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Perioperative hemodynamic monitoring and management

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Perioperative hemodynamic monitoring and management

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Editorial: Perioperative hemodynamic monitoring and management

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Editorial on the Research Topic
Perioperative hemodynamic monitoring and management

In recent years, perioperative hemodynamic monitoring techniques have made great strides as the accelerating introduction of non-invasive monitoring instruments such as critical care ultrasound (1, 2). As performing standardized hemodynamic monitoring is a significant routine for clinicians with respective specialties in intensive care unit, these strides enable them to produce better hemodynamic status observation, then provide timely while targeted interventions, and thereby improve patient prognosis. Furthermore, the concept of resuscitation has also undergone a radical transformation, changing from a cardiac output-centered strategy into a perfusion-driven strategy (3, 4).

On the Research Topic, prominent experts in the field of hemodynamic monitoring have been commissioned as guest editors. Also, clinicians and researchers worldwide are invited to present their latest findings and reflections, helping further the understanding of this pivotal theme. We hope to take this opportunity to bring the readers an introduction to the progress made in recent years in the aspect of perioperative hemodynamic monitoring and enhance current clinical practice.

We identified all nine papers on the Research Topic of "*Perioperative hemodynamic monitoring and management*" (https://www.frontiersin.org/research-topics/31049/perioperative-hemodynamic-monitoring-and-management), with 7 original research, 1 review, and 1 perspective. The topic focused on the most compelling spots of perioperative hemodynamic monitoring, including sedation, vasoactive medication usage, fluid responsiveness, goal-directed hemodynamic optimization protocol, and extracorporeal circulation support.

Fluid resuscitation has proven to be one of the most fundamental while crucial interventions for patients with circulatory failure (5). Two studies investigated the prediction of fluid responsiveness. Zhao et al. demonstrated that for patient who sustain spontaneous breathing, $\Delta CI > 7.5\%$ induced by unilateral PLR is able to predict fluid responsiveness in a comparative accuracy, which might bring amelioration for

patients who cannot undergo bilateral PLR. Morakul et al. reported that a reduction in perfusion index (PI) during lung recruitment maneuver (LRM) and the baseline pulse pressure variation (PPV) are better predictors of fluid responsiveness for patients who underwent elective open abdominal surgery than the baseline cardiac output (CO), mean arterial pressure (MAP) and pleth variation index (PVI). These studies provided novel methods to optimize perioperative fluid administration.

Sedation plays an indispensable role in hypotension during the operation. Qiu et al. conducted a prospective controlled study on patients undergoing endoscopic submucosal dissection. The research compared hemodynamic stability of the patients who received propofol or remimazolam bolus induction and thereafter intravenous infusion. The outcome indicated that remimazolam clinically and statistically reduced the occurrence of peri-anesthesia hypotension. The superiority of remimazolam in maintaining hemodynamic stability and preventing hypotension may partially contribute to its preferable preservation of CO. Additionally, since whether patient height is associated with the block level for spinal anesthesia remains controversial, Huang et al. demonstrated that without prophylactic fluid preloading or vasopressors the dosing algorithm of bupivacaine based on height provided sufficient anesthesia with an infrequent occurrence of hypotension.

Accurate prediction of outcomes in critically ill patients is essential for clinical research and monitoring care quality (6). Xing et al. established a clinical information and image parameters based outcomes prediction model for the in-hospital patients with acute aortic dissection (AAD) from emergency department. The team identified that age, Marfan syndrome, type A aortic dissection, surgical repair, and maximum false lumen diameter are vital influencing factors on the in-hospital AAD outcomes. The end product named 3-level type A aortic dissection clinical prognosis score (3ADPS) proved to be able to provide rapid and effective prediction of in-hospital prognosis of type A aortic dissection. Low cardiac output syndrome (LCOS) after cardiac surgery may result in tissue malperfusion, as well as dysfunction of multiple organs including the liver, kidney, lung, brain and gastrointestinal tract. To twist the situation of lacking machine learning prediction model for the occurrence of LCOS after cardiac surgery, Hong et al. constructed several LCOS predictive models employed with respective machine learning algorithms, which may help to stratify the risk factors, detect the emergence early, and ultimately improve the LCOS management.

Post-operative delirium is commonly reported among aged patients with increasing morbidity and mortality. Whether the perioperative goal-directed hemodynamic optimization algorithm could make improvements in cerebral oxygenation and delirium prevention remains controversial. Fuest et al. reported that the application of an algorithm in high-risk noncardiac surgical patients failed to make any progress in hemodynamic interventions, hemodynamics amelioration, and cerebral oxygenation increment. Any effect brought by the trial on the occurrence of post-operative delirium remains undetected. With regard to venous-arterial extracorporeal membrane oxygenation (V-A ECMO), the critical circulatory support apparatus to rescue patients from refractory cardiogenic shock. During the V-A ECMO weaning phase, to simulate diverse loading conditions and assess the ventricles performance, the V-A ECMO centrifugal pump flow requires continuous adjustment (7). Luo et al. reported a novel method to evaluate cardiac function during V-A ECMO support (Flow challenge test, FCT). During the test, afterload will be converted into preload which can lead to a hemodynamic challenge, and by extension, the FCT result is reliable to predict the CO value after V-A ECMO weaning.

As the core of Enhanced Recovery After Surgery (ERAS) protocols, the goal-directed fluid therapy (GDT) concept has aroused growing attention around the world. Dmytriiev et al. presented the analytical data, giving a comprehensive description of the perioperative targeted infusion therapy benefits and principles to reduce the peril of complications on a central hemodynamic parameters based foundation. Furthermore, the encouraging outcomes of GDT practice inspired clinicians to continue the research on a central hemodynamics monitoring basis to optimize benefits of surgical patients.

In summary, this Research Topic collected a series of research and review articles related to "*Perioperative hemodynamic monitoring and management*". All authors, reviewers, and editors who contributed are greatly appreciated. We hope that readers will enjoy this Research Topic, and the series will provide interested readers with new insights and inspiration for future research.

Author contributions

G-wT drafted the manuscript. XM, AV-B, ND, and KY edited the manuscript, contributed to the Research Topic, and approved the publication of this Editorial. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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ORIGINAL RESEARCH
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Changes in the Cardiac Index Induced by Unilateral Passive Leg Raising in Spontaneously Breathing Patients: A Novel Way to Assess Fluid Responsiveness

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Background: Evaluation of fluid responsiveness in intensive care unit (ICU) patients is crucial. This study was to determine whether changes in the cardiac index (CI) induced by a unilateral passive leg raising (PLR) test in spontaneously breathing patients can estimate fluid responsiveness.

Methods: This was a prospective study, and 40 patients with spontaneous breathing activity who were considered for volume expansion (VE) were included. CI data were obtained in a semirecumbent position, during unilateral PLR, bilateral PLR, and immediately after VE. If the CI increased more than 15% in response to the expansion in volume, patients were defined as responders.

Results: The results showed that a unilateral PLR-triggered CI increment of ≥7.5% forecasted a fluid-triggered CI increment of ≥15% with 77.3% sensitivity and 83.3% specificity with and an area under the receiver operating characteristic (ROC) curve of 0.82 [$P < 0.001$]. Compared with that for bilateral PLR, the area under the ROC curve constructed for unilateral PLR-triggered changes in CI (ΔCI) was not significantly different ($p = 0.1544$).

Conclusion: ΔCI >7.5% induced by unilateral PLR may be able to predict fluid responsiveness in spontaneously breathing patients and is not inferior to that induced by bilateral PLR.

Trial Registration: Unilateral passive leg raising test to assess patient volume responsiveness: Single-Center Clinical Study, ChiCTR2100046762. Registered May 28, 2021.

Keywords: fluid responsiveness, leg raising, cardiac index, pulse contour, volume expansion

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BACKGROUND

Circulatory failure is very common in intensive care unit (ICU) patients. In individuals with circulatory failure, fluid resuscitation is one of the most basic interventions for treatment (1). Nevertheless, only 50% of severely ill patients with acute circulatory failure benefit from intravascular volume expansion (2, 3). The expansion of blood volume harbors harmful effects in the absence of preload dependence (4). Treatment involving excessive intravenous fluid might result in pulmonary and peripheral edema along with complications of the abdomen and other compartments and may impair oxygen diffusion (5–7). It is therefore of great importance to effectively evaluate the patient's volume capacity status in the clinic (8).

Several dynamic indices of fluid responsiveness based on heart-lung interaction-induced variations in left ventricular stroke volume can be used in mechanically ventilated patients but not in spontaneously breathing patients. Passive leg raising (PLR) is a simple way to estimate volume responsiveness with good accuracy and can be used in spontaneously breathing patients (8). However, there are possible limitations to the PLR test, of which a few have been demonstrated, such as significant atrophy of the patient's unilateral lower extremity, necessity of venous compression stockings, deep vein thrombosis of the lower extremities, and lower extremity amputation. In the situations above, a patient cannot perform a classic bilateral passive leg lift test but can perform a unilateral PLR test. A minifluid challenge (∼100 ml of fluid) is able to predict stroke volume increases induced by 500 ml (9). It has been reported that bilateral PLR can recruit approximately 300 ml from the lower extremities (10), and therefore, we hypothesized that the blood volume mobilized by a unilateral PLR test may be sufficient to evaluate fluid responsiveness. No data are currently available concerning the unilateral PLR test in patients. This question is worth discussing.

In this study, we aimed to explore (1) whether cardiac index (CI) changes during a unilateral PLR could estimate fluid responsiveness in spontaneously breathing patients. (2) To compare changes in CI (ΔCI) triggered by classic bilateral PLR and unilateral PLR and the ability to estimate volume responsiveness.

Abbreviations: ICU, intensive care unit; ARDS, acute respiratory distress syndrome; SV, stroke volume; PLR, passive leg raising; CI, cardiac index; IAP, intra-abdominal pressure; PPV, pulse pressure variation; CVP, central venous pressure; SVV, stroke volume variation; SVI, stroke volume index; VE, volume expansion; SD, standard deviation; ROC, receiver operating characteristic; AUC, area under the ROC curve; ΔCI, percent changes in cardiac index; ΔPPV, percent changes in pulse pressure variation; ΔSVI, percent changes in stroke volume index; ΔSVV, percent changes in stroke volume variation.

PATIENTS AND METHODS

Patients

This single-center, prospective clinical study (ChiCTR2100046762) was conducted from June 1st, 2021, to July 15st, 2021, at Fudan University Shanghai Cancer Center. The study was approved by the hospital's Ethics Committee (No. 2104233-4), and all enrolled patients provided written informed consent for the clinical trial and were willing to participate.

Forty patients with spontaneous breathing activity who were considered for volume expansion were included. The inclusion

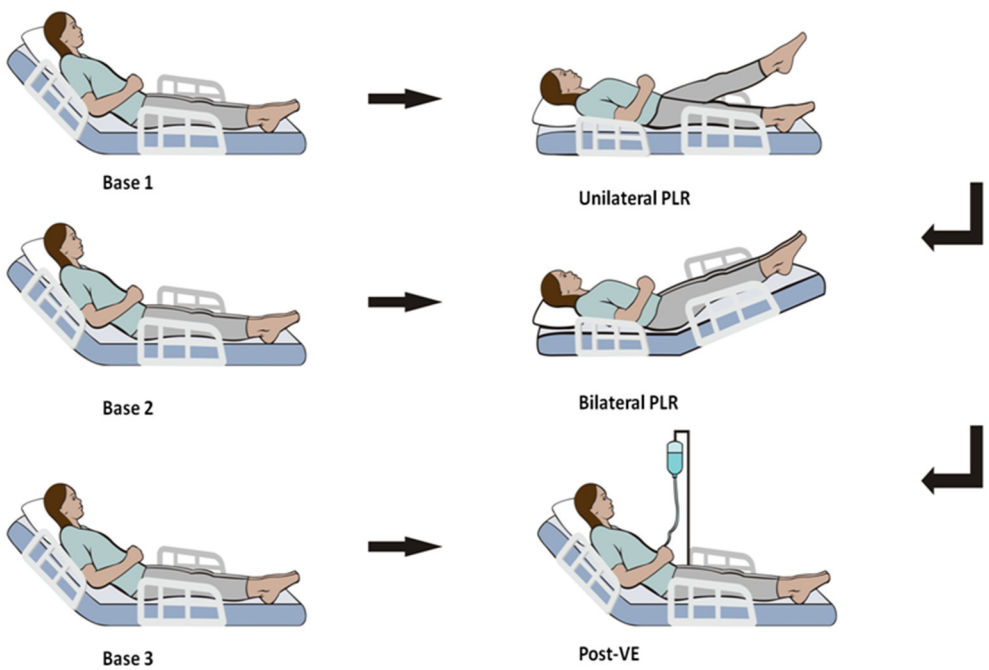

FIGURE 1 | Study protocol. PLR, passive leg raising; VE, volume expansion.

criteria were age over 18 years. The decision was made on the basis of clinical signs of inadequate tissue perfusion, such as (1) tachycardia; (2) mottled skin; (3) blood pressure <90/60 mmHg and/or mean arterial pressure of <75 mmHg; and (4) urine output below 0.5 ml/kg/minute for at least 2 h. When one of the inclusion criteria is met, we will judge whether the patient is in a state of hypovolemia, based on the patient's vital signs and clinical manifestations. Two experienced ICU doctors (at least 5 years of experience) are responsible for the patient enrollment. For disputes, all doctors will discuss together.

Patients were excluded if they had intra-abdominal hypertension (IAH, sustained elevation of intra-abdominal pressure above 12 mmHg), arrhythmia, pulmonary hypertension, severe heart valve disease, severe thoracic aortic abnormality, external cardiac pacemaker, head trauma, severe heart failure, or thrombotic stockings, or if they were uncooperative. Moreover, those not suitable for enrollment for other reasons, such as patients with clear hemorrhage or active bleeding and patients who needed immediate rescue, were also excluded.

Study Design and Measurements

Figure 1 illustrates the protocol steps of the current study. After 1 min of stabilization for each step, hemodynamic variables, such as heart rate, pulse pressure variation (PPV), systolic blood pressure, central venous pressure (CVP), CI, stroke volume variation (SVV), mean arterial pressure, stroke volume index (SVI) and diastolic blood pressure, were recorded. The initial value of the CI was estimated with a proprietary algorithm conducting an "autocalibration" by ProAQT/Pulsioflex, and data from the next steps were determined by pulse contour analysis with ProAQT/Pulsioflex.

Hemodynamic variables were measured during six sequential steps (**Figure 1**). The initial set of assessments was acquired in a semirecumbent position (45°) (named base 1), ensuring that the detected value was stable.

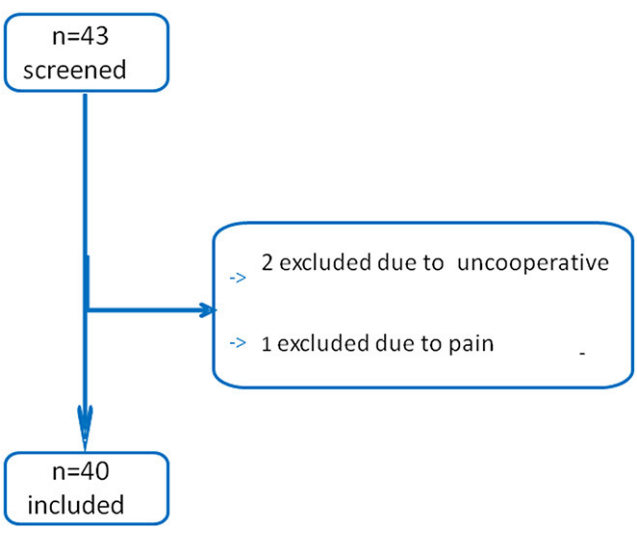

FIGURE 2 | Flow of patients through the study.

Next, we performed a unilateral PLR test. One of the legs was raised at a 45° angle by holding the patients' heels, while the patients' trunk and the other leg were in a supine posture. Therefore, the angle of the trunk with the lower raised leg remained unaltered at 135°. A second assessment set (named unilateral PLR) was documented at the maximal effect of unilateral PLR on the CI, occurring within 1 min.

The body position was then rendered to the base 1 posture, and the cardiac index was allowed to reach its baseline value. Then a third assessment set was documented (base 2).

To prevent possible pain from creating false-positives, the automatic technique was used for bed elevation. The patients' lower limbs were lifted to a 45° angle from the horizontal position, whereas the trunk was lowered to a horizontal position, and the angle of the trunk and the legs was still lifted at 135°. The fourth set of values (termed bilateral PLR) was measured when the CI reached its maximal value.

The patients were then shifted back to the base 1 position, and the fifth set of assessments was documented (base 3).

Finally, measurements were acquired immediately after volume expansion (VE) (500 mL of saline for 15–30 min) (designated post-VE).

Estimated CVP was measured at each study step, and the jugular venous pulse was evaluated to estimate CVP (11). Estimated CVP was measured at end-expiration and the averaged value from three sequential respiratory cycles was taken into account.

We haven't measure inferior vena cava. About half of the patients with upper abdominal surgery in our ICU, and the ultrasound quality were relatively poor. Moreover, the use of the inferior vena cava to assess volume responsiveness is controversial, and studies found that inferior vena cava showed poor accuracy to predict fluid responsiveness in spontaneous breathing patients (12–14).

Hemodynamic Monitoring

The ProAQT/Pulsioflex (Pulsion Medical Systems, Munich, Germany, termed "Pulsioflex" hereafter) was used to estimate the CI from pulse contour analysis, without any external calibration. It was connected to a radial arterial catheter. The values of CI, SVI, SVV, and PPV were inferred from the device.

Statistical Analysis

The calculation of the sample size was based on the comparison of two ROC curves (15). Expecting an AUC for the unilateral PLR-induced ΔCI of 0.70, anticipating an AUC for the bilateral PLR-induced ΔCI of 0.92, and selecting βas 0.2 andα as 0.05, we estimated that half of the patients would be preload responders. Thus, we planned to enroll 18 patients in each group.

After completing the study protocol, patients were divided into two groups: responders and non-responders to fluid loading. Patients with a CI increase of more than 15% by volume expansion from base 3 were classified as responders; otherwise, they were classified as non-responders.

The data distribution normality was screened with the Kolmogorov-Smirnov examination. Data are presented as the

TABLE 1 | Characteristics of the study population.

Parameters	Global population (40)	Non-responders (18)	Responders (22)	*P*-value
Patient's characteristics:				
Age (year)	59 ± 10	55 ± 8	61 ± 10	0.034
Male (*n*, %)	28 (70)	12 (30)	16 (40)	0.681
Weight (kg)	62.50 ± 9.19	61.28 ± 10.19	61.50 ± 8.53	1.000
Body mass index (kg/m^2)	22.21 ± 2.81	21.93 ± 2.95	22.61 ± 2.71	0.568
Apache II (ICU admision)	7 ± 3	8 ± 4	7 ± 2	0.897
Death in the ICU (*n,* %)	4 (10)	3 (7.5)	1 (2.5)	0.209
Mechanical ventilation (*n*, %)	8 (20)	3 (7.5)	5 (12.5)	0.074
Medical history:				
Congestive heart failure (*n*, %)	7 (17.5)	3 (7.5)	4 (10)	0.015
Chronic respiratory insufficiency (*n*, %)	5 (12.5)	2 (5)	3 (7.5)	0.037
Abdominal surgery (*n*, %)	8 (40)	3 (7.5)	5 (12.5)	0.074
Thoracic surgery (*n*, %)	4 (10)	2 (5)	2 (5)	0.044
ARDS (*n*, %)	8 (20)	4 (10)	4 (10)	0.050
Hypertension (*n*, %)	4(10)	2(5)	2(5)	0.044
Diabetes (*n*, %)	2(5)	1(2.5)	1(2.5)	0.079
Chronic renal failure (*n*, %)	2(5)	1(2.5)	1(2.5)	0.079
Cause of circulatory failure:				0.49
Hypovolemic shock (*n*, %)	19 (47.5)	8 (20)	11 (27.5)	
Cardiogenic shock (*n*, %)	7 (17.5)	4 (10)	3 (7.5)	
Septic shock (*n*, %)	7 (17.5)	3 (7.5)	4 (10)	
Obstructive shock (*n*, %)	2 (5)	0 (0)	2 (5)	
Anaphylactic shock (*n,* %)	1 (2.5)	0 (0)	1 (2.5)	
Other causes (*n*, %)	4 (10)	3 (7.5)	1 (2.5)	

ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

mean [standard deviation (SD)], median (interquartile range), or number (frequency in %).

The comparison of patient characteristics, medical history, and cause of circulatory failure between preload responders and non-responders was performed using a non-parametric Mann–Whitney U test for continuous variables and a chi-square test for categorical variables.

Comparison of hemodynamic variables between time points of the study was performed by the paired Student's *t* test or Wilcoxon test, based on the data distribution. Variables between preload responders and non-responders were analyzed using the two-sample Student's *t* test (normally distributed) or Mann-Whitney *U* test (non-normally distributed) as appropriate.

Receiver operating characteristic (ROC) curves were produced for unilateral PLR-induced changes in continuous variables (CI, PPV, SVI and SVV). The area under the ROC curve (AUC) for unilateral PLR-triggered ΔCI and bilateral PLR-triggered ΔCI were compared in all patients using a Hanley-McNeil test (15).

A two-tailed $p < 0.05$ showed statistical significance. Statistical analysis was implemented in MedCalc Statistical Software version 19.0.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019).

RESULTS

Forty-three patients were screened in this study (**Figure 2**). Two patients were excluded due to being uncooperative with the test, and another patient was excluded because of pain when performing a unilateral PLR test. All the other patients were included. Finally, 40 patients were included and analyzed, as shown in **Table 1**.

No patients received β-blockers. Every patient was breathed spontaneously. Eight patients (20%) were intubated and ventilated, and pressure support was in ventilation mode (fraction of inspired oxygen = 35 ± 5%, inspiratory pressure = 10 ± 4 cmH2O, and positive end-expiratory pressure = 5 cmH2O). Thirty-two patients were not intubated.

Twenty-two patients responded to the volume expansion, and 18 were non-responders. The impacts of unilateral PLR, bilateral PLR, and the expansion of volume on hemodynamic variables in responders and non-responders are shown in **Table 2**. As shown in **Table 3**, we found that unilateral PLR, the bilateral PLR test, and VE induced significant differences in ΔCI and ΔSVI between preload responders and preload non-responders.

