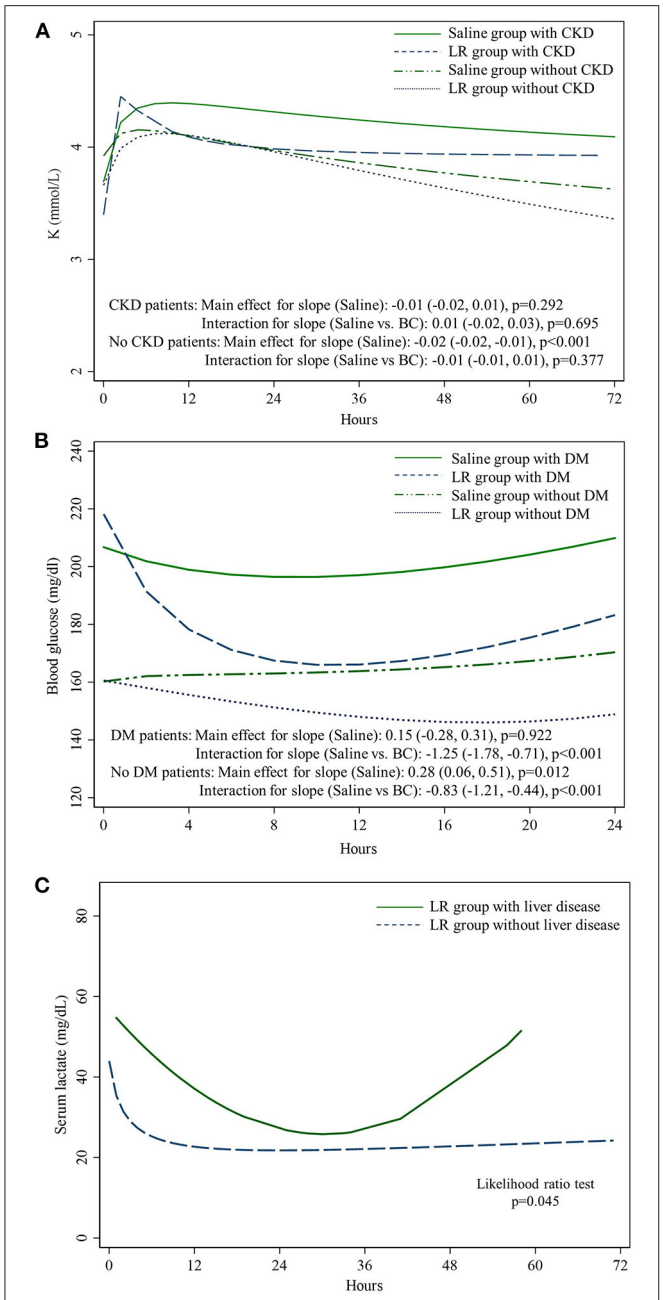

FIGURE 4 | Trends for **(A)** serum potassium among fluid types and chronic kidney status, **(B)** blood sugar changes among fluid types and diabetes status, **(C)** serum lactate in patient with or without moderate to severe liver disease. K, potassium; LR, lactated Ringer's; CKD, chronic kidney disease; DM, diabetes mellitus.

decreased the risk for high blood glucose. This could be explained by the fact that the balanced electrolyte distribution in lactated Ringers may help stabilize blood glucose levels. Finally, in patients with moderate to severe liver disease, lactate metabolism and thus the acidosis-prevention effect were impaired. This may explain why the lactate level remained high during and after resuscitation in liver disease patients.

The strength of this study was that we collected detailed comorbidity data and implemented standard care bundles, including regularly evaluating resuscitation targets to adjust fluid volume administration, collecting baseline laboratory data, and implementing standard glucose control and glucose target protocols. This helped to control all possible confounding factors. Our study also had some limitations. First, the choice of lactated Ringers or saline was dependent on physician preference. Second, resuscitation fluid volume and types before ICU admission were not available. The APACHE score in the lactated Ringers group was higher than that in the saline group. We consider this confounding factor in the adjusted regression model.

TABLE 4 | Adjusted glycemic variability and fluid types.

	Diabetes mellitus	APACHE	Lactated Ringer's group vs. Saline only
CoV (%)	1.64 (0.21, 3.08)*	0.14 (0.03, 0.24)**	−1.78 (−3.34, −0.23)*
MAGE	0.41 (0.06, 0.75)*	0.02 (−0.01, 0.05)	−0.51 (−0.89, −0.13)**
HBGI	5.47 (4.35, 6.60)***	0.05 (−0.04, 0.13)	−3.17 (−4.40, −1.95)***
LBGI	−0.22 (−0.85, 0.41)	0.09 (0.04, 0.13)***	0.03 (−0.66, 0.71)

** <0.05, ** <0.01, *** <0.001.*

CoV, coefficient of variation; MAGE, mean amplitude of glycemic excursion; HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index.

CONCLUSIONS

Lactated Ringers use was associated with lower mortality and shorter lengths of ICU and hospital stays, and these beneficial effects were observed in patients with chronic pulmonary disease, without chronic kidney disease, without chronic liver disease and without cerebral vascular disease. Lactated Ringers use was associated with higher serum lactate levels, especially in liver disease patients. The glucose levels during resuscitation were highest in diabetes patients receiving saline and lowest in non-diabetes patients receiving lactated Ringers.

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 protocol was approved by the Institutional Review Board of the Veteran General Hospital Taichung (IRB no. CF16017A). Written informed consent was not provided because identifications were deidentified by hospital.

AUTHOR CONTRIBUTIONS

C-HT: data curation and writing—original draft preparation. T-TC: conceptualization, methodology, data curation, and conceptualization. M-CC: conceptualization and validation. K-YC and S-MW: data curation and conceptualization. M-CS: software and validation. Y-KT: supervision conceptualization, reviewing, and editing. 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.2021.758902/full#supplementary-material

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Reintubation Summation Calculation: A Predictive Score for Extubation Failure in Critically Ill Patients

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Objective: To derive and validate a multivariate risk score for the prediction of respiratory failure after extubation.

Patients and methods: We performed a retrospective cohort study of adult patients admitted to the intensive care unit from January 1, 2006, to December 31, 2015, who received mechanical ventilation for ≥48 h. Extubation failure was defined as the need for reintubation within 72 h after extubation. Multivariate logistic regression model coefficient estimates generated the **R**e-**I**ntubation **S**ummation **C**alculation (RISC) score.

Results: The 6,161 included patients were randomly divided into 2 sets: derivation (n = 3,080) and validation (n = 3,081). Predictors of extubation failure in the derivation set included body mass index <18.5 kg/m^2 [odds ratio (OR), 1.91; 95% CI, 1.12–3.26; P = 0.02], threshold of Glasgow Coma Scale of at least 10 (OR, 1.68; 95% CI, 1.31–2.16; P < 0.001), mean airway pressure at 1 min of spontaneous breathing trial <10 cmH_2O (OR, 2.11; 95% CI, 1.68–2.66; P < 0.001), fluid balance ≥1,500 mL 24 h preceding extubation (OR, 2.36; 95% CI, 1.87–2.96; P < 0.001), and total mechanical ventilation days ≥5 (OR, 3.94; 95% CI 3.04–5.11; P < 0.001). The C-index for the derivation and validation sets were 0.72 (95% CI, 0.70–0.75) and 0.72 (95% CI, 0.69–0.75). Multivariate logistic regression demonstrated that an increase of 1 in RISC score increased odds of extubation failure 1.6-fold (OR, 1.58; 95% CI, 1.47–1.69; P < 0.001).

Conclusion: RISC predicts extubation failure in mechanically ventilated patients in the intensive care unit using several clinically relevant variables available in the electronic medical record but requires a larger validation cohort before widespread clinical implementation.

Keywords: critical care medicine, extubation failure, intensive care unit, mechanical ventilation, reintubation, predictive modeling, prediction scale

INTRODUCTION

Before extubating a mechanically ventilated patient, intensivists must evaluate the patient's risk of extubation failure (EF). This decision is usually based on the results of a rapid shallow breathing index (RSBI), which is most often assessed during the readiness evaluation to identify patients who may proceed with the spontaneous breathing trial (SBT), with either a T-piece or low-level pressure support (1–3). The RSBI is the ratio of respiratory frequency to tidal volume and is a commonly used weaning predictor (1–3). This method is not 100% predictive of extubation success (ES) by 72 h. The decision-making behind extubation is critically important, as failed extubation occurs in 10–20% of intensive care unit (ICU) patients (4, 5) and both delayed extubation as well as early extubation are associated with worse outcomes. Extubation delay is associated with ventilator-associated pneumonia (6, 7), increased length of stay, increased risk for downstream tracheostomy (8, 9) and increased mortality in brain-injured patients (8). Extubation failure after planned extubation is associated with adverse outcomes including increased hospital mortality, prolonged hospital stay, higher costs, and greater need for tracheotomy and transfer to post-acute care (10–13).

While there are numerous ventilator weaning predictors and types of SBTs (14, 15), there is a paucity of data on risk factors that predict EF prior to removal of the endotracheal tube. Predicting factors for ES and EF include amount of endotracheal secretions (8, 16, 17), cough strength (16, 18, 19), and mental status prior to extubation after a successful SBT (16, 20). Patients with moderate or abundant secretions have been 3–8 times more likely to fail extubation than those with few to no secretions (8, 19). Coplin et al. (16) stated that the Glasgow coma scale (GCS) score alone did not predict extubation outcome in brain-injured patients and should not be used to exclude extubation; however, other investigators reported that impaired mental status did predict EF (21, 22). Moreover, patients who fail extubation often retain carbon dioxide because of an imbalance among respiratory muscle strength and imposed load (1, 23–25). Patients extubated while developing hypercapnia ($PaCO_2$ >45 mmHg) during a successful SBT may also have an increased risk of mortality due to respiratory failure compared to those who do not develop hypercapnia during SBT (2).

Therefore, we hypothesized that recurrent respiratory failure requiring reintubation after initial extubation could be estimated using a composite score of known risk factors available in the electronic medical record (EMR). Our main objective was to derive a simple clinical prediction tool using a multivariate model and validate the **R**e-**I**ntubation **S**cale **C**alculation (RISC) score to predict respiratory failure requiring reintubation.

Abbreviations: ARDS, acute respiratory distress syndrome; AUC, area under the curve; EF, extubation failure; ES, extubation success; FOUR, Full Outline of UnResponsiveness; GCS, Glasgow coma scale; ICU, intensive care unit; MAP, mean airway pressure; OR, odds ratio; RISC, Reintubation Scale Calculation; RSBI, rapid shallow breathing index; SBT, spontaneous breathing trial.

METHODS

Study Population

We performed a retrospective cohort study to develop and validate the RISC score. Our study population included critically ill adults who were on mechanical ventilation for ≥48 h during their stay in a medical, surgical, or mixed ICU between January 1, 2006, and December 31, 2015 (**Figure 1**). The study was approved by the Mayo Clinic Institutional Review Board for the use of existing medical records of patients with prior research authorization.

Inclusion Criteria

We gathered data for patients who met the following criteria: age ≥18 years; intubation and mechanical ventilation for ≥48 h; adequate oxygenation, suggested by PaO_2 >60 mmHg at fraction of inspired oxygen of ≤0.4 with an extrinsic positive end-expiratory pressure (PEEP) <7 cmH_2O; successful SBT of 60 min and treating physician approval for extubation; cardiovascular stability (i.e., absence of active myocardial ischemia, heart rate <130 beats per min, absence of vasopressor use, and dopamine or dobutamine <5 mcg/kg/min); body temperature between 36°C and 38°C; serum hemoglobin ≥8 g/dL; adequate coughing during suctioning and suction frequency of no more than every 2 h; and baseline cough observed by airway care score during suctioning (8). We excluded patients with missing baseline variables, those who failed SBT, those with tracheostomies, and those who withdrew all support or received comfort care support after extubation.

Outcome Classification

Patients were grouped by ES or EF. ES was defined as the ability to maintain spontaneous unassisted respiration for ≥72 h after extubation. EF was defined as reintubation within 72 h after extubation.

Data Collection

We collected data retrospectively by using Mayo Clinic ICU DataMart and Unified Data Platform, which are extensive data repositories that contain a near real time standardized replica of Mayo Clinic's EMR. These databases contain patient clinical information along with their laboratory test results, respiratory therapy notes, mechanical ventilation data, medications, vital sign flowsheets, and other clinical and pathological information from sources within the institution and have been previously validated (26). ICU Datamart stored validated ICU ventilator data at 15-min intervals and 2 min intervals in a surgical setting. The validation of ventilator data was done by the respiratory therapist and recorded in EMR.

Patient data collected included age, Acute Physiology and Chronic Health Evaluation score, mechanical ventilation duration, history of chronic comorbidities, hemoglobin and blood chemistries, arterial blood gas values within 1 h after onset of SBT, date and time of extubation, use of drugs (e.g., paralytics, systemic corticosteroids, etc.) during mechanical ventilation, negative inspiratory pressure measured prior to SBT, and GCS score assessed by the patient's nurse at the time of extubation. The airway care score (8) was recorded if available. Additionally,

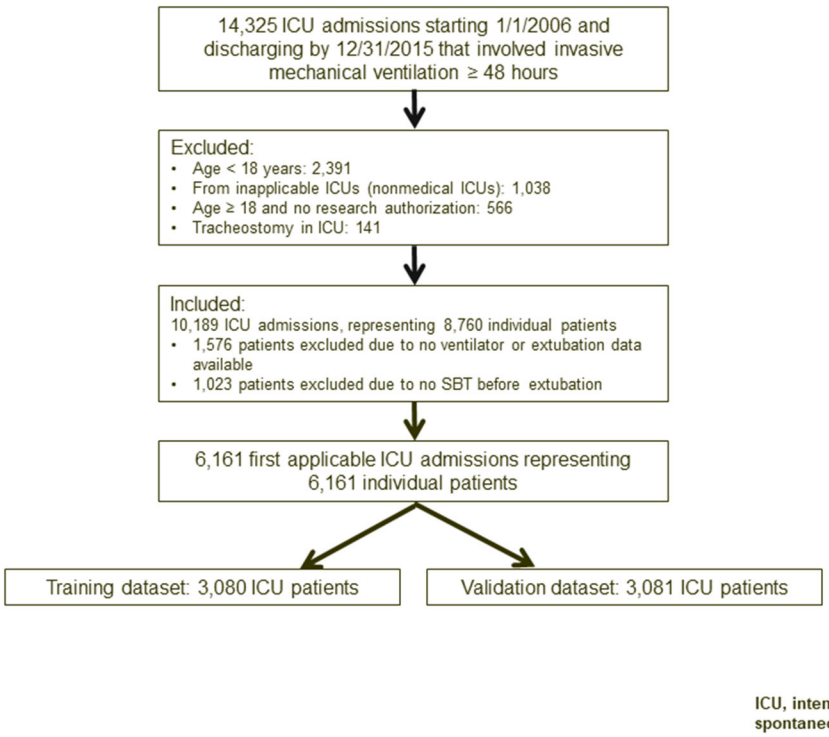

FIGURE 1 | Flowchart of study participants. ICU, intensive care unit; SBT, spontaneous breathing trial.

we collected data on respiratory variables including minute ventilation, respiratory rate, tidal volume, and at 1, 30, and 60 min during the SBT. We also collected RSBI recorded at 1 min (RSBI1), 30 min (RSBI30), and 60 min (RSBI60) during the SBT. We evaluated 2 pre-defined variables: (1) the RSBI30 to RSBI1 ratio as a percentage reflecting the change of RSBI from baseline to 30 min and (2) the RSBI60 to RSBI1 ratio as a percentage reflecting the change of RSBI from baseline to 60 min.

Data Analysis

The main outcome of interest was EF. Categorical variables were reported as frequency and percentage and continuous variables as mean ± standard deviation (SD) and median (25th, 75th). We used the Wilcoxon rank sum test to compare continuous and ordinal variables between patients with and without EF, and χ^2 or Fisher exact tests to compare categorical variable correlations. We used odds ratios (ORs) and 95% CIs to express a variable's strength for independently predicting EF in multivariate logistic regression models. Extreme outliers for variables ≥3 SD were verified manually in EMR. If the value was not available in the EMR, then we considered these erroneous values as missing in the final analysis. Probable predictor variables were chosen based on our clinical experience and information from other studies (11, 20, 27–36). Predictor variables that were significantly different between the success and failure groups ($P \leq 0.01$) for which no more than 5% data were missing were included in multivariate analysis. Variable reduction was done based on the correlation between predictors and the threshold used was 0.6. Prediction scores were developed based on the multivariate logistic regression model coefficient estimate. The smallest coefficient was first identified and assigned a score of 1. Then the scores for the other variables were equal to their corresponding model coefficients divided by this smallest coefficient and finally, all scores were rounded to integers. We developed the RISC score by assigning an amount to each of the risk factors based on their model coefficients. Discrimination of the score as a continuous variable was reported as C-index. Area under the curve (AUC) was also reported for scores at different cutoff points. Calibration of the score was evaluated by calibration plot comparing the predicted and observed risk of EF within 72 h. All statistical tests were 2-sided, with an α-level of 0.05 for statistical significance. Analysis was done using SAS version 9.4 (SAS Institute Inc.).

RESULTS

The 6,161 patients included in our study were randomly allocated into a derivation set ($n = 3{,}080$) and validation set ($n = 3{,}081$). In the derivation set, patients had a mean (SD) age of 61.7 (16.6) years, and 1,820 (59%) were men. Within 72 h, 393 patients (12.8%) experienced EF. Similarly, in the validation set, the mean (SD) age was 62.4 (16.6) years and 1,778 (58%) were men. Within 72 h, 353 patients (11.5%) experienced EF (**Table 1**). Patient endotracheal secretions, mechanical ventilation, and ICU admission diagnosis data for both sets are displayed in **Appendices A–C**.

TABLE 1 | Baseline demographic and hemodynamic instability and fluid status.

Characteristic	Derivation (n = 3,080)	Validation (n = 3,081)	Total (N = 6,161)	P-value
Extubation failure	393	353	746	0.12
Age, y				
Mean (SD)	61.7 (16.6)	62.4 (16.6)	62.0 (16.6)	0.08
Median (IQR)	63.4 (51.9–74.0)	64.0 (52.2–75.1)	63.8 (52.1–74.5)	
Sex, No. (%) Female	1,260 (40.9)	1,303 (42.3)	2,563 (41.6)	0.28
Male	1,820 (59.1)	1,778 (57.7)	3,598 (58.4)	
BMI (kg/m^2), No. (%)				
Missing	17	21	38	0.84
<18.5	91 (3.0)	86 (2.8)	177 (2.9)	
18.5–24.9	771 (25.2)	755 (24.7)	1,526 (24.9)	
25.0–29.9	883 (28.8)	896 (29.3)	1,779 (29.1)	
30.0–34.9	648 (21.2)	624 (20.4)	1,272 (20.8)	
≥35.0	670 (21.9)	699 (22.8)	1,369 (22.4)	
GCS score prior to extubation				
Missing	0	0	0	0.64
Mean (SD)	9.6 (2.5)	9.6 (2.5)	9.6 (2.5)	
Median (IQR)	10 (8–11)	10 (8–11)	10 (8–11)	
Total RBC volume (mL) given within 24 h prior to extubation				
Missing	1	3	4	0.56
Mean (SD)	106.9 (366.6)	115.4 (402.9)	111.2 (385.2)	
Total platelet volume (mL) given within 24 h prior to extubation				
Missing	1	2	3	0.14
Mean (SD)	23.9 (117.4)	27.9 (133.4)	25.9 (125.7)	
Total cryoprecipitate volume (mL) given within 24 h prior to extubation				
Missing	0	2	2	0.80
Mean (SD)	3.9 (57.3)	2.4 (25.8)	3.1 (44.4)	
Total urine output (mL) within 24 h prior to extubation				
Missing	0	2	2	0.37
Mean (SD)	2,315.0 (1,713.7)	2,258.9 (1,634.8)	2,287.0 (1,674.8)	
Median (IQR)	2,043.5 (1,052.3–3,350.3)	2,025.0 (1,040.0–3,199.0)	2,036.0 (1,045.0–3,276.0)	
Fluid balance (mL) 24 h prior to extubation				
Missing	2	2	4	0.17
Mean (SD)	563.6 (2,924.4)	677.0 (2,970.5)	620.3 (2,947.9)	
Median (IQR)	274.2 (−1,061.9 to 1,601.1)	374.0 (−966.7 to 1,604.1)	318.1 (−1,013.6 to 1,601.1)	

BMI, body mass index; GCS, Glasgow coma scale; IQR, interquartile range; RBC, red blood cell; SD, standard deviation.

Predictors of EF in the derivation set included underweight status (body mass index, <18.5 kg/m^2; OR, 1.91; 95% CI, 1.12–3.26; $P = 0.02$), GCS score of ≥10 (OR, 1.68; 95% CI, 1.31–2.16; $P < 0.001$), mean airway pressure (MAP) closest to 1 min after SBT start within 15 min <10 cmH_2O (OR, 2.11; 95% CI, 1.68–2.66; $P < 0.001$), fluid balance of ≥1,500 mL 24 h prior to extubation (OR, 2.36; 95% CI, 1.87–2.96; $P < 0.001$), and mechanical ventilation ≥5 days (OR, 3.94; 95% CI, 3.04–5.11; $P < 0.001$) (**Tables 2**, **3**). The derivation set had a C-index of 0.72 (95% CI, 0.70–0.75) (**Figure 2**).

Our logistic model in validation set demonstrated that as RISC increased by 1, the odds of having EF became 1.6-fold higher (OR, 1.58; 95% CI, 1.47–1.69; $P \leq 0.001$) (**Table 4**). Receiving operating curve analysis revealed the best cutoff for RISC was 4, which demonstrated a sensitivity of 0.80 and specificity of 0.54 with AUC of 0.67 (95% CI, 0.65–0.69) (**Appendix C**). Calibration plot of observed vs. predicted EF in the validation set is displayed in **Figure 3**. Using the above model, the validation set had a C-index of 0.72 (95% CI, 0.69–0.75). The RISC score ranged from 0 to 8 with a median of 4 (**Figure 4**).

DISCUSSION

We successfully developed a multivariable RISC score to predict extubation failure after a successful SBT with readily available bedside predictors. The RISC score predicts extubation failure

TABLE 2 | SBT and MV data for derivation and validation cohort.

Characteristic	Derivation (n = 3,080)	Validation (n = 3,081)	Total (N = 6,161)	P-value
Total ventilation hours				
Missing	0	1	1	0.22
Mean (SD)	192.4 (194.4)	187.8 (189.7)	189.6 (191.9)	
Median (IQR)	131.4 (79.5–230.7)	127.6 (75.3–221.2)	129.0 (76.5–225.0)	
Respiratory rate (breaths/min) closest to 1 min after SBT start within 15 min				
Missing	16	16	32	0.49
Mean (SD)	20.6 (8.0)	20.4 (7.6)	20.5 (7.8)	
Median (IQR)	20.0 (15.0–25.0)	19.0 (15.0–24.4)	19.2 (15.0–25.0)	
Expired V_T (in ml) closest to 1 min after SBT start within 15 min				
Missing	123	130	253	0.34
Mean (SD)	517.9 (204.3)	512.6 (198.7)	515.3 (201.5)	
Median (IQR)	489.0 (389.0–620.0)	480.0 (386.0–601.0)	480.0 (388.0–610.0)	
Expired V_T (in ml/kg) closest to 1 min after SBT start within 15 min				
Missing	123	130	253	0.06
Mean (SD)	6.4 (2.7)	6.3 (2.7)	6.4 (2.7)	
Median (IQR)	6 (4.7–7.7)	5.9 (4.5–7.6)	5.9 (4.6–7.6)	
RSBI[a] (breaths/min/L) closest to 1 min after SBT start within 15 min				
Missing	121	126	247	0.98
Mean (SD)	50.6 (44.3)	49.9 (41.3)	50.3 (42.9)	
Median (IQR)	40.0 (26.2–61.5)	40.8 (26.4–60.6)	40.4 (26.3–60.9)	
MAP (cmH_2o) closest to 1 min after SBT start within 15 min				
Missing	31	45	76	0.75
Mean (SD)	10.7 (3.6)	10.8 (3.7)	10.8 (3.6)	
Median (IQR)	10.0 (7.8–13.0)	9.9 (7.8–13.0)	9.9 (7.8–13.0)	
PIP (cmH_2o) closest to 1 min after SBT start within 15 min				
Missing	129	156	285	0.43
Mean (SD)	18.8 (6.4)	18.8 (6.2)	18.8 (6.3)	
Median (IQR)	18.0 (14.6–22.0)	18.0 (15.0–22.0)	18.0 (15.0–22.0)	
Plateau pressure (cmH_2o) closest to 1 min after SBT start within 15 min				
Missing	1,028	1,074	2,102	0.92
Mean (SD)	18.3 (6.2)	18.2 (5.8)	18.3 (6.0)	
Median (IQR)	18.0 (14.0–21.0)	17.0 (15.0–21.0)	17 (14.0–21.0)	
PEEP (cmH_2o) closest to 1 min after SBT start within 15 min				
Missing	0	0	0	0.53
Mean (SD)	7.5 (3.2)	7.5 (3.3)	7.5 (3.2)	
Median (IQR)	5 (5–10)	5 (5–10)	5 (5–10)	
PS (mmH_2O) closest to 1 min after SBT start within 15 min				
Missing	6	9	15	0.96
Mean (SD)	8.9 (4.0)	8.8 (3.5)	8.9 (3.8)	
Median (IQR)	10 (5–10)	10 (5–10)	10 (5–10)	
History of paralytic use, No. (%)				
No	1,096 (35.6)	1,145 (37.2)	2,241 (36.4)	0.20
Yes	1,984 (64.4)	1,936 (62.8)	3,920 (63.6)	
History of sedative use, No. (%)				
No	202 (6.6)	232 (7.5)	434 (7.0)	0.15
Yes	2,878 (93.4)	2,849 (92.5)	5,727 (93.0)	

IQR, interquartile range; MAP, mean airway pressure; MV, mechanical ventilation; PEEP, positive end–expiratory pressure; PIP, peak inspiratory pressure; PS, Pressure Support; RSBI, rapid shallow breathing index; SBT, spontaneous breathing trial; SD, Standard deviation; V_T, tidal volume.

[a]*RSBI, respiratory rate (f) in breaths/min/ V_T in L.*

TABLE 3 | Logistic regression model predicting extubation failure.

Variable	Label	Univariable		Multivariate		Score
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	
Underweight	Underweight	1.97 (1.18–3.27)	0.009	1.91 (1.12–3.26)	<0.02	1
GCS10	GCS score prior to CPAP mode ≥10	1.61 (1.27–2.05)	<0.001	1.68 (1.31–2.16)	<0.001	1
MAP10	MAP closest to 1 min after SBT start within 15 min <10	1.71 (1.38–2.13)	<0.001	2.11 (1.68–2.66)	<0.001	1
Fluid balance	Fluid balance 24 h prior to extubation ≥1,500	2.30 (1.85–2.86)	<0.001	2.36 (1.87–2.96)	<0.001	2
Ventday 5	Total ventilation days ≥5	3.54 (2.76–4.55)	<0.001	3.94 (3.04–5.11)	<0.001	3

CPAP, continuous positive airway pressure; GCS, Glasgow coma scale; MAP, mean airway pressure; OR, odds ratio; SBT, spontaneous breathing trial.

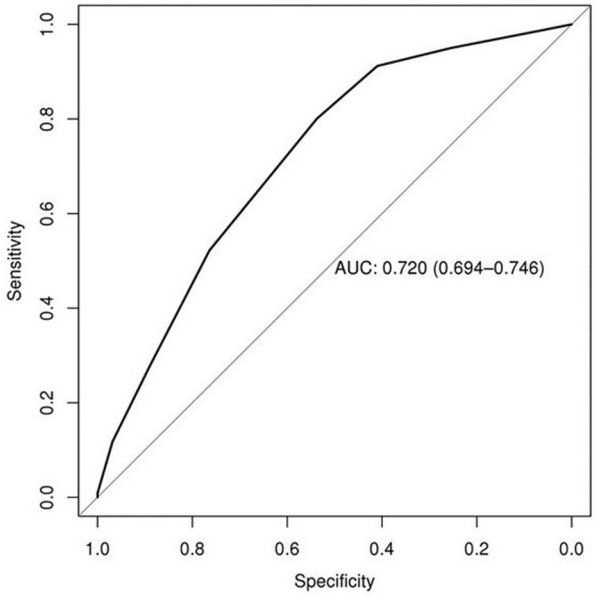

FIGURE 2 | AUC receiver operating characteristic curve. AUC indicates area under the curve.

TABLE 4 | Validation set: extubation within 72 h predicted by score.

Variable	OR (95% CI)	*P*-value	C-index
RISC score	1.58 (1.47–1.69)	<0.001	0.72

OR, odds ratio; RISC, Reintubation Summation Calculation.

with the best cut-off at ≥4 demonstrating a sensitivity of 0.80 and a specificity of 0.54 with AUC of 0.67. This is a modest value to determine extubation failure. RISC score provides several multivariate risk factors that can be externally validated in future deep learning and machine learning predictive models. We acknowledge this model is limited and some would argue that a clinically useful tool should have a higher AUC; however, external testing with larger data sets may be helpful in reproducing these results.

Neurologic impairment was found to be a possible risk factor for EF in our study and was validated previously in several studies (16, 19, 37–39). Mokhlesi et al. (37) verified that a moderate GCS score (9–12) can clinically predict reintubation, comparable to our results. We feel this is an important finding for clinicians caring for those patients with an "intermediate" GCS in their decision-making for extubation. GCS is inherently limited in finding lower cutoffs since a "V1-NT" is the subcomponent reported in intubated patients. Moreover, its components only grade Eyes (E1-4) and Motor (M1-6) which if maximal total 10 points (E4+M6), similar to our observed lowest cutoff. Some suggest using the **F**ull **O**utline of **U**n**R**esponsiveness (FOUR) score (40) might provide a more granular range (0–16) by including brainstem cranial nerve findings. We reviewed our data for FOUR score (40), but only had 228 patients, which is statistically underpowered to detect lower limits of this coma scale for reintubation risk. Only a future study using FOUR score with sufficient sample size may be able to detect this as a true reintubation risk, or in a future randomized trial in brain-injured patients similar to the one performed by WDF, which previously showed no difference in reintubation rates in GCS 10 or less patients with intact brainstem protective reflexes of cough/gag (9). We find documentation of protective airway or cranial nerve reflexes lacking in most and/or all coma scales, even in the FOUR score which focuses on pupillary reflexes for the brainstem. Furthermore, the FOUR score did not include gag/cough reflexes in the randomized trial by Manno et al. (9).

Another covariate of the RISC score is a MAP closest to 1 min after SBT start within 15 min <10 cmH_2O. MAP is dependent on peak inspiratory pressure, PEEP, and respiratory cycle time. Our finding of low MAP leading to extubation failure may be explained by a dyspneic patient with vigorous efforts. Mean airway pressure is a pressure monitoring metric used by mechanical ventilators that are closely connected to mean alveolar pressure and depict pressures on the lung parenchyma during ventilation (41). It's also connected to the oxygenation index (42). Peak inspiratory pressure, PEEP, and the inspiratory-to-expiratory time ratio with dynamic and real-time features are used to calculate MAP, which measures mechanical power impacted by the ventilator mode (43). A high MAP suggests that the patient's mechanical energy power is greater (43). Furthermore, MAP is a critical pressure parameter that influences a patient's hemodynamics. It has been established that higher MAP causes a reduction in cardiac output in infants during both normal and high-frequency mechanical

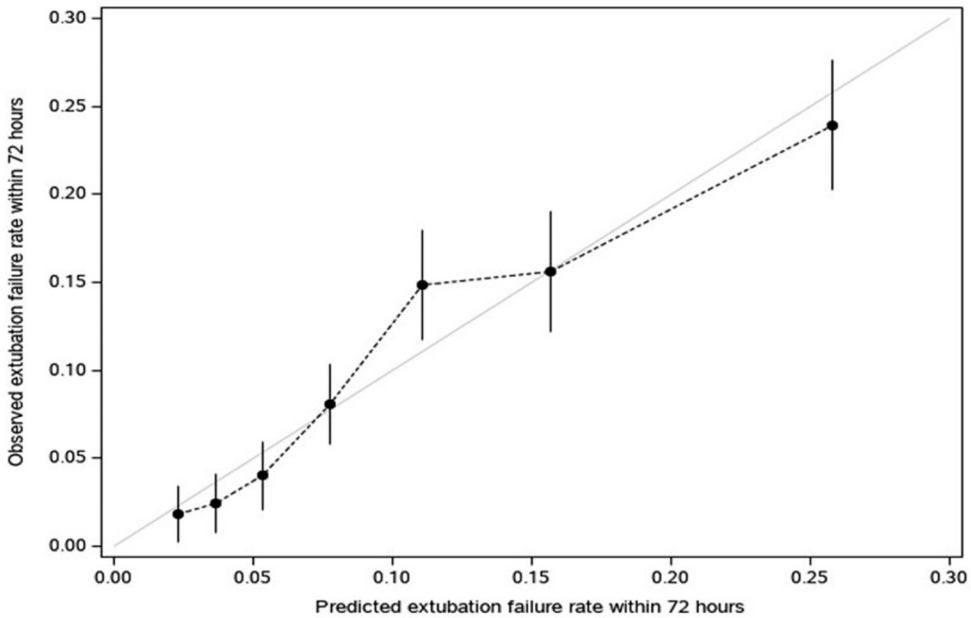

FIGURE 3 | Calibration plot of observed vs. predicted extubation failure in the validation set (dots convey the apparent calibration from the original model, in which predictions for extubation failure within 72 h are grouped into deciles (10 groups ranging from low to high likelihood) and each related to observed rates (vertical bars reflect 95% CI for the rate); For a reference of perfect calibration, the Y = X line is displayed).

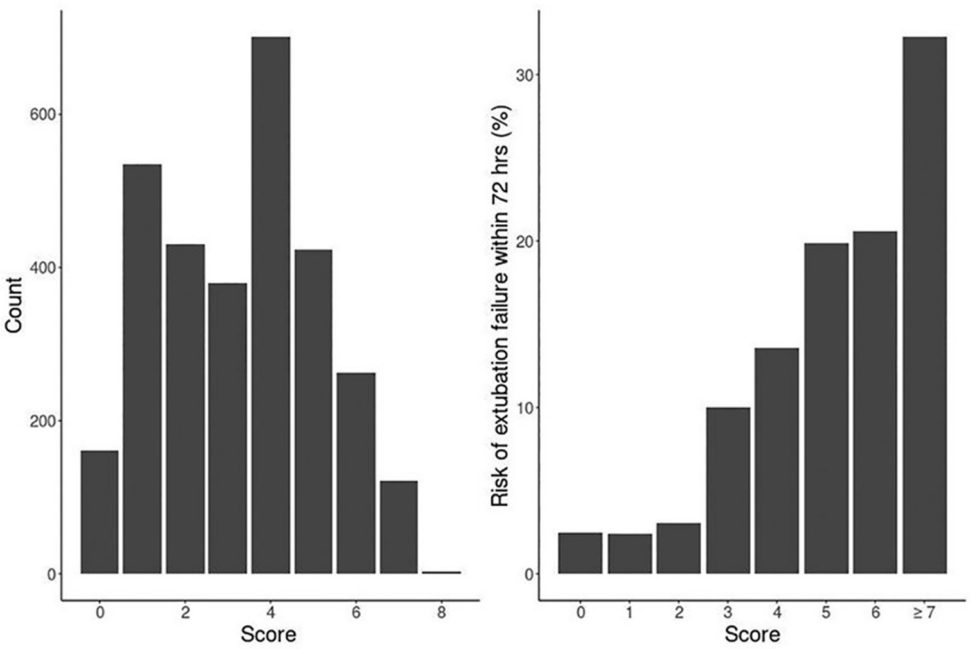

FIGURE 4 | Distribution of RISC score and the corresponding 72-h extubation failure rate (%).

ventilation (44, 45). In direct proportion to their effects on MAP, tidal forces and PEEP raise pulmonary vascular resistance (PVR) (46). As a result, MAP is becoming more linked to the prognosis of patients on mechanical ventilation. A patient that is not able to mount a high MAP may demonstrate insufficient respiratory mechanics from possibly, diaphragmatic weakness. Patients who are able to mount a high MAP may have more strength in respiratory muscles, and thus mechanics, thereby resulting in tolerance of extubation. In summary, we argue that MAP has several strengths over other conventional

mechanical ventilator parameters especially pressure indicators, and it has the ability to become a major bridge factor coupling respiratory mechanics and hemodynamics. However, we acknowledge there are factors potentially not assessed in this study during the transition from positive to negative pressure physiology, stressors on cardiac physiology, and potentially Co_2 accumulation that could theoretically occur before extubation.

Thille et al. (33) identified prolonged mechanical ventilation (duration <1 week) prior to weaning as a strong predictor for EF, similar to our results. We observed that underweight status was also associated with EF and an important factor since it underlies neuromuscular reserve. Malnutrition is reported in as much as 40% of critically ill patients, but data linking nutritional status to ventilator weaning issues are limited (47, 48). In the acute respiratory distress syndrome (ARDS) network trial (43); 4.7% of patients were identified as underweight. Underweight patients, defined as those with a body mass index <18.5 kg/m^2, may experience depressed ventilatory drive (49), limited muscle mass (50), and weaning difficulty (51). Obesity may be associated with a better prognosis ("obesity paradox") for some disease states, patients with ARDS (52) and those in the ICU in general (53, 54). Another important covariate in EF was positive fluid balance, as reported by Frutos-Vivar et al. (27). This is an important finding for clinicians to review prior to extubation attempts since diuretics could be given in future RISC-driven randomized trials on EF. D'Orio et al. (55) reported that a positive cumulative fluid balance may cause increased capillary leak and extravascular lung water and decreased lung compliance, leading to respiratory failure, both during SBT and in the immediate post-extubation period. Hence why restrictive fluid strategies are employed in ARDS patients (56). In an earlier study, positive cumulative fluid balance from hospital admission to weaning was correlated with EF (57). Therefore, it is highly plausible that positive fluid balance influences the respiratory outcome of patients.

To our knowledge, there are no comprehensive data sets analyzing all the variables we proposed in predicting ES, particularly with neurologic components. Most studies focus on RSBI as a predictor in the post-operative setting (27, 37, 58). RSBI is challenging however in patients in pain with tachypnea and some neurologic patients with abnormal brain-disordered breathing states. The closest study we found in the literature similar to ours was a neonatal extubation modeling study by Mueller et al. (54), who used artificial neural-networks, receiver operating characteristics, and regression modeling to predict ES. The authors looked at inspiratory to expiratory ratio, inspiratory time, MAP, tidal volume, and Sa_{O_2}. The authors found an AUC of 0.87, which is a fairly strong prediction for ES (59). Other studies have studied ES but these have been largely focused on operating room predictors and not global predictors (60). Rodriguez Blanco et al. (60) studied 78 surgery patients who had adequate ejection fraction and other standard clinical factors. This study did not adequately characterize the respiratory variables proposed and was of relatively small sample size. Similarly, data from a cohort of mechanically ventilated elderly patients were prospectively analyzed and used to develop a predictive model using a classification and regressive tree (CART) algorithm, also known as a decision tree to predict extubation outcome in patients following a successful SBT (29, 30). This CART model showed a good discrimination with an AUC of 0.94. However, calibration was moderate with a substantial mismatch between predicted and actual probabilities in the updated CART model (47).

Our study has several limitations. First, the retrospective design limits extrapolation to prospective and individualized patient care contexts. Retrospective studies can introduce selection and information biases. We were also not able to collect data on all clinical weaning predictors such as diaphragm movement, endotracheal secretions, and hypercapnic ventilatory response, Airway occlusion pressure in each patient. Second, our study lacked granular data on supplemental oxygen strategies post-extubation as recent literature supports high flow nasal cannula combined with non-invasive in preventing re-intubation (61, 62). Third, the study was completed at a single center with retrospective data collection, and thus does not allow inferences on causality derived from prospective data. Fourth, we were not able to collect echocardiographic measurements to be able to correlate positive fluid balance with ventricular dysfunction. Fifth, in our model, there may be some lack of variability using a retrospective cohort from the same center, and thus validation and accuracy may be overestimated. Sixth, some of the ventilator data captured in this study such as the reporting of a plateau pressure measurement during pressure support in a spontaneously breathing patient were from Puritan Bennett 840 ventilators (Medtronic). These ventilators record into the EMR what it believes are plateau pressures in any mode, even when an adequate inspiratory pause is absent. We have documented instances where vitals are being recorded at greater than the 15-min standard of the time for procedures or more while ventilator settings remained as they were. Lastly, our multivariate covariates within our RISC score model are generally known single risk factors of EF in the existing literature (27, 28, 33–35, 63). Therefore, our study should be considered with caution as exploratory only and requires prospective and external validation of the multivariate model before implementing into routine clinical decision making. This is especially true given data is from a single site that may reflect a unique culture not practiced by others.

Despite our limitations, this study has several strengths. A major strength is that it was done using a robust and clean dataset derived from a previously validated database (64). The study also included a large cohort of patients from a large, tertiary academic hospital. To date, there are no comprehensive data sets analyzing all the variables in predicting ES, especially with neurological components; therefore, we feel this study could represent the first adult human modeling study, and by the addition of more variables, an even more potentially accurate and precise model for predicting ES in the future. However, we still recommend external validation before generalizing and implementing these results as predictive models.

CONCLUSIONS

We developed the RISC score using several practical clinical parameters tested within a derivation and validation set. This

model provides risk-stratification for extubation and subsequent EF within 72 h in mechanically ventilated patients in the ICU. Overall, we identified 5 predictors of EF readily available at the bedside and in many EMRs: underweight status (body mass index <18.5 kg/m^2), GCS score ≥ 10, MAP closest to 1 min after SBT start within 15 min <10 cmH_2O, fluid balance of $\geq 1{,}500$ mL 24 h prior to extubation, and mechanical ventilation ≥ 5 days. External validation in a larger, multicenter study is required before clinical implementation.

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 Mayo Clinic Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

VB, NS, RK, and WF contributed to the conception and design of the study. VB and AM organized the database. VB and ZL performed the statistical analysis. 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.2021.789440/full#supplementary-material

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OPINION
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Motor Simulation as an Adjunct to Patient Recovery Process Following Intensive Care Unit Admission

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INTRODUCTION

Individuals commonly admitted to the intensive care unit (ICU) for acute respiratory failure, due to pulmonary or neuromuscular disease, shock and the need for airway protection or temporary respiratory support after major surgery, are generally placed on invasive mechanical ventilation support. The recovery processes of these patients is uncertain (the longer the duration of respiratory assistance, the more uncertain the vital prognosis) (1) and will take time even with the application of respiratory weaning process (i.e., spontaneous breathing periods alternated with respiratory assistance; enabling patients to gradually come back to unsupported spontaneous breathing) before leaving ICU (2). As these patients suffer from post-mechanical ventilation physical, cognitive, and mental sequelae, in addition to comorbidities (3), maximizing their recovery is therefore paramount to reduce any disabling experiences and to avoid the menace of relapse following discharge and consecutive risk of readmission (2).

It would be beneficial to adopt a multidisciplinary approach by pooling knowledge from the healthcare system—e.g., respiratory medicine and sport medicine—to advance the understanding of the (post-) ICU recovery process which will allow practitioners to set up the most beneficial rehabilitation program (4). In this view, based on neuroscience findings, we propose that Jeannerod's theory (5, 6) related motor simulation would be a useful complement to physiotherapy, motor rehabilitation and other accompanying interventions (e.g., speech therapy, nutritional, and psychological support) to optimize patients' return to autonomy.

WHAT IS MOTOR SIMULATION AND WHY INTRODUCING AFFERENT INFORMATION DURING MOTOR SIMULATION?

Ventilation support for 2–4 weeks and respiratory weaning care (i.e., alternating spontaneous breathing periods with respiratory assistance) result in significant muscle atrophy and weakness (3, 7). It imposes great challenge for optimal recovery from respiratory muscle fatigue due to patients' low breathing capacity, inability to perform basic movements and fatigability. Interestingly, motor simulation offers a motor learning/relearning alternative process without performing any movement (8). Briefly, an individual is engaged in motor simulation when he/she is able to imagine, observe or verbally describe a movement (**Figure 1**) (8). According to Jeannerod (5, 6), motor imagery or action observation (called covert stage) and action execution (called overt stage) share a common activation of cortical motor systems. Of interest, overt stages could be replayed off-line through motor simulation that enables the brain to represent the sensorial consequences and future states of simulated actions. In the field of neuroscience, systematic scientific reviews and meta-analysis have shown, first, that the imagination or the observation of a movement activates a

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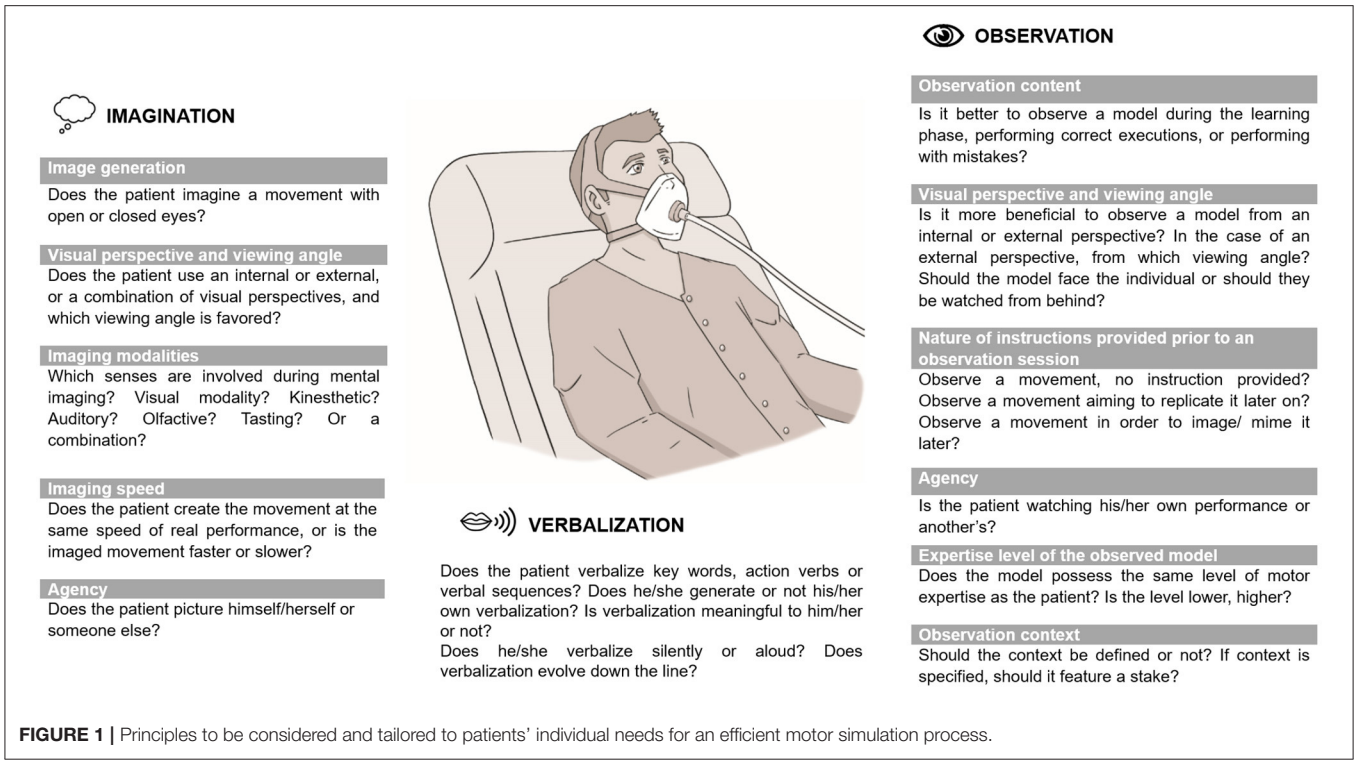

FIGURE 1 | Principles to be considered and tailored to patients' individual needs for an efficient motor simulation process.

premotor-parietal and primary somatosensory network similarly to the one involved during "real" movement execution (9); second, that premotor and primary motor areas are activated during arm or leg movement verbalization and execution (10); third and last, as suggested almost two decades ago (11), that human brain is provided by internal motor efference copies between simulated (imagined, observed, verbalized) and "real" movements (12–14). While simulating or performing movements, these internal forward models are enrolled to predict movement-induced future states and sensorial consequences. Thus, simulated movements are movements except for the fact they do not generate motor output which is blocked by a motor command inhibitory mechanism (5, 6).

However, during a motor simulation, the absence of sensorimotor feedback (i.e., sensorimotor consequences of the motor command) could inactivate the somatosensory processes underlying movement representation, thereby restricting the impact of motor simulation on motor learning/relearning process (15). In the same vein, others have argued that peripheral (proprioceptive and haptic) information is essential for accessing and maintaining motor representations stored in the brain and that, in their absence, these representations fade and even cease to be accessible (16). For instance, the effects of transient sensorimotor deprivation following orthopedic trauma in patients with no prior neurological deficits revealed motor execution impairments and maladaptive plasticity in the somatosensory and motor cortices including shrinkage of somatosensory cortical maps, decreased cortical excitability, reduced cortical thickness in the sensorimotor cortex, decreased of fractional anisotropy in the corticospinal tract and decreased interhemispheric inhibition from the impacted to the non-impacted hemisphere (8). The impaired functioning of internal forward models (referring to the interactions between motor commands and environment, useful to predict the sensory consequences of an action) accounts for these alterations. Though, these models need to be updated through experience (i.e., training that can be translated into changes in synaptic weights which will improve future forward model prediction) to operate reliably (11). Because of the lack of sensorimotor input (proprioceptive, haptic) in the case of immobilization for instance, forward models remain available but are no longer updated, generating an inaccurate prediction of sensory consequences, and thus initiating unskilled and inefficient movements (11). Consequently, integrating afferent information (i.e., proprioceptive and haptic) during motor simulation should be encouraged (i.e., mimicking a movement and handling an object related to a specific movement) (8). It has been reported that mimicking a movement concomitantly to its motor/mental simulation increases its technical quality and efficacy (17).

WHAT IS THE EVIDENCE FOR A POSITIVE IMPACT OF MOTOR SIMULATION IN REAL-WORLD CLINICAL PRACTICE?

Studies probing the effects of motor simulation interventions prescribed alongside motor rehabilitation to recover from detrimental effects of transient sensorimotor deprivation are

scarce in individuals without any neurological history (8). Notably, in patients over 60 years who underwent total hip and knee arthroplasty surgery were instructed to feel the sensations of movements they mentally simulated, results indicated some benefits through an increased motor performance following observation of locomotor tasks (18) and greater quadriceps strength subsequent to the imagination of knee flexion-extension (19). These positive outcomes are deemed to be due to equivalences between simulated and executed movements (18, 19), to the integration of proprioceptive information during motor simulation (8, 17), to the combination of motor rehabilitation and simulation sessions (18, 19), and to cortical plasticity in response to internal or external constraints such as motor learning or training interventions (8, 18, 19). The scientific community hence agrees that cortical changes in healthy individuals exposed to motor learning/training are seen in brain areas and networks related to the physical execution of movements.

WHY USING MOTOR SIMULATION FOR ICU AND POST-ICU PATIENTS?

Despite the lack of scientific evidence promoting motor simulation benefits to ICU and/or post-ICU patients so far, its integration in the rehabilitation process could appear as a very promising adjunct for the following reasons.

First, delivering early active mobilization and rehabilitation in ICU, when the cardiovascular, respiratory and neurological states of patients are stable (20), has been shown to improve the rehabilitation outcomes (improved muscle strength, functional capacity and mobility; increased number of ventilator-free day and discharged-to-home rate) (21). In this view, motor simulation can be helpful in the early rehabilitation process (i.e., when the patient is temporarily completely or partially unable to move, too weak to exercise or subject to the use of supportive devices), as it offers a motor learning/relearning alternative without requiring patient to perform any movement (8). Whenever possible, it is important to alternate motor simulation and movement execution, whether active or assisted, within the same session, as the benefit of this approach has been demonstrated (18, 19).

Second, because ICU patients suffer from sensory deprivation increased by the interference of sedative and analgesic medication, it is essential to provide visual, proprioceptive, haptic information during motor simulation (e.g., watching a video of a movement, mimicking it, handling an object related to this movement). Interestingly, as observing an object automatically potentiates actions associated to it (22), showing objects that patient used in their daily lives will activate action representations (e.g., reaching or grasping actions when a mug is shown).

Third, depending on an individual's ability to use motor simulation techniques (e.g., patients with poor imagery ability), on his/her fatigability, motivation and individual needs, a variety of different simulation packages could be offered for an optimal motor simulation process. The **Figure 1** summarizes the available motor simulation techniques that can be used alone or in combination (i.e., preferably associated with miming a movement and/or handling an object related to this movement to generate afferent information during (motor) simulation) and declined under varied modalities (8) to personalize the intervention in reference to the patient's requirements.

CONCLUDING REMARKS

The present opinion aimed to promote motor simulation as a plausible non-invasive, safe, easy to implement and low cost complementary adjunct among the healthcare delivery provided during the (post-) ICU recovery process. Hopefully, the ICU practitioners and their multidisciplinary healthcare professionals will consider motor simulation as a practical, relevant and therapeutic option to maximize patient's return to autonomy.

AUTHOR CONTRIBUTIONS

The authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication.

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A Study on the Outcome of Targeted Temperature Management Comparing Cardiac Arrest Patients Who Received Bystander Cardiopulmonary Resuscitation With Those Who Did Not, Using the Nationwide TIMECARD Multicenter Registry

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Background and Purpose: Targeted temperature management (TTM) is associated with decreased mortality and improved neurological function after cardiac arrest. Additionally, studies have shown that bystander cardiopulmonary resuscitation (BCPR) doubled the survival of patients with out-of-hospital cardiac arrest (OHCA) compared to patients who received no BPCR (no-BCPR). However, the outcome benefits of BCPR on patients who received TTM are not fully understood. Therefore, this study aimed to investigate the outcome differences between BCPR and no-BCPR in patients who received TTM after cardiac arrest.

Methods: The Taiwan Network of Targeted Temperature Management for Cardiac Arrest (TIMECARD) multicenter registry established a study cohort and a database for patients receiving TTM between January 2013 and September 2019. A total of 580 patients were enrolled and divided into 376 and 204 patients in the BCPR and no-BCPR groups, respectively.

Results: Compared to the no-BCPR group, the BCPR group had a better hospital discharge and survival rate (42.25 vs. 31.86%, $P = 0.0305$). The BCPR group also had a better neurological outcome at hospital discharge. It had a higher average GCS score (11.3 vs. 8.31, $P < 0.0001$) and a lower average Glasgow–Pittsburgh cerebral performance category (CPC) scale score (2.14 vs. 2.98, $P < 0.0001$). After undertaking

a multiple logistic regression analysis, it was found that BCPR was a significant positive predictor for in-hospital survival (OR = 0.66, 95% CI: 0.45–0.97, $P = 0.0363$).

Conclusions: This study demonstrated that BCPR had a positive survival and neurological impact on the return of spontaneous circulation (ROSC) in patients receiving TTM after cardiac arrest.