The maximal impact of PLR on the CI was detected within 1 min in all patients. ΔCI triggered by the unilateral leg raise test

TABLE 2 | Evolution of hemodynamic parameters in preload responders and non-responders.

Variable	Baseline1	Unilateral passive leg raising	Baseline 2	Bilateral passive leg raising	Baseline 3	Post volume expansion
Heart rate (beats/min)						
Preload responders	105 ± 12	105 ± 11	106 ± 11	103 ± 11	106 ± 12	96 ± 11*
Preload non-responders	107 ± 14	108 ± 11	107 ± 14	107 ± 14	107 ± 15	106 ± 12
Systolic arterial pressure (mmHg)						
Preload responders	108 ± 12	108 ± 12	109 ± 14	115 ± 12*	108 ± 13	124 ± 12*
Preload non-responders	108 ± 14	109 ± 14	108 ± 13	110 ± 14	109 ± 12	110 ± 15
Diastolic arterial pressure (mmHg)						
Preload responders	58 ± 9	59 ± 8	58 ± 7	57 ± 9	57 ± 7	62 ± 8*
Preload non-responders	62 ± 8	62 ± 8	60 ± 6	61 ± 7	61 ± 6	60 ± 6
CVP (mmHg)						
Preload responders	5 (5–6)*	7 (6–8)*!	5 (4–6)*	7 (6–8)*–	6 (5–6)*	7 (6–9)*#
Preload non-responders	9 (8–10)*	10 (9–11) *!	9 (8–9)*	10 (9–11)*–	9 (8–10)*	10 (8–11)*#
SVV (%)						
Preload responders	15 ± 7	15 ± 7	15 ± 6	14 ± 7–	16 ± 7	15 ± 7
Preload non-responders	12 ± 5	13 ± 4	13 ± 5	11 ± 4–	13 ± 5	12 ± 4
SVI (ml/m^2)						
Preload responders	31 ± 9	34 ± 10	31 ± 9	46 ± 10	31 ± 7	47 ± 8#
Preload non-responders	31 ± 8	33 ± 9	32 ± 9	34 ± 9	32 ± 8	34 ± 8
PPV (%)						
Preload responders	20 ± 5	21 ± 5	19 ± 6	20 ± 7	23 ± 6	21 ± 5
Preload non-responders	11 ± 4	11 ± 4	12 ± 3	12 ± 4	14 ± 4	13 ± 4
CI (L/min/m^2)						
Preload responders	3.25 ± 0.70	3.59 ± 0.71!	3.24 ± 0.63	3.79 ± 0.89–	3.20 ± 0.92	4.02 ± 1.03#
Preload non-responders	3.31 ± 0.66	3.51 ± 0.80!	3.36 ± 0.69	3.65 ± 0.69–	3.28 ± 0.83	3.69 ± 1.21#

$p < 0.05$ between preload responders and non-responders.
! $p < 0.05$ VS baseline 1.
– $p < 0.05$ VS baseline 2.
 # $p < 0.05$ VS baseline 3.
CVP, Central Venous Pressure; SVV, Stroke Volume Variation; SVI, Stroke Volume Index; PPV, Pulse Pressure Variation; CI, Cardiac Index.

was significantly higher in responders than in non-responders ($p = 0.0005$; **Figure 3**). In responders, the CI increased by 10.2 (8.4–11.9) % from baseline to unilateral PLR. In non-responders, the CI increased by 6.3 (5.2–7.3) % from baseline to unilateral PLR. In all patients, ΔCI triggered by the bilateral leg raise test was significantly higher in responders than in non-responders ($p<0.0001$; **Figure 3**). In responders, the CI increased by 16.9 (14.6–19.2) % from baseline to bilateral PLR. In non-responders, the CI increased by 9.1 (7.5–10.6) % from baseline to bilateral PLR. A correlation [r = 0.60 (0.35–0.77), $p<0.0001$] between ΔCI induced by unilateral and bilateral PLR tests (**Figure 4**) was found.

As shown in **Figure 5** and **Table 4**, the AUC established for the unilateral and bilateral PLR-triggered changes in PPV and SVV was significantly lower than that established for the unilateral PLR-triggered ΔCI and ΔSVI.

The results show that a unilateral PLR-triggered CI increment of ≥7.5% forecasted a fluid-triggered CI increment of ≥15% with 77.3% sensitivity and 83.3% specificity. Meanwhile, bilateral PLR-triggered increases in CI that were ≥9.8% forecasted a fluid-triggered CI increment of ≥15% with 95.5% sensitivity and 77.8% specificity (**Table 4** and **Figure 5**). The AUCs constructed for unilateral and bilateral PLR-triggered alterations in the CI were not significantly different ($p = 0.1544$) (**Figure 6**).

DISCUSSION

This prospective study found that CI changes induced by a unilateral PLR greater than approximately about 7.5% predicted fluid responsiveness and were not inferior to bilateral PLR. To the best of our knowledge, this is the first clinical trial to address this problem.

The classical bilateral PLR test triggers a sudden increase in cardiac preload because of blood autotransfusion from the lower limbs and the vast splanchnic territory, resulting in a cardiac output increase in patients that is dependent on the preload. Under physiological conditions, the volume of blood in the capacity veins of the lower limbs and the vast

TABLE 3 | Indices of preload responsiveness in preload responders and non-responders.

Variable	Effect of unilateral PLR	Effect of bilateral PLR	Effects of VE
ΔCI (% change)			
Preload responders	10 ± 4	17 ± 5	20 ± 8
Preload non-responders	6 ± 2	9 ± 3	13 ± 7
P preload responders preload vs. non-responders	<0.001	<0.001	<0.001
ΔSVV (% change)			
Preload responders	−3 ± 18	5 ± 23	3 ± 26
Preload non-responders	10 ± 50	11 ± 18	5 ± 27
P preload responders vs. preload non-responders	0.819	0.476	0.757
ΔSVI (% change)			
Preload responders	11 ± 5	17 ± 6	19 ± 7
Preload non-responders	6 ± 2	9 ± 4	12 ± 8
P preload responders vs. preload non-responders	<0.001	<0.001	0.001
ΔPPV (% change)			
Preload responders	6 ± 26	8 ± 31	9 ± 31
Preload non-responders	−14 ± 43	7 ± 26	8 ± 26
P preload responders vs. preload non-responders	0.312	0.638	0.492

PLR, passive leg raising; VE, volume expansion; ΔCI, percent changes in cardiac index; ΔPPV, percent changes in pulse pressure variation; ΔSVI, percent changes in stroke volume index; ΔSVV, percent changes in stroke volume variation.

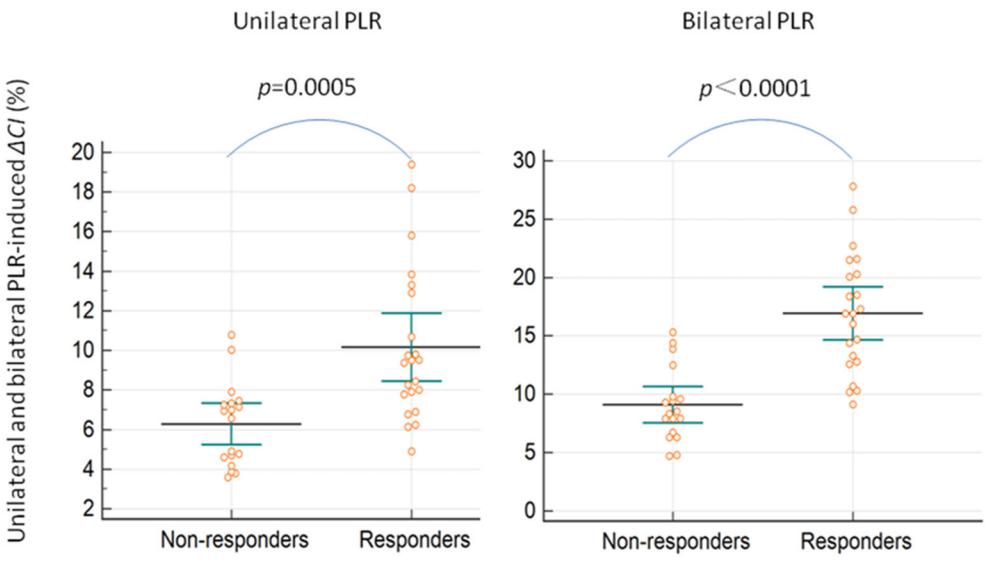

FIGURE 3 | Unilateral and bilateral PLR-induced ΔCI in preload responders and non-responders. ΔCI, percent changes in the cardiac index; PLR, passive leg raising.

splanchnic territory, returned during the classic bilateral PLR, is estimated at 300 ml (10). For the unilateral PLR test, the blood volume recruited should be <300 ml, similar to the "mini-fluid challenge," which can lead to a significant cardiac output response. This trial is based on the assumptions that a small quantity of fluid can remarkably raise the cardiac preload and that this rise in preload is adequate to test the preload dependence of the two ventricles (16), which is confirmed by the results.

Acutely, during unilateral PLR, the trunk was lowered, and the splanchnic blood volume likely participated in the increase in preload, not just the blood volume of the raised leg. In this regard, in future research, we may be able to assess the effects of lowering only the trunk on the CI, if we performed the PLR in two

steps [lowering the trunk and then elevating the leg(s)]. There is no relevant published report on this topic yet.

PPV is the most studied and used dynamic index in clinical practice and is a reliable indicator of preload responsiveness in patients with mechanical ventilation >8 ml/kg without spontaneous breathing. Taccheri et al. (17) found that Δ*PPV* can detect preload responsiveness during a bilateral PLR test in patients with mechanical ventilated at <8 ml/kg without spontaneous breathing. Hamazaoui et al. (18) found that in mechanically ventilated patients with spontaneous breathing, the Δ*PPV* induced by bilateral PLR could predict fluid responsiveness with moderate accuracy. However, in our study, the results showed that in patients with spontaneous breathing, Δ*PPV* was not a reliable marker of preload responsiveness during unilateral or bilateral PLR tests. Only 20% of patients received mechanical ventilation in our study, in contrast with two other studies which all patients received mechanical ventilation. Patients with spontaneous breathing without positive pressure ventilation may experience small changes in cardiac loading condition. In these patients, higher Δ*PPV* might be predictive of fluid responsiveness, but threshold have not defined (19). Further explorations are needed to determine whether Δ*PPV* induced by PLR can assess preload responsiveness in patients with spontaneous breathing activity.

The unilateral PLR test has some significant advantages. Some special situations are encountered in a clinical setting, such as disorders affecting one of the lower limbs rendering patients unable to perform a bilateral passive leg lift test. At this time, a unilateral PLR test can be used to evaluate the patient's volume capacity. Furthermore, unlike a fluid challenge test that may induce fluid overload, unilateral PLR increases preload by transferring blood pooled in the lower extremities to the compartment. The fluid is reversible when the patient is returns to the semirecumbent position, similar to the bilateral PLR test.

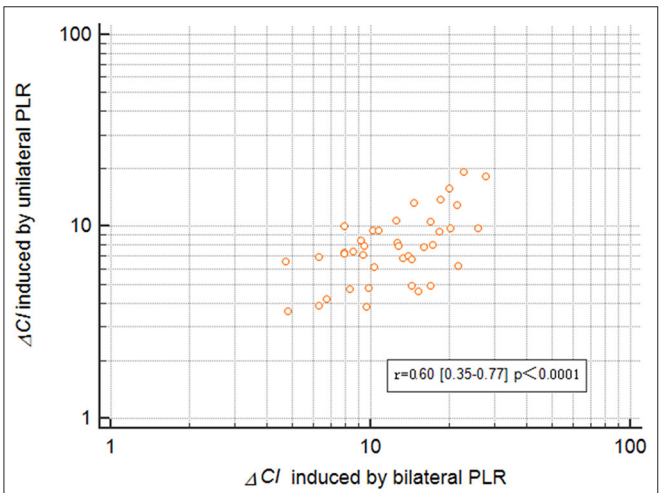

FIGURE 4 | Correlation ΔCI between inducetion by unilateral and bilateral PLR. ΔCI, percent changes in the cardiac index; PLR, passive leg raising.

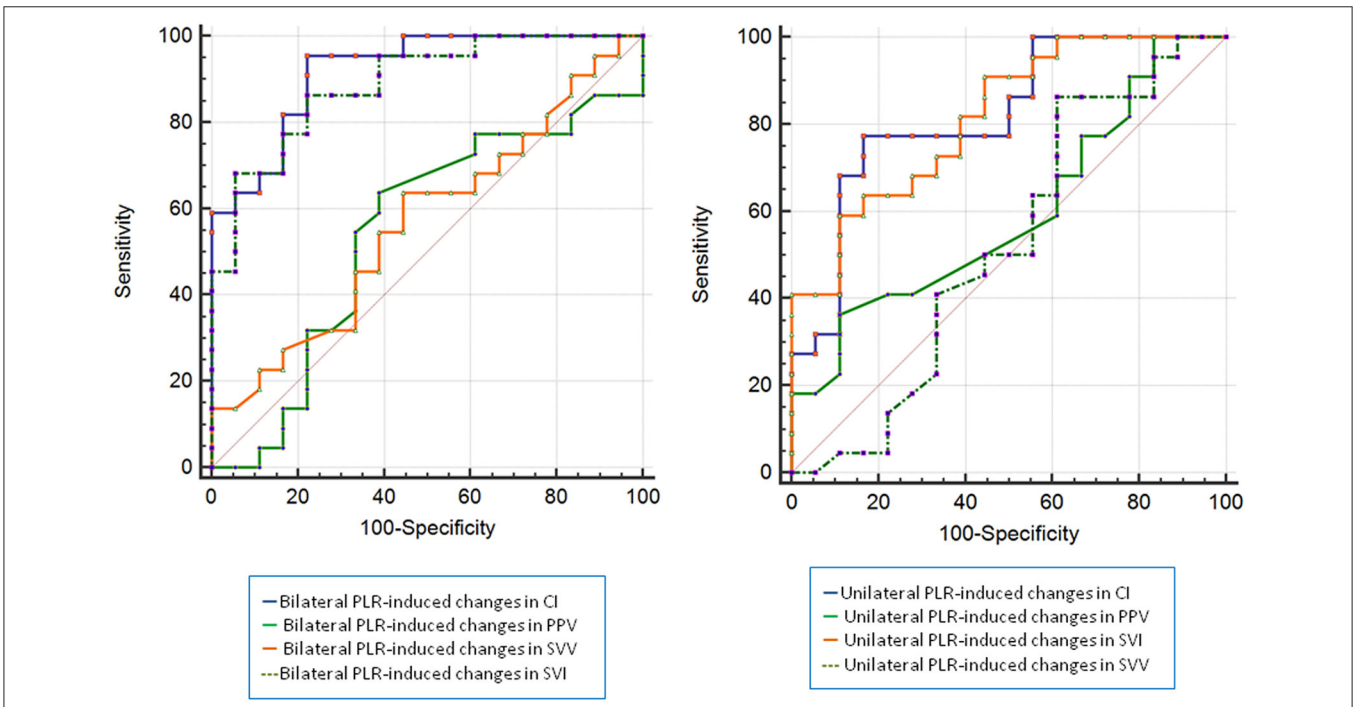

FIGURE 5 | ROC curves comparing changes in CI, PPV, SVI, and SVV to discriminate responders and non-presponders (left: bilateral PLR, right: unilateral PLR). CI, cardiac index; PPV, pulse pressure variation; SVI, stroke volume index; SVV, stroke volume variation; ROC, receiver operating characteristic.

TABLE 4 | Diagnostic ability of the unilateral and bilateral PLR-induced changes in CI, PPV, SVI and SVV to detect preload responsiveness.

Variable	AUC	*p*-value verse 0.50	Best cutoff value	sensitivity	specificity	positive predictive value	Negative predictive value	Positive likehood ratio	Negative likehood ratio	Youden index
Unilateral PLR-induced Δ*CI* (%)	0.82	<0.0001	7.5	77.2	83.3	85.0 (66.3–94.2)	75.0 (57.5–86.9)	4.64 (1.6–13.3)	0.27 (0.1–0.6)	0.6061
Unilateral PLR-induced Δ*PPV* (%)	0.60	0.2896								
Unilateral PLR-induced Δ*SVI* (%)	0.82	<0.0001	7.9	59.1	88.9	86.7 (62.7–96.2)	64.0 (51.2–75.1)	5.32 (1.4–20.6)	0.46 (0.3–0.8)	0.4798
Unilateral PLR-induced Δ*SVV* (%)	0.52	0.8256								
Bilateral PLR-induced Δ*CI* (%)	0.92	<0.0001	9.8	95.5	77.8	84.0 (68.8–92.6)	93.3 (67.0–99.0)	4.30 (1.8–10.2)	0.058 (0.008–0.4)	0.7323
Bilateral PLR-induced Δ*PPV* (%)	0.54	0.6441								
Bilateral PLR-induced Δ*SVI* (%)	0.89	<0.0001	11.0	86.4	77.8	82.6 (66.3–92.0)	82.4 (61.3–93.2)	3.89 (1.6–9.4)	0.18 (0.06–0.5)	0.6414
Bilateral PLR-induced Δ*SVV* (%)	0.57	0.4567								

PLR, passive leg raising; AUC, area under the receiver operating characteristic curve; ΔCI, percent changes in cardiac index; ΔPPV, percent changes in pulse pressure variation; ΔSVI, percent changes in stroke volume index; ΔSVV, percent changes in stroke volume variation n = 40; mean (95% confidence interval), p-value to the AUC.

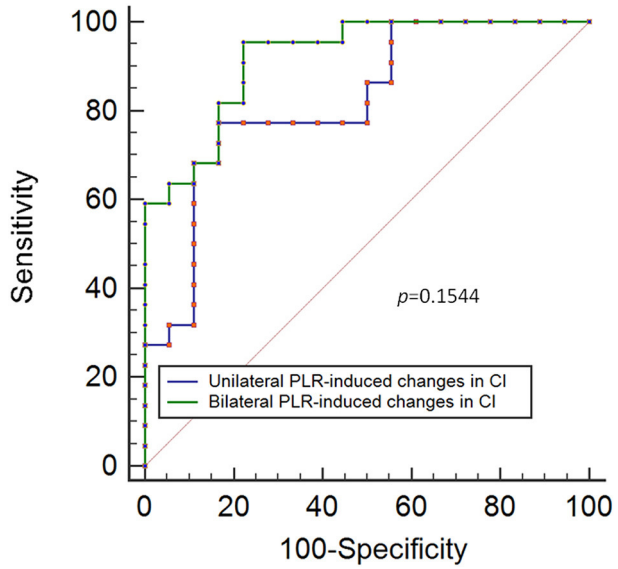

FIGURE 6 | ROC curves showing the ability of changes in CI induced by unilateral PLR and bilateral PLR to predict an increase in the CI of ≥ 15% during volume expansion. ROC: receiver operating characteristic; CI, cardiac index; PLR, passive leg raising.

Unilateral PLR may avoid this issue and still provide good volume forecasting.

There are some limitations to this study. First, performing the PLR test requires the ProAQT/Pulsioflex to estimate CI, which is invasive. Second, when the unilateral PLR test was performed, one of the lower limbs was manually lifted by holding the patients' heels. However, the maneuver was performed gently to prevent possible pain from lifting the leg. One patient was still excluded because of pain. There were only seven patients with septic shock, and none were placed under vasopressor support. Thus, these findings cannot be extrapolated to patients with septic shock who receive vasopressor support. Finally, this study was conducted using pro-AQT algorithms, and therefore, our results cannot be extrapolated to other algorithms. The hemodynamic parameters were average values obtained during the last 12 s. At any timepoint, the values resulted from both the former autocalibration and the pulse contour assessment that was run afterward. Data lag was inevitable.

CONCLUSION

Δ*CI* >7.5% induced by unilateral PLR may be able to predict fluid responsiveness in spontaneously breathing patients. In addition, the significance of this study may not lie in how accurately CI changes resulting from unilateral PLR can determine whether the volume response is positive, but may stem from the presentation of a new method that can be used to predict fluid responsiveness. This is especially true for

patients who cannot undergo bilateral PLR, but are eligible for unilateral PLR.

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 Ethics Committees of Shanghai Cancer Center, Fudan University, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZhiZ, ZhoZ, QL, and BZ: conception and design. LS, PW, and SZ: administrative support. ZX, QX, and FL: provision of study materials or patients. ZhiZ and ZhoZ: collection and assembly of data, data analysis, and interpretation. All authors wrote the manuscript and approved the final manuscript.

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Simple Death Risk Models to Predict In-hospital Outcomes in Acute Aortic Dissection in Emergency Department

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Objective: We sought to find a bedside prognosis prediction model based on clinical and image parameters to determine the in-hospital outcomes of acute aortic dissection (AAD) in the emergency department.

Methods: Patients who presented with AAD from January 2010 to December 2019 were retrospectively recruited in our derivation cohort. Then we prospectively collected patients with AAD from January 2020 to December 2021 as the validation cohort. We collected the demographics, medical history, treatment options, and in-hospital outcomes. All enrolled patients underwent computed tomography angiography. The image data were systematically reviewed for anatomic criteria in a retrospective fashion by three professional radiologists. A series of radiological parameters, including the extent of dissection, the site of the intimal tear, entry tear diameter, aortic diameter at each level, maximum false lumen diameter, and presence of pericardial effusion were collected.

Results: Of the 449 patients in the derivation cohort, 345 (76.8%) were male, the mean age was 61 years, and 298 (66.4%) had a history of hypertension. Surgical repair was performed in 327 (72.8%) cases in the derivation cohort, and the overall crude in-hospital mortality of AAD was 10.9%. Multivariate logistic regression analysis showed that predictors of in-hospital mortality in AAD included age, Marfan syndrome, type A aortic dissection, surgical repair, and maximum false lumen diameter. A final prognostic model incorporating these five predictors showed good calibration and discrimination in the derivation and validation cohorts. As for type A aortic dissection, 3-level type A aortic dissection clinical prognosis score (3ADPS) including 5 clinical and image variables scored from −2 to 5 was established: (1) moderate risk of death if 3ADPS is <0; (2) high risk of death if 3ADPS is 1–2; (3) very high risk of death if 3ADPS is more than 3. The area under the receiver operator characteristic curves in the validation cohorts was 0.833 (95% CI, 0.700–0.967).