Keywords: cardiac arrest, targeted temperature management, bystander cardiopulmonary resuscitation, witnessed collapse, electrical discharge, coronary intervention

INTRODUCTION

Post-cardiac arrest care plays a crucial role in the functional recovery of patients after cardiac arrest. Targeted temperature management (TTM) is an important post-cardiac arrest neuroprotective treatment for patients after the return of spontaneous circulation (ROSC) (1). Although the pharmacologic mechanisms are not fully understood, there is a possibility of attenuating post-arrest reperfusion injury to therapeutic hypothermia by reducing cerebral metabolism, thereby reducing the release of excitatory amino acids and the production of oxygen free radicals and restoring the mechanism of normal intracellular signaling (2). Studies have shown that TTM improves neurological outcomes in patients after cardiac arrest (3).

The neuroprotective effects of TTM can be influenced by several factors, including the initial rhythm of cardiac arrest, pre-admission ROSC, the provision of percutaneous coronary intervention, the cooling method for the maintenance phase of TTM, and bystander cardiopulmonary resuscitation (BCPR) (4, 5). BCPR provides blood circulation to vital organs after cardiac arrest, thus reducing the risk of brain damage. The survival and neurological benefits of BCPR have been rigorously investigated in existing literature (6). However, the outcome benefits of BCPR in patients receiving TTM have not been explored. This study, therefore, aimed to investigate the outcome differences between BCPR and no-BCPR (those who had not received BCPR) in patients receiving TTM after cardiac arrest.

MATERIALS AND METHODS

Study Design and Setting

We conducted a retrospective observational cohort study from January 2013 to September 2019 using data from the Taiwan Network of Targeted Temperature Management for Cardiac Arrest (TIMECARD) registry, a nationwide multicenter registry for cardiac arrest patients receiving TTM in post-cardiac arrest care (7).

The TIMECARD registry was managed by the Taiwan Society of Emergency and Critical Care Medicine. In participating hospitals, TTM was provided to patients with out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) with a Glasgow Coma Scale (GCS) score of <8 or those who could not obey verbal commands after ROSC. A temperature range between 32 and 36°C was maintained for at least 24 h, after which the body was slowly rewarmed at a rate of 0.2–0.5°C/h. Patients aged ≥ 18 years who received TTM after ROSC were included in this study.

Data Collection and Definitions

The primary variable in this study was whether the patient had received BCPR. In this study, BCPR was defined as "an attempt to perform basic cardiopulmonary resuscitation by someone who is not a part of an organized emergency response system," according to the Utstein templates for resuscitation (8). Covariates of patient-related factors such as age, sex, and comorbidities were included. Covariates of resuscitation parameters such as event time, event location, witnessed collapse, initial rhythms, cause of cardiac arrest, cardiopulmonary resuscitation (CPR) duration, electrical discharge therapy, and pre-hospital ROSC were also included.

The initial rhythm was determined using either a manual defibrillator or an automated external defibrillator (AED). Cardiac arrest is classified as cardiogenic or non-cardiogenic. Cardiogenic origin is defined as cardiac arrest caused by myocardial ischemia or infarction, hypertrophic cardiomyopathy, valvular disease, and heart failure. Non-cardiac causes include drowning, trauma, asphyxia, respiratory disease, malignancy, electrolyte imbalance, sepsis, and uncontrolled bleeding. Electrical discharge therapy included defibrillation and synchronized cardioversion with manual defibrillators or AEDs. ROSC was defined as a palpable pulse lasting >20 s. Blood pressure and heart rate were immediately measured after ROSC.

We also recorded the heart rate, mean arterial pressure, and the GCS score at ROSC, time from ROSC to targeted temperature range, the cooling method for the maintenance phase of TTM, cold saline infusion during TTM, and patients who received coronary angiography. The cooling methods for the maintenance phase of TTM were classified into external and internal cooling. External cooling included a traditional cold blanket and the Arctic Sun medical device, which modulates patient temperature by circulating cold water in pads directly adhered to the patient's skin. Internal cooling included an intravascular cooling device and extracorporeal membrane oxygenation (ECMO).

Outcomes Measures and Statistical Analysis

Results are expressed as n (%) for categorical variables. Descriptive statistics were reported as mean and standard deviation for continuous variables. The groups were compared using Pearson's chi-squared test for categorical data and Student's *t*-test for numerical data. We compared the survival, the

GCS score, and the Glasgow–Pittsburgh cerebral performance category (CPC) scale score between the BCPR group and the no-BCPR group while transferring out of ICU and again during hospital discharge. A comparison of mortality rates between BCPR and no-BCPR patients was also analyzed in a different subgroup. The multivariate logistic regression model was used to explore independent risk factors for in-hospital mortality. Odds ratio (OR) and 95% confidence interval (CI) were identified for each risk factor. Important significant risk factors were identified using the stepwise logistic regression model. All data were processed using SAS software (version 9.4; SAS Institute Inc., Cary, NC). A $P < 0.05$ was considered statistically significant.

RESULTS

Study Population

A total of 580 patients were enrolled in this study, of which 376 were in the BCPR group, and the remaining 204 were in the no-BCPR group. The basic characteristics of cardiac arrest patients who received TTM in the BCPR and no-BCPR groups are listed in **Table 1**. The mean age was 62.1 in the BCPR group and 67.3 in the no-BCPR group (**Table 1**).

Effect of BCPR on Survival and Neurological Outcomes in ROSC Patients Post-TTM

A survival benefit was found in the BCPR group. Compared to those in the no-BCPR group, BCPR patients who received TTM after ROSC had a higher survival rate at hospital discharge (42.25 vs. 31.86%, $P = 0.0305$, **Table 2**). However, there was no significant difference in the survival rate of patients in the BCPR and no-BCPR groups (52.66 vs. 49.51%, $P = 0.4686$, **Table 2**) while transferring out of ICU.

The BCPR group also had a better neurological outcome while transferring out of ICU. The BCPR group had more patients with GCS $\geq$8 than the no-BCPR group (55.84 vs. 35.64%, $P = 0.0010$, **Table 2**). Their average GCS score was higher (9.83 vs. 6.76, $P < 0.0001$, **Table 2**), and more patients in BCPR group were scored 1–2 on the CPC scale (45.69 vs. 24.75%, $P = 0.0004$, **Table 2**). The average CPC scale was also lower in the BCPR group (2.51 vs. 3.28, $P < 0.0001$, **Table 2**).

The data collected at hospital discharge also showed neurological benefits in patients in the BCPR group. The group had a higher average GCS score (11.3 vs. 8.31, $P < 0.0001$, **Table 2**) and a lower average CPC scale score (2.14 vs. 2.98, $P < 0.0001$, **Table 2**).

Effect of BCPR on Survival in Different Subgroups in ROSC Patients Post-TTM

The effect of BCPR on post-TTM survival in various subgroups is presented in **Table 3**. Compared to the patients in the no-BCPR group, the BCPR group had a lower mortality rate in male patients (50.60 vs. 65.38%, $P = 0.0059$), patients aged >65 (59.28 vs. 74.53%, $P = 0.0083$), patients with cardiac arrest on workday (53.11 vs. 64.71%, $P = 0.0366$), and patients with OHCA (54.09 vs. 64.36%, $P = 0.0271$). While studying BCPR patients with co-morbidities, a survival benefit was also found among patients with hypertension (56.42 vs. 67.89%, $P = 0.0458$), patients with dyslipidemia (55.41 vs. 78.79%, $P = 0.0210$), patients without chronic kidney disease (CKD) (51.64 vs. 61.40%, $P = 0.0401$), patients without end-stage renal disease (ESRD) under dialysis (51.37 vs. 61.88%, $P = 0.0224$), and patients without malignancy (53.13 vs. 63.64%, $P = 0.0211$). Two resuscitation-related parameters, heart rate <100 bpm at ROSC (52.02 vs. 66.67%, $P = 0.0228$) and mean arterial pressure (MAP) $\geq$65 mmHg at ROSC (50.65 vs. 61.90%, $P = 0.0182$), were associated with a lower mortality rate in the BCPR group.

Independent Risk Factors of In-Hospital Mortality in Patients With Cardiac Arrest Receiving TTM

We performed a multivariate logistic regression analysis to explore independent risk factors for in-hospital mortality. The adjusted odds ratio and 95% confidence interval of each risk factor are shown in **Table 4**. Bystander CPR was a significant positive predictor, with an adjusted odds ratio (OR) of 0.66 (95% CI: 0.45–0.97, $P = 0.0363$, **Table 4**) for in-hospital mortality. On the other hand, the unadjusted odds ratio of bystander CPR was 0.697 (95% CI 0.49–0.99, $P = 0.0436$).

In addition to bystander CPR, prehospital ROSC (OR = 0.55, 95% CI: 0.35–0.88, $P = 0.0123$, **Table 4**) and coronary angiography (OR = 0.48, 95% CI: 0.29–0.81, $P = 0.0056$, **Table 4**) were significant positive predictors in multivariate logistic regression model. On the contrary, ESRD under dialysis (OR = 2.53, 95% CI: 1.30–4.90, $P = 0.0061$, **Table 4**) and mean arterial pressure at ROSC < 65 mmHg (OR = 2.54, 95% CI: 1.52–4.25, $P = 0.00004$, **Table 4**) were significant negative predictors. Stepwise logistic regression for important factors was also analyzed. The odds ratio for each important factor is demonstrated in **Table 4**.

DISCUSSION

BCPR Improved Survival in Patients Post-TTM

This study aimed to investigate the outcome differences between BCPR and no-BCPR patients receiving TTM after cardiac arrest. Among patients who received TTM, BCPR was associated with a higher survival rate until hospital discharge than those who did not receive BCPR (42.25 vs. 31.86%, $P = 0.0305$, **Table 2**). The positive effects of BCPR on OHCA patients have been extensively investigated. According to a meta-analysis of 16 cohort studies, BCPR was associated with an ∼2-fold chance of survival of patients with OHCA compared to patients who received no-BCPR (OR = 1.95; 95% CI: 1.66–2.30) (6). Notably, our study proved the survival benefit of BCPR in patients with cardiac arrest, specifically in those receiving TTM. During cardiac arrest, the cerebral blood flow is extremely low (9). If patients with cardiac arrest received BCPR, they could have better cerebral blood flow, which consequently contributes to improved survival outcomes after TTM.

TABLE 1 | Basic characteristics for cardiac arrest patients receiving TTM between BCPR group and NO-BCPR group.

Variables	BCPR group (*N* = 376)		NO-BCPR group (*N* = 204)		*P*-Value
Male	251	(66.76%)	130	(63.73%)	0.4630
Age ≤ 65 years	182	(48.40%)	98	(48.04%)	0.9330
Comorbidities					
Diabetes mellitus	162	(43.09%)	77	(37.75%)	0.2122
Hypertension	218	(57.98%)	109	(53.43%)	0.2917
Coronary artery disease	104	(27.66%)	50	(24.51%)	0.4121
Dyslipidemia	74	(19.68%)	33	(16.18%)	0.2988
Heart failure	70	(18.62%)	40	(19.61%)	0.7713
Arrhythmia	52	(13.83%)	19	(9.31%)	0.1131
Chronic kidney disease	72	(19.15%)	33	(16.18%)	0.3747
ESRD under dialysis	47	(12.50%)	23	(11.27%)	0.6653
Malignancy	56	(14.89%)	17	(8.33%)	0.0229
Event time					
Workday	241	(64.10%)	119	(58.33%)	0.1720
Weekend	135	(35.90%)	85	(41.67%)	
Event location					
Out-of-hospital cardiac arrest	281	(74.73%)	188	(92.16%)	**<0.0001**
In-hospital cardiac arrest	95	(25.27%)	16	(7.84%)	
Witnessed collapse	341	(90.69%)	125	(61.27%)	**<0.0001**
Initial rhythm					
Shockable	142	(37.77%)	68	(33.33%)	0.2888
Non-shockable	234	(62.23%)	136	(66.67%)	
Cause of cardiac arrest					
Cardiac	207	(55.05%)	98	(48.04%)	0.1062
Non-cardiogenic	169	(44.95%)	106	(51.96%)	
CPR duration > 10 min	285	(75.80%)	166	(81.37%)	0.1232
Electrical discharge therapy	153	(40.69%)	79	(38.73%)	0.6444
Pre-Hospital ROSC	69	(18.35%)	48	(23.53%)	0.1378
Heart rate (bpm) at ROSC					
<100	173	(46.01%)	90	(44.12%)	0.6619
≥100	203	(53.99%)	114	(55.88%)	
MAP (mmHg) at ROSC					
<65	66	(17.55%)	36	(17.65%)	0.9774
≥65	310	(82.45%)	168	(82.35%)	
Glasgow coma scale (GCS) at ROSC					
<8	368	(97.87%)	199	(97.55%)	0.7766
≥8	9	(2.39%)	5	(2.45%)	
Time from ROSC to targeted temperature					
<12 h	252	(69.23%)	127	(65.13%)	0.3225
≥12 h	112	(30.77%)	68	(34.87%)	
Method for maintenance phase of TTM					
External cooling	332	(88.30%)	190	(93.14%)	0.0636
Internal cooling	44	(11.70%)	14	(6.86%)	
Cold saline infusion during TTM	148	(39.36%)	98	(48.04%)	0.0435
Received coronary angiography	127	(33.78%)	58	(28.43%)	0.1872

Values are expressed as numbers (percentage).

BCPR, bystander cardiopulmonary resuscitation; bpm, beats per minute; CPR, cardiopulmonary resuscitation; ESRD, end stage renal disease; MAP, mean arterial pressure; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

TABLE 2 | Survival and neurological outcomes for cardiac arrest patients receiving TTM between BCPR group and NO-BCPR group.

Outcomes	BCPR group ($N = 376$)		NO-BCPR group ($N = 204$)		*P*-Value
Survived at transferring out of ICU	198	(52.66%)	101	(49.51%)	0.4686
GCS at transferring out of ICU					
GCS < 8	87	(44.16%)	65	(64.36%)	**0.0010**
GCS ≥ 8	110	(55.84%)	36	(35.64%)	
Average (SD)	9.83	(4.77)	6.76	(4.05)	**<0.0001**
CPC at transferring out of ICU					
CPC 1–2	90	(45.69%)	25	(24.75%)	**0.0004**
CPC 3–5	107	(54.31%)	76	(75.25%)	
Average (SD)	2.51	(1.26)	3.28	(1.04)	**<0.0001**
Survived at hospital discharge	158	(42.25%)	65	(31.86%)	**0.0305**
GCS at hospital discharge					
GCS < 8	57	(34.55%)	30	(44.12%)	0.1697
GCS ≥ 8	108	(65.45%)	38	(55.88%)	
Average (SD)	11.3	(4.58)	8.31	(4.37)	**<0.0001**
CPC at hospital discharge					
CPC 1–2	91	(55.15%)	26	(38.24%)	**0.0189**
CPC 3–5	74	(44.85%)	42	(61.76%)	
Average (SD)	2.14	(1.27)	2.98	(1.18)	**<0.0001**

Values are expressed as mean (standard deviation) for continuous variables and numbers (percentage) for categorical variables.
BCPR, bystander cardiopulmonary resuscitation; CPC, Cerebral Performance Categories; GCS, Glasgow Coma Scale; ICU, intensive care unit; SD, standard deviation; TTM, targeted temperature management. Statistically significant data ($P < 0.05$) were expressed as bold values.

The positive survival impact of BCPR was significant among older patients (aged > 65 years) undergoing TTM (59.28 vs. 74.53%, $P = 0.0083$, **Table 3**). In a previous study, BCPR had a higher OR for 1-month survival in patients aged >71 years (OR = 5.1, 95% CI: 3.8–7.1) than in those aged ≤71 years (OR = 2.5, 95% CI: 1.9–3.3) (10). In terms of their response to TTM, a previous study showed that TTM was significantly associated with good neurologic outcomes in patients aged <65 years but had no association with outcomes in older patients (65–74 years: OR 1.49, 95% CI: 0.90–2.47; >75 years: OR 1.44, 95% CI: 0.79–2.34) (11). Although older patients may not benefit much from TTM, they can have better survival outcomes after receiving BCPR.

Our study showed that patients who received BCPR had a better chance of survival in post-TTM care when they did not have CKD (51.64 vs. 61.40%, $P = 0.0401$, **Table 3**), ESRD on dialysis (51.37 vs. 61.88%, $P = 0.0224$, **Table 3**), and malignancy (53.13 vs. 63.64%, $P = 0.0211$, **Table 3**). A previous study also suggested that BCPR had a stronger survival impact on patients with less severe comorbidities (12). One possible explanation is that additional comorbidities may hasten the electrical, hemodynamic, and metabolic decline in patients with cardiac arrest, making BCPR less effective in rescuing a patient (13).

Our findings showed that BCPR improved survival in patients with OHCA (54.09 vs. 64.36%, $P = 0.0271$, **Table 3**) but did not show a survival benefit in patients with IHCA. In patients who did not receive BCPR, the interval time between OHCA and EMS arrival was longer than the interval time between IHCA and CPR provided by the healthcare team. BCPR could significantly reduce the time from arrest to first CPR in patients with OHCA but not in patients with IHCA. This could be a possible reason why BCPR has different effects on survival between patients with OHCA and IHCA.

BCPR Preserved Pre-arrest Neurological Status in Patients Post-TTM

The result of our study demonstrated that BCPR was associated with better neurological outcomes. Similar results were reported in a previous study. According to a meta-analysis in 2018, favorable neurological outcomes were associated with a significantly higher odds ratio of BCPR (OR, 1.44; 95% CI: 1.14–1.82) in patients treated with TTM after cardiac arrest (14). Given that immediate CPR provides crucial blood flow to the brain and shortens ischemia time, BCPR has a positive impact on neurological outcomes in cardiac arrest patients treated with TTM. Therefore, community interventions to encourage BCPR should be undertaken to improve the functional outcomes of patients with cardiac arrest.

Other Independent Risk Factors of In-Hospital Mortality in Patients Post-TTM

Preexisting comorbidities in patients with cardiac arrest influenced their survival after TTM therapy. When adjusted for other variables, ESRD under dialysis (OR = 2.53, 95% CI: 1.30–4.90, **Table 4**) was an independent negative predictive factor for survival. Hirlekar et al. also demonstrated that renal disease (OR = 0.53, 95% CI: 0.53–0.72) reduced the chance of 30-d survival of patients with OHCA (15).

TABLE 3 | In-hospital mortality rates in different subgroups between BCPR group and NO-BCPR group.

Subgroups		BCPR (*N* = 376)		NO-BCPR (*N* = 204)		Subgroup *P*-value
		Death/Total	Mortality	Death/Total	Mortality	
Sex	Male	127/251	(50.60%)	85/130	(65.38%)	**0.0059**
	Female	80/125	(64.00%)	45/74	(60.81%)	0.6528
Age	≤65	92/182	(50.55%)	51/98	(52.04%)	0.8118
	>65	115/194	(59.28%)	79/106	(74.53%)	**0.0083**
Event time	Weekend	79/135	(58.52%)	53/85	(62.35%)	0.5719
	Workday	128/241	(53.11%)	77/119	(64.71%)	**0.0366**
Event location	OHCA	152/281	(54.09%)	121/188	(64.36%)	**0.0271**
	IHCA	55/95	(57.89%)	9/16	(56.25%)	0.9020
Diabetes mellitus	NO	107/214	(50.00%)	73/127	(57.48%)	0.1810
	YES	100/162	(61.73%)	57/77	(74.03%)	0.0613
Hypertension	NO	84/158	(53.16%)	56/95	(58.95%)	0.3703
	YES	123/218	(56.42%)	74/109	(67.89%)	**0.0458**
Coronary artery disease	NO	148/272	(54.41%)	96/154	(62.34%)	0.1121
	YES	59/104	(56.73%)	34/50	(68.00%)	0.1806
Dyslipidemia	NO	166/302	(54.97%)	104/171	(60.82%)	0.2167
	YES	41/74	(55.41%)	26/33	(78.79%)	**0.0210**
Heart failure	NO	161/306	(52.61%)	100/164	(60.98%)	0.0821
	YES	46/70	(65.71%)	30/40	(75.00%)	0.3107
Arrhythmia	NO	179/324	(55.25%)	115/185	(62.16%)	0.1287
	YES	28/52	(53.85%)	15/19	(78.95%)	0.0554
Chronic kidney disease	NO	157/304	(51.64%)	105/171	(61.40%)	**0.0401**
	YES	50/72	(69.44%)	25/33	(75.76%)	0.5062
ESRD under dialysis	NO	169/329	(51.37%)	112/181	(61.88%)	**0.0224**
	YES	38/47	(80.85%)	18/23	(78.26%)	1.0000
Malignancy	NO	170/320	(53.13%)	119/187	(63.64%)	**0.0211**
	YES	37/56	(66.07%)	11/17	(64.71%)	0.9172
Witnessed collapsed	NO	25/35	(71.43%)	56/79	(70.89%)	0.9530
	YES	182/341	(53.37%)	74/125	(59.20%)	0.2626
Initial rhythm	Non-shockable	147/234	(62.82%)	97/136	(71.32%)	0.0961
	Shockable	60/142	(42.25%)	33/68	(48.53%)	0.3916
Electrical discharge	NO	141/233	(60.52%)	89/125	(71.20%)	0.1318
	YES	66/153	(43.14%)	41/79	(51.90%)	0.2046
Prehospital ROSC	NO	181/307	(58.96%)	106/156	(67.95%)	0.0596
	YES	26/69	(37.68%)	24/48	(50.00%)	0.1852
Heart rate at ROSC	<100 bpm	90/173	(52.02%)	60/90	(66.67%)	**0.0228**
	≥100 bpm	117/203	(57.64%)	70/114	(61.40%)	0.5127
MAP at ROSC	<65 mmHg	50/66	(75.76%)	26/36	(72.22%)	0.6954
	≥65 mmHg	157/310	(50.65%)	104/168	(61.90%)	**0.0182**
Cause of cardiac arrest	Non-cardiogenic	108/169	(63.91%)	74/106	(69.81%)	0.3137
	Cardiogenic	99/207	(47.83%)	56/98	(57.14%)	0.1285

Values are expressed as numbers (percentage).

BCPR, bystander cardiopulmonary resuscitation; bpm, beats per minute; ESRD, end stage renal disease; MAP, mean arterial pressure; ROSC, return of spontaneous circulation. Statistically significant data (P < 0.05) were expressed as bold values.

Pre-hospital ROSC (OR = 0.55, 95% CI: 0.35–0.88, **Table 4**) was also an independent prognostic factor for survival in our study. Since chest compressions only generate 25–30% of the normal cardiac output (16), prolonged CPR increases cerebral damage (17). Therefore, a pre-hospital ROSC could result in good survival among TTM recipients by reducing the levels of brain damage prior to TTM.

Coronary angiography (OR = 0.48, 95% CI: 0.29–0.81, **Table 4**) had a positive effect on in-hospital survival in BCPR patients. Acute coronary syndrome is a major cause of OHCAs, requiring emergency coronary angiography for immediate

TABLE 4 | Independent risk factors of in-hospital mortality in cardiac arrest patients receiving TTM.

Variables	OR	(95% CI)	*P*-value
Multivariate logistic regression			
Male sex	1.07	(0.72–1.60)	0.7457
Age > 65	1.36	(0.92–2.01)	0.1265
Event time: weekend	1.19	(0.82–1.74)	0.3576
Diabetes mellitus	1.32	(0.87–2.02)	0.1976
Hypertension	0.89	(0.59–1.34)	0.5740
Coronary artery disease	1.24	(0.79–1.94)	0.3591
Heart failure	1.31	(0.78–2.22)	0.3078
Arrhythmia	0.82	(0.45–1.48)	0.5055
Chronic kidney disease	1.30	(0.76–2.22)	0.3384
ESRD under dialysis	2.53	(1.30–4.90)	**0.0061**
Dyslipidemia	1.12	(0.66–1.91)	0.6661
Malignancy	1.37	(0.78–2.40)	0.2772
Bystander CPR	0.66	(0.45–0.97)	**0.0363**
AED defibrillation	1.46	(0.66–3.21)	0.3531
Initial shockable rhythm	0.63	(0.27–1.47)	0.2822
Electrical discharge	0.86	(0.36–2.06)	0.7309
Prehospital ROSC	0.55	(0.35–0.88)	**0.0123**
Heart rate at ROSC ≥100 bpm	1.11	(0.76–1.62)	0.5866
MAP at ROSC < 65 mmHg	2.54	(1.52–4.25)	**0.0004**
Cardiogenic cardiac arrest	0.99	(0.61–1.62)	0.9696
Cold saline infusion	0.79	(0.54–1.15)	0.2138
Coronary angiography	0.48	(0.29–0.81)	**0.0056**
Stepwise multiple regression			
ESRD under dialysis	2.96	(1.57–5.58)	**0.0008**
Bystander CPR	0.67	(0.46–0.98)	**0.0391**
Prehospital ROSC	0.50	(0.32–0.77)	**0.0020**
MAP at ROSC < 65 mmHg	0.42	(0.25–0.69)	**0.0006**
Coronary angiography	0.37	(0.25–0.54)	**<0.0001**

AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; bpm, beats per minute; ESRD, end stage renal disease; MAP, mean arterial pressure; ROSC, return of spontaneous circulation. Statistically significant data (P < 0.05) were expressed as bold values.

diagnosis and treatment. Although immediate coronary angiography could delay TTM therapy for ∼1 h (18), current guidelines recommend immediate coronary angiography and percutaneous coronary intervention in resuscitated OHCA patients whose ECGs show ST-elevation myocardial infarction (19). Given that hemodynamic instability and cardiac dysfunction could worsen during TTM, percutaneous coronary intervention could provide better outcomes in TTM recipients by allowing revascularization of the coronary artery and supporting the hemodynamic status during post-resuscitation care (4).

Mean arterial pressure at ROSC < 65 mmHg was an independent negative predictor of in-hospital mortality in patients post-TTM. A previous retrospective cohort study also found that post-ROSC hypotension was an independent predictor of survival among patients who had ROSC after OHCA (20).

Study Limitations

Our study is subject to certain limitations. First, this was a retrospective, non-randomized study. Potential selection bias may exist due to differences in basic patient characteristics between the control and experimental groups. However, selection bias was limited by the large sample size in this study. Second, our analyses were based on observational data. Therefore, although our study showed correlations between BCPR, survival, and neurological outcomes, we could not prove causality. Third, TTM duration, targeted temperature, and cooling methods differed between hospitals due to their differing protocols. This may be an unknown bias that influences the overall survival and neurological outcomes.

Study Strengths

This is the first nationwide multicenter registry project to compare survival and neurological outcomes between cardiac patients under TTM care who had received BCPR with those who did not receive BCPR. A significant positive survival impact of BCPR was found in multiple subsets in the subgroup analysis. This study also identified independent risk and protective factors and their odds ratio for in-hospital mortality among patients who received TTM. Since this study proved that BCPR increases the neuroprotective effects of TTM, the public should be encouraged to offer more BCPR, which will improve post-TTM outcomes in cardiac patients.

CONCLUSIONS

This study demonstrated that BCPR had a positive survival and neurological outcome on the return of spontaneous circulation in patients post-TTM.

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 (IRB) of the Kaohsiung Veterans General Hospital approved this study (No. VGHKS18-EM3-02). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

W-CH: conception, study design, and critical revision of the manuscript. M-ST, L-KK, H-HH, C-HL, and K-CL: data acquisition, analysis, and interpretation, F-YL: drafting of the manuscript. All authors have read and approved the final manuscript.

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Impact of Oxygen Saturation on Mortality in Obese and Non-obese Critically Ill Patients With Mechanical Ventilation: A Retrospective Observational Study

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Background: The main aim of this study was to evaluate the effect of oxygen saturation on mortality in critically ill patients with mechanical ventilation according to obesity status.