Conclusion: Age, Marfan syndrome, type A aortic dissection, surgical repair, and maximum false lumen diameter can significantly affect the in-hospital outcomes of AAD. And 3ADPS contributes to the prediction of in-hospital prognosis of type A aortic

dissection rapidly and effectively. As multivariable risk prediction tools, the risk models were readily available for emergency doctors to predict in-hospital mortality of patients with AAD in extreme clinical risk.

Keywords: acute aortic dissection (AAD), in-hospital outcomes, maximum false lumen diameter, site of intimal tear, pericardial effusion, nomogram

INTRODUCTION

Acute aortic dissection (AAD), which belongs to a family of acute aortic syndromes including intramural hematoma (IMH), penetrating aortic ulcer (PAU), and thoracic aortic rupture, is a life-threatening clinical condition associated with high morbidity and mortality rates (1, 2). It requires prompt diagnosis and timely interventional therapy to optimize in-hospital and long-term outcomes. The incidence of AAD in Taiwan China is 4.3 cases per 100,000 people per year, similar to that in Europe and America (3, 4). It is three times more common in men than in women, although women present older than men at the onset of presentation and experience worse outcomes (5–7). Systemic hypertension, atherosclerosis, Marfan syndrome (commonly seen in patients aged < 50 years), cocaine use, bicuspid aortic valve, and iatrogenic causes by far are more frequent risk factors in AAD patients. And more patients are treated with interventional procedures timely: open surgery in type A AAD and endovascular therapy in type B AAD (8–12).

With its wide application and rapid accessibility, computed tomography angiography (CTA) has been the preferred diagnostic imaging modality in acute settings (5, 8). Some image features provided crucial diagnostic information, had prognostic value, and were helpful to optimize treatment. Previous studies on type B AAD suggested that the strongest independent predictors of complications including aneurysmal growth and the need for late intervention were an initial false lumen (FL) diameter $\geq$ 22 mm, a maximal aortic diameter $\geq$ 40 mm, a patent or partially thrombosed FL, and an initial entry tear (ET) $\geq$ 10 mm (13, 14). With these changes in care, the in-hospital mortality for type A AAD has decreased significantly from 31 to 22% (5, 6).

Even with the progress in clinical practice, diagnostic imaging, clinician awareness, and treatment strategy, AAD patients still died of time delay, risk transfer (especially type A AAD patients who are initially referred to community hospitals and then transferred to tertiary hospitals with expertise and whole experience), patient refusal (patients with advanced age, critical comorbidity, and those who cannot afford the operations), and the surgical procedure itself in clinical practice (1, 5, 15, 16). Whereas, early surgical repair can decrease crude mortality, there is sparse data on which patients will benefit from such therapy. Moreover, as emergency doctors in such acute settings, it remains a challenge for us to make a rapid and correct prognosis prediction for AAD patients. This study aimed to find a bedside prognosis prediction model based on clinical and image parameters to determine the in-hospital outcomes of AAD in the emergency department (ED).

Abbreviations: AAD, acute aortic dissection; CTA, computed tomography angiography; ET, entry tear; MFL, maximum false lumen diameter; 3ADPS, 3-Level type A aortic dissection clinical prognosis score; IMH, intramural hematoma; PAU, penetrating aortic ulcer; ED, emergency department; AAS, acute aortic syndrome; CTPA, computed tomography pulmonary angiography; C-index, concordance index; AUC, area under the receiver operating characteristic curve.

MATERIALS AND METHODS

Study Population

The acute aortic syndrome (AAS) database of ED of Zhongshan Hospital, Fudan University, was searched for training cohort patients with clinical suspicion of AAD diagnosed between January 2010 and December 2019 retrospectively. In addition, we prospectively enrolled validation cohort patients with clinical suspicion of AAD diagnosed between January 2020 and December 2021. The diagnostic criterion for AD was a classic double-lumen aorta with a visible intimal tear shown by CTA (17). Patients diagnosed as AAD by local hospitals, but in fact, the angiography in our hospital implied IMH only, PAU, or localized AD were excluded. Patients with incomplete image data, circumstantial evidence (e.g., computed tomography pulmonary angiography (CTPA) or echocardiogram showed the presence of AD), or lack of CTA in our hospital were also excluded. Furthermore, patients who visited our hospital after more than 14 days from symptom onset or postoperative follow-up were not included in this study. A flowchart to illustrate this study is shown in **Supplementary Figure 1**. The Stanford system was used to distinguish the anatomical classification of the affected aorta (18). The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (Shanghai, China). The informed consent was obtained from patients or their legal surrogates before enrolment.

Clinical and Image Parameters

All patients in two cohorts received standard medical treatment in ED, including blood pressure control, heart rate control, and pain relief when necessary (19). We collected the demographics, medical history, treatment options, and in-hospital outcomes. All enrolled patients underwent CTA in our hospital. A series of CT images were collected, including the extent of the dissection, the site of the intimal tear, the ET diameter, the maximal aortic diameter, the maximum false lumen diameter (MFL, the false lumen diameter of the aortic segment where the ratio of true lumen diameter to false lumen diameter is the most minor) (**Supplementary Figure 2**), and the presence of pericardial effusion. Three professional radiologists analyzed the image data systematically.

Statistical Analysis

Shapiro–Wilk test was used for testing the normality of all continuous variables. Normally distributed continuous variables were expressed as means ± SD, while abnormally distributed continuous variables were expressed as median (the 25th and 75th quartiles). Categorical variables were presented as frequencies and percentages (%). To determine significant variables between surviving and non-surviving groups in AAD and type A AAD derivation cohort, chi-squared tests were performed for categorical variables, and Wilcoxon rank-sum and one-way ANOVA tests were performed for continuous variables. Logistic regression was performed to develop fast-to-use prognostic models for AAD and type A AAD patients. All analyses were conducted using R (version 3.6.3) and SPSS (version 25). All statistical analyses were two-sided, and the significance level was set to $p < 0.05$.

Derivation and Validation of a Prognostic Model for AAD

The variables significantly associated with mortality in the AAD derivation cohort were enrolled into the multivariable regression. The AAD prognostic model was constructed based on the significant variables obtained from the multivariable analysis. The likelihood ratio test was used to compare the goodness-of-fit of nested models. The concordance index (C-index) was used to assess the discrimination performance of the nomogram, while the calibration curve was used to analyze the agreement between the nomogram and actual observation. The accuracy of the model was assessed by analyzing the area under the receiver operating characteristic curve (AUC). The prediction model was validated first internally by using 20 repetitions of 10-fold cross-validation within the derivation cohort, and then externally in the validation cohort by using predictions based on the derivation cohort. In the internal validation, discrimination and calibration of the model were assessed *via* cross-validated AUC and Nagelkerke *R* square. In the external validation, model performance was assessed by the same measures used for the primary analysis.

Derivation and Validation of 3ADPS for Type A AAD

Logistic regression was also performed to screen for risk factors in the type A AAD derivation cohort. Then 3-level type A aortic dissection clinical prognosis score (3ADPS) was constructed based on the significant variables obtained from the multivariable analysis. We assigned points for each variable according to the regression coefficient. The AUC was used to assess the accuracy of 3ADPS.

RESULTS

Baseline Characteristics of AAD Patients in the Derivation and Validation Cohorts

A total 939 patients who presented with AAD from January 2010 to December 2021 were collected. After excluding patients with incomplete image data, diagnosed as IMH or PAU, and visiting our hospital after more than 14 days from symptom onset and postoperative follow-up, 449 patients were enrolled in the derivation cohort and 120 in the validation cohort (**Supplementary Figure 1**).

TABLE 1 | Baseline characteristics of AAD patients in the derivation and validation cohorts.

	Derivation cohort ($n = 449$)	Validation cohort ($n = 120$)	*P*-Value
Age	61 (50, 69)	58 (47, 67)	0.107
Sex, male	345 (76.8%)	93 (77.5%)	0.878
Stanford A	132 (29.4%)	67 (55.8%)	<0.001
Stanford B	317 (70.6%)	53 (44.2%)	<0.001
Hypertension	298 (66.4%)	81 (67.5%)	0.816
Diabetes	35 (7.8%)	9 (7.5%)	0.914
MFS	13 (2.9%)	7 (5.8%)	0.121
History of aortic aneurysm	77 (17.1%)	8 (7.4%)	0.004
Surgical repair	327 (72.8%)	98 (81.7%)	0.048
Open surgery	91 (20.3%)	50 (41.7%)	<0.001
Endovascular therapy	237 (52.8%)	47 (39.2%)	0.008
In-hospital mortality	49 (10.9%)	14 (11.7%)	0.815

Of the 449 patients in the derivation cohort, 345 (76.8%) cases were male, and the mean age was 61 years. And 298 (66.4%) cases had a history of hypertension, 13 (2.9%) had a history of MFS, and 77 (17.1%) had a history of aortic aneurysm (AA). Surgical repair was performed in 327 (72.8%) cases in the derivation cohort. And the overall crude in-hospital mortality was 10.9%. In the validation cohort, 93 of 120 (77.5%) were male, and the mean age was 58. Baseline characteristics of the enrolled patients are presented in **Table 1**.

It should be noted that the number of patients with type A AAD and patients undergoing surgical repair in the validation cohort were significantly higher than those in the derivation cohort. As we all know, an institutional combination of multidisciplinary expertise in complex surgical repair and established resources and infrastructure are indispensable for the successful estimation and management of AAD, primarily type AAD (20, 21). More patients with type A AAD had been thus transferred to our hospital in recent 2 years, and the operation rate had also increased.

Comparison Between Surviving and Non-surviving AAD Patients in the Derivation Cohort

The comparison of clinical characteristics and image parameters between surviving and non-surviving groups of AAD patients in the derivation cohort are shown in **Supplementary Table 1**. There was no significant difference in gender and age between the two groups. Patients with type A AAD and Marfan syndrome (MFS) had a high risk of death ($p < 0.001$), with type A AAD in 99/400 (24.8%) patients of survivors and 33/49 (67.3%) of non-survivors and MFS in 8/400 (2%) patients of survivors and 5/49 (10.2%) of non-survivors. More patients in the surviving group received surgical repair (75.8 vs. 46.9%, $p < 0.001$) and had a

longer time window from symptom onset to operation (8 vs. 4 days, $p < 0.001$).

Image parameters showed that patients with dissection involving the aortic sinus, brachiocephalic trunk, left common carotid artery, and left subclavian artery had a worse prognosis (14.3 vs. 3, 28.6 vs. 8, 24.5 vs. 7.5, 22.4 vs. 8.5%, respectively, $p < 0.002$). Patients with an entry tear at the ascending aorta had a high risk of death (34.7 vs. 12.5%, $p < 0.001$). And the ET diameter and MFL diameter in the non-surviving patients were dramatically larger than that in the surviving group (7.1 vs. 3.9 mm, $p = 0.001$; 27.5 vs. 24.5 mm, $p = 0.019$, respectively). Additionally, patients with pericardial effusion were much more in the non-surviving group than in the surviving group (28.6 vs. 10%, $p < 0.001$).

TABLE 2 | Multivariate logistic analysis of potential prognostic factors in AAD patients.

Factor	Multivariable OR (95% CI)	*P*-Value
Age	1.051 (1.009, 1.094)	**0.017**
Stanford A	22.354 (4.665, 107.107)	**<0.001**
MFS	7.223 (1.185, 44.033)	**0.032**
Surgical repair	0.231 (0.090, 0.594)	**0.002**
Pericardial effusion	3.423 (1.124, 10.428)	**0.030**
Site of intimal tear		1.151
0 (none)		
1 (ascending aorta)		
2 (aortic arch)		
3 (thoracoabdominal aorta)		
Entery tear diameter	1.017 (0.939, 1.103)	0.676
Maximum false lumen diameter	1.049 (1.009, 1.092)	**0.017**

Bold values are used to indicate the significance of these indexes in multivariate analysis (P < 0.05).

Comparison Between Surviving and Non-surviving Type A AAD Patients in the Derivation Cohort

The comparison of clinical characteristics and image parameters between surviving and non-surviving groups of type A AAD patients in the derivation cohort are shown in **Supplementary Table 2**. Undoubtedly, more patients in the surviving group received surgical repair (79 vs. 37.5%, $p < 0.001$), and most of the patients in the surviving group received open surgery (71 vs. 37.5%, $p = 0.001$).

Image parameters showed that the ET diameter and MFL diameter in the non-surviving patients were relatively more extensive than in the surviving group (8.1 vs. 5 mm, $p =$

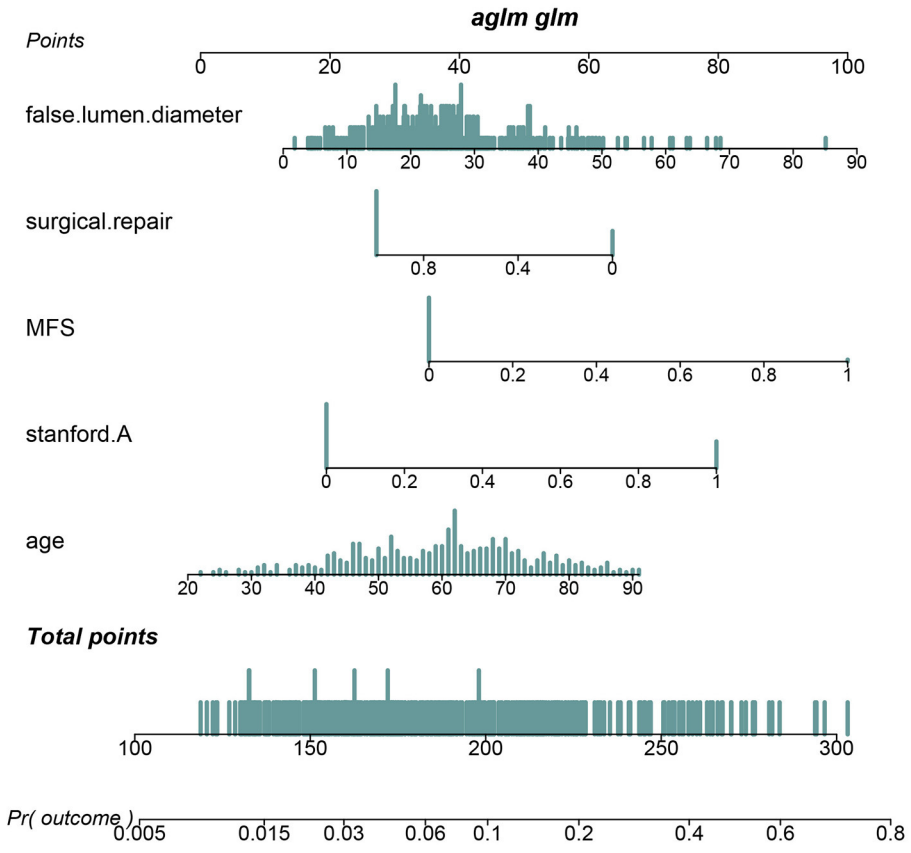

FIGURE 1 | A nomogram for predicting the in-hospital prognosis of patients with AAD.

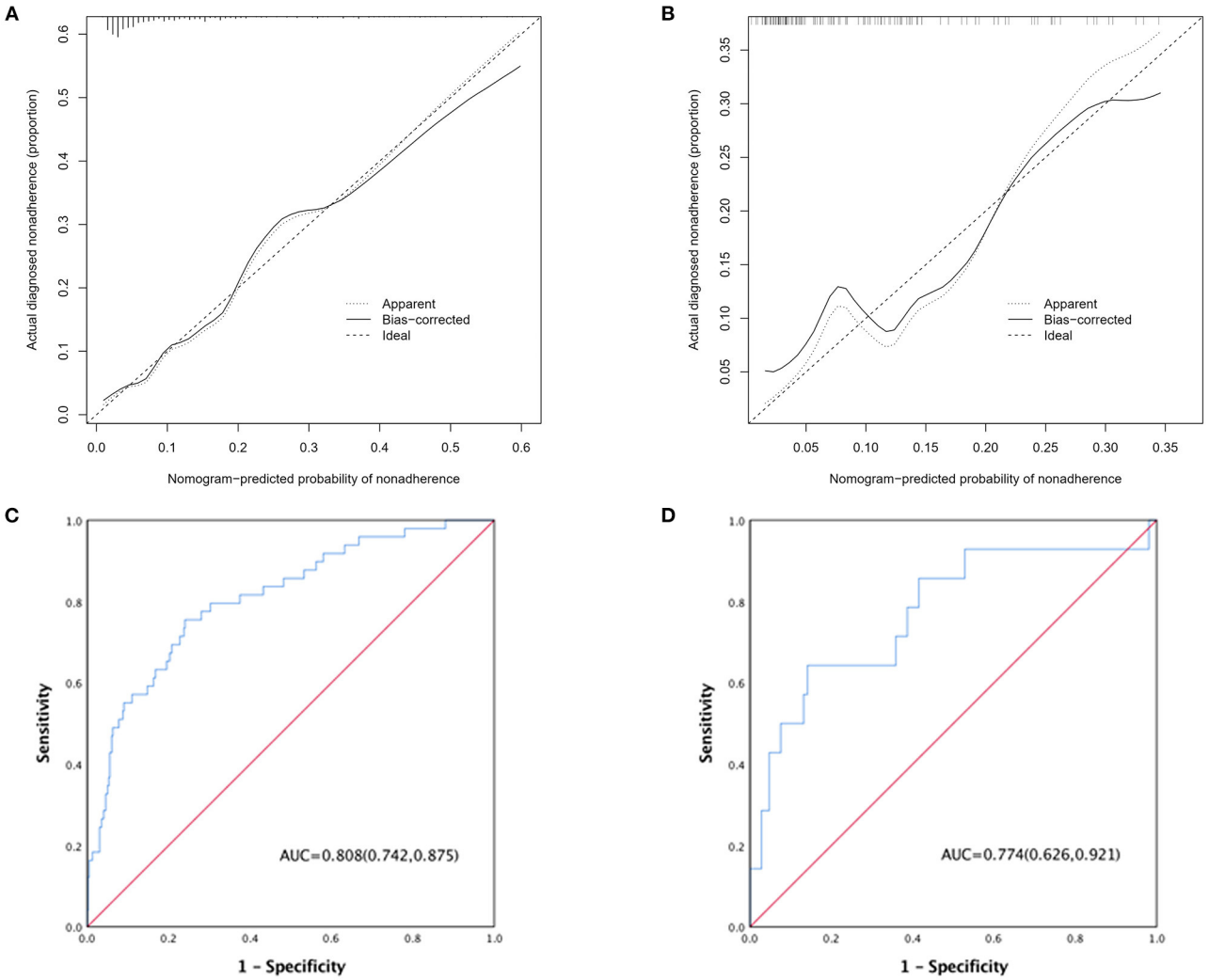

FIGURE 2 | (A) Calibration curve of the AAD nomogram in the derivation cohort, which depicts the calibration of the nomogram in terms of the agreement between the predicted risk of death and observed outcomes. The 45° dotted line represents an ideal prediction, and the solid line represents the bias-corrected predictive performance of the nomogram. The closer the solid line fits to the ideal line, the better the predictive accuracy of the nomogram; **(B)** calibration curve in the validation cohort; **(C)** ROC curve of the AAD nomogram in the derivation cohort; **(D)** ROC curve in the validation cohort.

0.003; 27.4 vs. 24.1 mm, $p = 0.096$, respectively). There was no significant difference in other image variables for type A AAD.

Logistic Regression Analysis and Final Prognostic Model Derivation and Validation in AAD Patients

Multivariate logistic regression analysis was performed to predict the in-hospital mortality in AAD patients. It showed that predictors of in-hospital mortality included age [odds ratio (OR), 1.051; 95% confidence interval (CI), 1.009–1.094; $p = 0.017$], type A AAD (OR, 22.354; CI, 4.665–107.107; $p < 0.001$), Marfan syndrome (OR, 7.223; CI, 1.185–44.033; $p = 0.032$), pericardial effusion (OR, 3.423; CI, 1.124–10.428; $p = 0.030$), and MFL diameter (OR, 1.049; CI, 1.009–1.092; $p = 0.017$). Surgical repair was protective against in-hospital death (OR, 0.231; CI, 0.090–0.594; $p = 0.002$; **Table 2**).

Pericardial perfusion was removed from consideration because it failed to offer a significant improvement in model fit, as suggested by the likelihood ratio test (**Supplementary Table 3**). Hence, the final prognostic model based on five variables, namely, age, type A AAD, Marfan syndrome, surgical repair, and MFL diameter, was constructed (**Figure 1**). The C-index value was 0.808 (0.742–0.875) in the derivation cohort and 0.774 (0.626–0.921) in the validation cohort. The calibration curves of the final prognostic model showed high consistencies between the predicted and observed survival probability in both the derivation (**Figure 2A**) and validation cohorts (**Figure 2B**). The AUCs of the final prognostic model in the derivation and validation cohorts were 0.808 (0.742–0.875; **Figure 2C**) and 0.774 (0.626–0.921; **Figure 2D**), respectively, which implied successful

TABLE 3 | Three-level type A aortic dissection clinical prognosis score (3ADPS).

Variable	Regression coefficient		Points
MFS	2.211	No	0
		Yes	2
Surgical repair	−2.197	No	0
		Yes	−2
Pericardial effusion	0.821	No	0
		Yes	1
Maximum false lumen diameter < 22 mm	Reference	<22 mm	0
22 mm ≤ False lumen diameter < 45 mm	1.704	22–45 mm	1
45 mm ≤ False lumen diameter	3.721	≥45 mm	3
Intimal tear in the aortic arch or descending aorta	2.689	No	0
		Yes	2
In-hospital death risk, total			
Moderate risk of death (<20%)	<0		
High risk of death (20–50%)	0–2		
Very high risk of death (>50%)	≥3		

discrimination. The model achieved an AUC of 0.7918 and an *R* square of 0.1515 in the 10-fold cross-validation.

Logistic Regression Analysis and 3ADPS Derivation and Validation in Type A AAD Patients

Multivariate logistic regression analysis of type A AAD patients showed that predictors of in-hospital mortality included Marfan syndrome (OR, 17.810; CI, 2.021–97.390; $p = 0.01$), the site of intimal tear ($p = 0.001$), pericardial effusion (OR, 3.431; CI, 1.008–11.675; $p = 0.049$), and MFL diameter (OR, 1.069; CI, 1.016–1.125; $p = 0.01$). Similarly, surgical repair was protective against in-hospital death (OR, 0.075; CI, 0.021–0.269; $p < 0.001$; **Supplementary Table 4**). The above 5 variables were included in the final model (3-level type A aortic dissection clinical prognosis score, 3ADPS), and we assigned points for each of them according to the regression coefficient. The final model was presented in **Table 3**.

The in-hospital outcome of type A AAD evaluated by 3ADPS and the distribution of 3ADPS in the derivation cohort were presented in **Figure 3**. According to the predefined cutoff values, a 3ADPS < 0 represents a moderate risk of death (<20%), a 3ADPS of 0–2 represents a high risk of death (<50%), a 3ADPS more than 3 represents a very high risk of death (50% or greater) (**Table 3**). In the derivation cohort, the AUC was 0.871 (0.807–0.935) (**Figure 4A**).

For the validation cohort, the in-hospital outcome of type A AAD evaluated by 3ADPS and the distribution of 3ADPS in the derivation cohort are presented in **Figure 3**. In the validation cohort, the AUC was 0.833 (0.700–0.967) (**Figure 4B**).

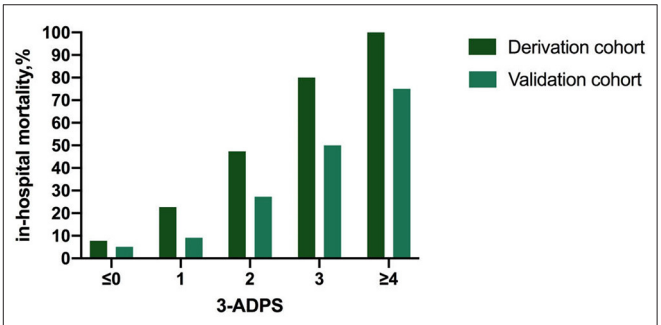

FIGURE 3 | The in-hospital outcome of type A AAD was evaluated by 3ADPS and the distribution of 3ADPS in the derivation and validation cohorts.

DISCUSSION

It is reported that untreated patients with AAD have a significant mortality rate of 1–2% per hour immediately after symptom onset, primarily type A AAD (3, 5). Previous studies showed that in-hospital mortality for type A AAD was up to 26% for open surgical procedures and 58% for medical management (6, 22). Therefore, it is necessary but full of challenges for emergency doctors to determine the in-hospital prognosis of AAD patients for successful management. This study aimed to construct bedside risk prediction tools mainly based on image parameters to determine the in-hospital outcomes of AAD in ED.

This study identified that age, type A AAD, Marfan syndrome, surgical repair, pericardial effusion, and MFL diameter were independent predictors of mortality in AAD patients. The clinical symptoms and signs of elderly patients are often atypical, leading to delayed diagnosis and a bad prognosis. IRAD reported that patients aged ≥ 70 years had an overall higher in-hospital mortality than patients aged < 70 years (43 vs. 28% for type A AAD, 16 vs. 10% for type B AAD, $p < 0.05$) (5, 17, 23), which was consistent with our results. It is well-known that Marfan syndrome is the most common heritable connective tissue aortic disorder and causes aortic root enlargement in 60–80% of patients (11, 24). Therefore, type A was more

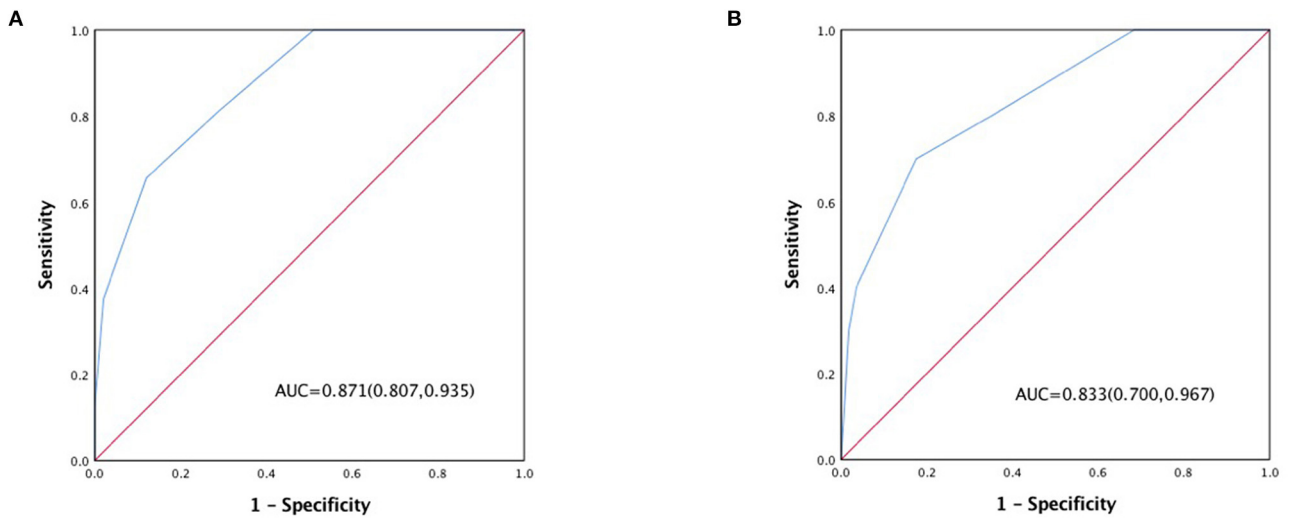

FIGURE 4 | (A) ROC curve of the 3ADPS in the derivation cohort and **(B)** ROC curve in the validation cohort.

frequent than type B in patients with Marfan syndrome, and the majority of patients with type A AAD and Marfan syndrome with dissection involving only the ascending aorta or more segment and aortic rupture had higher in-hospital mortality if not surgically repaired in time. This study confirmed it in the derivation cohort (mortality rate in non-surviving patients 10.2 vs. 2% in surviving patients, $p < 0.001$, **Supplementary Table 1**).

There is a consensus that AAD is an urgent surgical emergency, primarily type A AAD, and IRAD data have further confirmed that patients treated medically alone had remarkably higher in-hospital mortality than those who received surgical repair simultaneously (58.1 vs. 23.9%). Since the late 1990s, most patients with type A AAD have been managed surgically, rising from 79 to 90% (5, 8). More operative procedures, including a valve-sparing root repair, an ascending with hemi or complete arch replacement, and frozen elephant trunk deployment if needed, were implemented in recent years. And in-hospital mortality rate of type A AAD decreased significantly from 31 to 22% over time, mainly because of decreased surgical mortality (8, 15). Endovascular management tends to be the first-line therapy for type B AAD patients complicated by malperfusion syndrome, progression of dissection, rapid aortic expansion, or instability hemodynamic, while medical management was still reserved for patients who had an uncomplicated course (14, 25). This study implied that more AAD patients in the surviving group received surgical repair than the non-surviving group (75.8 vs. 46.9%, $p < 0.001$), and more type A AAD patients in the surviving group received open surgery compared with the non-surviving group (71 vs. 37.5%, $p = 0.001$), which were following previous reports.

The presence of pericardial effusion indicates the destruction of the integrity of the outer aortic wall. Patients with pericardial effusion are more likely to have a periaortic hematoma, and pericardial tamponade may occur when pericardial effusion suddenly increases. The mortality of patients with pericardial tamponade remained dramatically high, and periaortic hematomas were identified to be an independent predictor for AAD (26, 27). CTA can easily identify the presence of pericardial effusion, and echocardiography can also be performed. These image findings provided important diagnostic information, had prognostic value, and were helpful to optimize treatment. Bossone, Eduardo et al. found that evidences of pericardial effusion, pericardial tamponade, and periaortic hematoma were more frequent in non-survivors (51.1 vs. 40.9%, $p = 0.04$; 34.5 vs. 11.3%, $p < 0.001$; 23.8 vs. 14.7%, $p = 0.02$, respectively), (28). As expected, both the univariate and multivariate regression analysis of this study suggested that pericardial effusion was a satisfactory predictor of mortality in patients with AAD [3.600 (1.787, 7.254), $p < 0.001$; 3.423 (1.124, 10.428), $p = 0.03$; respectively]. Thus, the presence of pericardial effusion indicates a poor prognosis and should warrant urgent surgical intervention.

Several image variables such as initial false lumen diameter and patent or partially false lumen thrombosis have been proved to be high-risk features indicating unstable disease (including aneurysmal growth and need for late intervention) in apparently stable type B AAD patients. In addition, a larger false lumen implied poorer organ perfusion and was confirmed to be associated with an unsatisfactory long-term survival in type B AAD (14, 29). In contrast, few studies have focused on the relationship between false lumen diameter and in-hospital prognosis in type A AAD. This study showed that larger maximum false lumen (MFL) diameter was more frequent in non-survivors both in AAD and type A AAD derivation cohorts (27.5 vs. 24.5 mm, $p = 0.019$; 27.4 vs. 24.1 mm, $p = 0.096$, respectively). Accordingly, multivariate regression analysis also implied MFL is a good predictor of mortality both in AAD and type A AAD derivation cohorts (OR, 1.049, $p = 0.017$; OR, 1.06927.4, $p = 0.01$, respectively). In addition, patients with an intimal tear originating in the aortic arch or thoracoabdominal aorta were confirmed to suffer a poor in-hospital outcome in the type A AAD derivation cohort, which was due to the greater extent of

dissection and the independent entity from the perspective of the pathology undoubtedly. Also, the site of the intimal tear (aortic arch and thoracoabdominal aorta) was a perfect predictor of mortality in the type A AAD derivation cohort by multivariate regression analysis (OR, 71.738, $p = 0.001$; OR, 136.125, $p < 0.001$, respectively).

Once the patient with AAD presents to the emergency room, simple bedside tools for estimating in-hospital outcomes were helpful for emergency doctors to make a rapid and correct prognosis prediction and ensure management without any delay. Meanwhile, family members could also be fully informed of the patient's risk conditions and consider available treatment. The final prognostic model of AAD incorporating age, Marfan syndrome, type A AAD, surgical repair, and MFL diameter, showed good calibration and discrimination in the derivation and validation cohorts. As for type A AAD, 3ADPS was confirmed acceptable calibration and accuracy. As multivariable risk prediction tools, the models were readily available for emergency doctors to predict in-hospital mortality of AAD patients in extreme clinical risk.

Nevertheless, this study has some limitations. It is a single-center study and lacks external validation cohorts. The population for each cohort is relatively small. And there was a bias in the number of type A and B AAD between the two cohorts, which was due to more patients with type A AAD transferred to our hospital because of the multidisciplinary expertise and excellent infrastructure. The nomogram and 3ADPS strategy need to be formally validated in a more enormous prospective, multicenter implementation study.

CONCLUSIONS

The age, Marfan syndrome, type A AAD, surgical repair, and MFL diameter can significantly affect the in-hospital outcomes of AAD. And 3ADPS contributes to the prediction of in-hospital prognosis of type A AAD rapidly and effectively. The simple bedside tools for estimating in-hospital outcomes were helpful for emergency doctors to make a rapid and correct prognosis prediction for AAD patients in extreme clinical risk and then ensure management without any delay.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the Ethics Committee of Zhongshan Hospital Fudan University (Shanghai, China) (Record Number B2019-319R). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GG and CY conceived, designed, and coordinated the study. LX and YH drafted this manuscript. MT, ZD, XZ, and SG were responsible for collecting and measuring the imaging data. DC, YY, and FL were responsible for collecting clinical data. YZ and CC were responsible for data analysis. All authors read, approved, and contributed to 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.2022.890567/full#supplementary-material

Supplementary Figure 1 | A flowchart of this study.

Supplementary Figure 2 | (A) On the oblique coronary section, line-a is a line drawn parallel to the curve aortic ascendens or arch, and line-b is a line perpendicular to line-a. The red arrow shows the direction of blood flow in the true lumen, and the dark red arrow shows the direction of blood flow in the false lumen; **(B)** On cross-section, line-a is a line drawn parallel to the curve aortic ascendens or arch, and line-b is a line perpendicular to the line-a. A reproducible manual method was used to measure the maximal diameter of FL and the minimal diameter of TL on line-b.

Supplementary Table 1 | Comparison between surviving and non-surviving AAD patients in the derivation cohort.

Supplementary Table 2 | Comparison between surviving and non-surviving type A AAD patients in the derivation cohort.

Supplementary Table 3 | Likelihood ratio test of different prediction models regarding in-hospital outcome of AAD in the training cohort. AAD, acute aortic dissection; MFS, Marfan syndrome; MFL, maximum false lumen; AIC, Akaike Information Criterion.

Supplementary Table 4 | Multivariate logistic analysis of potential prognostic factors in type A AAD patients.

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Conflict of Interest: ZD was employed by Suzhou Zhi Zhun Medical Technology Co., Ltd., and SG was employed by CANON Medical Systems (China) Co., Ltd. Shanghai Huidr Information Technology Co., Ltd assisted in following up with the patients.

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

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A Height-Based Dosing Algorithm of Bupivacaine in Spinal Anesthesia for Decreasing Maternal Hypotension in Cesarean Section Without Prophylactic Fluid Preloading and Vasopressors: A Randomized-Controlled Non-Inferiority Trial

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Background: There is a high incidence of maternal hypotension in spinal anesthesia for cesarean section. The aim of the study is to investigate whether there is a height-based dosing algorithm of bupivacaine that provides adequate anesthesia with less maternal hypotension.

Methods: There were 2 groups of 280 parturients who did not receive prophylactic fluid preloading: Test and Conventional group. In Test group, a height based dosing algorithm was used to confirm the dose of bupivacaine in parturients without prophylactic vasopressors. In the Conventional group, a constant dose of bupivacaine was used. The complications and quality of anesthesia were evaluated.

Results: In the Conventional group, the shorter participants had higher incidence of hypotension, faster sensory block time, and more participants with complete motor block ($p = 0.030$, 2.957×10^{-14}, and 0.012). In the Test group, the incidence of hypotension, sensory block time, and number of participants with complete motor block did not change with height ($p = 0.199$, 0.617, and 0.209). The height-based dosing algorithm of bupivacaine decreased the incidence of hypotension ($p = 0.004$), induced lower sensory block level and less degree of motor block ($p = 3.513 \times 10^{-7}$ and 5.711×10^{-11}). The quality of analgesia, quality of muscle relaxation, and degree of intraoperative comfort were similar in both groups ($p = 0.065$, 0.498, and 0.483).

Conclusions: The height influences the dose of bupivacaine in spinal anesthesia; without prophylactic fluid pre-loading and vasopressors, the height-based dosing

algorithm of bupivacaine is suitable, and meets the cesarean section' requirement with less maternal hypotension.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03497364.

Keywords: anesthesia, spinal, bupivacaine, cesarean section, height, hypotension

INTRODUCTION

Spinal anesthesia is popularly applied for cesarean section due to high-quality anesthesia and no inhibitory effect of general anesthetics on the fetus (1, 2). Unfortunately, there is a high incidence of maternal hypotension, which is attributed to special physiological changes in parturients (3) and sympathetic block (1). Mild hypotension may result in a series of side effects [e.g., hypoxemia and acidosis in fetus (4), and nausea, vomiting, and dizziness in parturient] (5). For severe hypotension, the life of the parturient and fetus may be threatened (6). In obstetric anesthesia, it has been deemed to be the Holy Grail for effectively preventing or treating maternal hypotension resulted from spinal anesthesia (2).

For decreasing the maternal hypotension, the fluid preloading (colloid or crystalloid) (7) and/or vasopressors (ephedrine or phenylephrine) (8) is often prophylactically used. In late pregnancy, the blood volume and cardiac load of the parturient significantly increase, which may be further exacerbated by fluid preloading. Ephedrine may increase the incidence of fetal acidosis (9), which may be associated with poor neonatal outcome (10). Phenylephrine may induce bradycardia (11), and decrease cardiac output (8). Consequently, for parturient or fetus, it may be beneficial that avoiding prophylactic fluid preloading and/or vasopressors.

It is controversial whether the patient height is related to the block level for spinal anesthesia. In several studies, there is no statistical association between block level and height (12, 13). The dose of the local anesthetic does not change with height in many studies (1, 4, 14). However, vertebral column length can influence the block level (15). In Norris's study, the height accounts for 10.6% of the variation in the length of the spine, there is a statistical correlation between vertebral column length and height (13). Thus, the block level theoretically depends on height, which is verified in two studies (16, 17). In spinal anesthesia, as the dose of local anesthetic decreases, the block level lowers, the maternal hypotension decreases, but inadequate muscle relaxation and analgesia may increase (18). Based on above analysis, we hypothesize that in spinal anesthesia, even without prophylactic fluid preloading and vasopressors, there is a height-based dosing algorithm of local anesthetic that provides adequate anesthesia for cesarean section with less maternal hypotension.

To test our hypothesis, for cesarean section, spinal anesthesia with bupivacaine was carried out, the dose of bupivacaine was adjusted according to height in this study. In this manner, for cesarean section, we attempted to found a suitable dose of bupivacaine in spinal anesthesia.

MATERIALS AND METHODS

General

Ethical approval for this study protocol was obtained from the Ethics Committee of Shenzhen People's Hospital of Jinan University, and this study was registered at ClinicalTrials.gov on April 12, 2018 (NCT03497364). The full protocol was available in pubmed (https://www.ncbi.nlm.nih.gov/pubmed/31101694). **Figure 1** provided the study flow chart. Parturients (scheduled for cesarean section, aged 18–45 years) were recruited after February 8, 2018, and were randomly divided into 2 groups, Test and Conventional groups. Before anesthesia, all parturients were prohibited to drink clear liquids for 2–3 h, and eat non-fatty solids for 6–8 h. Written informed consent was acquired from all parturients. Parturients with pre-eclampsia, cardiovascular disease, systolic blood pressure (SBP) < 90 mmHg, multiple births, placental abnormalities, fetal abnormalities, and combined spinal-epidural anesthesia (CSE) contraindications were excluded from the study.

Intervention

Before entering the operation room (OR), the heart rate (HR), and blood pressure of the parturients were measured. Once entering the OR, electrocardiogram, HR, blood pressure, and SPO_2 were monitored. Supplementary oxygen (2 L/min) was given via a facemask. In the forearm vein, venipuncture was carried out. Then, Ringer's lactate (1,000 ml) was slowly infused into parturients in both groups (2 ml/kg/h).

To furthest decrease incomplete analgesia and muscle relaxation, we performed CSE instead of spinal anesthesia in this study. CSE was performed at the L3–4 interspace in left lateral position by the experienced doctors, who had been trained about how to more identically perform CSE before starting this study. Isobaric bupivacaine was marketed in our hospital. We were accustomed to use isobaric bupivacaine in spinal anesthesia for cesarean section all the time. In the Test group, 1.15–1.7 ml isobaric bupivacaine (5 mg/ml) from ChaoHui drug company (ShangHai, China) was applied. The bupivacaine dose was adjusted according to the height of the parturients (0.05 ml/2–3 cm, **Table 1**) (19). In the Conventional group, 1.8 ml isobaric bupivacaine (5 mg/ml) was applied (20). The direction of side opening on spinal needle was toward the cephalic in both groups. After intrathecal injection, the parturients were immediately placed the supine position with a left lateral tilt (15 degree). Ringer's lactate was quickly infused in both groups (10 ml/kg/h) (21). Prophylactic phenylephrine was infused via micropump (0.25 $\mu g.kg^{-1}.min^{-1}$ (i.e., 2.5 ml/h) in the Conventional group (22). Normal saline was infused (2.5 ml/h) in the Test group. Prophylactic fluid preloading was not applied for all participants.

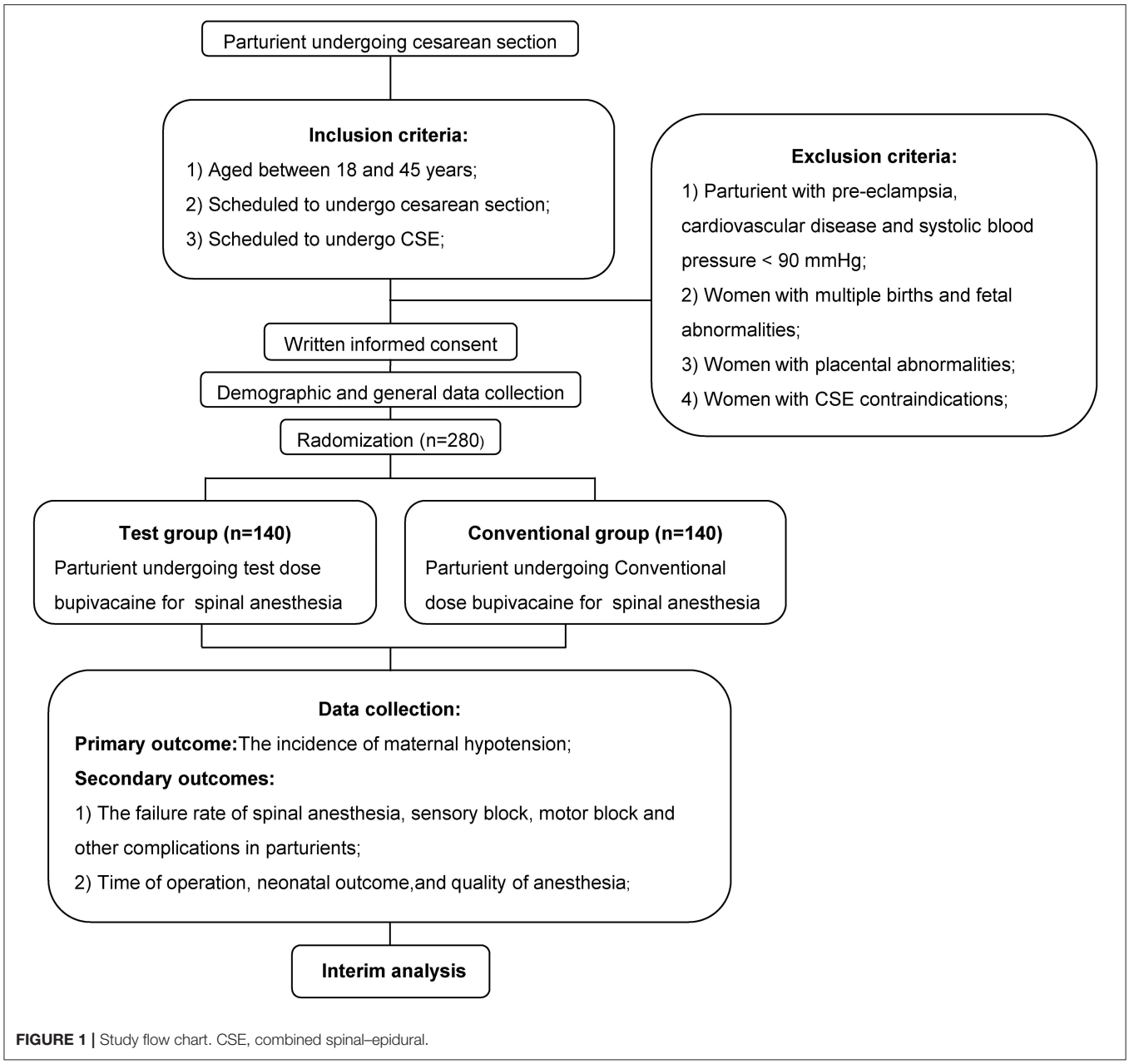

FIGURE 1 | Study flow chart. CSE, combined spinal–epidural.