Methods: We conducted an observational study in mechanically ventilated patients admitted to the ICU retrospectively. Demographic, arterial blood gas, ventilator setting, interventions, and peripheral oxygen saturation (Spo_2) during the first 24 h were recorded and analyzed between non-obese and obese patients. The main exposure included Spo_2, time-weighted mean Spo_2 (TWM-Spo_2), and proportion of time spent in different Spo_2 (PTS-Spo_2) levels. The primary outcome was hospital mortality. We used multivariable logistic regression models to assess the relationship between Spo_2 and mortality, as well as the interaction between PTS-Spo_2 and obesity status.

Results: A total of 25,100 patients were included, of which 10,564 (42%) were obese patients. After adjusting for confounders, compared with TWM-Spo_2 of 94–98%, TWM-Spo_2 of <=88% (OR 3.572; CI [2.343, 5.455]; $p < 0.001$) and of 89–93% (OR 1.514; CI [1.343, 1.706]; $p < 0.001$) were both associated with higher risk of mortality. PTS-Spo_2 of 99–100% was associated with increased risk of mortality for obese patients (OR 1.028; 95% CI 1.010–1.046; $p = 0.002$; $P_{interaction=}$ 0.001), while PTS-Spo_2 of 89–93% was associated with increased risk of mortality (OR 1.089; 95% CI 1.051–1.128; $p < 0.001$; $P_{interaction=}$ 0.001) for non-obese patients.

Conclusions: For obese and non-obese critically ill patients with mechanical ventilation, the impact of oxygen saturation on hospital mortality is different.

Keywords: obesity, intensive care unit, mechanical ventilation, oxygen saturation, mortality

INTRODUCTION

Obesity has emerged as one of the leading health concerns over the past century (1). In the United States, for the years 2013 and 2014, the overall obesity prevalence was 37.7% (2). Moreover, for adult obesity and severe obesity, the prevalence will continue to increase (3). Recent studies estimate by 2030 nearly 1 in 2 adults will have obesity (4, 5). At the same time, obese patients are over-represented in primary care (6). The similar circumstance is also reflected in critically

ill patients where a recent study reported a prevalence of around 20% for the year 2012 (7, 8). Moreover, obese patients represent a specific population that seemed to be associated with high morbidity and increased resource utilization, who require an adapted ICU management (7–10).

The provision of supplemental oxygen is a ubiquitous intervention for mechanically ventilated patients. However, excessive oxygen could also be injurious (11, 12). British Thoracic Society (BTS) recommends, for morbidly obese patients who are at the risk of hypoventilation, even without evidence of coexistent obstructive sleep apnea, targeted oxygen saturation of 88–92% should be titrated (grade D) (13). Two small trials conducted in morbidly obese patients showed exposure to hyperoxia caused elevated partial pressure of carbon dioxide ($Paco_2$) and hypoventilation (14, 15). However, for patients with milder obesity, the literature is really sparse, especially concerning the impact in the critical setting. Moreover, the BTS or Thoracic Society of Australia and New Zealand guidelines did not cover the area of ICU (13, 16). Given the epidemiologic and specific pathophysiologic changes observed in obese patients, one could hypothesize that the obesity status could be an important confounder in the relationship between supplemental oxygen and outcomes. To the best of our knowledge, no study has specifically evaluated the relationship between supplemental oxygen and hospital mortality outcome in obese critically ill patients with mechanical ventilation.

The main aim of this study was to analyze the influence of the obesity status on the relationship between oxygen saturation and the hospital mortality in mechanically ventilated patients. The hypothesis was the impact of the supplemental oxygen on mortality in non-obese and obese critically ill patients with mechanical ventilation may be different.

METHODS

Setting

This study used data stored in the high-resolution eICU (eicu-crd.mit.edu) database, which comprises 200,859 admissions for 139,367 unique patients between 2014 and 2015 at 208 hospitals located throughout the United States. The database contains parameters that were available in the routine ICU clinical information system, including admission diagnosis, APACHE IV score and components, laboratory measurements, vital signs, medications, and special treatments. The elaborate description of eICU can be found elsewhere (17).

The eICU database was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2). The institutional review board (IRB) approval was exempt due to the retrospective and re-identification design. The author (certification number: 28795067) was approved to access the database for research aims after completing the National Institutes of Health web-based training course, which was "Protecting Human Research Participants."

Study Population

All recorded patients in the eICU database were eligible for inclusion. The first ICU stay was selected for those who were admitted to ICU for more than once. We selected adult patients with invasively mechanical ventilation during the first 24 h after admission to ICU. Patients were excluded for the following reasons: (1) ICU length of stay <24 h, (2) Incomplete hospital mortality recording, (3) Missing Spo_2 data, (4) Percentage of recorded Spo_2 <=50%, values of Spo_2 < 70% were excluded based on such values were likely to be not accurate, (5) Missing height or weight data, (6) Missing APACHE IV score, (7) Ventilation with ambient air, i.e., fraction of inspired oxygen (Fio_2) = 21%.

Clinical Variables

The following information data during the first 24 h of admission were extracted: age, gender, height, weight, ethnicity, comorbidities, admission diagnosis, ICU types, Acute Physiology and Chronic Health Evaluation (APACHE) IV score and components, and sequential organ failure assessment (SOFA) score. The use of dialysis, vasopressors, mechanical ventilation setting during the first 24 h were also collected. However, we could not extract the pattern of mechanical ventilation. Patients with a body mass index (BMI) $\geq$30 kg/(m^2) were defined as obese according to the international standards (18), where BMI was calculated as body weight /(height^2).

We included all arterial blood gas (ABG) samples that were obtained during the first 24 h admitted to the ICU. The time-weighted mean partial pressure of arterial oxygen (Pao_2) (TWM-Pao_2), $Paco_2$ (TWM-$Paco_2$), pH (TWM-pH), and Fio_2 (TWM-Fio_2) were calculated for every patient. The time-weighted mean (TWM) data was calculated as an area under the curve (AUC) by integrating all time-sequence data divided by the whole time (24 h). The duration of the first measured value represented the time from admission (0 h) to the first measurement time. The duration for the last measured value was the measurement time to 24 h in the ICU. TWM- Pao_2, TWM-$Paco_2$, and TWM-pH were considered as categorical variables, and patients with missing ABG data of Pao_2, $Paco_2$, and pH were considered as a unique category, respectively.

The Spo_2, which was obtained during the first 24 h after ICU admission, were generally recorded from bedside vital signs monitors as 5-min median values. According to the BTS guideline for oxygen use in adults in healthcare and emergency settings (13), four categories were generated, which were <=88%, 89–93%, 94–98%, and 99–100%. TWM-Spo_2 was calculated for every patient, and patients were classified into different Spo_2 categories. We separately calculated the proportion of time spent in Spo_2 (PTS-Spo_2) of four categories during the first 24 h, defined as the time in each Spo_2 category divided by total time. For each patient, PTS-Spo_2 in each of the four predefined categories ranged from 0 to 100%, and the total proportion was 100%. A similar method was used in other studies (19, 20).

We selected the hospital mortality, defined as dead at hospital discharge as the primary outcome.

Statistical Analysis

Categorical variables were reported as numbers and percentages and were analyzed with Chi-square test or Fisher's exact test as appropriate. Continuous variables are shown as median and

interquartile range (IQR) or mean and standard deviation (SD), which were compared using Wilcoxon rank-sum test or Student's *t*-test, respectively. As for outliers in the database, which were defined as the recording lies outside the 3 × IQR range, were re-checked and replaced by the 5th or 95th percentile. As for missing values, the number was clearly stated for each variable. Patients with missing data of Pao_2, $Paco_2$, and pH were considered as a categorical variable, and multiple imputation was performed for missing data of TWM-Fio_2.

First, a descriptive analysis was performed in non-obese and obese patients, including baseline characteristics and clinical parameters. Then, a univariate analysis was done according to survival at hospital discharge in non-obese and obese patients. We used the multivariable logistic regression models to assess the relationship between TWM-Spo_2 categories and hospital mortality after adjusting for covariates. The association between each PTS-Spo_2 of different categories and hospital mortality was investigated with multivariable logistic regression. The variables that were considered clinically relevant or that showed a univariate relationship with the outcome ($p < 0.10$) were selected into the multivariable model. A stepwise backward elimination method with a significance level of 0.05 was used to build the final model. The variance inflation factor was used to examine the multicollinearity, and the Hosmer-Lemeshow goodness-of-fit test to assess the calibration of the models.

PTS-Spo_2 of different categories was compared between non-obese and obese patients. The interaction between PTS-Spo_2 (as a continuous variable) and obesity status (obese and non-obese, as a categorical variable) was explored by the multivariable logistic regression model.

As for the data extraction, PostgreSQL (version 10, www.postgresql.org) was used. A two-sided *p*-value of < 0.05 was considered statistically significant. We used the R software (version 3.5.1, www.r-project.org) to conduct all the statistical analyses.

RESULTS

Figure 1 showed the flow chart of the study. After exclusion, a total of 25,100 patients met our inclusion criteria, of which 10,564 (42%) were obese patients and 14,534 (58%) were non-obese patients. The median BMI in the total population was 28.3 (IQR 23.9–34.4) kg/m^2, of which the non-obese was 25 (IQR 22–27) kg/m^2 and the obese was 36 (IQR 33–42) kg/m^2. The median age was 65 (IQR 54–75) years, 13,632 (54%) was male. 4,242 (17%) patients were non-survivors at hospital discharge. Demographics and baseline characteristics between the obese and non-obese were presented in **Table 1**.

In non-obese patients, the median age was 67 (IQR 55–78) and the hospital mortality was 18%. BMI of non-obese patients was higher in survivors than in non-survivors (25 vs. 24, $p < 0.001$). Non-obese patients with comorbidities of hypertension or chronic renal insufficiency had higher hospital mortality (**Table 1**). Non-obese survivors had a higher percentage of TWM-Spo_2 of 99–100% (**Table 2**).

In obese patients, the median age was 63 (IQR 53–72) and hospital mortality was 15%, which was lower than non-obese patients ($p < 0.001$). Obese survivors had higher BMI than non-survivors (36 vs. 35, $p = 0.014$). Obese patients had a higher percentage of hypertension, diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease, and chronic renal insufficiency than the non-obese. Interestingly, obese survivors had a higher percentage of diabetes mellitus (33% vs. 30%, $p = 0.009$). Obese survivors had lower percentage of TWM-Spo_2 of 99–100% (11% vs. 14%) and higher percentage of TWM-$Paco_2$ > 45 mmHg (30 vs. 26%) (**Table 2**). Obese patients had lower PTS-Spo_2 of 99–100% than non-obese patients (39.8% vs. 54.8%, $p < 0.001$) (**Table 3**).

The relationship between TWM-Spo_2 categories and hospital mortality, which was assessed by the multivariable logistic models after adjusting confounders, was comparing with 94–98% category, <=88% category (OR 3.572; CI [2.343, 5.455]; $p < 0.001$) and 89–93% category (OR 1.514; CI [1.343, 1.706]; $p < 0.001$) both had higher odds ratio for hospital mortality, while 99–100% category was not associated with hospital mortality (**Figure 2A** and **Supplementary Table 1**). After multivariable analysis, PTS-Spo_2 of <=88% (OR 1.445; CI [1.356, 1.541]; $p < 0.001$; per 10% increase) and PTS-Spo_2 of 89–93% (OR 1.080; CI [1.052, 1.108]; $p < 0.001$; per 10% increase) had higher odds ratio for hospital mortality, PTS-Spo_2 of 94–98% (OR 0.968; CI [0.955, 0.981]; $p < 0.001$; per 10% increase) had lower odd ratio for hospital mortality, and PTS-Spo_2 of 99–100% (OR 0.997; CI [0.986, 1.009]; $p = 0.636$; per 10% increase) was not associated with high risk of hospital mortality (**Figure 2B** and **Supplementary Tables 2–5**).

The multivariable models including the interaction between PTS-Spo_2 and obesity status (non-obese and obese) showed that there was a significant interaction between PTS-Spo_2 and obesity status (**Table 3**). While the PTS-Spo_2 of 99-100% was not significantly associated with hospital mortality outcome (OR 1.004; 95% CI 0.990-1.018; p = 0.597; per 10% increase) in non-obese patients, it was associated with increased risk of mortality in obese patients (OR 1.028; 95% CI 1.010-1.046; p = 0.002; per 10% increase) (**Figure 3A**). While the PTS-Spo_2 of 89-93% was significantly associated with increased risk of hospital mortality outcome (OR 1.089; 95% CI 1.051-1.128; p < 0.001; per 10% increase) in non-obese patients, it was not associated with hospital mortality in obese patients (OR 1.022; 95% CI 0.985-1.060; p = 0.235; per 10% increase) (**Figure 3B**). **Supplementary Figure 3** showed the interaction between PTS-Spo_2 of <= 88% and 94-98% and obesity status (obese and non-obese).

DISCUSSION

The results of our study provide evidence to support our hypothesis. The impact of supplemental oxygen on hospital mortality was different in non-obese and obese critically ill patients with mechanical ventilation. Spo_2 of 99–100% was associated with a higher hospital mortality for obese patients but was not statistically significant for non-obese patients. Spo_2 of

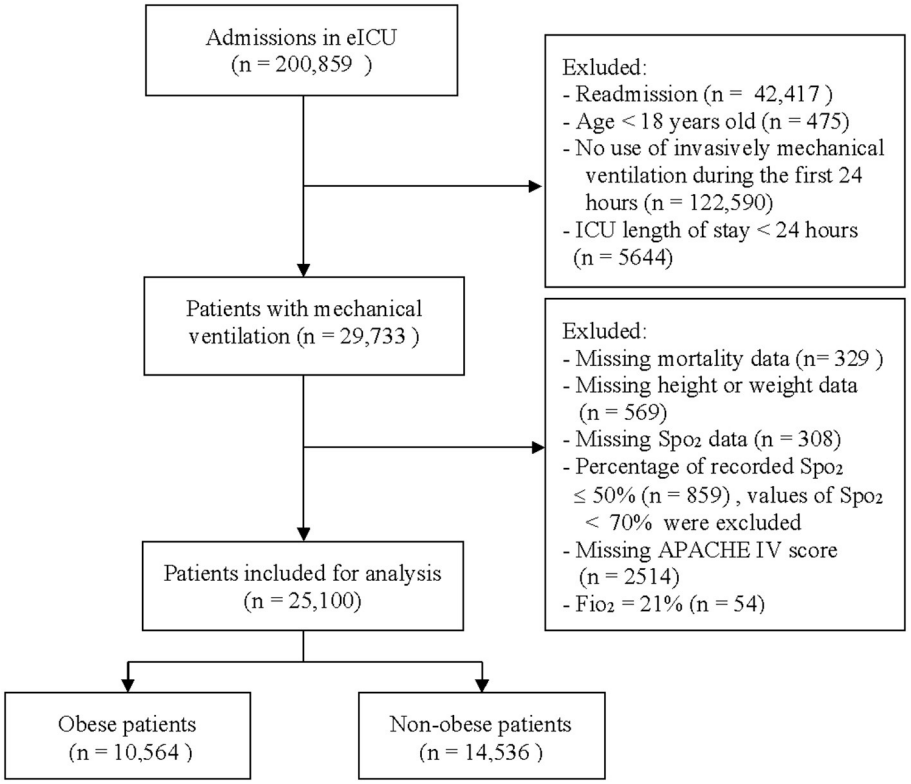

FIGURE 1 | Flow chart of subject selection. eICU, telehealth intensive care unit; Spo_2, peripheral oxygen saturation; Fio_2, fraction of inspiration oxygen.

94–98% was associated with decreased risk of hospital mortality outcome for both obese and non-obese patients. Spo_2 of 89–93% was associated with higher mortality for non-obese patients, but not statistically significant for obese patients. Spo_2 of <=88% was associated with an increased risk of hospital mortality outcome in both non-obese patients and obese patients. This is the first study to assess the relationship between supplemental oxygen and mortality in the specific population of obese critically ill patients with mechanical ventilation. The results of the present study showed that supplemental oxygen therapy should consider the obesity status into account.

The Oxygen-ICU randomized clinical trial showed among critically ill patients with an ICU length of stay of 72 h or longer, conservative therapy (Spo_2 94–98%) vs. conventional therapy (Spo_2 97–100%) resulted in lower ICU mortality (11). However, ICU-ROX trial found in adults undergoing mechanical ventilation in the ICU, conservative oxygen therapy (Spo_2 91–96%), as compared with usual oxygen therapy (Spo_2 ≥91%), did not significantly affect the number of ventilator-free days or mortality (21). In the present study, compared with the TWM-Spo_2 94–98% category, TWM-Spo_2 of 99–100% was not associated with hospital mortality. However, when considering the dose of Spo_2, PTS-Spo_2 of 94–98% was associated with lower hospital mortality in overall patients. The results of our study were consistent with the two RCTs.

There were some explanations of the differences observed between the non-obese and obese groups. First, obese patients can cause hypoxemia by decreasing lung volumes and may be at risk for hyperoxia-induced hypercapnia (22, 23). Two small trials conducted in morbidly obese patients with obesity hypoventilation syndrome (OHS) showed an elevated baseline $Paco_2$. After a 20-min exposure to hyperoxia, the patients had a mean increase in $Paco_2$ of about 4.4 mmHg (14, 15). However, whether hyperoxia-induced hypercapnia occurs in patients with milder obesity and without hypoventilation is unclear. Denault et al. found in obese patients with mean BMI 34 kg/m^2 after cardiac surgery, there was no clinically important increase in $Paco_2$ associated with higher Spo_2 values (24). Second, obese patients had higher rate of comorbidities, like COPD, chronic heart failure, diabetes mellitus, of which hyperoxia could exacerbate the outcome (25, 26). In the present study, percentage of COPD or heart failure was higher in obese than non-obese patients. Interestingly, in obese patients, survivors had a higher percentage of diabetes mellitus than non-survivors, which was not the case in the non-obese patients. Vught LA et al. also found diabetes was not associated with adjusted 90-day mortality risk in critically ill patients admitted with sepsis (27). Third, hyperoxia may result in nitric oxide depletion and induction of oxidative stress on the adipose tissue, which may exacerbate the critical illness (28).

TABLE 1 | Baseline characteristics of study patients.

Variables	Total (n = 25,100)		Non-obese (n = 14,536)		*P*-value	Obese (n = 10,564)		*P*-value
	Non-obese (n = 14,536)	Obese (n = 10,564)	Survivors (n = 11,865)	Non-survivors (n = 2,671)		Survivors (n = 8,993)	Non-survivors (n = 1,571)	
Age, years	67 (55, 78)	63 (53, 72)	66 (54, 77)	72 (60, 81)	<0.001	63 (53, 72)	67 (57, 75)	<0.001
Gender: male	8147 (56)	5485 (52)	6636 (56)	1511 (57)	0.561	4678 (52)	807 (51)	0.654
BMI	25 (22, 27)	36 (33, 42)	25 (22, 27)	24 (21, 27)	<0.001	36 (33, 42)	35 (32, 41)	0.014
Ethnicity					0.665			0.532
Caucasian	11154 (77)	8233 (78)	9083 (77)	2071 (78)		7005 (78)	1228 (78)	
African American	1602 (11)	1322 (13)	1322 (11)	280 (10)		1142 (13)	180 (11)	
Hispanic	549 (4)	325 (3)	448 (4)	101 (4)		276 (3)	49 (3)	
Asian	295 (2)	59 (1)	245 (2)	50 (2)		47 (1)	12 (1)	
Native American	85 (1)	101 (1)	74 (1)	11 (0)		84 (1)	17 (1)	
Other/Unknown	851 (6)	524 (5)	693 (6)	158 (6)		439 (5)	85 (5)	
Comorbidities								
Hypertension	7095 (49)	6166 (58)	5722 (48)	1373 (51)	0.003	5267 (59)	899 (57)	0.333
Diabetes mellitus	2525 (17)	3471 (33)	2046 (17)	479 (18)	0.411	3000 (33)	471 (30)	0.009
COPD	3188 (22)	2560 (24)	2608 (22)	580 (22)	0.784	2205 (25)	355 (23)	0.108
Heart failure	2380 (16)	2525 (24)	1921 (16)	459 (17)	0.22	2098 (23)	427 (27)	0.001
Cirrhosis	252 (2)	180 (2)	192 (2)	60 (2)	0.03	136 (2)	44 (3)	<0.001
Chronic renal insufficiency	1879 (13)	1615 (15)	1480 (12)	399 (15)	0.001	1320 (15)	295 (19)	<0.001
ICU types					<0.001			<0.001
Med-SurgICU	7735 (53)	5691 (54)	6328 (53)	1407 (53)		4902 (55)	789 (50)	
Cardiac ICU	924 (6)	683 (6)	687 (6)	237 (9)		504 (6)	179 (11)	
CCU-CTICU	1168 (8)	942 (9)	982 (8)	186 (7)		818 (9)	124 (8)	
CSICU	516 (4)	366 (3)	441 (4)	75 (3)		321 (4)	45 (3)	
CTICU	662 (5)	445 (4)	608 (5)	54 (2)		409 (5)	36 (2)	
MICU	1446 (10)	1102 (10)	1144 (10)	302 (11)		912 (10)	190 (12)	
Neuro ICU	995 (7)	615 (6)	770 (6)	225 (8)		500 (6)	115 (7)	
SICU	1090 (7)	720 (7)	905 (8)	185 (7)		627 (7)	93 (6)	
Diagnosis					<0.001			<0.001
Respiratory	3231 (22)	2550 (24)	2711 (23)	520 (19)		2278 (25)	272 (17)	
Sepsis	2135 (15)	1448 (14)	1625 (14)	510 (19)		1170 (13)	278 (18)	
Cardiac surgery	1619 (11)	1257 (12)	1577 (13)	42 (2)		1217 (14)	40 (3)	
Neurological	1920 (13)	1129 (11)	1568 (13)	352 (13)		950 (11)	179 (11)	
Cardiovascular	1064 (7)	1041 (10)	895 (8)	169 (6)		916 (10)	125 (8)	
Cardiac arrest	1181 (8)	898 (9)	637 (5)	544 (20)		474 (5)	424 (27)	
Trauma	774 (5)	384 (4)	645 (5)	129 (5)		323 (4)	61 (4)	
Gastrointestinal	675 (5)	336 (3)	548 (5)	127 (5)		293 (3)	43 (3)	
Others	1937 (13)	1521 (14)	1659 (14)	278 (10)		1372 (15)	149 (9)	

Data are median (interquartile range) or No/Total (%).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; CCU, Coronary Care Unit; CTICU, Cardiothoracic ICU; CSICU, Cardiac Surgery ICU; MICU, Medical ICU; SICU, Surgical ICU.

The results of the current study suggest that compared with non-obese patients, excessive oxygen may be injurious for obese patients. However, targeted oxygenation was still unknown. BTS guideline recommends for morbidly obese patients (BMI > 40 kg/m_2), a target saturation of 88–92% should be titrated to maintain (grade D) (13). However, the literature was really sparse. In the present study, for obese patients with mechanical ventilation, Spo_2 of <=88% may be associated with poor outcome, 89–93% was not associated with mortality, 94–98% was associated with lower mortality, and 99–100% was associated with higher mortality. The results suggested Spo_2 99–100% was not appropriate for obese patients. On the other hand, in obese patients, non-survivors had a higher percentage of TWM-Pao_2 of 120–300 mmHg and >300 mmHg, which also suggested hyperoxia may be detrimental for obese patients.

For overall and non-obese patients, PTS-Spo_2 of 89–93% was associated with increased hospital mortality in the present study. The contribution of modest hypoxemia to mortality is unknown. The recommendation of oxygen supply by guidelines mainly based on the normal ranges of Spo_2 (13, 16). A North

TABLE 2 | Clinical data during the first 24 h and interventions.

Variables	Total (n = 25,100)		Non-obese (n = 14,536)		*P*-value	Obese (n = 10,564)		*P*-value
	Non-obese (n = 14,536)	Obese (n = 10,564)	Survivors (n = 11,865)	Non-survivors (n = 2,671)		Survivors (n = 8,993)	Non-survivors (n = 1,571)	
TWM-Spo_2					<0.001			<0.001
<=88%	71 (0)	58 (1)	22 (0)	49 (2)		37 (0)	21 (1)	
89–93%	1016 (7)	1341 (13)	740 (6)	276 (10)		1118 (12)	223 (14)	
94-98%	10249 (71)	7994 (76)	8476 (71)	1773 (66)		6889 (77)	1105 (70)	
99–100%	3200 (22)	1171 (11)	2627 (22)	573 (21)		949 (11)	222 (14)	
TWM-Pao_2, (mmHg)					<0.001			<0.001
<60	368 (3)	327 (3)	274 (2)	94 (4)		270 (3)	57 (4)	
60–120	5269 (36)	5139 (49)	4285 (36)	984 (37)		4381 (49)	758 (48)	
120–300	5199 (36)	2718 (26)	4203 (35)	996 (37)		2239 (25)	479 (30)	
>300	403 (3)	155 (1)	320 (3)	83 (3)		120 (1)	35 (2)	
Missing, *N* (%)	3297 (23)	2225 (21)	2783 (23)	514 (19)		1983 (22)	242 (15)	
TWM-$Paco_2$, (mmHg)					<0.001			<0.001
<35	2951 (20)	1387 (13)	2240 (19)	711 (27)		1040 (12)	347 (22)	
35–45	5549 (38)	3799 (36)	4622 (39)	927 (35)		3245 (36)	554 (35)	
>45	2618 (18)	3079 (29)	2129 (18)	489 (18)		2667 (30)	412 (26)	
Missing, *N* (%)	3418 (24)	2299 (22)	2874 (24)	544 (20)		2041 (23)	258 (16)	
TWM-pH					<0.001			<0.001
<7.35	3579 (25)	3132 (30)	2641 (22)	938 (35)		2547 (28)	585 (37)	
7.35–7.45	5783 (40)	4069 (39)	4920 (41)	863 (32)		3513 (39)	556 (35)	
>7.45	1633 (11)	941 (9)	1318 (11)	315 (12)		779 (9)	162 (10)	
Missing, *N* (%)	3541 (24)	2422 (23)	2986 (25)	555 (21)		2154 (24)	268 (17)	
Mechanical ventilation setting								
Fio_2, %	50 (40, 60)	55 (40, 70)	50 (40, 60)	60 (50, 80)	<0.001	50 (40, 70)	60 (50, 80)	<0.001
RR	15 (12, 18)	16 (14, 20)	14 (12, 18)	16 (14, 20)	<0.001	16 (14, 18)	18 (14, 23)	<0.001
Tidal volume, ml/kg	6.7 (6.9, 7.6)	7 (6.3, 8.2)	6.7 (5.9, 7.7)	6.6 (5.8, 7.5)	<0.001	7.1 (6.3, 8.3)	7 (6.3, 8)	0.005
PEEP, cmH_2O	5 (5, 5)	5 (5, 7)	5 (5, 5)	5 (5, 8)	<0.001	5 (5, 7)	5 (5, 8)	<0.001
Plateau pressure, cmH_2O	19 (16, 24)	22 (18, 27)	19 (15, 23)	21 (17, 26)	<0.001	22 (18, 27)	24 (20, 29)	<0.001
APACHE-IV	69 (52, 90)	65 (49, 87)	65 (49, 84)	92 (72, 113)	<0.001	62 (47, 81)	94 (71, 118)	<0.001
SOFA	6 (4, 9)	6 (4, 8)	6 (4, 8)	8 (6, 11)	<0.001	6 (4, 8)	9 (6, 11)	<0.001
Vasopressors	3361 (23)	2323 (22)	2377 (20)	984 (37)	<0.001	1725 (19)	598 (38)	<0.001
Dialysis	601 (4)	351 (3)	499 (4)	102 (4)	0.393	283 (3)	68 (4)	0.02
Total ventilation days	3 (2, 5)	3 (2, 6)	2 (2, 4)	4 (2, 7)	<0.001	3 (2, 5)	4 (3, 8)	<0.001
Duration of ICU stay	3 (2, 6)	3 (2, 7)	3 (2, 6)	4 (2, 7)	<0.001	3 (2, 6)	4 (2, 8)	<0.001
Duration of hospital stay	8 (5, 13)	8 (5, 14)	8 (5, 14)	6 (3, 11)	<0.001	8 (5, 14)	6 (3, 11)	<0.001

Data are median (interquartile range) or No/Total (%).