Maternal hypotension was defined by SBP < 90 mmHg or 70% of baseline value. From anesthesia initiation to delivery, when maternal hypotension occurred, this parturient was defined as a parturient with hypotension. Maternal hypotension was treated with phenylephrine (100 μg). Bradycardia (<60 beat/min) was treated with atropine (0.5 mg). Nausea and vomiting were treated with metoclopramide (10 mg). According to anatomical structure, for cesarean section, it is recommended that the highest sensory block level should reach dermatome level dominated by the fourth thoracic nerve (T4) (23). However, in different studies, the highest sensory block level is required to reach T4, T5, T6, or T8 (5, 14, 20, 24–26). In some parturients, even though the highest sensory block level reaches T4, they still feel slight pain (23). In our clinical practice, when the highest sensory block level reaches T8 at 10 min after anesthesia, the anesthesia is adequate. Therefore, at 10 min after anesthesia, if the sensory block level did not reach T8, spinal anesthesia was regarded as a failure (24, 25). The parturients without successful spinal anesthesia were excluded from the study. For parturients without successful spinal anesthesia, 2% lidocaine + 0.75% ropivacaine (15 ml) was given via epidural space until the level of sensory block is not lower than T8 (24, 25) or the anesthetic technique was changed to general anesthesia. For parturients with successful spinal anesthesia, when the parturients felt pain after taking out the fetus, fentanyl (0.1 mg) via a vein and/or 2% lidocaine + 0.75% ropivacaine (15 ml) via the epidural space were carried out.

Data Acquisition

Before anesthesia, demographic data, baseline data, and general data were recorded. After bupivacaine injection, the HR, blood pressure, respiratory rate and SPO_2 were immediately collected. The level of sensory block was measured via hypoalgesia. If the hypoalgesia level reached T8, anesthesia was considered to be sufficient for cesarean section (24, 25). Motor block was evaluated with the modified Bromage scale (26).

After taking out the fetus, APGAR scores at 1 and 5 min were assessed. For blood gas analysis, blood sample was taken from umbilical artery. The complications (hypotension, dizziness, nausea, vomiting, dyspnea, and bradycardia) were recorded. After cesarean section, the time from anesthesia initiation to skin incision, time from skin incision to delivery and operation duration were computed. The quality of analgesia (judged by the anesthetist), the quality of muscle relaxation (judged by the surgeon) and the degree of intraoperative comfort (judged by the patient via asking how you feel during operation) were recorded as excellent, good, fair, or poor (14).

TABLE 1 | The relationship between the height of the parturient and dose of 0.5% bupivacaine.

Height of parturient (cm)	Dose of 0.5% bupivacaine (ml)
173–174	1.70
170–172	1.65
168–169	1.60
165–167	1.55
163–164	1.50
160–162	1.45
158–159	1.40
155–157	1.35
153–154	1.30
150–152	1.25
148–149	1.20
145–147	1.15

This table was from the published full protocol in BMJ Open (https://www.ncbi.nlm.nih.gov/pubmed/31101694).

Statistical Analysis

Sample Size Calculation

For maternal hypotension, there is an incidence of 30% in Geng et al.'s study (27). A $\geq$ 15% difference in the incidence of maternal hypotension was considered to be significant in a clinical setting. A non-inferiority one-sided test was performed with this equation ($n = \frac{2 \bullet p \bullet (1-p) \bullet (z_{(1-\alpha)} + z_{(1-\beta)})^2}{\Delta^2}$) for sample size calculation (28). Assuming a power of 0.80 and a type I error protection of 0.05, 116 subjects were required in each group. To compensate for dropouts and protocol violations, we planned to recruit at least 280 parturients in this study.

Outcome Analysis

Statistical analysis was performed using SPSS 13.0 software package. All continuous data were presented as the mean (*SD*). With chi-square test, the enumeration data were analyzed. With Student's *t*-test (Normally distributed data) or Mann-Whitney U-test/Kruskai-Wallis H (Non-normally distributed data), the continuous data were analyzed. A p-value <0.05 were deemed significant.

TABLE 2 | Parturient characteristics.

	Test group ($n = 127$)	Conventional group ($n = 131$)	Z, t or χ^2	p
Age (years)	32.181 (5.417)	31.122 (4.785)	−1.665	0.096
Height (cm)	158.854 (4.875)	158.657 (4.834)	0.327 #	0.744
Weight (kg)	67.053 (9.551)	68.221 (10.249)	−0.395	0.693
Weeks of gestation	37.504 (2.407)	37.939 (2.063)	−1.854	0.064
Previous cesarean	71	67	0.412	0.521
Initial SBP (mmHg)	123.221 (16.468)	119.412 (14.533)	−1.509	0.131
Initial HR (beats/min)	86.969 (13.751)	84.336 (13.138)	−1.704	0.084
Time from anesthesia initiation to skin incision (min)	19.024 (7.411)	19.046 (7.651)	−0.177	0.860
Time from skin incision to delivery (min)	8.394 (4.794)	7.565 (4.127)	−1.711	0.087
Operation duration (min)	55.732 (15.938)	54.710 (13.967)	−0.153	0.878
Concomitant disease				
Hypertension	10	9	0.005	0.944
Diabetes	25	23	0.078	0.780
HGB < 90 g/L	3	7	0.842	0.359
Hyperthyroidism	2	1	0.001	0.978
Hypothyroidism	1	4	0.754	0.385
Abnormal liver function	1	0	2.414×10^{-4}	0.988
Macrosomia	0	2	0.473	0.491

Indicated that Student's t-test was used. For other continuous data, Mann-Whitney U-test was used.

TABLE 3 | Incidence of side effects in parturients.

	Test group ($n = 127$)	Conventional group ($n = 131$)	χ^2	p
Hypotension	18	39	8.231	0.004
Number of hypotensive recordings				
0	109	92	14.268	0.003
1–2	16	22		
3–4	2	15		
≥5	0	2		
Dizziness	6	17	4.440	0.035
Nausea	3	12	4.272	0.039
Vomiting	1	6	2.224	0.136
Bradycardia	4	15	5.353	0.021
Dyspnea	0	7	5.098	0.024

TABLE 4 | Characteristics of spinal anesthesia.

	Test group ($n = 127$)	Conventional group ($n = 131$)	Z or χ^2	p
Unsuccessful spinal anesthesia	3	2	0.001	0.979
Time $_{sensoryblocktoT8}$ (min)	4.858 (1.521)	3.733 (1.583)	−6.029	1.647×10^{-9}
Sensory level at 10 min after anesthesia				
>T2	2	16	42.883	3.513×10^{-7}
T2	9	25		
T3	13	29		
T4	24	24		
T5	36	20		
T6	26	14		
T7	13	3		
T8	4	0		
Time $_{completemotorblock}$ (min)	13.053 (7.115)	6.674 (5.400)	8.948	3.618×10^{-19}
Number $_{completemotorblock}$	61	113	41.194	1.379×10^{-10}

RESULTS

Characteristics of Parturients

This study excluded 13 parturients from the Test group and 9 parturients from the Conventional group due to a variety of factors (e.g., unsuccessful spinal anesthesia and protocol violations). The demographic data, general data, baseline data, and concomitant disease of parturients were similar in both groups (**Table 2**).

Complications, Sensory Block, and Motor Block of Parturients

The incidence of hypotension (primary outcome), dizziness, nausea, dyspnea and bradycardia, and number of hypotensive recordings were fewer in Test group than those in Conventional groups (**Table 3**). The incidence of vomiting was no statistically different in both groups (**Table 3**). The sensory block levels of three parturients in Test group and two parturients in Conventional groups were lower than T8 at 10 min after anesthesia (**Table 4**). For sensory block, in comparison with both in Test groups, the time for sensory block to reach T8 (Time $_{sensoryblocktoT8}$) was faster, and the sensory level at 10 min after anesthesia was higher in the Conventional group (**Table 4**). For motor block, 15 parturients in Test group and two parturients in the Conventional groups could not reach complete block, and not be included to compute the time to complete motor block (Time $_{completemotorblock}$). In comparison with both in Test groups, the Time $_{completemotorblock}$ was faster, and the numbers of parturients with complete motor block at 10 min after anesthesia (Number $_{completemotorblock}$) were more in Conventional group (**Table 4**).

In Test group, the incidence of hypotension, Time $_{sensoryblocktoT8}$ and Number $_{completemotorblock}$ were similar in parturients with different height (**Table 5**). In Conventional group, as the height increased, the incidence of hypotension and Number $_{completemotorblock}$ decreased, the Time $_{sensoryblocktoT8}$ increased (**Table 5**).

Quality of Anesthesia and Neonatal Outcome

For quality of analgesia, although "good" parturients were more in Test group, there was no statistical difference between 2 groups (**Table 6**). For "good" parturients, no matter whether the highest sensory block level reaches T4, they usually felt slight transitory pain during taking out the fetus. This slight transitory pain was

TABLE 5 | Comparison among different heights in Test and Conventional groups.

	Test group				Conventional group			
	n	**Hypotension**	**Time** $_{\text{sensoryblocktoT8}}$ **(min)**	**Number** $_{\text{completemotorblock}}$	***n***	**Hypotension**	**Time** $_{\text{sensoryblocktoT8}}$ **(min)**	**Number** $_{\text{completemotorblock}}$
145–149 cm	1	1	/	0	3	3	1.333 (0.577)	3
150–154 cm	22	2	5.136 (1.781)	13	20	8	2.400 (0.503)	18
155–159 cm	45	6	4.956 (1.445)	17	49	17	3.286 (0.816)	42
160–164 cm	42	6	4.690 (1.423)	24	46	9	4.239 (1.079)	38
165–169 cm	15	3	4.667 (1.759)	7	12	2	6.500 (1.624)	6
170–174 cm	2	0	4.000 (0.000)	0	1	0	/	0
χ^2		7.298	2.657	7.154		12.347	69.456	14.664
P		0.199	0.617	0.209		0.030	2.957×10^{-14}	0.012

/ indicated that the mean could not be obtained, because the sample size was 1.

related with pressing the uterus by surgical assistant, and could be completely endured by the parturients. The quality of muscle relaxation and degree of intraoperative comfort were similar in both groups (**Table 6**). As for neonatal outcome, there was no statistical difference in both groups (**Table 7**).

DISCUSSION

Potential Factors Influenced Dose of Bupivacaine

In comparison with patients in other surgical department (e.g., orthopedics department), a relatively small dose of bupivacaine can induce a higher sensory block level in spinal anesthesia for cesarean section (20). That is, the parturient is more sensitive to the dose of bupivacaine, which should be adjusted based on some factors. Weight is a controversial factor. There are some studies showed that the dose of bupivacaine should (29, 30) or not (13, 31, 32) be adjusted according to weight. In addition, in some studies, only in parturients with high body mass index, weight is an interference factor (33, 34). In our practice, parturients with high body mass index are small, and weight does not seem to influence the block level. Theoretically, the injection speed can influence the spread of bupivacaine, but this is not found in clinical practice (35). Age is also an interference factor, but the interference effect occurs only in the elderly (36, 37). The parturients are young. The direction of side opening on spinal needle, position of parturients and punctured interspace may also influence the spread of bupivacaine (15, 38). However, we had identically limit that the direction of side opening was toward the cephalic, the parturients were immediately placed the supine position with a left lateral tilt after intrathecal injection and the punctured interspace was L3–4. Increasing evidences show that height is an important factor influenced the dose of bupivacaine (16, 17, 30, 39). Furthermore, height is a continuous variable, has a large change range in parturients. Therefore, height was selected as the only adjusted factor for the dose of bupivacaine in this study.

Dose of Bupivacaine Depended on Height

The height is related with vertebral column length (13). The vertebral column length can influence the block level (13), which is associated with the injected dose of local anesthetic in the subarachnoid space (18). In addition, in parturients, high abdominal pressure decreases the volume of the subarachnoid space (40, 41). If the dose of bupivacaine is constant, the incidence of hypotension, Time $_{\text{sensoryblocktoT8}}$ and Number $_{\text{completemotorblock}}$ changed with height (**Table 5**). Therefore, the height influences the block level, which is consistent with the results in 2 studies (16, 17). That is, the dose of bupivacaine depends on height, and should be adjusted according to height. When the dose of bupivacaine changed with height, the incidence of hypotension, Time $_{\text{sensoryblocktoT8}}$ and Number $_{\text{completemotorblock}}$ changed little in parturients with different height (**Table 5**). Therefore, the height based dosing

TABLE 6 | Quality of anesthesia.

	Quality of analgesia		Quality of muscle relaxation		Degree of intraoperative comfort	
	Test group ($n = 127$)	Conventional group ($n = 131$)	Test group ($n = 127$)	Conventional group ($n = 131$)	Test group ($n = 127$)	Conventional group ($n = 131$)
Excellent	106	122	114	124	104	101
Good	17	7	7	4	16	25
Fair	2	2	3	2	5	3
Poor	2	0	3	1	2	2
χ^2	7.229		2.377		2.458	
P	0.065		0.498		0.483	

TABLE 7 | Neonatal outcome.

	Test group ($n = 127$)	Conventional group ($n = 131$)	Z or χ^2	p
Male	72	70	0.161	0.689
Weight (kg)	3.120 (0.552)	3.136(0.513)	−0.338	0.735
1 min Apgar score	9.882 (0.544)	9.863 (0.642)	−0.276	0.783
5 min Apgar score	9.976 (0.198)	9.977 (0.195)	−0.031	0.975
Blood gas analysis				
PH	7.276(0.043)	7.229 (0.442)	−0.654	0.513
PO_2	17.535 (4.203)	17.977 (4.398)	−0.512	0.608
PCO_2	52.535 (6.185)	54.557 (8.667)	−1.928	0.054
BE	−2.244 (2.298)	−2.137 (2.411)	−0.486	0.627

algorithm of bupivacaine in this study is reasonable, especially using a low dose of bupivacaine (16, 17).

The height of parturient is associated with the block onset time (42) and block level (29), and is regarded as a risk factor for hypotension (29). However, in some studies, the variation in block spread of the subjects with same height is very large, the height does not influence the block level of spinal anesthesia (13, 31). This may be due to that the dose of bupivacaine is more in these studies than it in our study, and the effect of height on block level is undetectable (39).

Height Based Dosing Algorithm of Bupivacaine Induced a Low Incidence of Complications Even Without Prophylactic Fluid Pre-loading and Vasopressors

In spinal anesthesia, the motor and sensory block levels depend on the dose of local anesthetic (18, 27). In comparison with the Conventional group, the dose of bupivacaine was adjusted according to height and was smaller in Test group. Therefore, the Time $_{\text{sensoryblocktoT8}}$ or Time $_{\text{completemotorblock}}$ increased the sensory block level at 10 min or Number $_{\text{completemotorblock}}$ decreased in Test group (**Table 4**). This implies that the degree of sympathetic block was deeper, and the range of sympathetic block was wider in the Conventional group than both in Test group. The hypotension depends on the range and degree of a sympathetic block (1). Therefore, the maternal hypotension was less in Test group (**Table 3**).

Other complications are often correlated with hypotension (5). Thus, the incidence of other complications also decreased in Test group (**Table 3**), which is consistent with previous studies (5). Theoretically, hypotension may decrease blood flow volume of umbilical artery, and induce hyoxemia and acidosis in fetus (4). Although the incidence of hypotension was higher in Conventional group (**Table 3**), the hypotension were timely rectified with phenylephrine. The neonatal outcome was not different in both groups (**Table 7**) (19).

Height Based Dosing Algorithm of Bupivacaine Provided Adequate Anesthesia

Theoretically, the highest sensory block level should reach T4 for adequate analgesia in cesarean section (5, 23). Actually, the requirement of highest sensory block level is T4, T5, T6, or T8 in different studies (5, 14, 20, 24–26). In this study, the highest sensory block level was required to be T8. In previous experience of other researchers (23) and in this study, even though the highest sensory block level reaches T4, some parturients still feel slight pain. The incidence of pain in this study (**Table 6**) was similar to it in other studies (34). No matter whether the highest sensory block level reaches T4, the pain usually occurred during taking out the fetus. We consider this pain was mostly attributed to pressing the uterus by surgical assistant, and was not related with the sensory block level. Our results showed that T8 was suitable requirement of highest sensory block level. This may be partly due to 2 reasons. Firstly, before taking out the

fetus, the operative region locates on anesthesia of abdomen and, and is relatively narrow. Secondly, after taking out the fetus, we timely applied analgesic via a vein or local anesthetic via the epidural space.

For quality of analgesia, although more "good" parturients felt slight transitory pain in Test group, there was no statistical significance between 2 groups (**Table 6**) and these parturients could completely endure this pain. Moreover, the sensory block level $\geq$ T8 is taken as adequate analgesia for cesarean section (24, 25). In Test groups, the sensory block level could reach T8 at 10 min after anesthesia in most parturients (**Table 4**). Consequently, we consider the height based dosing algorithm of bupivacaine provides adequate analgesia.

In Test group, although the Number $_{\text{completemotorblock}}$ is less, the motor block level could reach modified Bromage scale = 2 in all parturients. The quality of muscle relaxation in Test group was similar to it in Conventional group (**Table 6**). In addition to pain, the degree of intraoperative comfort is also related with other complications (e.g., nausea, vomiting, dizziness, and dyspnea). Although parturients with slight pain were more in Test group (**Table 6**), parturients with other complications were more in Conventional group (**Table 3**). The degree of intraoperative comfort was similar in both groups (**Table 6**). Taken together, the height based dosing algorithm of bupivacaine provides adequate anesthesia, which is further supported by that smaller dose of bupivacaine in spinal anesthesia can meet the requirement of cesarean section (20).

In comparison with it in Conventional group, the dose of bupivacaine in Test group was less, and the time to reach adequate anesthesia was later (**Table 4**). This is supported by other studies (30, 42). However, the height based dosing algorithm of bupivacaine did not delay the operation duration, because the time to reach adequate anesthesia was 4.858 (1.521) min, which was approximate to the time of skin disinfection, placing sterile surgical drape and wearing sterile surgical clothes for surgeon. Furthermore, the parturients included in this study were not in extreme critical situation. In Harten et al.' study (29), for parturients in extreme critical situation emergency, the height-based dosing algorithm of bupivacaine is not recommended, because the time to reach adequate anesthesia is longer than it in our study. This time difference may be partly attributed to the different definition of adequate anesthesia and racial difference (29).

Strengths and Limitations

In spinal anesthesia, we clarified the relation between the parturient height and bupivacaine dose, and verified it is feasible that spinal anesthesia for cesarean section is carried out under condition of no prophylactic fluid pre-loading and vasopressors. Our study helps to decrease the dangerousness of parturients and fetuses with lower incidence of complications, and alleviate the stress of anesthetist.

There are two limitations in this study. First, the number of parturients with height $\geq$ 165 cm was too small (**Table 5**). For higher parturient (women in Europe and America), the height based dosing algorithm of bupivacaine need to be further studied. Second, we used a small dose of bupivacaine in Test group, the sensory block level is lower (**Table 4**) and may recover to < T8 more quickly (20). In some parturients, analgesic via a vein or local anesthetic via the epidural space needs to be timely supplied. In addition, opiates (morphine, fentanyl, and sufentanil) may be applied into subarachnoid space to improve the quality of analgesia (43, 44). We did not inject the opiates and bupivacaine together, because we did not observe an obvious improvement in quality of analgesia after adding the opiates in our practice. This is consistent to Siddiqui et al.'s study (30).

CONCLUSIONS

The dose of bupivacaine depended on height; 0.5% bupivacaine (1.15–1.7 ml, isobaric) varying with the height (0.05 ml/2–3 cm) is a suitable algorithm; the height based dosing algorithm of bupivacaine provided sufficient anesthesia with a low incidence of hypotension in the case of no prophylactic fluid preloading and vasopressors.

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 Ethics Committee of Shenzhen People's Hospital of Jinan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BH and ZH conceived, designed, and revised the experiments. BH, QH, CH, and ZZ performed the experiments. QH, GW, and YL analyzed the data. ZH contributed reagents, materials, and analysis tools. BH wrote the paper. All authors contributed to the article and approved the submitted version.

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Prediction of Fluid Responsiveness by the Effect of the Lung Recruitment Maneuver on the Perfusion Index in Mechanically Ventilated Patients During Surgery

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Introduction: Excessive or inadequate fluid administration during perioperative period affects outcomes. Adjustment of volume expansion (VE) by performing fluid responsiveness (FR) test plays an important role in optimizing fluid infusion. Since changes in stroke volume (SV) during lung recruitment maneuver (LRM) can predict FR, and peripheral perfusion index (PI) is related to SV; therefore, we hypothesized that the changes in PI during LRM (ΔPI_{LRM}) could predict FR during perioperative period.

Methods: Patients who were scheduled for elective non-laparoscopic surgery under general anesthesia with a mechanical ventilator and who required VE (250 mL of crystalloid solution infusion over 10 min) were included. Before VE, LRM was performed by a continuous positive airway pressure of 30 cm H_2O for 30 sec; hemodynamic variables with their changes (PI, obtained by pulse oximetry; and ΔPI_{LRM}, calculated by using [(PI before LRM—PI after LRM)/PI before LRM]*100) were obtained before and after LRM. After SV (measured by esophageal doppler) and PI had returned to the baseline values, VE was infused, and the values of these variables were recorded again, before and after VE. Fluid responders (Fluid-Res) were defined by an increase in SV $\geq$10% after VE. Receiver operating characteristic curves of the baseline values and ΔPI_{LRM} were constructed and reported as areas under the curve (AUC) with 95% confidence intervals, to predict FR.

Results: Of 32 mechanically ventilated adult patients included, 13 (41%) were in the Fluid-Res group. Before VE and LRM, there were no differences in the mean arterial pressure (MAP), heart rate, SV, and PI between patients in the Fluid-Res and fluid non-responders (Fluid-NonRes) groups. After LRM, SV, MAP, and, PI decreased in both groups, ΔPI_{LRM} was greater in the Fluid-Res group than in Fluid-NonRes group (55.2 $\pm$ 17.8% vs. 35.3 $\pm$ 17.3%, $p < 0.001$, respectively). After VE, only SV and cardiac

index increased in the Fluid-Res group. ΔPI_{LRM} had the highest AUC [0.81 (0.66–0.97)] to predict FR with a cut-off value of 40% (sensitivity 92.3%, specificity 73.7%).

Conclusions: ΔPI_{LRM} can be applied to predict FR in mechanical ventilated patients during the perioperative period.

Keywords: perfusion index (PI), fluid responsiveness, lung recruitment maneuver, mechanical ventilation, perioperative period

INTRODUCTION

Perioperative fluid administration has a crucial role during perioperative management. Both excessive (1–3) and insufficient fluid infusion (4, 5) are related to poor outcomes including the development of organ dysfunction or death in patients undergoing abdominal surgery. The benefit of hemodynamic parameters such as cardiac output (CO) or stroke volume (SV)-guided fluid infusion on mortality or postoperative complication such as surgical site infection, acute kidney injury, has been demonstrated in recent meta-analyses (6, 7). However, this benefit seems to be limited in high-risk surgical patients (8, 9). Nevertheless, in the FEDORA trial (10), the advantage of CO-guided volume expansion (VE) or vasopressor titration on the development of acute kidney injury or pulmonary edema during post operative period in low-to-moderate-risk surgical patients undergoing major abdominal surgery has been demonstrated.

Dynamic parameters such as pulse pressure variation (PPV) or stroke volume variation (SVV) predict fluid responsiveness better than static parameters such as mean arterial pressure (MAP) or central venous pressure (CVP) (11–13). Nevertheless, the abilities of PPV or SVV to predict fluid responsiveness in patients with either open abdominal wall (14), abdominal hypertension (15), or in surgical patients during general anesthesia (16) are limited. Cannesson et al. (16) demonstrated inconclusive evidence of the ability of PPV to detect fluid responsiveness in ∼25% of patients during general anesthesia. However, to measure the dynamic change of PPV and SVV during a transient increase in the intrathoracic pressure lung recruitment maneuver (LRM) (17, 18) or tidal volume challenge (19–21) improved the accuracy of PPV or SVV to predict fluid responsiveness. Nevertheless, PPV or SVV require arterial catheter insertion with its inherent risk (22); therefore, a non-invasive measure such as pleth variation index (PVI) using pulse oximetry might be an alternative measurement (23–25).

Peripheral perfusion index (PI), which shows the ratio between pulsatile and non-pulsatile portions, is obtained using pulse oximetry, similar to PVI, which is a measure of the dynamic changes in PI that occur during one or more complete respiratory cycles. PI depends on SV, CO, and peripheral vascular tone (26, 27). Therefore, PI can be used to track changes in the systemic hemodynamic parameters (28). However, studies reporting changes in PI during LRM in surgical patients are limited. Therefore, in this study, we hypothesized that PI would be reduced during LRM and this change might predict fluid responsiveness in surgical patients.

MATERIALS AND METHODS

Study Design

This prospective diagnostic study was conducted in operating rooms at the Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand, from November 2020 to April 2021. The study protocol was approved by the local ethical committee (approval number COA. MURA2020/1844). The informed consent was obtained from each patient on the day before surgery. Patients were included if they were aged ≥18 years, were scheduled for elective non-laparoscopic surgery under general anesthesia with a controlled mechanical ventilation, and required their first VE during perioperative period. We excluded patients who had uncontrolled hemodynamic status (29, 30), intracranial hypertension, severe chronic obstructive pulmonary disease, broncho alveolar fistula, severe emphysema, and those with pre-existing comorbidities including severe left and right ventricular dysfunction, severe pulmonary hypertension (30, 31), severe obesity (BMI >40 kg/m^2), and pregnancy.

After anesthesia induction, an endotracheal tube and arterial catheter were placed in all included patients. The dose or type of anesthesia agents and an anesthesia mechanical ventilator were managed by the attending anesthesiologists. An anesthesia machine ventilator was set to achieve a low tidal volume (6–8 mL/kg predicted body weight, aiming for an expired ratio of 1:2), positive end-expiratory pressure (PEEP) of 3–5 cm H_2O, respiratory rate that was adjusted to obtain an appropriate end-tidal carbon dioxide ($EtCO_2$) amount between 30 and 35 mmHg, and an inspiratory oxygen fraction (FiO_2) was set to achieve an SpO_2 of at least 95%.

Demographic data were recorded from medical record. Continuous blood pressure, continuous electrocardiogram, heart rate (HR), $EtCO_2$, and SpO_2 (measured by pulse oximetry), were monitored during the perioperative period. VE, defined as 250 mL of crystalloid solution infusion over 10 min, was decided by the attending physicians. Esophageal Doppler probe (DCQ ODM, Deltex, Chichester, Sussex, UK) and PI (on the third or fourth finger) were placed before the initiation of LRM until the end of VE. The esophageal Doppler probe was positioned to attain the best aortic blood velocity signal. LRM had been performed before surgery began and thus with closed abdomen by applying a continuous positive airway pressure (CPAP) of 30 cm H_2O for 30 s before VE was infused. Systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, CO, SV, PVV, SVV, PVI, and PI were obtained before LRM as the first baseline values (T1) and after LRM (T2). After SV and PI returned to their baseline values (variations

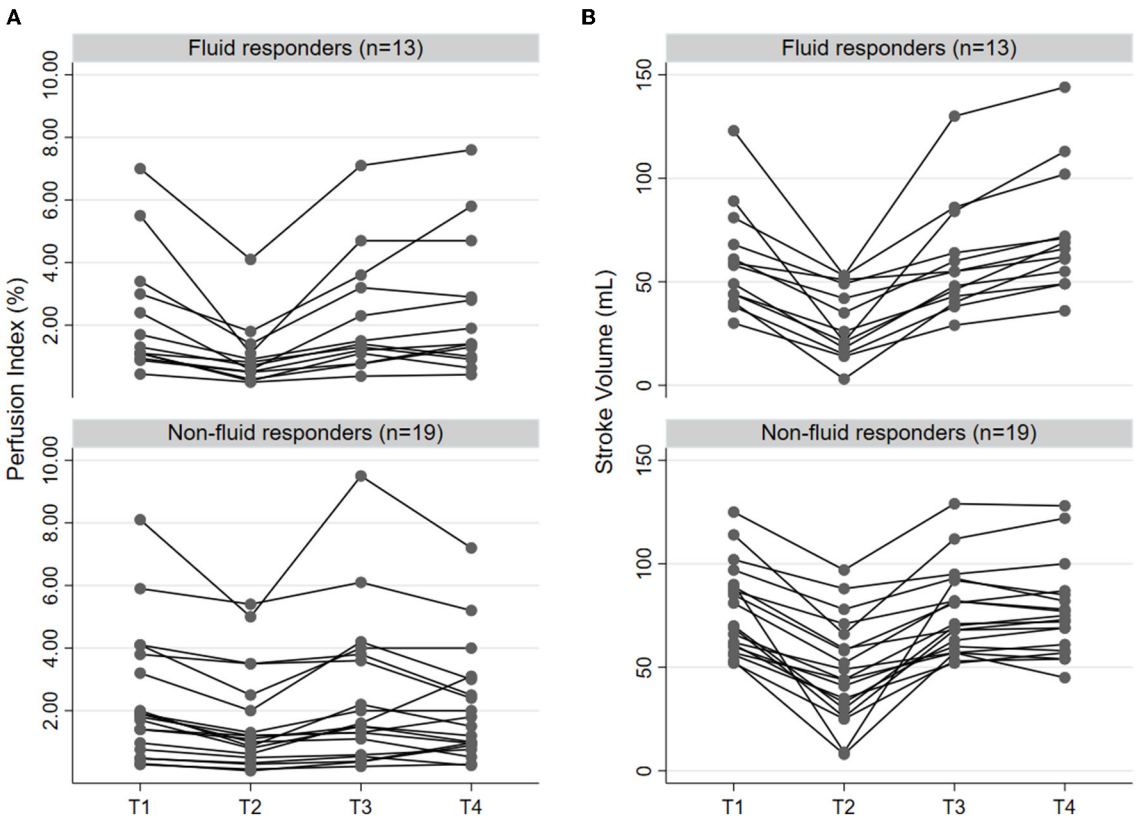

FIGURE 1 | Individual change of prefusion index **(A)** and stroke volume **(B)** according to the status of fluid responsiveness ($n = 13$) and non-responsiveness ($n = 19$) in four time points, including before LRM (T1), after LRM (T2), before VE (T3), and immediately after VE (T4). LRM, lung recruitment maneuver; VE, volume expansion.

<10%), hemodynamic variables and PI were obtained as the second baseline values (T3); then, VE was infused and these hemodynamic variables and PI were recorded immediately after VE (T4) [Supplemental Digital Content (SDC), **Figure 1**]. Changes in hemodynamic variables and PI during LRM and VE were recorded and presented as relative percent change from the baseline value before LRM and VE, respectively. These were calculated using the following formula:

Before (T1) vs. after LRM (T2)

$$\text{Relative change of SV } (\Delta SV_{LRM}) = ([SV_{T1} - SV_{T2}]/SV_{T1})*100$$

$$\text{Relative change of CO } (\Delta CO_{LRM}) = ([CO_{T1} - CO_{T2}]/CO_{T1})*100$$

$$\text{Relative change of MAP } (\Delta MAP_{LRM}) = ([MAP_{T1} - MAP_{T2}]/MAP_{T1})*100$$

$$\text{Relative change of PPV } (\Delta PPV_{LRM}) = ([PPV_{T2} - PPV_{T1}]/PPV_{T1})*100$$

$$\text{Relative change of PVI } (\Delta PVI_{LRM}) = ([PVI_{T2} - PVI_{T1}]/PVI_{T1})*100$$

Before (T3) vs. after VE (T4)

$$\text{Relative change of SV } (\Delta SV_{VE}) = ([SV_{T4} - SV_{T3}]/SV_{T3})*100$$

$$\text{Relative change of CO } (\Delta CO_{VE}) = ([CO_{T4} - CO_{T3}]/CO_{T3})*100$$

$$\text{Relative change of MAP } (\Delta MAP_{VE}) = ([MAP_{T4} - MAP_{T3}]/MAP_{T3})*100$$

SV, SVV, and CO were derived from the esophageal Doppler. PPV was derived from the Philips® IntelliVue MP 50 monitor. All the patients were grouped according to whether they were fluid responders or not, which was defined by an increase in SV (obtained by esophageal Doppler) ≥10% after VE. All the patients were included once.

PI Measurements

PI, a unit expressed as a percentage, was measured using a pulse oximeter, the Radical-7 Pulse CO-Oximeter device (Masimo Corporation, Irvine, CA, USA) with an adult disposable spectrophotometric sensor, ReSposable™ R2–25 (Masimo Corporation, Irvine, CA, USA). The PI was calculated as the ratio of the pulsatile over non-pulsatile amplitudes detected by the sensor. The short-time method was used to display the PI values during LRM. A percent decrease in PI according to the LRM (ΔPI_{LRM}) was calculated using this formula:

$$\text{Relative change of PI } (\Delta PI_{LRM}) = ([PI_{T1} - PI_{T2}]/PI_{T1})*100$$

Sample Size Calculation

The sample size was calculated based on the assumption that ΔPI_{LRM} could determine fluid responsiveness at an AUC of 0.80, corresponding to a good discriminative ability for the diagnostic test. The null hypothesis value of AUC was set at 0.50. The proportion of fluid responders was 45%, corresponding to a fluid

responsiveness ratio (negative-to-positive) of 1.222. The risk of alpha error at 5% and beta error at 10% were accounted for. In total, 27 patients were needed. The sample size was calculated using Obuchowski's method (32) via a web tool for ROC curve analysis (version 1.3.1) (33). To counteract the 15% dropout rate, 32 patients were planned for inclusion.

Statistical Analysis

Continuous data are expressed as the mean ± standard deviation (SD). Categorical data are expressed as counts (n) and percentages (%). The comparison of hemodynamic parameters before (T1) and after LRMs (T2) and before (T3) and after VE (T4) were performed using the paired *t*-test or Wilcoxon signed rank test as appropriate. Comparisons between fluid responders and non-responders were performed using the two-tailed Student *t*-tests or the Wilcoxon test as appropriate. The diagnostic performances of ΔPI_{LRM}, ΔSV_{LRM}, ΔCO_{LRM}, and ΔMAP_{LRM} for detecting fluid responsiveness were estimated by the area under the receiver operating characteristic curves (AUCs). Sensitivity (Sn), specificity (Sp), positive predictive value, negative predictive value, positive likelihood ratio (LR+), and negative likelihood ratio (LR-) were reported accordingly. The best cut-off value was determined by the Youden Index (Sn + Sp−1).

The gray zone approach to identifying inconclusive ranges of ΔPI_{LRM} that could not determine whether the patients were fluid responders or non-responders, was constructed using two approaches. First, the bootstrap resampling of 1,000 replications was performed to identify the best cut-off point and its 95% confidence interval (CI) (representative of the gray zone). Second, the three class responses for ΔPI_{LRM}, including inclusion, inconclusion, and exclusion, were determined. Thresholds related to the Sn <90% and Sp <90% were set. Then, the remaining area was deemed inconclusive or designated a gray zone. The larger size from the two approaches was used to indicate the gray zone (34, 35). Correlation was performed by linear correlation, according to the data distribution. A p-value < 0.05 was considered statistically significant. All analyses were performed using the STATA statistical software version 16.0 (StataCorp LP, College Station, Tx, USA).

RESULTS

Patient Characteristics

The baseline characteristics of the 32 patients included in this study are shown in **Table 1**. Thirteen (40.6%) patients were fluid responders and 19 were not. There were no differences in baseline characteristics between fluid responders and fluid non-responders (SDC, **Supplementary Table 1**).

TABLE 1 | Patient baseline characteristics ($n = 32$).

Variables	Results
Age (years)	60 ± 10
Male, *n* (%)	20 (62.5%)
Height (cm)	160.0 ± 6.8
Body weight (kg)	60.4 ± 12.1
Predicted body weight (kg)	55.3 ± 7.6
Body mass index (kg/m^2)	23.5 ± 4.2
Body surface area (m^2)	1.62 ± 0.16
ASA physical status, *n* (%)	
I	2 (6.2%)
II	15 (46.9%)
III	15 (46.9%)
Operative sites, *n* (%)	
Liver	14 (43.8%)
Pancreas	11 (34.4%)
Renal	3 (9.4%)
Gynecology	3 (9.4%)
Breast	1 (3.0%)
Tidal volume (mL)	480 ± 48
Tidal volume/predicted body weight (ml/kg)	8.7 ± 0.7
Respiratory rate (breaths/min)	12.8 ± 1.4
Plateau pressure (cm H_2O)	16.1 ± 2.2
Driving pressure (cm H_2O)	11.2 ± 2.2
Positive end expiratory pressure (cm H_2O)	5.0 ± 1.0
Vasopressor usage, *n* (%)	5 (15.6%)
Sevoflurane, *n* (%)	22 (68.8%)
Desflurane, *n* (%)	10 (32.3%)

ASA, American Society of Anesthesiologists.

The Effect of LRM on Hemodynamic Variables and PI in Fluid Responders vs. Non-responders

Before LRM, there were no differences in MAP, CO, PVI, PI between fluid responders and non-responders (**Table 2**). PVV and SVV were greater in fluid responders than in non-responders (**Table 2**). After LRM, CO, SV, MAP, PI reduced, while PVI, PPV, and SVV increased in both groups (**Table 2**). ΔPI_{LRM} were greater in fluid responders than in non-responders (55.2 ± 17.8% vs. 35.3 ± 17.3%, $p = 0.004$, respectively). ΔSV_{LRM} (49.4 ± 21.5% vs. 39.8 ± 21.4%, $p = 0.222$, respectively), ΔMAP_{LRM} (26.3 ± 10.9% vs. 19.5 ± 9.6%, $p = 0.073$, respectively), ΔPVI_{LRM} (45.3 ± 10.0% vs. 35.9 ± 6.4%, $p = 0.410$, respectively), and ΔPPV_{LRM} (58.1 ± 84.8% vs. 95.9 ± 102.5%, $p = 0.297$, respectively) did not differ between fluid responders and non-responders. Individual changes in PI and SV in fluid responders and non-responders are presented in **Figure 1**.

The Effect of VE on Hemodynamic Variables and PI in Fluid Responders vs. Non-responders

Before VE, MAP, CO, SV, and HR did not differ between fluid responders and non-responders (**Table 2**). After VE, only SV increased in fluid responders while MAP and HR were not different before and after VE in fluid responders (**Table 2**). PI did not change after VE in both groups (**Table 2**). Changes in PI and SV in fluid responders and non-responders during VE are shown in **Figure 1**.

TABLE 2 | Hemodynamic parameters before and after lung recruitment maneuver and volume expansion.

Hemodynamic parameters	Lung recruitment maneuve		*P*-value	Volume expansion		*P*-value
	Before (T1)	After (T2)		Before (T3)	After (T4)	
Perfusion index						
Fluid responders ($n = 13$)	2.30 ± 1.98	1.01 ± 1.04	0.002	2.25 ± 1.93	2.52 ± 2.21	0.197
Fluid non- responders ($n = 19$)	2.35 ± 2.08	1.65 ± 1.60	<0.001	2.41 ± 2.35	2.08 ± 1.81	0.110
Stroke volume (mL)						
Fluid responders ($n = 13$)	60.3 ± 25.4	30.8 ± 17.2	<0.001	59.8 ± 26.9	73.0 ± 29.8	<0.001
Fluid non-responders ($n = 19$)	77.7 ± 21.4$^{\$}$	48.1 ± 24.6$^{\$}$	<0.001	75.9 ± 21.0	76.1 ± 21.9	0.881
Cardiac output (L/min)						
Fluid responders ($n = 13$)	4.28 ± 1.30	1.78 ± 0.99	<0.001	4.25 ± 1.49	5.05 ± 1.84	<0.001
Fluid non-responders ($n = 19$)	5.13 ± 1.69	2.78 ± 1.61	<0.001	4.83 ± 1.56	4.95 ± 1.62	0.328
Systolic blood pressure (mmHg)						
Fluid responders ($n = 13$)	113 ± 18	78 ± 15	<0.001	108 ± 19	116 ± 16	0.013
Fluid non-responders ($n = 19$)	114 ± 18	92 ± 14	<0.001	107 ± 17	122 ± 24	<0.001
Diastolic blood pressure (mmHg)						
Fluid responders ($n = 13$)	64 ± 17	52 ± 13	<0.001	63 ± 15	63 ± 14	0.958
Fluid non-responders ($n = 19$)	61 ± 8	52 ± 10	<0.001	58 ± 8	66 ± 13	<0.001
Mean arterial pressure (mmHg)						
Fluid responders ($n = 13$)	82 ± 16	60 ± 13	<0.001	80 ± 15	83 ± 13	0.068
Fluid non-responders ($n = 19$)	81 ± 13	66 ± 15	<0.001	77 ± 11	88 ± 17	<0.001
Heart rate (beats/min)						
Fluid responders ($n = 13$)	75 ± 17	71 ± 15	0.051	75 ± 16	73 ± 15	0.325
Fluid non-responders ($n = 19$)	67 ± 14	62 ± 15	<0.001	64 ± 13$^{\$}$	65 ± 15	0.215
Pleth variability index (%)						
Fluid responders ($n = 13$)	13.9 ± 4.8	18.9 ± 4.2	<0.001	–	9.7 ± 3.2	–
Fluid non-responders ($n = 19$)	12.0 ± 6.8	15.5 ± 7.5	<0.001	–	12.6 ± 6.5	–
Pulse pressure variation (%)						
Fluid responders ($n = 13$)	18.8 ± 7.5	24.5 ± 7.4	<0.001	–	12.0 ± 8.2	–
Fluid non-responders ($n = 19$)	10.0 ± 5.8**	17.2 ± 6.9*	<0.001	–	6.0 ± 3.5$^{\$}$	–
Stroke volume variation (%)						
Fluid responders ($N = 13$)	25.2 ± 13.0	43.3 ± 14.0	0.003	–	18.4 ± 8.0	–
Fluid non-responders ($N = 17$)	17.9 ± 6.3$^{\$}$	27.3 ± 15.4$^{\$}$	0.036	–	18.8 ± 12.2	–

Data are expressed as mean ± SD. $^{\$}p < 0.05$ *comparing between fluid responders and non-responders at the same period of time.* $^{*}p < 0.01$ *comparing between fluid responders and non-responders at the same period of time.* $^{**}p < 0.001$ *comparing between fluid responders and non-responders at the same period of time.*

Baseline Parameters at T1 and Changes in PI During LRM to Predict Fluid Responsiveness

ΔPI_{LRM} [0.81 (0.66–0.97)] and PPV_{T1} [0.82 (0.66–0.99)] showed higher AUCs than ΔCO_{LRM}, ΔSBP_{LRM}, ΔMAP_{LRM}, PVI_{T1}, and PI_{T1} to predict fluid responsiveness (**Table 3**; **Figure 2**) with cut-off values ≥40% [Sn of 92.3% (95% CI, 64.0–99.8%); Sp of 73.7% (95% CI, 48.8–90.9%); positive predictive value of 70.6% (95% CI, 44.0–89.7%); negative predictive value of 93.3% (95% CI, 68.1–99.8%); and LR+ of 3.51 (95% CI, 1.63–7.57)]. ΔPI_{LRM} had similar AUC with PPV_{T1}, $p = 0.806$.

Correlation of ΔPI_{LRM}, PVI, PI, and PPV_{T1} With Changes in SV

ΔPI_{LRM} and PPV_{T1} showed significant correlations with ΔSV_{VE} ($r^2 = 0.36$, $p = 0.040$ and $r^2 = 0.40$, $p = 0.028$, respectively) and ΔSV_{LRM} ($r^2 = 0.16$, $p = 0.020$ and $r^2 = 0.17$, $p = 0.038$, respectively) (**Figure 3**). The relative change of PI and SV were correlated when considering all interventions (both LRM and VE) ($r^2 = 0.14$, $p = 0.028$, concordance rate = 29.64%) (SDC, **Figure 2**). There was a significant correlation between PVI_{T1} and ΔSV_{VE} ($r^2 = 0.25$, $p = 0.036$), but not with ΔSV_{LRM}.