TWM, time-weighted mean; Spo_2, peripheral oxygen saturation; Pao_2, partial pressure of arterial oxygen; $Paco_2$, partial pressure of arterial carbon dioxide; Fio_2, fraction of inspired oxygen; RR, respiratory rate; PEEP, positive end-expiratory pressure; APACHE, Acute Physiology, and Chronic Health Evaluation; SOFA, sequential organ failure assessment.

American study found Spo_2 at sea level for adults with two standard deviation range is 94–98% (29). However, the standard reference ranges obtained from healthy volunteers may differ from the analogous range generated from data of ICU patients (30). Another larger observational study of over 37,000 patients admitted to four acute medical admissions units found that median Spo_2 was 98% (IQR 97–99%) for young adults and 96% (IQR 95–98%) for old adults (31). They also found for patients with initial Spo_2 values of 89, 90, 91, 92, and 93% had higher mortality and the 95% confidential intervals did not overlap with those initial Spo_2 values of ≥95% (31). However, clearly, there were limitations to the raw results without adjusting for confounders.

The present study has several other strengths. First, a total of 25,100 patients was extracted from ICUs in 166 hospitals, which allowed for the adjustment of multiple confounding factors, making the findings more generalizable. Second, the total observations of Spo_2 were 6,925,863, the average observations of Spo_2 were 276 for each patient, accounting for the time of 95.8% in the first 24 h, which made the results robust. Third, we calculated both the TWM-Spo_2 and PTS-Spo_2, which considered the dose of Spo_2.

TABLE 3 | Adjusted odds ratio for hospital mortality in patients with different PTS-Spo_2 categories.

Proportion of time (%) spent in Spo_2 categories	Non-obese (n = 14,536)	Obese (n = 10,564)	Adjusted ORs for hospital mortality (95% CI)	*P*-Value	*P* for interaction
<=88%, median (IQR)	0 (0, 0.8)	0 (0, 1.1)	1.570 [1.435, 1.723]	<0.001	0.01
89–93%, median (IQR)	1.3 (0, 7.8)	3.4 (0.4, 14.3)	1.100 [1.062, 1.138]	<0.001	0.001
94–98%, mean (SD)	37 (28.3)	47.6 (27.8)	0.977 [0.961, 0.994]	0.008	0.007
99–100%, mean (SD)	54.8 (34)	39.8 (33.3)	1.000 [0.986, 1.014]	0.985	0.001

PTS, proportion of time spent; Spo_2, peripheral oxygen saturation; SD, standard deviation; OR, odd ratio; CI, confidence interval.
All models included age, BMI categories (obese and non-obese), admission diagnosis, diabetes mellitus, Sequential Organ Failure Assessment score (not including points for the respiratory part), TWM-Fio_2, TWM-$Paco_2$ categories, and TWM-pH categories as covariates. Four categories (i.e., four multivariable logistic models including four categories and other covariates) of proportion of time spent in Spo_2 were selected into the models separately, and the interaction between proportion of time spent in Spo_2 and BMI categories were explored.
BMI, body mass index; TWM, time-weighted mean; Fio2, fraction of inspiration oxygen; Paco2, partial pressure of arterial carbon dioxide.
An odd ratio is calculated per 10% increase in time in each given band.

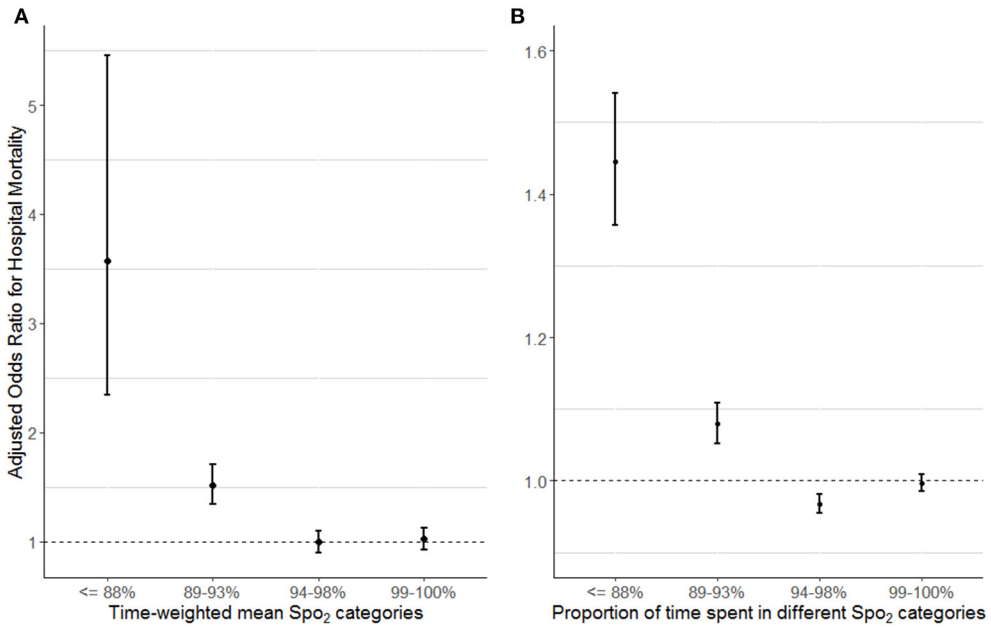

FIGURE 2 | Left **(A)** Adjusted odds ratio for hospital mortality according to different TWM-Spo_2 categories. The adjusted odds ratio for each Spo_2 level and 95% confidence intervals (error bars) were calculated (TWM-Spo_2 of 94–98% as reference). Right **(B)** Adjusted odds ratio for hospital mortality according to PTS-Spo_2 categories separately. An odds ratio is calculated per 10% increase in time in each given category. All models (i.e., five models, one for "**A**" and four for "**B**") were separately adjusted for age, BMI categories, admission diagnosis, diabetes mellitus, Sequential Organ Failure Assessment score (not including points for the respiratory part), TWM-Fio_2, TWM-$Paco_2$, and TWM-pH categories. TWM, time-weighted mean; Spo_2, peripheral oxygen saturation; PTS, proportion of time spent; BMI, body mass index; Fio_2, fraction of inspiration oxygen; $Paco_2$, partial pressure of arterial carbon dioxide. Full multivariable models see **Supplementary Tables 1–5**.

However, several obvious limitations should be mentioned. First, the retrospective design in nature was subjected to the inherent limitations. This study design may only show statistical associations and but not causality between PTS-Spo_2 and hospital mortality. Second, although the multivariable logistic regression to was used to adjust for potential confounders, the potential confounding factors (e.g., altitude, smoking status et al.) which were not included in the analysis, could lead to biased results. Third, some data could be invalidated due to the acquisition directly from the bedside vital sign monitors. Some of the data had not been checked and verified by a bedside care provider, i.e., the measurements may be noisy and may not reflect the true status. However, the Spo_2 values recorded by the nurse and observed by the monitor at the same time were highly correlated (**Supplementary Figure 4**). Fourth, we only extracted the data for the first 24 h, which could not represent the entire course of stay in ICU. Fifth, we arbitrarily classified the Spo_2 into four categories, <=88%, 89–93, 94–98%, and 99–100%, the rationality may need further research. Sixth, although Spo_2 is widely used for clinical practice for continuously assessing the oxygenation in critically ill patients, blood gasses analyses are still the golden standard, especially in assessing the severity of hypoxemia

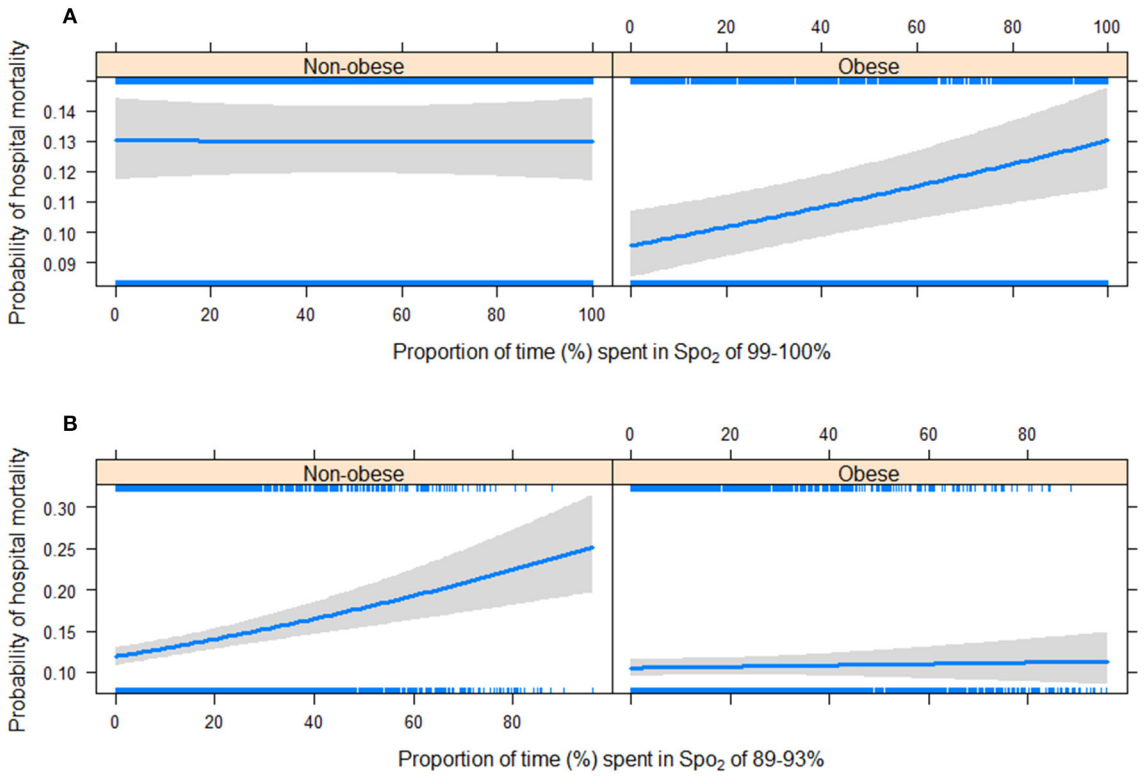

FIGURE 3 | Interaction between PTS-Spo_2 and obesity status (obese and non-obese). Upper **(A)** While the PTS-Spo_2 of 99–100% was not significantly associated with hospital mortality outcome (OR 1.004; 95% CI 0.990–1.018; $p = 0.597$; per 10% increase) in non-obese patients, it was associated with increased risk of mortality in obese patients (OR 1.028; 95% CI 1.010–1.046; $p = 0.002$; per 10% increase). Lower **(B)** While the PTS-Spo_2 of 89–93% was significantly associated with increased risk of hospital mortality outcome (OR 1.089; 95% CI 1.051–1.128; $p < 0.001$; per 10% increase) in non-obese patients, it was not associated with hospital mortality in obese patients (OR 1.022; 95% CI 0.985–1.060; $p = 0.235$; per 10% increase). PTS-Spo_2, proportion of time spent in peripheral oxygen saturation, OR odds ratio, CI confidential interval.

and other gas exchange anomalies. Spo_2 may not display the real oxygenation status. Finally, we excluded patients without APACHE IV score, whose diagnoses were mainly burns and certain organ transplantation (17, 32), which may cause biases.

CONCLUSIONS

The impact of supplemental oxygen on hospital mortality was different in non-obese and obese critically ill patients with mechanical ventilation. Spo_2 of 99–100% was associated with higher mortality for obese patients, while Spo_2 of 89–93% was associated with higher mortality for non-obese patients.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: eicu-crd.mit.edu.

ETHICS STATEMENT

The eICU was exempt from Institutional Review Board (IRB) approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2). Due to the HIPAA compliant de-identification in this database, our institutional IRB requirement was waived.

AUTHOR CONTRIBUTIONS

DZ and TL conceived this study and reviewed and modified the final manuscript. DZ extracted the data. TL, DZ, DW, and CW designed and performed the statistical analyses. DZ, TL, QL, RZ, and DZ wrote the first draft of the manuscript. All authors read, 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.2022.839787/full#supplementary-material

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ORIGINAL RESEARCH
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Methods for Measuring and Identifying Sounds in the Intensive Care Unit

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Background: Despite many studies in the field examining excessive noise in the intensive care unit, this issue remains an ongoing problem. A limiting factor in the progress of the field is the inability to draw conclusions across studies due to the different and poorly reported approaches used. Therefore, the first goal is to present a method for the general measurement of sound pressure levels and sound sources, with precise details and reasoning, such that future studies can use these procedures as a guideline. The two procedures used in the general method will outline how to record sound pressure levels and sound sources, using sound level meters and observers, respectively. The second goal is to present the data collected using the applied method to show the feasibility of the general method and provide results for future reference.

Methods: The general method proposes the use of two different procedures for measuring sound pressure levels and sound sources in the intensive care unit. The applied method uses the general method to collect data recorded over 24-h, examining two beds in a four-bed room, via four sound level meters and four observers each working one at a time.

Results: The interrater reliability of the different categories was found to have an estimate of >0.75 representing good and excellent estimates, for 19 and 16 of the 24 categories, for the two beds examined. The equivalent sound pressure levels (L_{Aeq}) for the day, evening, and night shift, as an average of the sound level meters in the patient room, were 54.12, 53.37, and 49.05 dBA. In the 24-h measurement period, talking and human generated sounds occurred for a total of 495 (39.29% of the time) and 470 min (37.30% of the time), at the two beds of interest, respectively.

Conclusion: A general method was described detailing two independent procedures for measuring sound pressure levels and sound sources in the ICU. In a continuous data recording over 24 h, the feasibility of the proposed general method was confirmed.

Moreover, good and excellent interrater reliability was achieved in most categories, making them suitable for future studies.

Keywords: intensive care unit, noise, sound level meters, hospital, decibels, sound pressure levels, sound sources

INTRODUCTION

Patients admitted to the intensive care unit (ICU) are constantly exposed to high sound pressure levels due to the complex nature of their treatment, involving numerous medical devices, alarms, and staff involved. Moreover, in previous research the already high sound pressure levels in the ICU have been found to be increasing by 0.38 dBA per year during the day, and by 0.42 dBA per year at night (1). The average daytime sound pressure levels have increased from 57 dBA in 1960 to 72 dBA in 2005, and nighttime levels have risen from 42 dBA to 60 dBA during the same period. Consequently, sound pressure levels in the ICU continue to exceed the recommended 45 dBA during the day, and 30 dBA at night, set forth by the World Health Organization (1–8).

One of the most difficult aspects of addressing the excessive sound pressure levels in the ICU is understanding what the precise causes of the high sound pressure levels are. Literature has presented evidence suggesting that in the ICU setting, staff-generated sounds are the greatest contributor to the total sound pressure levels recorded (2, 9), particularly in close proximity to the bed (10). Other major sources of sound in the ICU are attributed to activities such as hand washing, opening packages, storage drawers, telephones, and pagers (2, 4, 11). This is in line with a study by Vreman et al. (6) which found that overall alarms only contributed to a minor proportion of overall sound pressure levels in the ICU, however, other studies suggest a more significant role of monitor alarms (2, 12, 13). Understanding the true sources of sound is of importance due to its role in patient and staff health. In patients, changes in cardiovascular performance (14), sleep disruptions (15), and adverse clinical outcomes (16) have been linked to sound pressure levels >50 dBA. Patient outcomes can also be affected by alarm fatigue and burnout experienced by ICU professional repeatedly exposed to high sound pressure levels (12, 17).

Despite the existing literature on the topic, progress in addressing the known problems in this field is slow. One reason for this is the difficulty drawing comparisons between studies addressing this topic (11, 18). The lack of a defined procedure, methods, and parameters, for measuring and identifying sound within the ICU setting has resulted in numerous papers on the topic (9, 11, 18). For example, there are differences in the number, type, and location of the devices used. Some studies may use one or two recording devices placed near the patient head (19), while others may place them closer to the foot of the bed (20), or even in the hallway (21). Alternately, there are studies which use six or more devices (2, 21). Recording duration also varies between studies, with some recording continuously (19), while others record only intervals (21, 22). The devices used for the analysis also vary, with some using microphones (10, 23) or sound level meters (19, 24), while another may use previously recorded sounds (9). Differences also exist for observers identifying sound sources, with some studies using a single observer (3) and other using multiple observers (4). The checklists used for identifying or grouping sound sources is also unique to each paper and often difficult to replicate due to a lack of details. The checklists may be made up of more generalized groups (2, 9), while others may use more detailed lists or include additional precisions per group (3, 4, 9, 25). As such, it is relevant to the field to tackle this lack of consistency so that progress can be made in reducing high sound pressure levels, an issue that concerns hospitals worldwide (1, 2, 4, 9, 26).

For this reason, the current paper aims to standardize the assessment of sound levels and sound sources in the ICU, outlining a generalizable method with repeatable procedures and clear parameters. By providing a detailed description of the proposed steps, as well as the reasoning behind the choices, the goal is to provide a baseline that can be used for future investigations into the sound pressure levels and sound sources in the ICU. To show the feasibility of the general method, and to act as a reference, data from a 24-h recording period at two beds, in a four-bed patient room, collected using the proposed procedures, is presented. It is expected that by using the proposed procedures as a guideline, future studies will not only be able to successfully record sound pressure levels and sound sources in the ICU environment for single- and multi-day experiments, but also be comparable among each other.

MATERIALS AND METHODS

The general method is composed of two procedures that can be conducted simultaneously but independently (**Figure 1**). One procedure outlines how sound pressure levels can be measured using sound level meters, while the second procedure outlines how to identify sound sources using observers. These two procedures will be described in more detail below.

General Method

Sound Pressure Levels Procedure

Sound Equipment

Sound pressure levels are recorded using sound level meters. To be consistent with the literature, it is recommended that the decibel range of the device is appropriate for the sounds of interest (for example 30–90 dB). At least one sound level meter should be used per bed, plus one additional sound level meter outside of the patient room to capture sound in the surrounding environment. This means that if measuring a four-bed patient room, to examine all four beds four devices would be required, one above each bed, plus one for the outside the patient room, such as in the hallway. For recording using the sound level meters, there are a number of settings possible. It is recommended that the A-weighted filter is selected as it discriminates against low and high frequencies, comparable to

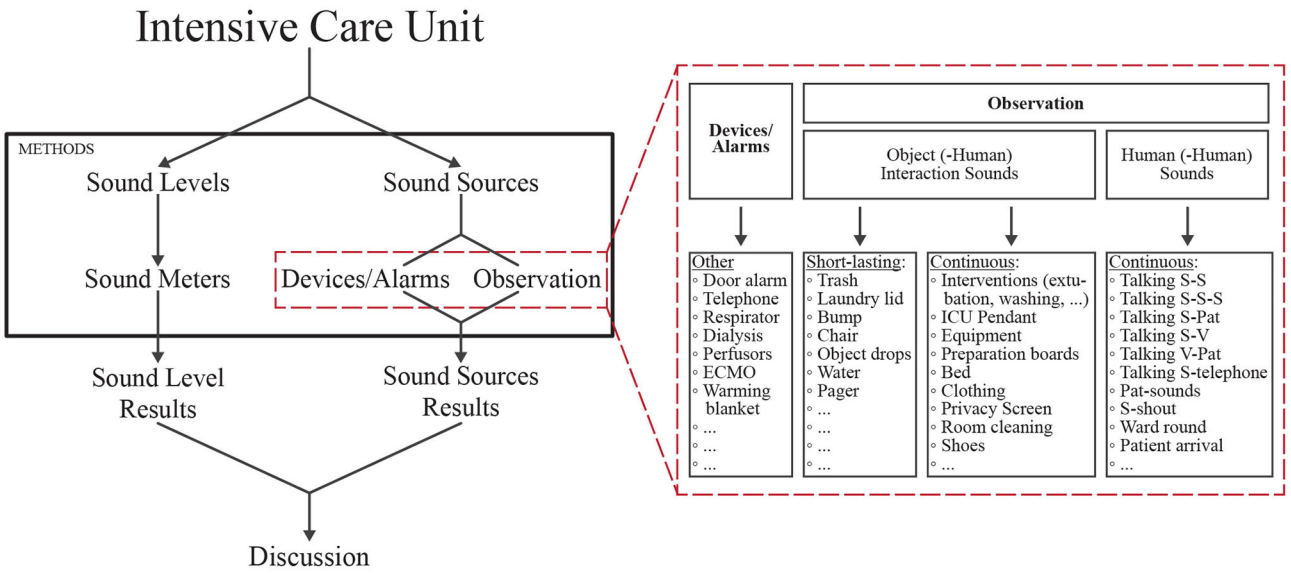

FIGURE 1 | Schematic outlining the two parallel methods for examining sound in the ICU setting. Left: The sound pressure levels in the ICU can be determined objectively using sound level meters. Right (red dashed box): details showing how the sound sources in the ICU can be determined via device alarms or via observers. These two components of sound in the ICU can be combined to create an overall picture of sound in the ICU. Staff (S); patient (Pat); visitor (V); extracorporeal membrane oxygenation (ECMO); intensive care unit (ICU). Full list of abbreviations, sound sources and descriptions can be found in the **Supplementary Table 1**.

the response of the human ear, and is standard weighting for indoor measurements (6, 27). Additionally, a fast time weighting is also recommended due to its higher resolution and similarities to the integration time of the human ear. The equivalent continuous sound level represents a stead sound pressure level around which the actual noise level fluctuates over a given time. When using A-weighted measurements, the equivalent sound level is denoted as L_{Aeq} (**Supplementary Equation 1**) (28). Similarly, the maximum, fast, A-weighted sound level measured (L_{AFmax}) represents the maximum sound pressure level reached during a defined recording period, using an A-frequency weighting and a fast time weighting.

For higher data quality, and to be able to record over longer periods, it is important that the devices are placed in an easily accessible place near a power-source. Certain devices need a continuous power source and have limited space for saving the data, therefore, data must be downloaded from the devices regularly, without interrupting the daily work of the ICU staff. Additional considerations pertaining to the individual device is whether the device can be disinfected, what the appropriate size is for the setting, and how it can be placed in or attached to the desired location. To ensure accurate sound pressure level recordings it is important that the sound level meters are placed in such a manner that they are not quickly noticed in an attempt to limit influencing the hospital staff. If the sound level meters are too easily noticed, this may create a bias in that sound pressure levels decrease (2, 4).

Medical Equipment

Within the ICU setting there are various stationary and movable devices which may be in a patient room at any given time. Many of these devices provide the possibility to extract the alarm information retrospectively, directly from the device itself, thereby easing the task of human-observers tracking the sound sources. For example, depending on the device, it may be possible to collect the occurrence of alarms concerning hemodynamics, dialysis, oxygenation, and perfusions following the observation period. Other patient-related alarms such as heart rate, blood pressure, blood saturation, and respiration rate, could also potentially be collected via the vital sign monitoring system. Miscellaneous alarms, such as doorbells or emergency reanimation alarms, might also be logged. Therefore, a query into the ability of retrieving such information from devices should be performed prior to beginning any observation period.

Sound Source Procedure

Checklist Development

To create a sound source checklist a dual bottom-up approach, based on the literature and clinical observations, was used. A baseline list of sound sources in the ICU was generated using previous work on the topic (2–4, 25). Next, an explorative approach was chosen to determine what types of sound sources exist in the patient room, both from a patient and staff perspective. This was done by having a member of the study team shadow a nurse working in the ICU for several h. Following this observation period, the findings were compared to and merged with those noted in the literature.

As the number of sound sources increased, it became unrealistic to be able to identify and note everything in parallel. Furthermore, sounds had to be differentiated into continuous and short-lasting sounds. To reduce complexity, observation periods were separated into five-min intervals and sound sources

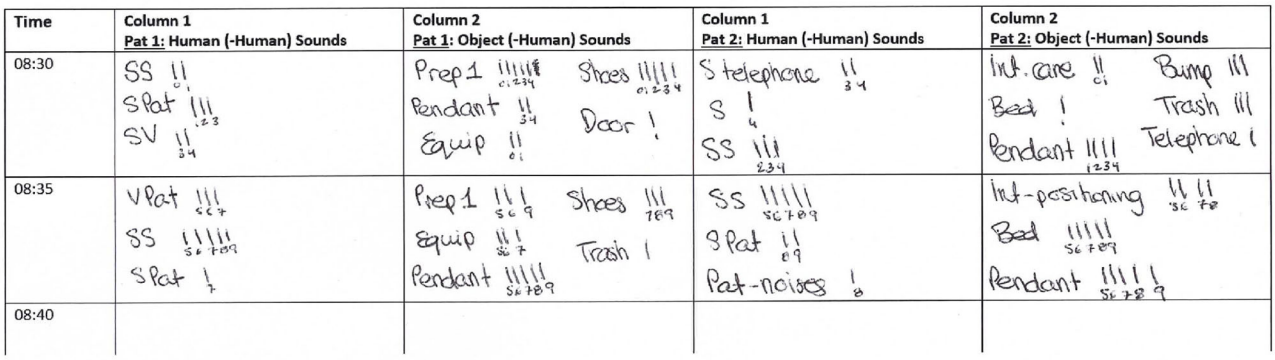

FIGURE 2 | Example observer sheet showing how two beds would be documented. The two columns on the left represent bed 1, and the two columns on the right represent bed 2. For each bed, the left column is where human (-human) sounds such as talking should be listed. For each bed, the right column is where object (-human) sounds should be noted such as sounds coming from the equipment, medical pendant, or shoes. Staff (S); staff-staff (SS); staff-patient (SPat); staff-visitor (SV); visitor-patient (VPat); preparation board one (Prep1); equipment (Equip); patient-noises (Pat-noises); intervention (Int). Full list of abbreviations, sound sources, and descriptions can be found in the **Supplementary Table 1**.

were grouped as either human (-human) or object (-human) interactions. Subsequently, the categorization was then tested and further adapted as new sounds were added and sounds were shifted from one classification to the other.

To further ease the challenge of noting all sound sources individually, clusters were created. For example, clusters such as equipment, preparation board, medical pendant, and interventions were created. A preliminary list of clusters was then assembled (**Supplementary Table 1**), to which new items could be added during the observation period.

Parameters and Scoring

The classification of sounds as continuous and short-lasting during the development of the checklist was important for defining how the groupings should be scored. Continuous sounds are those considered to last anywhere from more than a few sec to a min and should be scored as a duration. If a continuous sound occurs within a 5-min interval, the category of the sound (e.g., pendant, intervention, etc.) is noted, and a stroke is written down to indicate that it occurred in a single min. If the sound occurs again in the same min (e.g., from 8:30–8:31) no new stroke is added. If, however, the sound occurs again in a different min (e.g., from 8:31-8:32) another stroke is added (**Figure 2**). If a sound is categorized as continuous, a maximum of five strokes can be reached, representing that a sound occurred at most for 5 min. To make it easier for the observer and to avoid mistakes, the min in which a sound occurs can be noted as a small number under each stroke (**Figure 2**). This way, when the same sound is captured, it is quickly recognizable whether a new stroke must be made, or whether it still counts toward the already existing stroke. For continuous sounds, a score for each sound source is then achieved by adding up the total number of min the sound was heard which represents the maximum length of time it could have been heard.

On the other hand, if a short-lasting sound is heard, it should be scored as a frequency, and every occurrence should be noted by adding a stroke to the observation sheet (**Figure 2**). Here the number of strokes is not limited to five. Short-lasting sounds are those that cannot be continuous. For example, if a door closes or an object is dropped the sound cannot last more than a few sec. For short-lasting sounds, the total number of occurrences can be determined by adding up all the strokes.