The Gray Zone of ΔPI_{LRM}

Figure 4 depicts the gray zone approach for the ΔPI_{LRM}. A decrease in ΔPI_{LRM} of <35% could guide the decision-making for fluid non-responders with a Sn ≥90%. In contrast, a decrease in ΔPI_{LRM} of more than 60% could detect fluid responsiveness with a Sp ≥90%. Over 21.9 and 50.0% of our population, respectively, could undergo guided decision-making by the ΔPI_{LRM} regarding whether to receive VE or not. However, in 28.1% of the population, this was inconclusive.

TABLE 3 | The changes in hemodynamic parameters and their AUCs in predicting fluid responsiveness.

Hemodynamic parameters	Fluid responders (n = 13)	Fluid non-responders (n = 19)	AUC	95% CI
A decrease in hemodynamic parameters following lung recruitment maneuver				
ΔPI_{LRM} (%)	55.23 ± 17.82	35.32 ± 17.32	0.81	0.66–0.97
ΔSV_{LRM} (%)	49.42 ± 21.49	39.79 ± 21.44	0.65	0.45–0.86
ΔCO_{LRM} (%)	58.92 ± 18.70	47.39 ± 22.87	0.70	0.51–0.88
ΔSBP_{LRM} (%)	30.42 ± 11.56	20.22 ± 10.50	0.72	0.54–0.91
ΔDBP_{LRM} (%)	19.12 ± 10.59	14.55 ± 8.99	0.60	0.38–0.82
ΔMAP_{LRM} (%)	26.27 ± 10.93	19.47 ± 9.61	0.67	0.47–0.88
ΔHR_{LRM} (%)	5.08 ± 8.93	7.12 ± 7.50	0.43	0.22–0.64
Respiratory variation of hemodynamic parameters at T1				
PVI_{T1} (%)	13.92 ± 4.77	12.00 ± 6.82	0.67	0.48–0.87
PPV_{T1} (%)	18.85 ± 7.55	9.53 ± 6.00	0.82	0.66–0.99
SVV_{T1} (%)	25.91 ± 12.56	17.88 ± 6.28	0.69	0.46–0.92

AUC, area under the curve; CI, confidence interval; CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; LRM, lung recruitment maneuver; MAP, mean arterial pressure; PI, perfusion index; PPV, pulse pressure variation; PVI, pleth variability index; SBP, systolic blood pressure; SV, stroke volume; SVV, stroke volume variation. ΔSV_{LRM}; relative reduction rate of SV between T1 and T2, ΔCO_{LRM} relative reduction rate of CO between T1 and T2, ΔSBP_{LRM} relative reduction rate of SBP between T1 and T2, ΔDBP_{LRM} relative reduction rate of DBP between T1 and T2, ΔMAP_{LRM} relative reduction rate of MAP between T1 and T2, and ΔHR_{LRM} relative reduction rate of HR between T1 and T2.

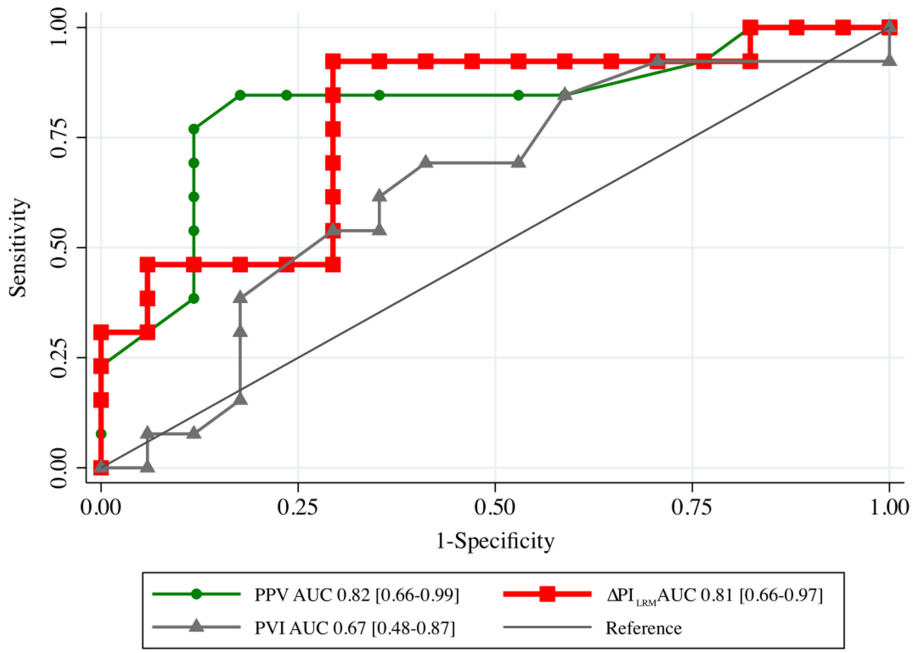

FIGURE 2 | The area under the receiver operating characteristic (AUC) curves generated from the changes in PI following LRM (ΔPI_{LRM}), PPV and PVI before lung recruitment maneuver (T1) to predict fluid responsiveness. LRM, lung recruitment maneuver; PPV, pulse pressure variation; PVI, pleth variation index.

DISCUSSION

In this study, we demonstrated that a reduction in PI during LRM and the baseline PPV had better ability to predict fluid responsiveness in surgical patients who underwent elective open abdominal surgery than the baseline MAP, CO, and PVI.

Predicting fluid responsiveness plays an important role in optimizing perioperative fluid infusion. Inappropriate fluid administration including inadequate fluid infusion during perioperative period are related to the development of acute kidney injury or an increase in postoperative complications such as infection, which is associated with mortality (1–5). Dynamic hemodynamic parameters which rely on heart-lung interactions, such as PPV and SVV are better indicators to predict fluid responsiveness than static hemodynamic variables such as MAP or CVP (11–13). However, PPV and SVV are less

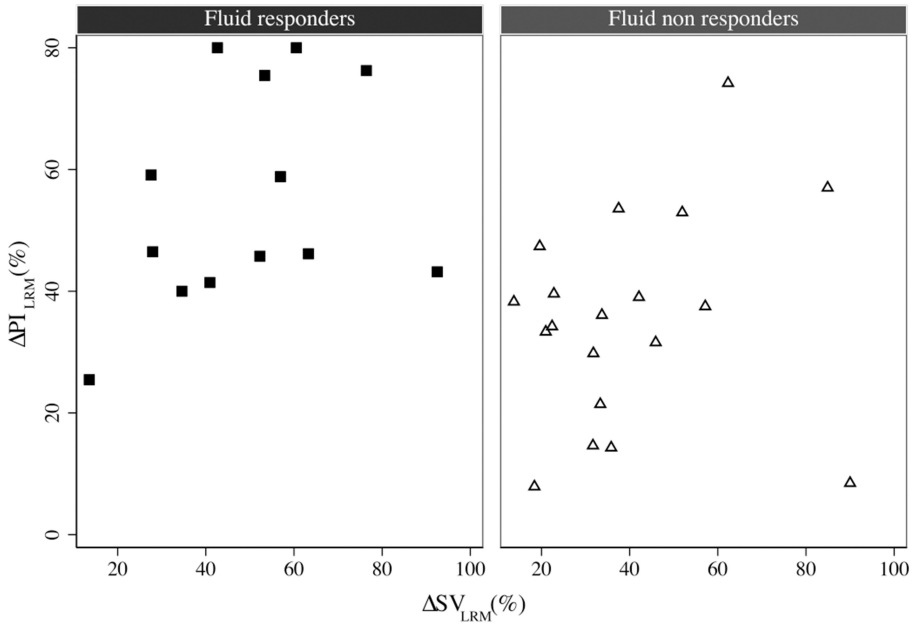

FIGURE 3 | The correlation between ΔSV_{LRM} and ΔPI_{LRM} in fluid responders (square) and non-responders (triangle), $r^2 = 0.16$, $p = 0.020$. LRM, lung recruitment maneuver; SV, stroke volume; PI, perfusion index.

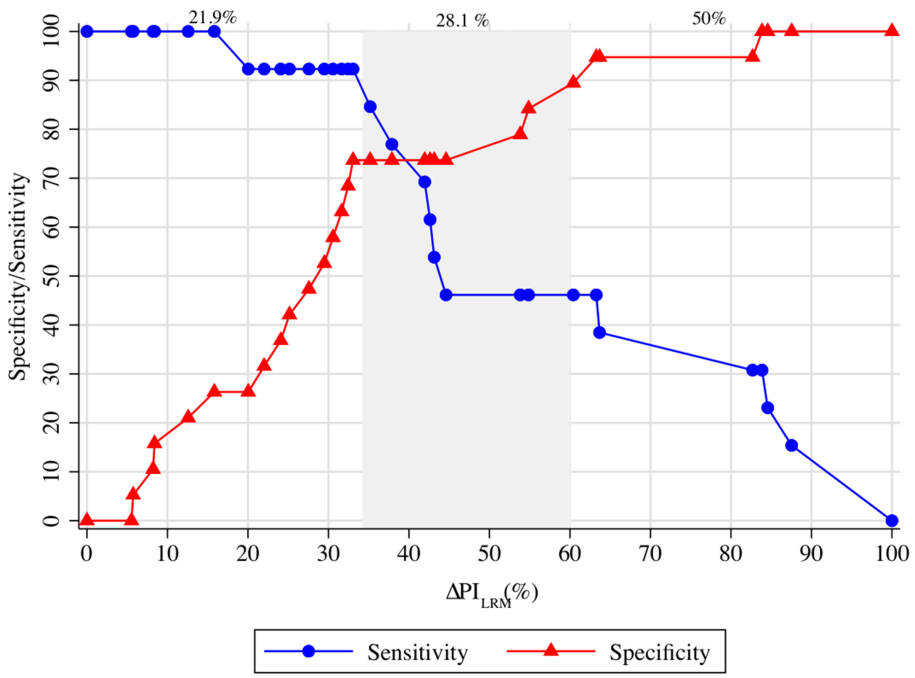

FIGURE 4 | The gray zone approach of ΔPI_{LRM} and ΔSV_{VE}. ΔPI_{LRM} <35.0% represents fluid non-responsiveness with a sensitivity >90%. Moreover, ΔPI_{LRM} >60.0% represents fluid responsiveness with a specificity >90%. The inconclusive zone of ΔPI_{LRM} is spread between 35.0 and 60.0%, which represents 28.1% of the population. LRM, lung recruitment maneuver; SV, stroke volume; PI, perfusion index.

reliable in patients under mechanical ventilator with tidal volume <6 mL/kg (15). To overcome these limitations, end-expiratory occlusion test (36) and LRM (17, 18) are applied to evaluate the dynamic response of PPV or SVV.

Biais et al. (18) and Watanabe et al. (17) showed that a decrease in SV after LRM indicate fluid responsiveness during perioperative period. However, a change in SV during LRM in this study did not differ between fluid responders and

non-responders, and it did not indicate fluid responsiveness. This finding can be explained by the differences in the sites of operation and devices between their publications (17, 18) and our study. The patients in this present study underwent open abdominal surgery whereas those in Biais et al. (18) and Watanabe et al. (17) underwent neurological and spine surgery, respectively. Additionally, SV in their publications (17, 18) were obtained by pulse contour analysis while in this present study, it was derived by esophageal Doppler. LRM might interfere with the aortic signal, leading to SV (37).

The PI signal represents the peripheral perfusion and depends on the global blood flow (SV and CO) and peripheral vasomotor tone. Thus, low PI could indicate either vasoconstriction and/or low SV (26, 27). While, high PI suggests vasodilatory state or high CO (38). When performing a preload test, as vascular tone does not change during this transient test, changes in PI track changes in CO (28). Courson et al. (35) demonstrated that a reduction in PI after LRM can predict fluid responsiveness in patients undergoing neurological surgery. In this study, we showed that the ΔPI_{LRM} was related with changes in SV during LRM and after VE and ΔPI_{LRM} was a good indicator to predict fluid responsiveness in patients undergoing open abdominal surgery; similar to the baseline PPV. Therefore, these findings confirmed the use of PI to detect a change in SV during LRM or VE. Moreover, ΔPI_{LRM} can be applied in patients with mechanical ventilator who are not requiring arterial catheter to detect fluid responsiveness. Furthermore, in this study, ΔPI_{LRM} had better ability to indicate fluid responders than PVI at baseline. This finding is similar to that of a previous meta-analysis (39), which reported that PVI reliability to predict fluid responsiveness in surgical patients under mechanical ventilators might be reduced. Nevertheless, further studies should be performed to validate these findings. Regarding the reduction in MAP and SV, LRM should be performed with caution in patients with hypotension or those requiring vasopressors.

In this study, PI did not change after VE in both fluid responders and non-responders. Ryu et al. (40) reported that sevoflurane and desflurane affected the PI values by inducing vasodilatation. Patients in this study received sevoflurane or desflurane, suggesting that in these patients, PI might have affected various vasoplegia states because of the anesthetic agents. This might explain the unchanged PI values after VE in fluid responders and non-responders (40, 41).

In fluid non-responders, PI and SV also decreased; this may be explained by the negative effect of the increase in the intrathoracic pressure during LRM on hemodynamic variables (29, 30) and volume status (42), or the degree of vasoplegia due to the anesthetic agents (40, 41). Moreover, the decrease in SV in fluid non-responders was similar to that reported by Biais et al. (18) and Watanabe et al. (17).

Our study also had some limitations. The first related to the esophageal Doppler technique. The cross-sectional area of the descending aorta was not applied in our technique. Therefore, this could lead to an underestimation of SV (37). Although with some considerations, this technique remains acceptable for tracking the trending ability when comparing it with the pulmonary artery thermodilution technique (43). Second, we performed LRM on patients in the supine position who mostly underwent open-abdominal surgery. The study period with LRM were performed before the surgery started; therefore, the results cannot be inferred to patients in other positions or other clinical situations, including laparoscopic surgery. The utilization of such a high tidal volume (8.7 ± 0.7 mL/predicted kg) in our study may limit the applicability of our ΔPI_{LRM} in a low tidal volume setting (6–8 mL/predicted kg). Moreover, a higher tidal volume, rather than a lower tidal volume, could emphasize the effects of LRM and thus produce a greater ΔPI_{LRM}, even in patients with good lung compliance and good transmission of pleural pressure. Therefore, confirming this hypothesis requires further investigations. Third, the sample size calculation did not take into account the accuracy of the esophageal Doppler to detect the changes in SV. Therefore, the number of participants in this study might be smaller than the actual required sample size. Fourth, an inconclusive zone of ΔPI_{LRM} between 35 and 60% needs further attention. Another test to predict fluid responsiveness is needed for these populations. Fifth, LRM in this study was performed shortly after an induction of the anesthetic agents; therefore, the effect of LRM on hemodynamic status might have been impacted by the degree of vasodilatation due to the anesthetic agents. Nevertheless, fluid administration in patients with various vasoplegia during anesthetic period should be based on clinical decision.

Despite these limitations, a reduction in PI after LRM obtained non-invasively by pulse oximetry can be applied as an indicator to predict fluid responsiveness in patients undergoing abdominal surgery, similar to the baseline PPV.

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 study protocol was approved by the Institutional Review Board of Human Research Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (COA. MURA2020/1844). The study was registered with the Thai Clinical Trials Registry, code TCTR20201202001 (http://www.thaiclinicaltrials.org/show/TCTR 20201202001), on 2 December 2020. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM and NP created the conception and designation of the study. PPer wrote and submitted the proposal. PPer and SM obtained

the data. NP, SM, PPin, and KT analyzed and interpreted the results. PPer and PPin drafted the work. NP, SM, WM, and KT substantively revised the manuscript. SM provided the greatest contribution to the study. All authors read and approved the final version 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.2022.881267/full#supplementary-material

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Perioperative Hemodynamic Optimization in Patients at Risk for Delirium – A Randomized-Controlled Trial

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Background: Post-operative delirium is common in elderly patients and associated with increased morbidity and mortality. We evaluated in this pilot study whether a perioperative goal-directed hemodynamic optimization algorithm improves cerebral oxygenation and can reduce the incidence of delirium.

Materials and Methods: Patients older than 70 years with high risk for post-operative delirium undergoing elective non-cardiac surgery were randomized to an intervention or control group. Patients in the intervention group received a perioperative hemodynamic optimization protocol based on uncalibrated pulse-contour analysis. Patients in the control group were managed according to usual standard of care. Incidence of delirium until day seven was assessed with confusion assessment method (CAM) and chart review. Cerebral oxygenation was measured with near-infrared spectroscopy.

Results: Delirium was present in 13 of 85 (15%) patients in the intervention group and 18 of 87 (21%) in the control group [risk difference −5.4%; 95% confidence interval, −16.8 to 6.1%; P = 0.47]. Intervention did not influence length of stay in hospital or in-hospital mortality. Amounts of fluids and vasopressors applied, mean arterial pressure, cardiac index, and near-infrared spectroscopy values were comparable between groups.

Conclusion: The hemodynamic algorithm applied in high-risk non-cardiac surgery patients did not change hemodynamic interventions, did not improve patient hemodynamics, and failed to increase cerebral oxygenation. An effect on the incidence of post-operative delirium could not be observed.

Clinical Trial Registration: [Clinicaltrials.gov], identifier [NCT01827501].

Keywords: outcome, post-operative delirium, goal-directed hemodynamic monitoring, goal-directed therapy, frailty

INTRODUCTION

Delirium is a common post-operative complication in the elderly (1). It is defined as an acute neuropsychiatric disorder characterized by fluctuations in attention, awareness, and cognition. The incidence depends on several factors like age, number of comorbidities, pre-operative cognitive or functional impairment, and type of surgery (2–4). Particularly in patients admitted to the intensive care unit (ICU) the incidence is between 50 and 80% (5) and their length of stay in ICU and hospital is prolonged. As a consequence, delirium is both a huge burden on a patient's wellbeing and on the healthcare system overall (6, 7). To prevent delirium multimodal and multidisciplinary interventions should be implemented during hospital stay and particularly in the perioperative course (8).

Since maintaining a sufficient perfusion is a general principle in anesthesia, the patient's hemodynamic status could be one target point of intervention. Sufficient perfusion and oxygen delivery are essential in order to avoid impairment of the brain (9). In sepsis-associated delirium a correlation with cerebral perfusion pressure has been demonstrated as one of many contributing factors (10). In addition, the correlation between intraoperative hypotension and post-operative delirium has been shown in a recent clinical trial not exclusively for sepsis but also involving surgical patients (11). Furthermore, poorer cerebral perfusion pressure was associated with a higher risk of post-operative delirium as well as longer duration and higher severity of delirium, independent of demographic and medical predictors in a cohort of lung-transplant recipients (12). This indicates that individual adjustment of cerebral perfusion in terms of goal-directed hemodynamic optimization could be an approach to reduce the incidence of delirium *via* improvement of cerebral oxygenation especially in elderly patients (13). Uncalibrated pulse contour analysis requires only an arterial line and cardiac index is calculated with an algorithm using bodyweight and height of the patient. It allows efficient, continuous monitoring, targeting of optimal cardiac output and facilitates management of vasopressors and fluid administration during high-risk surgery (14, 15). As a consequence, intraoperative cerebral perfusion and oxygenation might be optimized by being able to target cardiac output measures. The hypothesis of our study is, that goal-directed hemodynamic optimization will improve cerebral perfusion and consequently cerebral oxygenation and thereby reduce the incidence of delirium in a high-risk population compared with standard therapy.

METHODS

We performed a prospective, randomized, single-center study at a university hospital in Munich, Germany. Patients older than 70 years with a high risk of developing post-operative delirium were included and randomized into two treatments arms: intervention and control group.

The study was approved by the ethics committee of the Technical University of Munich (Ethikkommission der Technischen Universität München, Ismaninger Straße 22, 81675 München; Approval Number: 5687/13 S on February 28th, 2013 and October 24th, 2018; Chairperson Prof. Dr. G. Schmidt) and prospectively registered at Clinical Trials (April 2013; NCT01827501). There was one amendment to the study in 2018, when a new German law for data protection regulation has come into force and the patient information sheet had to be updated. The study was conducted in accordance with the Declaration of Helsinki.

Eligibility Criteria and Randomization

Patients were screened for eligibility during the pre-anesthesia visit. Inclusion criteria were age above 70 years, major elective non-cardiac surgery (defined by a scheduled surgery time $\geq$90 min) and a high risk for delirium (screening score $\geq$6 points; see below). Surgical procedures included all types of surgery except cardiac, major aortic, and neurosurgery. Patients with emergency procedures and patients who had general anesthesia within the last 30 days were excluded. Further exclusion criteria were valvular disorders grade II or higher as well as history of major aortic surgery, as these factors are known to distort the uncalibrated pulse contour analysis. A detailed interview with the patient and/or his caregivers was conducted by a research team member during the pre-anesthesia visit to assess the patient's risk for delirium. Several predisposing and precipitating factors were identified and scored with one or two points according to **Table 1**. The scoring system is a modification of the risk score described by Marcantonio based on the work of Inouye (16, 17). We included only patients with a score of $\geq$6 points in the study as these patients have a high risk of at least 30% for delirium (18).

A research team member evaluated the patients' eligibility, informed the patient in detail about the study, and obtained written informed consent. He enrolled the patient and assigned him to intervention or control group in a 1:1 ratio. The randomization list was generated by a study team member using a random generator without blocks (Microsoft Excel for Mac 14.0). For each randomization number we prepared a paper-based folder with all required materials including the group assignment. Only the folder with the lowest number was accessible to the study team member responsible for the allocation.

Pre-operative Predisposing Factors

A Mini-Mental-State exam (MMSE) was performed to detect dementia or cognitive impairment (MMSE $\leq$ 24: mild cognitive impairment; MMSE > 20 and < 24: dementia) and the Confusion assessment method (CAM-) Score was obtained (19, 20). Patients with present delirium were excluded. Above that, activities of daily life were assessed to determine the presence of frailty according to the Clinical Frailty Scale (CFS) (21). As already determined in large multicentric international trials, patients with a CFS 5–8 were considered as frail (22). Above that, functional disability is present, when sensory or visionary aids are necessary, walking sticks, rollators or wheelchairs are required or patients need feeding, e.g., by a percutaneous endoscopic gastrostomy. To determine high medical comorbidities and cardiovascular risk factors medical records including clinical charts and nursing records were reviewed. Data collection included patient biometrics, comorbidities, clinical parameters

TABLE 1 | Screening score: risk factors for delirium.