Observer Shifts

When considering what type of observer shifts to use, the first step would be to decide how long the measurement period should last, and how many people are available to act as observers. The advantage of having multiple observers is the ability to continuously record sound sources over longer time periods and potentially even over multiple days. It also ensures the ability to maintain concentration levels during times of peak activity and avoid alarm and noise fatigue (12, 13). For this reason, daytime observers should alternate in their shifts. To help further decrease fatigue, observers should also be allowed a 10-min break every h, during which they can leave the room. Changes in observers should occur during these breaks as it allows the study team a chance to debrief, clarifying certain questions, or provide updates which may help the subsequent observer. If possible, observer changes should also not occur during staff shift changes to avoid missing data for these known periods of high sound pressure levels.

The length of shifts presented in the literature ranges from 10 min (3) to 3 h (26), with some also alternating observers (5). While it could be argued that shorter shifts may be better for maintaining concentration, there are other advantages to longer observation shifts. For example, the more time spent in the patient room, the more familiar the observer becomes with what is occurring in the room. As there is often a lot happening simultaneously it can be overwhelming when an observation shift begins, as the observer must first familiarize themselves with the current situation in the room. While some studies cite the involvement of nurses and doctors (4), we propose that the observers can be anyone familiar with the hospital setting.

Based on these factors, using four observers, the following observation shifts are proposed as an example, with breaks always occurring from:20 to:30 every h:

Observer 1: 6:30–8:20, 11:30–14:20, 17:30–20:20
Observer 2: 8:30–11:20, 14:30–17:20
Observer 3: 20:30–1:20
Observer 4: 1:30–6:20

It should be noted that it is recommended that objective measurements using sound level meters overlap temporally with the data collected by human observers pertaining to sound sources. This way it is possible to support any claims based on subjective measurements with objective recordings.

Interrater Reliability

Based on guidelines outlined by Koo and Li (29) the intraclass correlation coefficient (ICC) estimates and their 95% confidence intervals should be calculated based on a mean-rating (k = number of raters), absolute-agreement, two-way-mixed-effects model. Scoring suggestions provided by Koo and Li (29) should also be followed to interpret the results. Estimates above 0.90 are considered excellent and estimates between 0.75 and 0.90 are considered good. Those between 0.50 and 0.75 are moderate, and those below 0.50 are poor. It should be noted that when the variance in the samples is low, in this case the ICC is likely to be low as well, or cannot even be calculated (30).

Applied Method

Sound Pressure Level and Source Procedure

To show the feasibility of the proposed methods, and provide data for future comparisons, a reference recording was carried out. The reference recording was conducted for 24-h, with four observers and four sound level meters, looking at two beds in a four bed ICU room.

Interrater Reliability

Prior to conducting the reference recording, the interrater reliability of the four observers was tested. A total of 6 h were recorded: three during the day shift (8:00–11:00) to represent a busier observation period, and three during the evening shift (20:00–23:00) to represent a calmer observation period. During each three-h period, each of the four observers was compared to the other three observers, for a total of 30 min overlap per observer pair. ICC calculations were subsequently completed using the psych package in R version 4.0.4 (R Core) (31) and the two-way mixed-effects model and scoring described in section Interrater Reliability were used. For ease of computation, and to increase the number of data points for analysis, the individual items scored were grouped into categories. The detailed list of the categories can be found in **Supplementary Table 2**.

Setting

The preliminary scoring for interrater reliability, and the reference 24-h recording, was performed in the Department of Intensive Care Medicine in a mixed medical-surgical ICU at the University Hospital Bern, Switzerland. The corresponding department of Intensive Care is the sole provider for adult critically ill patients in the tertiary care academic center (University Hospital of Bern, Inselspital). Assessments were performed in a 16-bed subunit. The methods presented in this paper were approved by the local ethics committee via waiver as no identifiable patient data was collected (KEK 2020-01294).

The mixed medical-surgical ICU at the University Hospital Bern has three ICU wards with similar structural designs. The ward chosen for these assessments has 16 beds spread across double-bed and four-bed rooms, with a central nursing station outside the patient rooms (**Figure 3**). The four-bed rooms are bracketed by a two-bed room on one side, and a four-bed room on the opposite side (**Figure 3**). These rooms are connected via sliding doors which are generally left open to create a sense of unity between the spaces. There are also two large double sliding doors at either end of the ward, at the foot end of the beds, leading into the main corridor. The central nursing station is located across the corridor from these large sliding doors, permitting ICU staff at the station to maintain a view of the patient beds (**Figure 3**). To obtain a representative sound measure, two neighboring beds in the four-bed room, on the side closest to the adjoining four-bed room, were selected for reference observations (shaded area **Figure 3**). These positions were selected as they are located near the middle of the ward, thereby, providing a representative measure of sound pressure levels throughout the entire ward. To provide naturalistic conditions for the 24-h reference recording, beds could be occupied or unoccupied over the recording period. For this reason, no patient was present in bed 2 for around four and a half h, approximately between 10:45–15:15.

For every two beds in a room, there are two preparation boards inside the room, one with a sink and one without (**Figure 3**). These preparation boards are mainly used to prepare medications, and to store and unpack material. At each bed, there are also two -medical pendants, one on each side of the bed (**Figure 3**). Nurses use these pendants to administer medications and during patient care, as well as to access patient data and update electronic patient charts via an integrated patient data management system. In the hallway directly outside the four-bed room there are additional, mobile, preparation boards and equipment that can be used in the hallway or brought directly into the patient room. The described setup may not be equivalent across all ICUs, but the goal was to propose a method that is as independent as possible. Nevertheless, there may be certain differences in the individual setting and researchers should make the appropriate changes to the proposed methods based on their own setup.

Sound Equipment

For the reference recording presented in this paper, a total of four sound level meters were used. Three devices were class II personal sound dosimeters (Extech-SL400, Extech Instruments, USA) and one was a class I sound level meter (PCE-430, PCE Germany GmbH, Germany). Generally speaking, class I sound level meters are referred to as 'precision' grade, whereas class II meters are referred to as 'general purpose' (27, 32). This is related to the fact that class I devices have a wider frequency range and are considered as being more accurate than class II devices due to their narrower tolerances at the higher frequencies

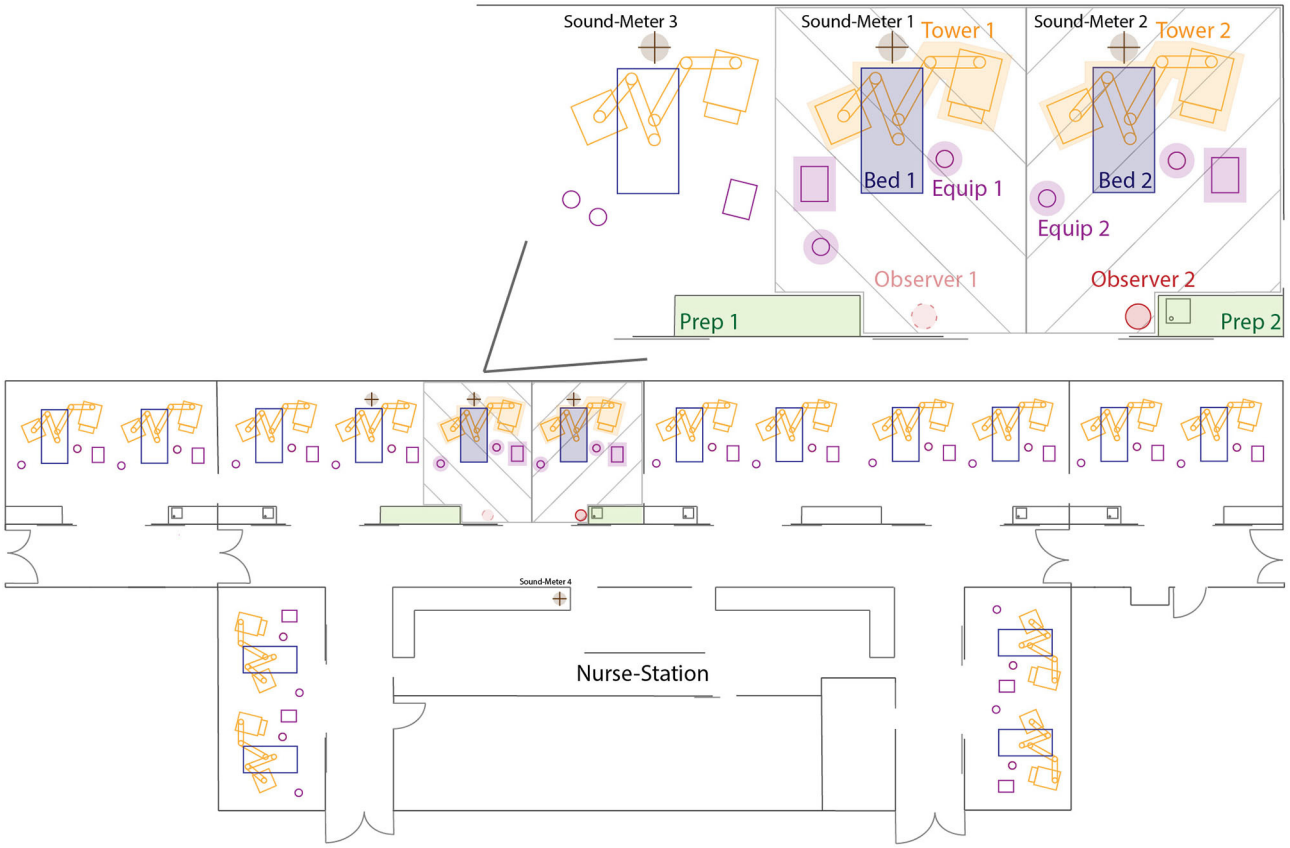

FIGURE 3 | Schematic display of the ICU ward on which the measurements took place. In the upper right, the two beds examined for the 24-h reference recording and inter-rater reliability are displayed in more detail. Observer 1 chair was only present while collecting data for the interrater reliability test. Green zones represent the preparation board, the pink items represent free-standing equipment in the room, orange zones represent the medical pendant on either side of the bed, the placement of the patient bed is depicted in dark blue, and the crossed brown circles represent the location of the sound level meters above the beds and at the nursing station. Shaded areas represent the two bed places examined for the reference recording and interrater reliability. Full list of abbreviations can be found in the **Supplementary Table 1**.

(27). However, for most applications these differences are not noticeable. All devices were calibrated by the manufacturer and were used with a sample rate of 1 Hz.

Each of the three class II sound level meters were placed above one of three beds (**Figure 3**). The sound level meters were attached directly above the head-end of the patient bed, at a height of approximately 2.5 meters above the ground and 0.4 meters from the ceiling. Due to the moveable nature of the bed and medical pendants on either side of the bed, it was decided not to attach the sound level meter directly to these structures. Placing the sound level meters above the bed also meant that the positioning was consistent over the duration of the 24-h recording as it was not attached to a single bed and would not be moved if a patient was admitted or discharged, or if the space was cleaned.

Another consideration is that in multi-bed rooms, it is possible that beds close to the wall may be quieter as they only have a neighboring patient on one side. As can be seen in **Figure 3**, the setup looked at two beds in the same room, one toward a wall, and one toward the middle of the room, with the two directly beside one another. The third, class II, device was placed above the neighboring bed to act as a control so it could be determined if loud sounds were coming from that side of the room. The reasoning was that if sound level meter 3 measured higher decibels than sound level meters 1 and 2 in **Figure 3**, it could be concluded that something producing high sound pressure levels was occurring on the left side of the room.

The class I device was placed in the hallway at the nurses' station located directly outside the patient room of interest (**Figure 3**). Since it was expected that sounds from outside the patient room would cause higher peaks than inside the room, the class I device was placed in the hallway as it had a slightly larger decibel range than the class II devices. The device was placed in such a manner that it was minimally noticeable to anyone walking past the nurses' station.

Data Collection

Four observers conducted the 24-h continuous reference recording, each working alone. The observer sat to the right of the door as depicted in **Figure 3** (see observer 2). For the reference

recording, the observer shifts described in section Observer Shifts were used, with the end time extended by30 min. This was done so that the data could be analyzed by shift, with a start time of 7:00, which corresponded to the start of the morning shift in this particular hospital. While all sounds were noted individually and scored as described in section Parameters and Scoring, further groups, as done for the ICC calculations, were made for ease of the final analysis. A detailed list of groupings can be found in **Supplementary Table 2**. All sounds that were logged either directly in the equipment itself, or in a database, were not additionally noted by the observer in the room.

To verify that the presence of the observer did not influence the sound pressure levels measured, follow-up recordings were conducted for an additional 24-h, 8, 15, and 22 days after the original recording day. Follow-up measurements were done with sound level meters only, with no observer present in the room. The follow-up measurements also ensured that the day measured was representative of the norm, and not by chance much louder or quieter.

RESULTS

Interrater Reliability

ICC estimates >0.90 (excellent) were achieved for 12 of the 24 categories which were heard during the day (**Table 1**). ICC estimates greater than 0.90 were achieved for eight of the 24 categories which were heard during the evening (**Table 1**). ICC estimates between 0.75 and 0.90 (good) were achieved for seven of the 24 categories during the day and eight of the 24 categories during the evening. ICC estimates between 0.50 and 0.75 (moderate) were achieved for two of the 24 categories during the day and for one of the 24 categories during the evening. ICC estimates below 0.50 (poor) were achieved for one of the 24 categories for both day and evening. No estimate could be computed for one of the 24 categories during the day and for six of the 24 categories during the evening due to lack of variance due to random effect. There was one category which did not occur during the day but did occur at evening, so no estimate was given for the day. Full results from the ICC can be found in **Table 1**.

Applied Sound Pressure Level and Source Results

Sound Pressure Levels

Analysis of the 24-h reference recording found elevated sound pressure levels across the three shifts (**Figure 4**). Using the sound pressure levels recorded by the class I device placed at the nurses' station the L_{Aeq} values, corresponding to the average A-weighted sound energy received over time, were calculated to be 52.55, 51.06, and 49.00 dBA during the day, evening, and night shifts, respectively. Recordings from the three class II devices placed in the patient room resulted, as an average of the three devices, in L_{Aeq} levels of 54.12, 53.37, and 49.05 dBA during the day, evening, and night shifts, respectively. The maximum sound pressure levels measured with an A-frequency weighting and fast-time weighting (L_{AFmax}), were 76.50, 85.59, and 79.47 dBA for the class I device, during the day, evening, and night shifts respectively. For the same shifts, the average L_{AFmax} of the class II devices were 71.20, 72.20, and 66.87 dBA. For full results per shift see **Table 2**.

Results from the follow-up recordings, during the 24-h recording and eight, fifteen-, and twenty-2-days post-recording, found L_{Aeq} levels of 50.87, 51.55, 51.68, and 52.05 dBA, from the device in the hallway at the nurses' station. The average decibel levels of the three devices above the beds in the patient room were 51.83, 51.97, 52.99, and 50.57 dBA, for the same time periods. The L_{AFmax} values on the initial recording day and follow-ups were 79.85, 78.82, 76.88, and 76.72 dBA for the device in the hallway, and 70.26, 71.02, 73.62, and 68.84 dBA for the devices above the beds. For full results per shift see **Supplementary Table 3**.

Sound Sources

Overall, during the 24-h reference recording, for bed 1 (**Figure 3**) talking and human generated sounds occurred for 495 min, making up 39.29% of the time (**Table 2**). For bed 2 (**Figure 3**), talking and human generated sounds occurred for 470 min, making up 37.30 % of the time (**Table 2**). For bed 1, other sound sources which were responsible for making up the highest percentage of sounds were the preparation board (290 min, 23.02%), oxygen related patient interventions (279 min, 22.14%), monitor alarms (245 min, 17.6%), the pendant (193 min, 15,32%), sounds coming from staff clothing like shoes and accessories on clothing (126 min, 10.00 %), and free-standing equipment in the room (89 min, 7.06 %) (**Table 2**). In the area around bed 2, the sound sources responsible for making up the highest percentage of sounds were oxygen related patient interventions (272 min, 21.59%), the pendant (212 min, 16.83%), monitor alarms (177 min, 12.3%), free standing equipment in the room (132 min, 10.48%), diagnostic interventions like measuring temperature or conducting an x-ray (128 min, 10.16%), sounds coming from staff clothing like shoes and accessories on clothing (126 min, 10.00%), and the preparation board (101 min, 8.02%) (**Table 2**).

DISCUSSION

In this paper we address two aspects related to measuring sound pressure levels and sound sources in the ICU. First, we fill a gap in the literature on the topic of sound pressure level measurements in the ICU. Currently, studies on the topic are inconsistent in terms of the sound level meters used, placement of recording devices, and parameters for the recordings, making it difficult to reproduce the work (3, 5, 26). Second, studies about the sound sources in the ICU environment lack comparability due to poor study documentation and differences in which parameters were observed, scoring criteria, and the number of observers (9, 11, 18). To address these shortcomings, we have demonstrated a feasible, and reliable method for multi-day measurements which is adaptable to individual needs in a constantly changing environment.

Interrater Reliability

Overall, the interrater reliability estimates for these sounds were largely found to be high, with the majority of the estimates

TABLE 1 | Full ICC estimates obtained using a two-way mixed-effects model during the day and evening observation periods.

	Description	Day			Evening		
		Estimate	F(*p*)	95% Interval	Estimate	F(*p*)	95% Interval
Human (-Human) Sounds	Staff < 3 people talking (out of ward round)	0.93	13 ($p < 0.001$	0.89–0.95	0.95	20 ($p < 0.001$)	0.93–0.97
	Patient talking	0.95	19 ($p < 0.001$)	0.92–0.96	0.98	54 ($p < 0.001$)	0.97–0.99
	Staff ≥ 3 people talking (out of ward round)	0.94	17 ($p < 0.001$)	0.91–0.96	0.27	1.4 (*0.094*)	0.70–0.86
	Patient Sounds	0.96	26 ($p < 0.001$)	0.93–0.97	0.77	4.4 ($p < 0.001$)	0.66–0.85
	Staff sounds	0.66	3 ($p < 0.001$)	0.50–0.77	–	–	–
	Staff during ward round ≥ 3 people talking	0.99	90 ($p < 0.001$)	0.98–0.99	0.80	4.9 ($p < 0.001$)	0.70–0.86
	Staff during ward round < 3 people talking	0.99	190 ($p < 0.001$)	0.99–1.00	0.80	4.9 ($p < 0.001$)	0.70–0.86
Object (-Human) Interaction Sounds	Oxygen	0.99	120 ($p < 0.001$)	0.99–0.99	0.99	122 ($p < 0.001$)	0.99–0.99
	Pendant	0.90	10 ($p < 0.001$)	0.85–0.93	0.89	9.1 ($p < 0.001$)	0.84–0.93
	Preparation board	0.96	26 ($p < 0.001$)	0.94–0.97	0.95	21 ($p < 0.001$)	0.93–0.97
	Clothing Accessories	0.84	6.2 ($p < 0.001$)	0.76–0.89	0.50	2 (*0.0015*)	0.27–0.66
	Free standing equipment	0.82	5.7 ($p < 0.001$)	0.74–0.88	0.90	10 ($p < 0.001$)	0.85–0.93
	Diagnostic	0.98	40 ($p < 0.001$)	0.96–0.98	1	5.1e+14 (*0*)	1.00–1.00
	Bed–related	0.87	7.6 ($p < 0.001$)	0.81–0.91	1	5.1e+14 (*0*)	1.00–1.00
	Unknown intervention	–	–	–	–	–	–
	Continuous maintenance	1	4.9e+14 (*0*)	1.00–1.00	–	–	–
	Admission and discharge	0.96	25 ($p < 0.001$)	0.94–0.97	–	–	–
	Activity of daily living: non–mobilization	0.98	46 ($p < 0.001$)	0.97–0.99	0.96	25 ($p < 0.001$)	0.94–0.97
	Activity of daily living: mobilization	0.89	9.4 ($p < 0.001$)	0.84–0.93	0.97	39 ($p < 0.001$)	0.96–0.98
	Privacy screens	0.79	4.9 ($p <$ s)	0.69–0.86	–	–	–
	Nursing	N/A	N/A	N/A	–	–	–
	Short–lasting activities	0.45	1.9 (*0.0046*)	0.20–0.63	0.82	5.6 ($p < 0.001$)	0.73–0.88
	Short–lasting maintenance	0.78	4.5 (*6.8e−10*)	0.67–0.85	0.84	6.4 (*1e−13*)	0.76–0.89
	Ringing	0.73	3.7 (*4.9e−8*)	0.60–0.82	0.80	4.9 (*7.9e−11*)	0.70–0.86

Detailed explanations of the groups can be found in ***Supplementary Table 2****. Estimate represents the estimated correlation value; F(p) represents the F statistic and its associated p-value; 95% Interval represents the 95% confidence interval of the estimate; N/A (not applicable) indicates the sound was heard during one, not both, of the observation periods, while '-' indicates that there was not enough variance in the data to compute the ICC.*

falling into the strong and almost perfect categories. Measuring the interrater reliability is important to ensure the accuracy and feasibility of the proposed methods for collecting data regarding the ICU sound sources. Another important reason for examining the interrater reliability of the observers is to determine the extent of bias introduced by having changing observers (4, 5). Having a high interrater reliability decreases the probability of bias being introduced by using multiple observers. This is important as it allows for a longer period of time to be observed as the study is not limited to a single observer (3). In addition to not being limited to a single observer, by confirming a high interrater reliability prior to the start of the study, replicability can be enhanced.

While the ICC estimates measured in the study are already quite high, there are still some categories, such as clothing accessories and garbage and laundry bins, that could be improved. However, slight differences in scoring are to be expected, for example, at the beginning of an intervention or due to prior knowledge of the ICU environment. An observer familiar with the intervention may recognize it sooner and score it as such, whereas an observer less familiar with such an intervention may continue scoring individual

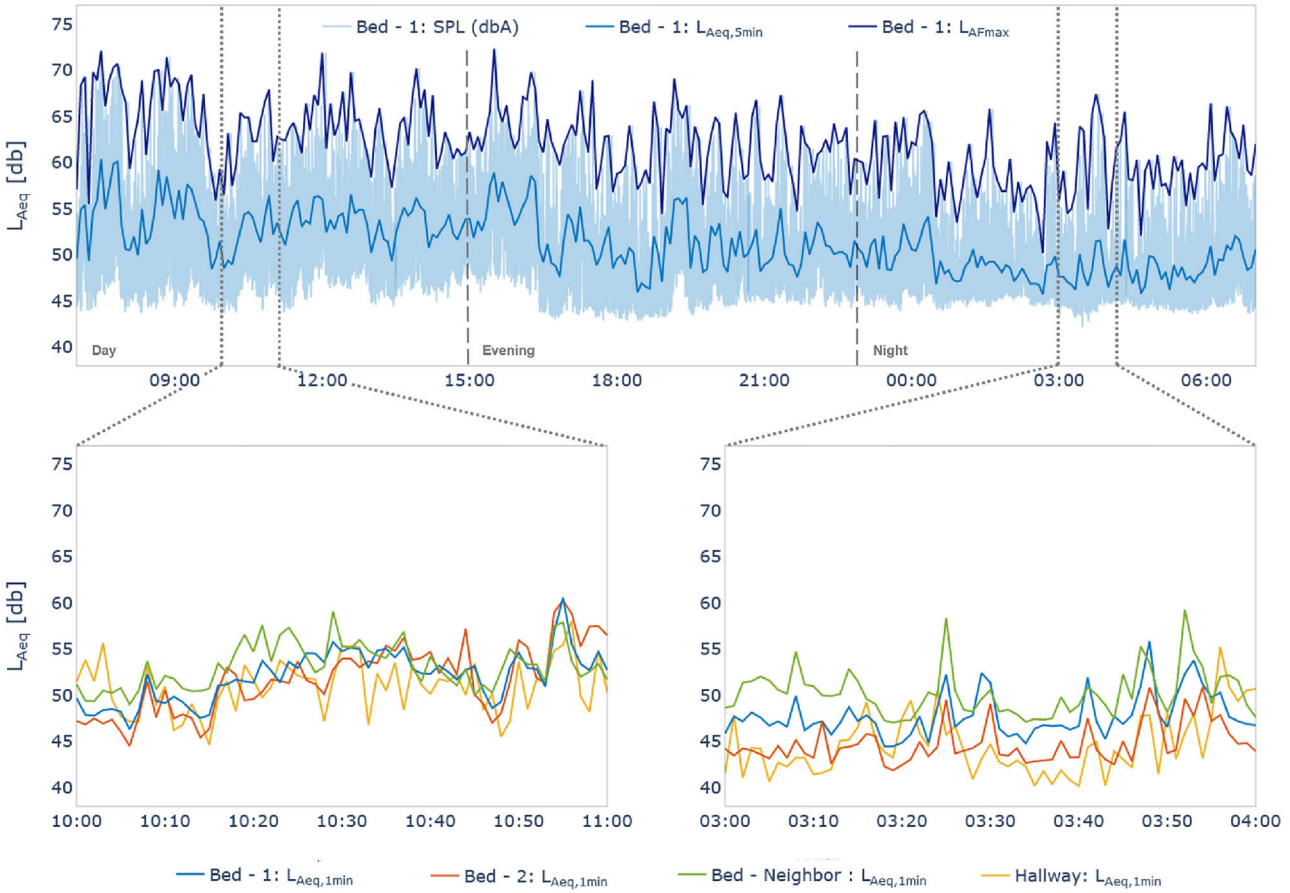

FIGURE 4 | (Top) 24-h overview of sound pressure levels measured by the class II device positioned over bed 1 (**Figure 3**). Dark blue shows the $L_{FAmax,}$ and the light blue trend shows the L_{Aeq} calculated over 5-min. The shaded area represents the raw sound pressure levels (SPL). (Bottom) Sub-figures show 1-minL_{Aeq} values for all devices (one class I, three class II) illustrating the different levels of alignment between the devices over two 1-h snapshots. Vertical dashed lines (15:00 and 23:00) indicate shift changes.

aspects of the scene before recognizing it as pertaining to an intervention. Therefore, to improve the interrater reliability, it is recommended that non-medically trained observers spend time prior to the study observing the ICU environment so that they are qualified to identify the different sound sources.

Sound Pressure Level Measurements

The results of this study are consistent with the literature (4, 5, 9, 11). Namely, sound pressure levels exceed those recommended by health authorities, and as expected, sound pressure levels decrease in the evening and at night compared to during the day (**Figure 4**; **Table 2**). While the data presented here only represents a single day, it can be assumed that by continuously recording for longer periods, the day-to-day and weekly variations in sound pressure levels could accurately be captured and assessed. Another advantage of recording sound pressure levels continuously over days and weeks is that it could capture work shift (i.e., day, evening, night) and staff related changes in sound pressure levels. It would be interesting to confirm whether the trends seen in the different work shifts presented here occur daily and over longer-periods.

Our proposed setup and procedure for recording sound pressure levels in the ICU environment addresses current concerns about the lack of clear, long-term, measurement protocols (9, 18). Not only is the proposed method replicable, but it is also adaptable based on specific needs making it independent of any given ICU or specific patient room. This is an important consideration so that future studies on the topic are comparable, more robust, and generalizable. Moreover, the 24-h reference recording provides a reference measurement structure. Compared to previous studies, the proposed method also provides a more accurate representation of the entire sound situation by continuously measuring the sound pressure levels, not only focusing on peak sound pressure levels (3).

As can be seen in the results, there are moments during the 24-h reference recording where the three class II devices align

TABLE 2 | Overall time of sound source occurrence in min over the 24-h observation period, and percent occurrence per 8-h shift.

	Description	Bed 1				Bed 2			
		Overall	Day	Evening	Night	Overall	Day	Evening	Night
Human (-Human) Sounds	Staff < 3 people talking (out of ward round)	299 min	21.88%	35.66%	13.81%	284 min	40.94%	24.58%	1.90%
	Patient talking	141 min	-	11.33%	11.43%	116 min	12.47%	11.33%	3.81%
	Staff ≥ 3 people talking (out of ward round)	67 min	6.59%	9.40%	-	91 min	18.59%	2.89%	-
Object (-Human) Interaction Sounds	Oxygen	279 min	-	25.90%	30.95%	272 min	-	34.22%	30.95%
	Pendant	193 min	14.82%	19.52%	11.67%	212 min	22.12%	24.58%	3.81%
	Preparation board	290 min	21.41%	28.67%	19.05%	101 min	14.59%	8.91%	1.19%
	Monitor Alarms	245 min	10.8%	12.3%	29.8%	177 min	9.4%	15.0%	12.3%
	Clothing accessories	126 min	13.41%	7.95%	8.57%	126 min	17.41%	9.64%	2.86%

The top three human (-human) sounds and top five object (-human) interaction sounds, as determined by the total sum between the two beds, are shown here. Results for each category can be found in ***Supplementary Table 4****.*

quite well despite their physical distances, and moments where they differ quite substantially. Therefore, a limitation of this design is that there is no correct number of devices which can be recommended. For example, if looking at just the data from the left sub-figure (10:00–11:00), one might conclude that due to the similar recordings of the three devices, only one would have sufficed. However, looking at the right sub-figure (3:00–4:00) it appears that there is on average a 5 dBA difference between device 1 and device 3, thereby supporting the use of the three devices.

Future analyses will be specific to the goals of each individual investigation. However, based on the literature, we propose some basic guidelines, which can be applied to sound pressure level data to draw preliminary conclusions, regardless of the final analyses. First, we propose the calculation of the L_{Aeq} and L_{AFmax} using 5-min epochs to generate a trend representative of the data. Second, we recommend analyzing the data based on 5- min windows. Taking a window that is too large may mask relevant data, however, taking a window that is too small may make interpretation more difficult due to an increased complexity and high number of peaks which may mask the high general sound levels. Moreover, in the case that data is also collected from observers, the 5-min epochs would match those of the observer. Third, it would be relevant to examine the data based on work-shifts present in the ICU of interest. There are staff and organizational differences between work shifts which may play a role regarding sound pressure levels. Therefore, we propose examining the variables of interest such as maximum sound pressure level or average sound pressure level, taking work shifts into account.

Sound Source Measurements

Consistent with the literature, major sound sources found using the presented method are conversations among the staff, patient interventions, monitor alarms, as well as equipment and devices in the room (2, 5, 9). While there were slight differences between the two beds considered, the absence of a patient in bed 2 for approximately four and a half h likely played a major role. Between the two beds, many of the sources generating the most sound were consistent, such as oxygen related interventions, monitor alarms, the medical pendants, free standing equipment in the room, and the preparation boards. Unfortunately, a lack of detailed descriptions and over generalized groupings in the literature make more precise comparisons to previous studies difficult.

In addition to facing problems generalizing data, previous studies examining the same question also faced several limitations. For example, studies with one, or multiple, in person observers may have generated a bias due to their presence in the study room influencing how the staff worked (2, 4). The bias here was limited in a few ways. First, the nursing team present for the observation period was informed of the study prior to its start and were also asked to continue working as normal, ignoring the study team. The staff were also asked not to interact with the observer, and informed that nothing being written down by the observer could not be link to specific individuals.

Bias was further reduced by having the observer present continuously. Even if the ICU staff adapted their behavior when the observer was first present in the room, it is unlikely that they would have been able to sustain such a change for more than a short time. This would have been especially difficult in the stressful, life-or-death situations often encountered in the ICU. This is supported by the results from the follow-up recordings, which were obtained in the absence of an observer and were in line with the values recorded when the observer was present. This supports the notion that even if a slight influence of the observers is present initially, it is likely not sufficient to generate a noticeable influence the sound pressure levels in the room.

Similarly, we propose some basic guidelines for how analyses of sound source measurements should be conducted. More

specifically, we propose two basic methods for examining the data of interest, based on how it was scored. Both methods can be adapted based on the recording duration of interest, ranging from 5-min epochs to multiple days. For continuous data scored as duration, it is recommended to present the results as the total min it was noted for and calculate the percentage of the total recording time. For example, if talking is scored as occurring for 720 min (twelve h), this would correspond to 50% of the total 24-h recording time. For short-lasting sounds scored as frequency, it is recommended to calculate the number of occurrences for each category of interest. While previously presented in the literature, definitions used for the analysis often lacked (e.g., over how long the percentage was calculated). Thereby, by using the procedure described in this paper it would become easier to compare results across studies, which will be important in decreasing sound pressure levels in the ICU.

CONCLUSION

Elevated sound pressure levels are an ongoing problem in the ICU, with few comparable studies on the topic. Here a clearly defined, reliable, and replicable method for both measuring sound pressure levels and sound sources in this highly complex setting, both short- and long-term, is presented. Moreover, a 24-h recording is provided for future studies to use as a reference and shows that it is feasible to conduct a recording using the proposed method.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

AUTHOR CONTRIBUTIONS

AN, NR, SK, and SG designed the study, collected data, analyzed the data, and were involved in the writing, editing and reviewing of the manuscript. M-MJ, MH, BZ, JS, and TN assisted in the data collection, study design, and were involved in editing and reviewing 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.2022.836203/full#supplementary-material

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Predictive Risk Factors at Admission and a "Burning Point" During Hospitalization Serve as Sequential Alerts for Critical Illness in Patients With COVID-19

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Background: We intended to establish a novel critical illness prediction system combining baseline risk factors with dynamic laboratory tests for patients with coronavirus disease 2019 (COVID-19).

Methods: We evaluated patients with COVID-19 admitted to Wuhan West Union Hospital between 12 January and 25 February 2020. The data of patients were collected, and the illness severity was assessed.

Results: Among 1,150 enrolled patients, 296 (25.7%) patients developed into critical illness. A baseline nomogram model consists of seven variables including age [odds ratio (OR), 1.028; 95% confidence interval (CI), 1.004–1.052], sequential organ failure assessment (SOFA) score (OR, 4.367; 95% CI, 3.230–5.903), neutrophil-to-lymphocyte ratio (NLR; OR, 1.094; 95% CI, 1.024–1.168), D-dimer (OR, 1.476; 95% CI, 1.107–1.968), lactate dehydrogenase (LDH; OR, 1.004; 95% CI, 1.001–1.006), international normalised ratio (INR; OR, 1.027; 95% CI, 0.999–1.055), and pneumonia area interpreted from computed tomography (CT) images (medium vs. small [OR, 4.358; 95% CI, 2.188–8.678], and large vs. small [OR, 9.567; 95% CI, 3.982–22.986]) were established to predict the risk for critical illness at admission. The differentiating power of this nomogram scoring system was perfect with an area under the curve (AUC) of 0.960 (95% CI, 0.941–0.972) in the training set and an AUC of 0.958 (95% CI, 0.936–0.980) in the testing set. In addition, a linear mixed model (LMM) based on dynamic change of seven variables consisting of SOFA score (value, 2; increase per day [l/d], +0.49), NLR (value, 10.61; l/d, +2.07), C-reactive protein (CRP; value, 46.9 mg/L; l/d, +4.95), glucose (value, 7.83 mmol/L; l/d, +0.2), D-dimer (value, 6.08 μg/L; l/d, +0.28),

LDH (value, 461 U/L; l/d, +13.95), and blood urea nitrogen (BUN value, 6.51 mmol/L; l/d, +0.55) were established to assist in predicting occurrence time of critical illness onset during hospitalization.

Conclusion: The two-checkpoint system could assist in accurately and dynamically predicting critical illness and timely adjusting the treatment regimen for patients with COVID-19.

Keywords: coronavirus disease 2019, critical illness onset, risk factor, "burning point", predictive model, sequential alerts

INTRODUCTION

The emergence of SARS-CoV-2 variants, with stronger transmissibility or ability to evade humoral immunity, has ushered in a new stage of the pandemic coronavirus disease 2019 (COVID-19) (1). Globally, 248,467,363 cumulative cases including 5,027,183 deaths have been confirmed until 5 November 2021, with hundreds of thousands of new cases increasing daily.[1] In total, 5–20% of hospitalized patients with COVID-19 were admitted to the intensive care unit (ICU), with the mortality rate reportedly standing between 26 and 61.5% (2–6). The condition of patients with critical illness tends to deteriorate over a very short period of time, frequently leading to acute respiratory distress syndrome (ARDS) or multiple-organ failure, and even death (7, 8).

The ongoing pandemic with the high fatality rate of patients with critical illness necessitates the discovery of reliable prognostic predictors. So far, several studies (9–12) have reported predictive models for patients with critical illness and with COVID-19. Other studies suggested the prognostic value of longitudinal changes in clinical variables including ventilatory ratio (VR), platelet count, fibrinogen, and D-dimer (13, 14). However, these models had not integrated the baseline characteristics and the longitudinal analysis and were unable to predict disease progression during hospitalization. Here, we introduced a novel two-checkpoint prediction system based on both baseline characteristics at patient admission and longitudinal data collected during hospitalization. A crucial turning point—"burning point" was found before patients deteriorated to a critical condition (such as ICU admission), which was incorporated into this warning system. The two-checkpoint prediction system is a workable early warning system, including the first warning at admission and the second alert as early as 5 days before critical illness onset (CIO) to predict the occurrence and possible time of critical illness in patients with COVID-19.

MATERIALS AND METHODS

Study Design and Participants

A total of 1,224 Laboratory-confirmed adult patients with COVID-19 (≥ 18 years old) were consecutively admitted to Wuhan West Union Hospital between 12 January and 25 February 2020. Among which, 74 patients were excluded including 57 patients transferred to other hospitals and 17 patients who died within 24 h after admission. The remaining 1,150 participants were included in our study, and they all had a definite clinical outcome (death or discharge) as of early-May 2020 (the study flowchart is shown in **Figure 1A**). This study was approved by the Institutional Review Board of Medical Ethics Committee of Union Hospital, Huazhong University of Science and Technology (NO.0036). Written informed consent was waived by the Committee for this critical situation of emerging infectious diseases.

Criteria and Definitions

The diagnosis and discharge criteria for COVID-19 were consistent with previous reports (10, 15). According to the interim criteria of WHO (16) and the guidelines by the National Health Commission (trial version 7.0), critical COVID-19 illness was evaluated retrospectively and confirmed based on respiratory infection, including one of the following: (1) ARDS needing mechanical ventilation, (2) sepsis leading to life-threatening organ dysfunction, and (3) septic shock. Otherwise, the patients were identified as non-critical patients. The CIO was recorded as the beginning time of moderate/severe ARDS requiring mechanical ventilation, or the time point at which sepsis caused the life-threatening multiple organ dysfunction or the septic shock developed or the patient was admitted to ICU. We introduced a new concept—"burning point" and defined it as a critical turning point at which the condition was exacerbated before CIO, and some indicators started to change significantly and continuously. The period from the burning point to CIO was deemed a high-risk period for CIO. The first alert comes from the baseline warning system at admission, and the second alert comes from the "burning point" warning system during hospitalization. ARDS was diagnosed according to the Berlin definition (17). Sepsis and septic shock were defined based on the 2016 Third International Consensus Definition (18). The sequential organ failure assessment (SOFA) score was calculated as previously reported (19). Definitions of various organ injuries were described in **Supplementary Materials**.

Data Collection

A total of 87 baseline variables, covering demographics, comorbidities, symptoms, laboratory findings, imaging features, SOFA score, and admission time, were collected from electronic

[1]https://covid19.who.int

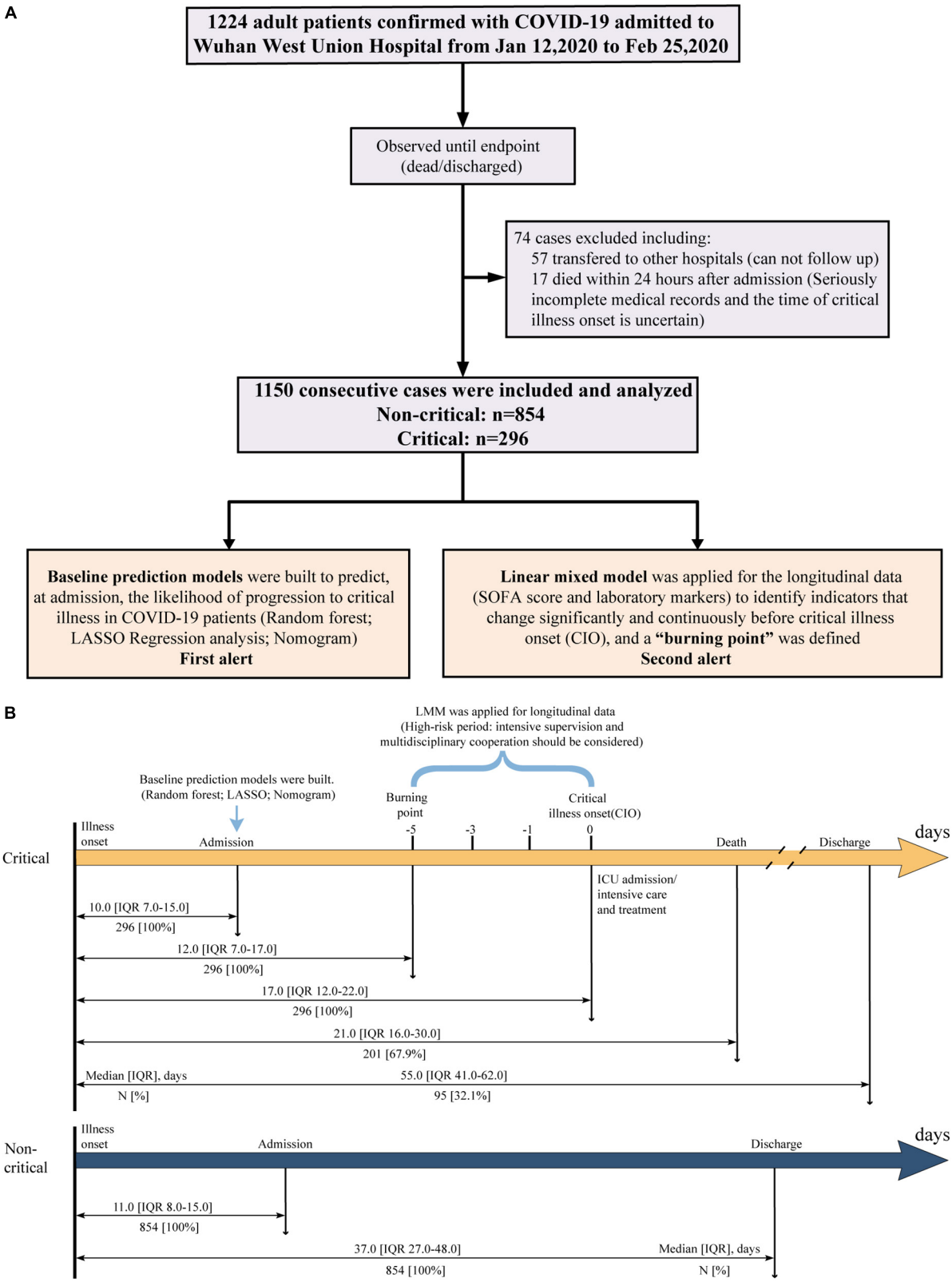

FIGURE 1 | Study flowchart **(A)** and schematic diagram of timeline **(B)**.

medical documents. The baseline computed tomography (CT) images were interpreted independently by two senior radiologists experienced in chest radiology. For all participants, the SOFA score and all laboratory data (47 items in total) were recorded from admission to discharge or death. At least two experienced doctors carefully went through the medical records of each critical patient to determine the time of the CIO. All of these data were summed up in a standardized form.

Descriptive Analysis

Categorical variables were presented as frequencies (n) and percentages (%). The continuous variables with normal or non-normal distribution were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)]. To compare the differences in baseline variables between critical and non-critical participants, we used the independent sample t-test or Mann–Whitney U-test for continuous variables, χ^2-test, Fisher's exact test, or Mann–Whitney U-test were employed for categorical (binary or ordinal) variables wherever appropriate.

Variable Selection and Model Construction

To ensure the data integrity and avoid potential selection bias, variables or patients with a missing rate of less than 40% were all included. As a result, 81 variables and 1,118 patients remained. The random forest machine learning method was employed to impute the missing values (20). Principal component analysis (PCA) was then conducted by using the R package "factoextra" (21) to evaluate the distribution of patients and the most relevant variables for critical illness. No cases were labeled as outliers and excluded in this process. Thereafter, a total of 1,118 remaining patients were randomized into training and testing sets at a ratio of 7:3 (Training set, N = 783 [Non-critical/Critical: 587/196]; Testing set, N = 335 [Non-critical/Critical: 241/94]).

Three predictive models [i.e., the machine-learning-based random forest, the least absolute shrinkage and selection operator (LASSO) logistic regression, and the multivariable logistic regression models] were built to predict, at admission, the likelihood of progression to critical illness in patients with COVID-19. Briefly, we chose the predictors selected by both the random forest and LASSO regression models as candidate risk factors to conduct a multivariable logistic regression analysis and then developed a nomogram scoring system. Finally, the three models were further compared and validated (**Supplementary Tables S1–6** and **Supplementary Figures S1–4**).

Longitudinal Data Analysis

The SOFA score and 46 laboratory markers (47 indicators in total) were recorded successively in all the 1,150 hospitalized patients with COVID-19. To find out the indicators that changed significantly during the period of critical illness development, the linear mixed model (LMM) implemented in the R package "lme4" (22) was used to explore the association between time and indicators by taking age and sex as fixed effects.

All tests were two-sided, and a p-value less than 0.05 was considered statistically significant. R software (version 3.6.2, R Foundation) was used for all analyses.

RESULTS

Features and Outcomes of Patients With Non-critical and Critical COVID-19

In our study, we collected data from 1,150 consecutively admitted patients. All the participants were studied until discharge or death (**Figure 1A**). Among them, 296 of 1,150 patients (25.7%) were identified to be critically ill. As shown in **Table 1**, the overall mortality was 17.5% (201/1,150), while up to 67.9% in critically ill. All non-critical patients were discharged, and their hospital stay time was significantly shorter than critical patients discharged (23.0 vs. 43.0, $p < 0.0001$). The median age of non-critical and critical patients was 59.0 (IQR, 48.0–68.0) and 68.0 (61.0–76.0) years, respectively. There were more male patients in the critical group than in the non-critical group (64.2% vs. 46.6%, $p < 0.0001$). Over half of the patients had fever (81.4%) and cough (68.3%) at admission. In total, 778 (68.7%) patients had at least one comorbidity, including hypertension (33.6%), diabetes (20.4%), and coronary heart disease (10.9%) as the top three comorbidities. Sepsis (48.1%) was the most frequent complication, followed by acute liver injury (31.4%), ARDS (31.1%), acute cardiac injury (13.5%), and acute kidney injury (13.1%). The frequencies of complications were significantly higher in critical patients (all $p < 0.0001$). Both the SOFA score at admission (3.00 vs. 1.00, $p < 0.0001$) and the highest SOFA score during hospitalization (6.00 vs. 1.00, $p < 0.0001$) were significantly higher in critical patients. The baseline CT features and laboratory findings among critical and non-critical patients were also summarized in **Table 1**. The time from illness onset to admission, "burning point," CIO, death, or discharge was listed in **Figure 1B**.

Baseline Predictor Selection in the Training Set

The baseline laboratory results of critical and non-critical patients with COVID-19 were shown in **Table 1** and **Supplementary Table S7**. The random forest and LASSO regression analysis were conducted in the training set, respectively, with the top 20 important variables remaining after random forest analysis and 19 variables selected by the latter (**Supplementary Tables S3**, **4** and **Supplementary Figure S2**). The nine variables selected by both random forest and LASSO regression models were used in the subsequent multivariable logistic regression analysis, with two variables [neutrophils (NEUs) and C-reactive protein (CRP)] excluded for their high correlation, respectively, with neutrophil-to-lymphocyte ratio (NLR) and lactate dehydrogenase (LDH) and relatively lower area under the curve (AUC) value (**Figure 2A**). These seven variables included age (odds ratio [OR], 1.028; 95% confidence interval [CI], 1.004–1.052; p = 0.023), SOFA score (OR, 4.367; 95% CI, 3.230–5.903; $p < 0.001$), NLR (OR, 1.094; 95% CI, 1.024–1.168; p = 0.008), D-dimer (OR, 1.476; 95% CI,

TABLE 1 | Baseline characteristics and outcomes of critical and non-critical patients with COVID-19.

Variables	All patients, (*n* = 1,150)	Non-critical patients, (*n* = 854)	Critical patients, (*n* = 296)	*p*-value
Demographics				
Age, median (IQR), years	62.0 (52.0, 70.0)	59.0 (48.0, 68.0)	68.0 (61.0, 76.0)	<0.0001
Sex				
Male, *n* (%)	588 (51.1)	398 (46.6)	190 (64.2)	<0.0001
Female, *n* (%)	562 (48.9)	456 (53.4)	106 (35.8)	
Initial symptoms, *n*/N (%)				
Fever	912/1,120 (81.4)	688/844 (81.5)	224/276 (81.2)	0.895
Highest temperature, median (IQR),°C	38.20 (37.50, 39.00)	38.00 (37.50, 39.00)	38.50 (37.63, 39.00)	0.065
Sore throat	44/1,091 (4.0)	34/828 (4.1)	10/263 (3.8)	0.817
Fatigue	531/1,104 (48.1)	390/835 (46.7)	141/269 (52.4)	0.150
Myalgia	238/1,096 (21.7)	192/832 (23.1)	46/264 (17.4)	0.057
Cough	759/1,113 (68.3)	576/842 (68.4)	184/271 (67.9)	0.868
Sputum production	361/1,104 (32.7)	262/836 (31.3)	99/268 (36.9)	0.095
Chest tightness	348/1,104 (31.5)	241/835 (28.9)	107/269 (39.8)	0.0008
Dyspnea	307/1,099 (27.9)	184/831 (22.1)	123/268 (45.9)	<0.0001
Running nose	22/1,095 (2.0)	14/828 (1.7)	8/267 (3.0)	0.191
Vomiting	83/1,100 (7.5)	71/833 (8.5)	12/267 (4.5)	0.036
Nausea	71/1,100 (6.5)	60/838 (7.2)	11/262 (4.2)	0.083
Diarrhea	171/1,103 (15.5)	131/834 (15.7)	40/269 (14.9)	0.800
Headache	69/1,098 (6.3)	59/828 (7.1)	10/270 (3.7)	0.052
Asymptomatic	13/1,120 (1.2)	12/870 (1.4)	1/250 (0.4)	0.291
Comorbidities, *n*/N (%)				
Hypertension	381/1,133 (33.6)	249/837 (29.7)	132/296 (44.6)	<0.0001
Diabetes	231/1,133 (20.4)	139/837 (16.6)	92/296 (31.1)	<0.0001
Coronary heart disease	123/1,133 (10.9)	76/837 (9.1)	47/296 (15.9)	0.0012
Cerebrovascular disease	49/1,133 (4.3)	16/837 (1.9)	33/296 (11.1)	<0.0001
Malignancy	64/1,133 (5.6)	40/837 (4.8)	24/296 (8.1)	0.033
Chronic bronchitis	27/1,133 (2.4)	21/837 (2.5)	6/296 (2.0)	0.640
Asthma	14/1133 (1.2)	12/837 (1.4)	2/296 (0.7)	0.479
Chronic obstructive pulmonary disease	19/1,133 (1.7)	9/837 (1.1)	10/296 (3.4)	0.017
Kidney disease	50/1,133 (4.4)	32/837 (3.8)	18/296 (6.1)	0.104
Liver disease	54/1,133 (4.8)	45/837 (5.4)	9/296 (3.0)	0.105
Others	360/1,133 (31.8)	258/837 (30.8)	102/296 (34.5)	0.248
Number of comorbidities, *n*/N (%)				
≥1	778/1,133 (68.7)	524/837 (62.6)	254/296 (85.8)	<0.0001
≥2	392/1,133 (34.6)	250/837 (29.9)	142/296 (48.0)	
≥3	150/1,133 (13.2)	94/837 (11.2)	56/296 (18.9)	
≥4	36/1,133 (3.2)	18/837 (2.2)	18/296 (6.1)	
Complications, *n*/N (%)				
Sepsis	553/1,149 (48.1)	258/854 (30.2)	295/295 (100)	<0.0001
Acute respiratory distress syndrome	358/1,150 (31.1)	66/854 (7.7)	292/296 (98.6)	<0.0001
Acute liver injury	361/1,149 (31.4)	187/854 (21.9)	174/295 (59.0)	<0.0001
Acute cardiac injury	155/1,149 (13.5)	31/854 (3.6)	124/295 (42.0)	<0.0001
Acute kidney injury	150/1,149 (13.1)	42/854 (4.9)	108/295 (36.6)	<0.0001
Baseline CT findings, *n*/N (%)				
Pneumonia area (Lesion ratio to lung)				
Small area (≤ 35%)	485/1,109 (43.7)	450/849 (53.0)	35/260 (13.5)	<0.0001
Medium area (35–65%)	493/1,109 (44.5)	347/849 (40.9)	146/260 (56.2)	
Large area (> 65%)	131/1,109 (11.8)	52/849 (6.1)	79/260 (30.4)	
Uni-/bilateral pneumonia				
Unilateral pneumonia	164/1,109 (14.8)	137/849 (16.1)	27/260 (10.4)	0.022
Bilateral pneumonia	945/1,109 (85.2)	712/849 (83.9)	233/260 (89.6)	

(Continued)

TABLE 1 | (Continued)

Variables	All patients, (*n* = 1,150)	Non-critical patients, (*n* = 854)	Critical patients, (*n* = 296)	*p*-value
Features and location of pulmonary lesions				
Central	2/1,109 (0.2)	1/849 (0.1)	1/260 (0.4)	<0.0001
Peripheral	282/1,109 (25.4)	240/849 (28.3)	42/260 (16.2)	
Both	825/1,109 (74.4)	608/849 (71.6)	217/260 (83.5)	
Consolidation	858/1,109 (77.4)	623/849 (73.4)	235/260 (90.4)	<0.0001
Patchy exudation	1,030/1,109 (92.9)	784/849 (92.3)	246/260 (94.6)	0.218
Ground-glass opacity	964/1,109 (86.9)	722/849 (85.0)	242/260 (93.1)	0.0008
White lung	42/1,109 (3.8)	9/849 (1.1)	33/260 (12.7)	<0.0001
Pleural effusion	152/1,109 (13.7)	98/849 (11.5)	54/260 (20.8)	0.0002
Lymph node enlargement	91/1,109 (8.2)	73/849 (8.6)	18/260 (6.9)	0.389
SOFA score, median (IQR)				
SOFA score at admission	1.00 (0.00, 2.00)	1.00 (0.00, 1.00)	3.00 (2.00, 4.00)	<0.0001
Highest SOFA score during hospitalization	1.00 (1.00, 3.00)	1.00 (0.00, 2.00)	6.00 (4.00, 11.00)	<0.0001
Representative baseline laboratory findings, median (IQR) or mean (± *SD*)				
Neutrophil-to-lymphocyte ratio	3.80 (2.23, 6.93)	3.18 (1.99, 5.24)	8.48 (5.02, 13.07)	<0.0001
Lactate dehydrogenase, U/L	256.00 (195.00, 362.75)	234.00 (187.00, 308.00)	412.00 (301.00, 558.50)	<0.0001
D-dimer, μg/mL	0.51 (0.25, 1.00)	0.44 (0.22, 0.87)	0.83 (0.42, 1.73)	<0.0001
International normalized ratio	1.02 (0.95, 1.10)	1.01 (0.95, 1.07)	1.08 (1.00, 1.19)	<0.0001
Outcomes and timeline				
Discharged, *n*/N (%)	949/1,150 (82.5)	854/854 (100.0)	95/296 (32.1)	<0.0001
Deceased, *n*/N (%)	201/1,150 (17.5)	0/854 (0.0)	201/296 (67.9)	
Time from illness onset to admission, median (IQR), days	11.0 (7.0, 15.0)	11.0 (8.0, 15.0)	10.0 (7.0, 15.0)	0.045
Time from admission to death, median (IQR), days	10.0 (6.0, 18.0)	–	10.0 (6.0, 18.0)	–
Time from admission to discharge, median (IQR), days	25.0 (17.0, 37.0)	23.0 (16.0, 34.0)	43.0 (31.0, 50.0)	<0.0001

Data were presented as n/N (%), median (IQR) or mean (± SD). p-values were calculated by Mann–Whitney U-test, χ^2-test, or Fisher's exact, if not specified. IQR, interquartile range; SD, standard deviation; SOFA, sequential organ failure assessment.

1.107–1.968; $p = 0.008$), LDH (OR, 1.004; 95% CI, 1.001–1.006; $p = 0.003$), INR (OR, 1.027; 95% CI, 0.999–1.055; $p = 0.059$), and pneumonia area interpreted from CT images (medium vs. small [OR, 4.358; 95% CI, 2.188–8.678; $p < 0.001$]; and large vs. small [OR, 9.567; 95% CI, 3.982–22.986; $p < 0.001$]) (**Figure 2A**).

First Alert: A Baseline Nomogram Model for the Prediction at the Admission of the Risk for Critical Illness

For easy clinical application, we developed a nomogram scoring system in the training set based on the seven aforementioned variables to predict, at admission, the likelihood of progression to critical illness in patients with COVID-19, which could figure out the predicted probability of a patient developing critical illness during hospitalization (**Figure 2B**). Internal 10,000 bootstrap resamples exhibited that the nomogram had good distinguishing power, with its AUC reaching 0.960 (95%CI, 0.941–0.972), comparable to the other two models (random forest: 1.000 [95%CI, 1.000–1.000] and LASSO regression: 0.971 [95%CI, 0.955–0.981]) (**Figure 2C**). The non-parametric bootstrap test in the validation dataset showed that there were no statistically significant differences in AUCs among the three models (all $p > 0.05$) (**Supplementary Table S5**). In addition, the calibration curve of the nomogram model suggested that the predictive probability for critical illness fitted very well with the actual probability in both the training and the testing set (**Figure 2D**). In the testing set, the H–L test further confirmed the good performance of this model ($p = 0.863$) (**Supplementary Table S6** and **Supplementary Figure S3**). Importantly, we performed a sensitivity analysis for this nomogram model based on the variables without missing values, yielding an AUC of 0.948 ($p = 0.43$) and 0.929 ($p = 0.26$), respectively, in the training and testing set (**Figure 2C** and **Supplementary Table S5**). As shown in **Figures 2E,F**, the decision curve analysis (DCA) and clinical impact curves proved that this nomogram worked well in supporting clinical decision-making, not much different from the other two predictive models. In addition, the nomogram scoring system was finally transformed into an online predictive tool: https://hust-covid19.shinyapps.io/Critical-illness-Predictive-Tool/ (**Supplementary Figure S4**).

Differences in Dynamic Changes of Sequential Organ Failure Assessment Score and Laboratory Markers Between Critical and Non-critical Patients

We compared the change patterns of SOFA score and 46 laboratory variables in 296 critical and 854 non-critical patients from illness onset to 26 days later by plotting line charts (**Figure 3** and **Supplementary Figures S5–7**). Most of the indicators were substantially higher in critical patients than in non-critical patients during the whole observation period, including a sustained high level of the SOFA score, inflammatory

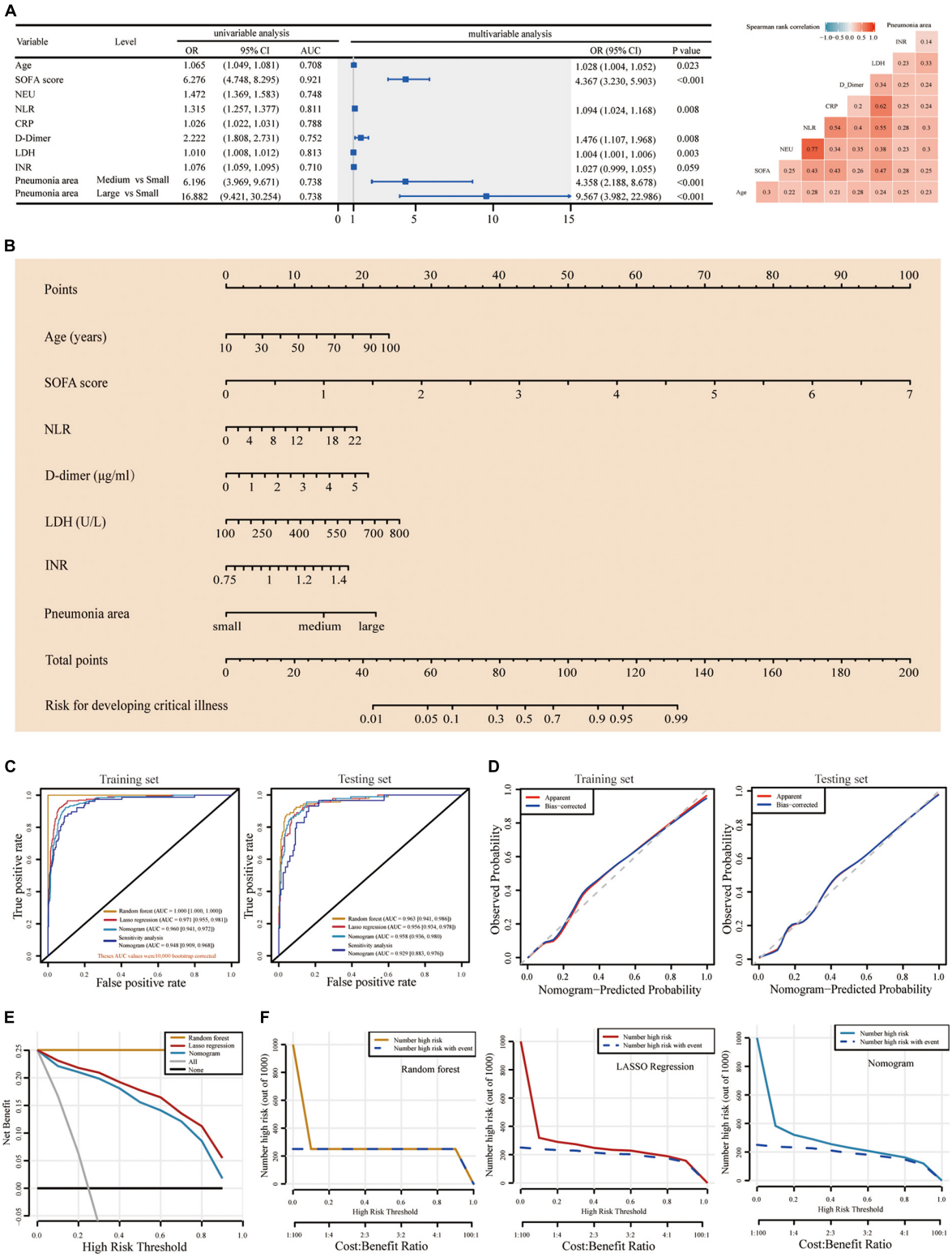

FIGURE 2 | Construction of and comparison among the three baseline predictive models. **(A)** Univariable logistic analysis of the nine variables selected by both random forest and LASSO predictive models. Multivariable logistic analysis of the seven remained variables, with NEU and CRP excluded according to the spearman rank correlation for the nine variables. **(B)** The predictive nomogram scoring system was developed in the training set, with age, SOFA score, NLR, D-dimer, LDH, INR, and pneumonia area interpreted from CT images incorporated. **(C)** Four ROC plots for three predictive models (random forest, LASSO regression analysis-based model, and multivariable logistic regression analysis-based nomogram) and sensitivity analysis of nomogram, in training and testing set, respectively.

(Continued)

FIGURE 2 | The AUCs and 95% CIs for these models were computed with 10,000 bootstrap resample in the training set. **(D)** Calibration plots of the nomogram in training and testing set. The ideal calibration curve (gray dotted line), raw calibration curve (red curve), and the bootstrap-corrected calibration curve (blue curve) were displayed. **(E)** DCA comparing the clinical utility of the random forest (yellow line), LASSO (red line), and nomogram (ocean blue line) models. The gray line and horizontal solid black line reflect the corresponding net benefit if some intervention strategies conducted in all or no patients across the full range of threshold probabilities at which a patient would undergo special intervention to avoid critical illness. **(F)** Clinical impact curves of random forest (yellow line), LASSO regression (red line), and nomogram (ocean blue line)-based predictive model. They were evaluated by the predictive performance of risk stratification for 1,000 people and the corresponding cost–benefit ratio. The yellow, red, and ocean blue lines represent the number of people classified as high risk by each model under different threshold probability; the blue dotted curve is the number of truly positive people under different threshold probability. LASSO, least absolute shrinkage and selection operator; LDH, lactate dehydrogenase; SOFA, sequential organ failure assessment; ROC, receiver operating characteristic curve; NLR, neutrophil-to-lymphocyte ratio; DCA, Decision curve analysis; AUC, area under the curve; CRP, C-reactive protein; NEU, neutrophil.

biomarkers [NLR, CRP, white blood cells (WBCs), NEUs, procalcitonin (PCT), and ferritin], coagulation indices [D-dimer, prothrombin time (PT), international normalised ratio (INR), and activated partial thromboplastin time (APTT)], organ dysfunction indicators [LDH; creatine kinase (CK), brain natriuretic peptide (BNP), creatine kinase muscle-brain isoform (CK-MB), myoglobin, hypersensitive cardiac troponin I (hsTNI); total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (ALP), aspartate aminotransferase (AST), Globin, total bile acid (TBA), γ-glutamyl transpeptidase (GGT), Alanine aminotransferase (ALT); blood urea nitrogen (BUN), cystatin C (Cys-C)]), and metabolism parameter (glucose). However, some indicators were persistently lower in critical patients than in their non-critical counterparts, and these indicators were indicative of immune damage (lymphocytes and eosinophils), coagulation disorder (platelets), impaired liver function (A/G), and malnutrition (hemoglobin, RBCs, TP, prealbumin, and albumin). Importantly, several laboratory markers started to rise or drop on the 8th (7th–9th) day after illness onset in critical patients, such as NEUs, NLR, D-dimer, LDH, BUN, PCT, myoglobin, globin (all rose), lymphocyte, albumin, A/G, and HDL-C (all dropped) (**Figure 3**, **Supplementary Figures S5–7**, and **Supplementary Notes**).

Second Alert: A "Burning Point"—Identified by Studying the Dynamic Changes Before Critical Illness Onset in Patients With Critical Illness

We further examined the dynamic changes of these 47 indicators before and after the CIO in 296 critical patients. As shown in **Figure 3** and **Supplementary Figures S5–7**, boxplots showed the dynamic changes in laboratory findings and SOFA score starting from the CIO in critical patients. Indicators, including SOFA score, NLR, CRP, PCT, ferritin (four inflammatory biomarkers), lymphocytes (immune indicator), D-dimer (coagulation index), LDH (organ dysfunction variable), glucose (metabolic indicator), TP, and albumin (two nutrient indicators), were abnormal from the beginning and started to progress substantially and continuously on the 5th day before the CIO. Some other indices, including WBCs, NEUs, hemoglobin, RBCs, platelet, BUN, CK, BNP, and DBIL, were virtually within the normal range from the beginning but become abnormal upon approaching CIO, which indicated the same change in the pattern within the 5 days before CIO. Moreover, indicators, including PT, INR, and ALP, were not only constantly within the reference value range but also began to change persistently on the 5th day before CIO (all in **Figure 3** and **Supplementary Figures S5–7**). Based on the above facts, the "burning point" was identified to be on the 5th day before CIO, a critical turning point indicating that CIO was only 5 days away, at which several indicators would experience further clear and continuous changes. This "burning point" appeared 12 (IQR, 7–17) days after illness onset (**Figure 1B**). As shown in **Table 2** and **Supplementary Table S8**, LMM analysis revealed 26 out of 47 indicators changed significantly and continuously within 5 days before CIO, involving aspects of hematology, coagulation function, inflammation, energy and metabolism, cardiac, liver, and renal functions. The seven most significant and representative indicators were selected as reference indicators for clinical judgment. They were SOFA score [value, 2; increase per day (I/d), +0.49; $p < 0.001$], NLR (value, 10.61; I/d, +2.07; $p < 0.0001$), CRP (value, 46.9; I/d, +4.95 mg/L; $p < 0.0001$), glucose (value, 7.83; I/d, +0.2 mmol/L; $p = 0.0066$), D-dimer (value, 6.08; I/d, +0.28 μg/L; $p < 0.0001$), LDH (value, 461; I/d, +13.95 U/L; $p = 0.0008$), and BUN (value, 6.51; I/d, +0.55 mmol/L; $p < 0.0001$), each being presented as median value at the 5th day before CIO plus average daily increment between burning point and CIO [in square bracket] (**Figure 3** and **Table 2**). The dynamic changes of all these 47 indicators after the CIO have been shown in **Supplementary Table S9**.

DISCUSSION

In this study, on the basis of the analysis of 1,150 consecutive patients with COVID-19 who were admitted to Wuhan West Union Hospital from 12 January to 25 February 2020, we established a reliable baseline predictive model and developed an online tool to predict, at admission, the risk for the development to critical illness, which can be used as the first warning sign (the first alert). Moreover, in critical patients, we retrospectively identified a "burning point," a warning sign that CIO was only 5 days away, and several indicators would experience significant and continuous changes. The "burning point" can serve as a second warning sign (the second alert), which can give clinicians precious time to take proactive measures before CIO. The two-checkpoint system can tell us "who" and "when" the critical illness will be developed in patients with COVID-19.

The predictors incorporated into the baseline predictive model were selected based on the random forest and LASSO regression analysis, which can provide a double guarantee for the selected predictors, ensuring the accuracy of the baseline

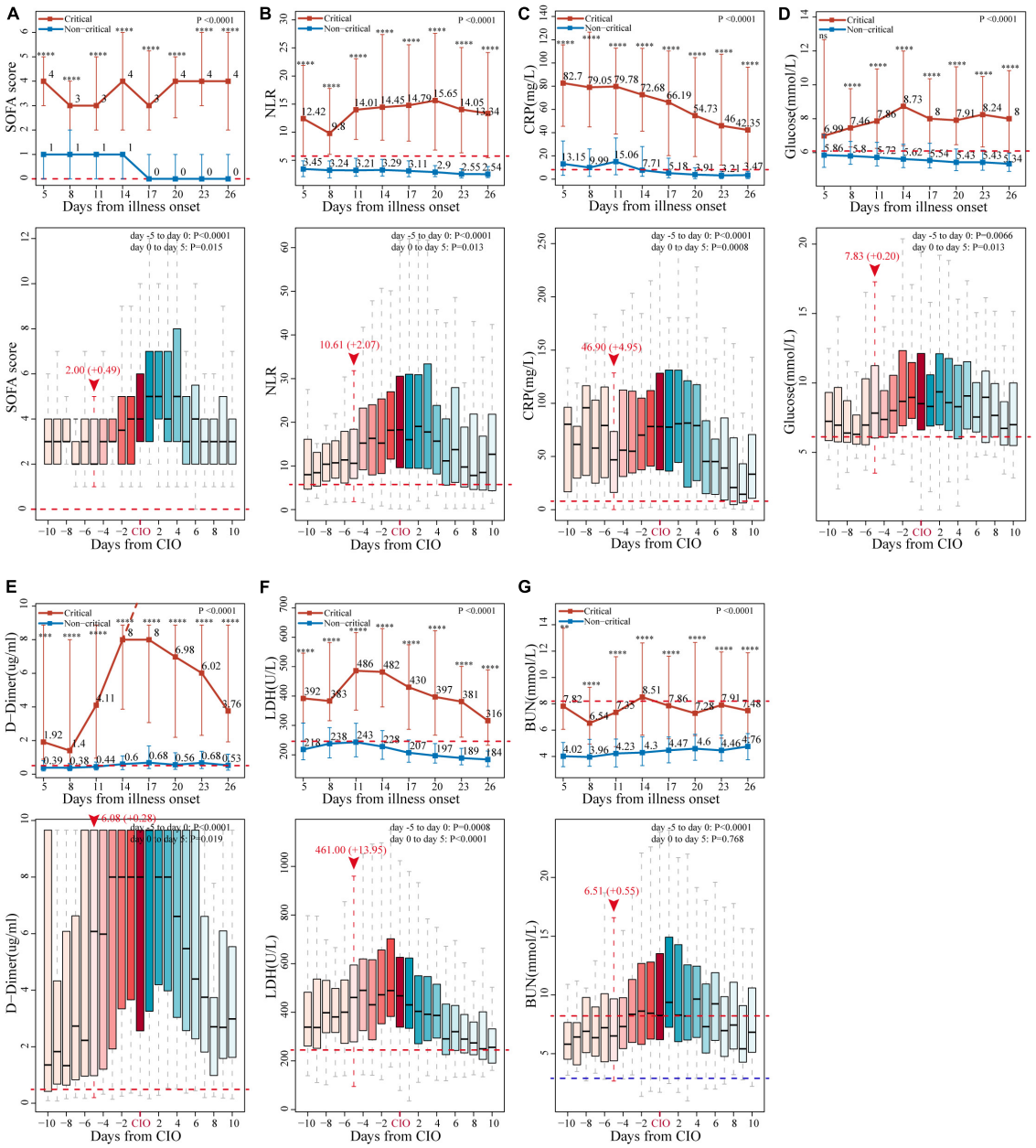

FIGURE 3 | Change patterns of seven representative indicators in critical and non-critical COVID-19 patients. The dynamic changes of **(A)** SOFA score, **(B)** neutrophil-to-lymphocyte ratio (NLR), **(C)** C-reactive protein (CRP), **(D)** glucose, **(E)** D-dimer, **(F)** lactate dehydrogenase (LDH), and **(G)** blood urea nitrogen (BUN), starting from illness onset between critical and non-critical patients (line chart), and those starting from critical illness onset (CIO) in critical patients (boxplot). The horizontal red dotted line and the horizontal blue dotted line represent the upper and lower limits of the reference value range of each indicator, respectively. In line chart, the results are reported as median (IQR), *p*-values of the comparison of each marker at each timepoint and the overall change trend between critical and non-critical patients have also been displayed (**$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, and ns for no significance). The values of D-dimer after day 14 exceeded the upper limit of detection, as indicated by the dashed line. In the boxplot, the day of "burning point" is designated as day 0 and highlighted by vertical red dotted line and red arrow, above which are indicator's median value at the day of "burning point" and its average daily increment from "burning point" to CIO, they are expressed in the form of median value (+ increment per day), *p*-values for the change of the seven markers in critical patients from days 5 to 0 and days 0 to 5 have also been given, respectively. All the indicators' values and *p*-values were calculated and analyzed by the linear mixed model, which have been adjusted for age and sex.

model. Meanwhile, the model was translated into a nomogram system. Actually, the differentiating power of this nomogram scoring system was comparable to that of the aforementioned two models, yielding an AUC of 0.960 (95%CI, 0.941–0.972) (vs. 1.00 [95%CI, 1.00–1.00] vs. 0.971 [95%CI, 0.955–0.981]) in the training set and an AUC of 0.958 (95%CI, 0.936–0.980) (vs. 0.963 [95%CI, 0.941–0.986] vs. 0.956 [95%CI, 0.934–0.978]) in the testing set. The accuracy of this model was also fully validated

TABLE 2 | Dynamic changes of SOFA score and laboratory findings before the critical illness onset (CIO).

Variables	Day-5	Day-3	Day-1	Day-0 Critical illness onset	Estimate	Std. error	Pr (> |t|)
Representative variables, median (IQR)							
SOFA score	2.00 (2.00–4.00)	3.00 (3.00–4.00)	4.00 (2.00–5.00)	4.00 (3.00–6.00)	0.492	0.033	<0.0001
NLR	10.61 (7.25–17.99)	16.33 (7.96–24.03)	18.19 (11.58–27.00)	18.29 (9.59–30.55)	2.068	0.264	<0.0001
CRP, mg/L	46.90 (16.23–73.52)	54.93 (35.62–111.10)	78.20 (41.03–111.97)	78.00 (37.36–128.24)	4.951	0.958	<0.0001
Glucose, mmol/L	7.83 (6.10–11.09)	8.01 (6.37–10.55)	8.96 (7.45–11.36)	8.50 (6.62–12.12)	0.201	0.074	0.0066
D-dimer, μg/mL	6.08 (1.01–8.50)	8.00 (1.93–8.50)	8.00 (3.73–8.50)	8.00 (2.60–8.50)	0.282	0.067	<0.0001
LDH, U/L	461.00 (278.50–594.50)	431.00 (287.00–616.00)	489.00 (383.00–702.50)	467.50 (339.00–625.50)	13.951	4.157	0.0008
BUN, mmol/L	6.51 (4.39–9.67)	8.36 (5.96–11.32)	8.45 (6.27–12.75)	8.25 (6.20–13.52)	0.547	0.096	<0.0001

The linear mixed model has been adjusted for age and sex.
SOFA, sequential organ failure assessment; NLR, neutrophil-to-lymphocyte ratio; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein.

by the internal 10,000 bootstrap and external testing set through the H–L test and calibration plots. The sensitivity analysis in the training (p = 0.43) and testing set (p = 0.26) further proved the good performance of this nomogram model. Furthermore, the DCA and clinical impact curves verified that this model worked effectively in supporting clinical decision-making. The nomogram system contained seven risk factors, including age, SOFA score, NLR, D-dimer, LDH, INR, and pneumonia area. All of them are easily obtained since they are included in the essential examinations at admission. Several studies (8, 23–25) have demonstrated that advanced age was an independent risk factor for death in patients with COVID-19. A higher SOFA score at admission was associated with increased odds of in-hospital death for patients with COVID-19 (15). Previous studies (11, 15, 26–28) showed that NLR, D-dimer, LDH, BUN, troponin, CRP, and PCT were risk predictors for the fatal outcome related to COVID-19. INR was reportedly higher in deceased patients than in convalescent patients with COVID-19 (29). Overall, the risk factor-based nomogram model is simple, effective, and amenable to clinical application, especially when transformed into a web-risk calculator, which can serve as the first alert for predicting critical illness in patients with COVID-19.

In addition, the longitudinal data analysis of critical and non-critical patients with COVID-19 demonstrated that almost all indicators showed conspicuous differences between those two groups, and several laboratory markers started to rise or drop on the 8th (7th–9th) day after illness onset in critical patients, supporting the hypothesis that the acute phase starts from the 7th to 10th day after illness onset of COVID-19, as proposed by a previous study (30). Collectively, differences in the aforementioned laboratory markers between critical and non-critical populations suggested that critical patients experienced long term coagulopathy, inflammatory activation, lymphocyte exhaustion, malnutrition, metabolic disorders, myocardial injury, liver dysfunction, and kidney injury. These findings can help us gain insight into the pathogenesis of COVID-19 and distinguish between critical and non-critical patients.

Moreover, we further looked into the dynamic changes in these 47 indicators before and after the CIO in 296 critical patients. The median time from illness onset to CIO was 17.0 (IQR, 12.0–22.0) days. We found that, prior to CIO, critical patients also suffered from severe coagulopathy (elevated D-dimer and declined PLT), inflammatory activation (elevated NEUs), lymphocyte exhaustion, myocardial damage (ascendant LDH and BNP), impaired liver function (elevated TBIL, AST, GGT, and ALT), kidney injury (ascendant BUN and Cys-C), malnutrition (reduced TP, albumin, and hemoglobin), and metabolic disorders (elevated glucose). Most importantly, we noticed that many laboratory markers started to have further and continuous changes on the 5th day before CIO. It indicates a turning point, at which the patient's condition began to deteriorate before the CIO appeared. We designated this point as the "burning point," which occurred 12 (IQR, 7–17) days after illness onset. This "burning point" corresponded exactly to a point in the early acute phase of COVID-19 proposed by Lin et al. (30). Furthermore, results of LMM revealed that 26 out of 47 indicators changed significantly and continuously within the 5 days before CIO, covering almost all the aspects of the above-mentioned abnormities. For clinical application, we selected the seven most significant and representative indicators as reference indicators and calculated their median values at the "burning point" (at the 5th day before CIO) and their average daily increments from "burning point" to CIO. These indicators were SOFA score, LDH, BUN (two organ-dysfunction indicators), CRP (inflammatory biomarkers), NLR (immune indicator), glucose (metabolism index), and D-dimer (coagulation indicator). In practice, we can judge whether a patient has passed the "burning point" on the basis of the time after illness onset, the value of each indicator at the "burning point" and its daily change increment. The appearance of a "burning point" indicates that CIO is only 5 days away, which can serve as the second alert before critical illness developed in patients with COVID-19.

Although the vaccine against COVID-19 is in full swing (31–33), there are still no special and effective treatments (34, 35). Intensifying multidisciplinary treatments, such as enhanced nutritional support, anticoagulation [low-molecular weight heparin (LMWH)], anti-inflammatory (γ-globulin, etc.), respiratory support (mechanical ventilation), and replacement therapy [continuous renal replacement therapy (CRRT)], are adopted to save lives of critical patients with COVID-19 (2, 36, 37). But the implementation of the above-mentioned intensive treatments usually started after the occurrence of critical illness. A recent study (30) about COVID-19 proposed that early initiation of intravenous γ-globulin and LMWH

anticoagulant therapy was effective in improving the prognosis of patients with COVID-19. Since the "burning point" in this study represented the starting point at which the patient's condition began to deteriorate before CIO, the high-risk period between the "burning point" and CIO might provide a precious time window for earlier intensive care and multidisciplinary interventions, thereby avoiding the aggravation to critical illness and improving survival.

Our study had several limitations. First, it was a single-center study. However, consecutively enrollment, large sample size (1,224), and low exclusion rate (74/1,224) reduce bias to some extent. Second, emerging SARS-CoV-2 variants characterized by increased transmissibility and decreased pathogenicity changed the landscape of the pandemic (38). However, considering that the mechanism of critical illness caused by different SARS-CoV-2 variant strains is similar to severe inflammatory syndrome (39), our predictive model may be used to predict the risk of critical illness due to infection by these variants and even other similar diseases. In addition, the methods section in our study has a greater reference value for similar studies and can be generalized to other critical diseases. Third, since all data were from China, the conclusion should be further validated in other countries.

CONCLUSION

In conclusion, the baseline risk factors-based nomogram (the first alert) can be employed at admission to identify the high-risk patients who might progress to critical illness. During hospitalization, the "burning point" (the second alert) could be identified in patients with COVID-19 based on the time after illness onset, the value of each indicator at the "burning point," and their daily change increments. The appearance of the "burning point" indicates that CIO was only 5 days away. The two sequential alerts allow early identification of deterioration of patients' condition, which is critical in optimizing medical intervention and reducing the mortality rate of patients with COVID-19.

DATA AVAILABILITY STATEMENT

The original data presented in this 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 Institutional Review Board of Medical Ethics Committee of Union Hospital, Huazhong University of Science and Technology. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YJ and ZY designed the study. JX, HL, FW, GM, and LD collected and summarized the clinical data. ZY, XT, and CD checked all the data. XH, KW, ZY, and ZW cleaned and analyzed all data. ZY, MZ, XT, and KW drafted the manuscript. YJ, JX, and XH revised the final manuscript. YJ was the guarantor and attested that all listed authors meet authorship criteria and no others meeting the criteria have been omitted. All authors approved the final draft of 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.2022.816314/full#supplementary-material

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