Risk factor category	Predisposing factors	Precipitating factors
Major (2 points)	• Advanced age (≥80 years)	• High-risk surgical procedure*
	• Dementia (MMSE <20) or recent delirium, not resolved	• Planned intensive care unit stay ≥2 days
Minor (1 point)	• Older age (70–79 years)	• Moderate-risk surgical procedure*
	• Mild cognitive impairment (MMSE ≤24)	• General anesthesia
	• History of stroke	• Planned intensive care unit stay <2 days
	• Functional disability (MET <4, paresis, hearing aid, glasses)	
	• Laboratory abnormalities	
	• High medical comorbidity, including cardiovascular risk factors	
	• Alcohol/sedative abuse	
	• Depressive symptoms	

**High-risk surgical procedures include open vascular and major abdominal surgery.*
**Moderate-risk surgical procedure include orthopaedic, ear, nose and throat, gynaecologic and urologic surgery.*
MMSE, Mini-Mental-State Examination; MET, Metabolic Equivalent of Task.

and laboratory findings. The risk of the surgical-procedures was determined according to the German Society of Anesthesia (23).

Perioperative Treatment

After transfer to the operating theater, an arterial line was introduced *via* Seldinger technique in the radial (3 French) or femoral (4 French) artery under local anesthesia before induction of anesthesia. Following the induction of general anesthesia with sufentanil, propofol and rocuronium the patient was intubated. Anesthesia was maintained with sufentanil, rocuronium and sevoflurane. Depth of anesthesia was recorded using entropy and was kept between 40 and 60. A central venous catheter was placed when necessary, according to the attending specialist.

In the goal-directed hemodynamic optimization group (group intervention) hemodynamic management was performed according to a previously published algorithm obtained by pulse contour analysis using the PulsioFlex® device (PULSION Medical Systems SE; Feldkirchen; Germany) (see **Figure 1**) (24). Evaluation of the algorithm was started before induction of anesthesia and continued until discharge from the post-anesthesia care unit (PACU).

For volume therapy Ringer's acetate was used. Every patient received a basal infusion with a dosage of 1 ml/kg per hour according to our standard care. The algorithm was based on the two factors mean arterial blood pressure and cardiac index. If both factors were in a sufficient range (MAP > 70 mmHg, cardiac index > 2.5 L/kg/m^2), no intervention was necessary. In case of insufficient mean arterial pressure or cardiac index, the patient received a fluid bolus of 250 ml Ringer's acetate in 5–10 min followed by another assessment of the algorithm. If after a fluid bolus the stroke volume index did not increase, drug therapy was initiated. Norepinephrine was used as vasopressor, Dobutamine as inotropic medication.

The goal-directed optimization was terminated, when the patient fulfilled the standard criteria for discharge from recovery room: the pain level was ≤3 according to the numeric rating scale (NRS), the hemodynamic situation was stable without catecholamines, the pulmonary situation was stable, and the patient fully awake and compliant.

In the control group an arterial line was placed as well and hemodynamic management was performed according to heart rate and blood pressure without using extended monitoring like pulse contour analysis or any other goal-directed hemodynamic monitoring. Ringer's acetate was used for fluid replacement at the attending anesthetist's discretion. Here, the responsible anesthetist was blinded to the results of the goal-directed hemodynamic monitoring which was obscured by the study team.

In both groups other medication like antibiotics, anticoagulants, or pain medication was administered according to the intraoperative standard operating procedure protocol of the department of anesthesia and intensive care medicine. Patients in all groups received red blood cell transfusion, when hemoglobin value dropped below 8 mg/dl or in case of cardiac impairment such as ST-depression. Coagulation factors and fresh frozen plasma were substituted according to the coagulation status assessed with rotational thromboelastometry (ROTEM^{TM}).

Near-Infrared Spectroscopy

To test our hypothesis, that goal-directed hemodynamic optimization reduces delirium by improving perfusion and consequently enhancing oxygenation, it was necessary to measure the oxygen concentration of the tissue. In the last years NIRS has been introduced in daily clinical practice (25). The device is safe, non-invasive and was used in our patients to assess the oxygen concentration in the brain. In this study, the INVOS^{TM} (Medtronic GmbH, Earl-Bakken-Platz 1, 40670 Meerbusch, Germany) cerebral somatic oximeter with two adult sensors placed on the left and right side of the forehead was used.

To evaluate the difference to pre-operative values, the monitoring was established before induction of anesthesia in both groups. In the intervention group values from NIRS monitoring were available to the responsible anesthetist. However, they were not included in the hemodynamic optimization algorithm. Thus, it was left to the treating anesthesiologist to react individually to possible insufficient NIRS values in the intervention group.

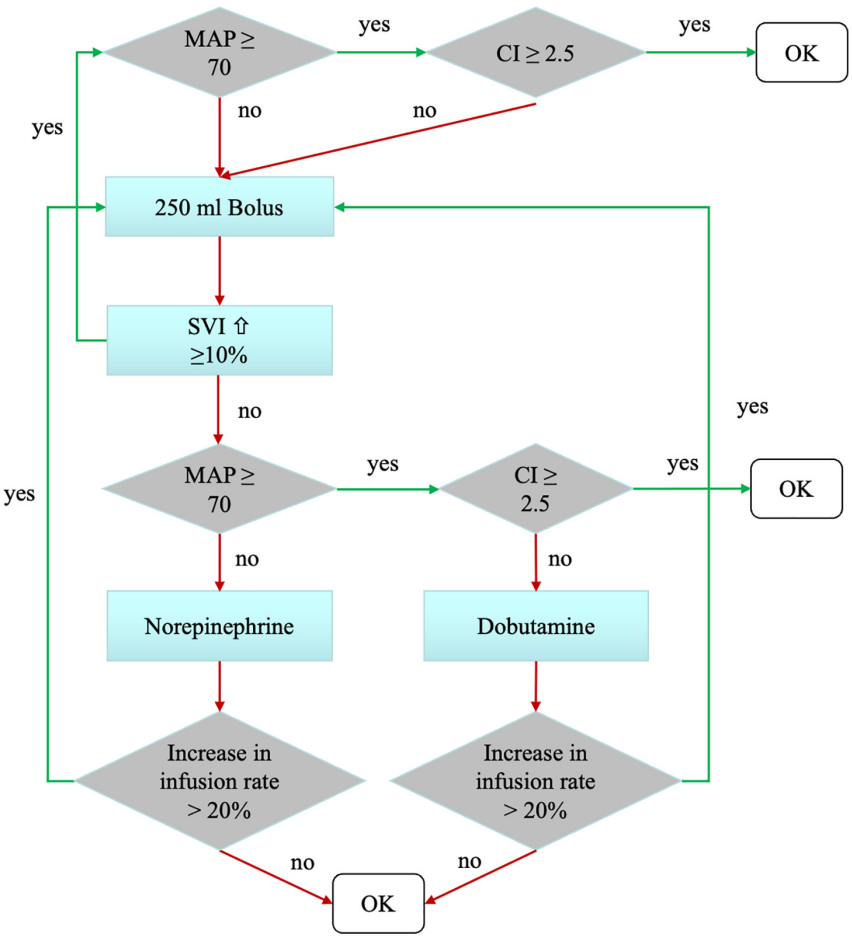

FIGURE 1 | Hemodynamic treatment algorithm in the intervention group. The hemodynamic goals were mean arterial pressure (MAP) >70 mmHg and a cardiac index (CI) >2.5 L/kg/m^2. Hemodynamics were evaluated routinely every 30 min, as well as at times of hemodynamic instability. We tested fluid responsiveness using a volume challenge of 250 mL Ringer's acetate. Depending on changes in the stroke volume index (SVI), the patient received either volume or catecholamines in a titrated manner.

Anesthesiologists in the control group were blinded to the NIRS monitoring.

Data Collection

Following data were recorded: demographics (age, sex, and co-morbidities) and information obtained during the pre-anesthesia visit including predisposing factors for delirium, surgical and anesthesiologic data extracted from the anesthesia and surgical protocol (including medication and administered fluids, goal-directed hemodynamic monitoring parameters as well as NIRS and entropy), parameters obtained during the post-operative visit that can be extracted from the clinical charts on the ward, length of stay in hospital, and follow-up data like mortality after 1 year.

Detection of Delirium, Post-operative Visit and Follow-Up

For detection of delirium the CAM Score (19, 26, 27) was obtained from every patient once daily until day 7 after surgery. This was done by a member of the study team who had been thoroughly trained. If delirium was present, the severity was also assessed using CAM-S (28, 29). Delirium often occurs during the night. Since the visit by the study team took place during the day, we decided to improve detection of delirium by inspecting the patient files to review delirium associated medication like haloperidol and by exchanging information with the ward team. This ensured that even in the event of a poor handover of the night shift to the day shift, abnormalities during the night became apparent and could thus be evaluated with the treating team if necessary. Furthermore, inadequate qualification of the nursing staff (such as inexperienced in delirium symptoms and their clinical presentation) could thus be compensated for *via* the evaluation of the patient record. As delirium can be triggered by pain the NRS was registered daily. If the patient was admitted to ICU, the CAM was also obtained there. As in anesthetized and ventilated patients obtaining the CAM is not possible, we performed an additional sensitivity analysis and assigned

these patients to the delirium group assuming worst outcome (worst-case imputation). Furthermore, a second MMS-Test was performed in every patient on day 7 or the day before discharge, whichever occurs first. Patients were subsequently followed for up to 1 year after surgery *via* telephone interview to assess mortality. In cases where we were not able to reach the patient, we reviewed the hospital record for information about survival during the last year.

Primary and Secondary Endpoints

Primary endpoint was the incidence of delirium until day 7. Duration of delirium as well as the day it first occurred were investigated as secondary endpoints. Further secondary endpoints were: length of stay in hospital, in-hospital mortality, and mortality after 1-year.

Blinding

Patients were blinded to group allocation and intervention throughout the trial. Anesthesiologists treating the patient during surgery and in the PACU were not blinded but in the control group they were not able to assess the parameters of the goal-directed hemodynamic and NIRS monitoring. Nurses and physicians treating the patient on ICU or normal ward after surgery were blinded to group allocation. The outcome assessor was not blinded to the intervention.

Statistical Analyses

Data analysis was performed with R version 4.1.0. Continuous variables are presented as median [interquartile range (IQR)]. Categorical variables are presented using absolute numbers and frequencies. Effect sizes were calculated using differences in median for continuous variables and risk difference (RD) for binary variables. In addition to effect sizes null hypothesis tests were conducted *via* Mann-Whitney *U*-tests for continuous variables and by χ^2–tests for binary variables. To validate our results, we performed a sensitivity analysis using worst-case imputation. A two-sided *P*-value of less than 0.048 was considered statistically significant.

Sample Size Calculation

By using a screening score we intended to included patients with an expected delirium-incidence above 30%. As in most interventional studies the risk for post-operative delirium could be reduced by one third these figures could have been used for sample size calculation (4, 6). However, 6 or more points in the screening score correspond to a wide range of delirium-incidence between 30 and 50%. As the actual incidence had a significant impact on the number needed per group, we *a priori* planned an interim analysis after 100 included patients to assess the new sample size according to a modification of the O'Brian-Fleming technique (30). In the interim analysis the incidence of delirium was 3/47 (6%) in the intervention and 11/52 (21%) in the control group ($P = 0.04$; Fisher's exact test; 1 patient excluded as pre-set surgery time was not adhered). As the difference of delirium between the two groups was not significant with a pre-defined $\alpha < 0.002$ to finish the study, the sample size needed per group was adjusted. Thereafter, based on two-tailed χ^2-test, assuming an $\alpha = 0.048$ and a power of 80%, the analysis disclosed 86 patients per group. The calculation was performed *via* DataTab (URL).[1] As a result, of the *a priori* planned interim analysis, the targeted sample size was now set to 172.

RESULTS

Between May 2013 and December 2019, 172 patients were included in the study. Follow-up was finished in February 2021. **Figure 2** shows the CONSORT diagram of the study. Surgical procedures included all departments with abdominal surgery being the most frequent. 85 patients were randomized into the intervention group. 87 patients received standard care. Baseline characteristics were comparable between the two groups regarding screening score, frailty, and pre-medical condition (**Table 2**).

Components of the Goal-Directed Therapy and Cerebral Oxygenation

The number of crystalloids, colloids, blood products, and vasopressors infused was comparable between groups. Patients in the intervention group received more inotropes. Regarding hemodynamics patients in the control group had an increased MAP, whereas cardiac index was higher in the intervention group (**Table 3**). NIRS monitoring showed comparable cerebral oxygenation (median and delta from pre-induction) in both groups during surgery [median NIRS total: control 68 (IQR 78 to 96) vs. intervention 81 (75 to 88); median difference 2.8; 95% confidence interval (CI) −0.9 to 6.0; $P = 0.09$; **Table 3**] and in the PACU (**Table 3**).

Primary Outcome

Delirium was present in 13 patients in the intervention group (15%) and in 18 in the control group (21%) (RD, −5%; 95% CI, −16.8 to 6.1%; $P = 0.47$) (**Table 4**). The type of delirium assessment (CAM score or chart review) had no influence on the results (**Table 4**). In an additional sensitivity-analysis with anesthetized patients included in the group of delirium (worst-case imputation), there was no difference between groups (23 vs. 18%) (RD, −5%; 95% CI, −17 to 7%; $P = 0.50$). Length of delirium as well as severity of delirium was not significantly different between groups [2 (1 to 3) vs. 1 (1 to 2)], difference in medians, 1; 95% CI 1 to 2; $P = 0.27$).

Secondary Outcomes

There was no significant difference between groups regarding length of stay in hospital as well as in-hospital-mortality (**Table 4**). One-year mortality was reduced in the intervention

[1] https://datatab.net

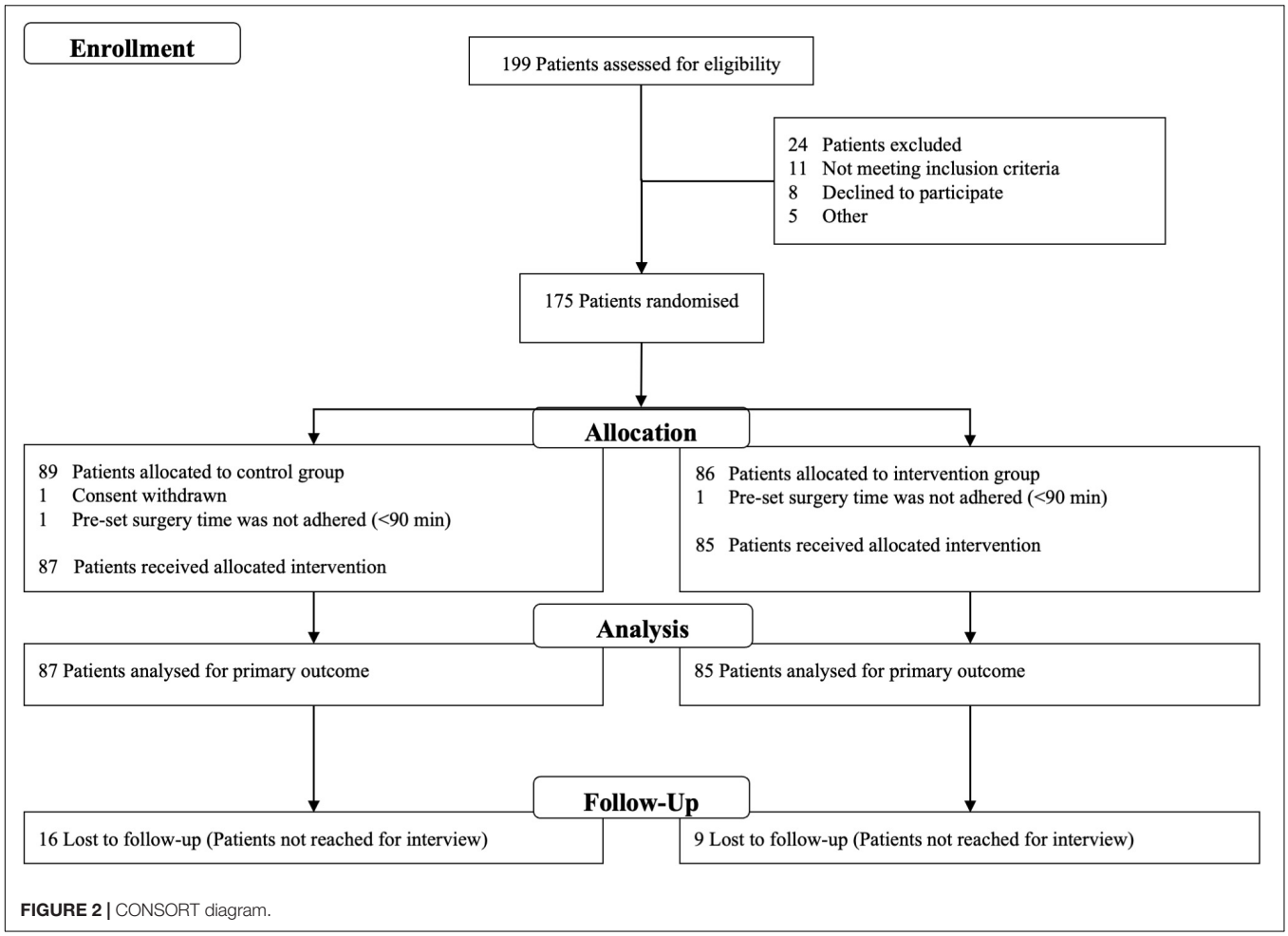

FIGURE 2 | CONSORT diagram.

group (12 vs. 24%) (RD, −14%; 95% CI, −25.4 to −1.5%; $P = 0.03$) (**Table 4**).

DISCUSSION

In this single-center, randomized-controlled pilot trial a goal-directed hemodynamic optimization algorithm did not lead to significantly different therapeutic interventions, and thus did not result in different hemodynamics or values of cerebral oxygenation. Consequently, the algorithm applied did not reduce post-operative delirium in elderly high-risk patients. There was no effect on secondary endpoints like length of stay in hospital as well as in-hospital-mortality. This monocentric trial does not support the use of this goal-directed hemodynamic optimization algorithm in the prevention of post-operative delirium.

The incidence of post-operative delirium with 21% in the control group and 15% in the intervention group ($P = 0.47$) was low compared to an anticipated occurrence of delirium of a least 30% in our high-risk population (3). There was a large difference in the incidence of delirium in the intervention group between the interim analysis (6%) and the final analysis (15%). Therefore, the intended level of power was not achieved. The reasons for this can only be speculated, as there were no changes to the study protocol or study team after the interim analysis. The missing effect of the intervention, nevertheless, is in line with the investigations from other authors. In a systematic review and meta-analysis multicomponent strategies were able to reduce the incidence of delirium in elderly patients with scheduled non-cardiac surgery. Strategies during the perioperative period (optimization of pain management or anesthesia) could only rarely improve the rate of delirium (4). However, in the special subgroup of patients in the prone position goal-directed fluid therapy improved hemodynamics and cerebral oxygenation and reduced the incidence of post-operative cognitive dysfunction (31, 32). Also, non-pharmacological multicomponent approaches were more effective. In our study pain management was sufficient in both groups and therefore no influencing factor for delirium. To this point monitoring depth of anesthesia is the best of the perioperative components to reduce delirium, especially to guide anesthetic titration during surgery and avoid long periods of burst suppression (33, 34). It must be emphasized that the evidence on this topic is still insufficient. Although delirium reduction of up to 30% was reported in the cited meta-analyses, the ENGAGES trial published in 2019 showed

TABLE 2 | Characteristics after randomization into the two groups.

	Control *N* = 87	**Intervention *N* = 85**
Age (yr), median [IQR]	79 [74 to 82]	77 [74 to 82]
Female, n/total N (%))	37 (43%)	36 (42%)
BMI, median [IQR]	24.6 [23.0 to 28.7]	24.7 [22.5 to 27.4]
Delirium risk score, median [IQR]	7 [6 to 8]	7 [7 to 8]
Delirium risk score components, n/total N (%)		
6	28 (32%)	19 (23%)
7	28 (32%)	35 (41%)
8	20 (23%)	22 (26%)
9	7 (8%)	7 (8%)
10	4 (5%)	2 (2%)
ASA, median [IQR]	3 [2 to 3]	3 [2 to 3]
ASA III, n/total N (%)	57 (66%)	63 (74%)
Clinical frailty scale, median [IQR]	4 [3 to 4]	4 [3 to 5]
Clinical frailty scale components, n/total N (%)		
1-4	67 (77%)	61 (72%)
5-9	20 (23%)	24 (28%)
Preoperative MMSE, median [IQR]	27 [25 to 29]	28 [26 to 29]
Preoperative MMSE components, n/total N (%)		
Dementia	1 (1%)	3 (3%)
Cognitive impairment	21 (24%)	15 (18%)
Unobtrusive	65 (75%)	67 (79%)
Surgical department, n/total N (%)		
Abdominal surgery	66 (76%)	54 (64%)
Vascular surgery	5 (6%)	14 (16%)
Orthopedics	12 (14%)	13 (15%)
Trauma surgery	4 (4%)	4 (5%)
Type of surgery, n/total N (%)		
High-risk surgery (open vascular abdominal, oesophageal)	7 (8%)	6 (7%)
Moderate-risk Surgery (abdominal, orthopedic)	74 (85%)	75 (88%)
Anesthesia time (min), median [IQR]	274 [203 to 364]	278 [218 to 407]
Surgical time (min), median [IQR]	190 [115 to 260]	180 [130 to 300]
Comorbidities, n/total N (%)		
Diabetes mellitus	24 (28%)	21 (25%)
Arterial hypertension	70 (81%)	66 (78%)
Cardiac risk factors, n/total N (%)	65 (75%)	71 (84%)
Coronary artery disease	39 (45%)	38 (45%)
Heart failure	20 (23%)	21 (25%)
Arrhythmia	13 (15%)	32 (38%)
History of stroke, n/total N (%)	7 (8%)	10 (12%)
History of delirium, n/total N (%)	2 (2%)	2 (2%)

BMI, Body-Mass-Index; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental-State Examination; IQR, interquartile range.

different results (35). Here, BIS-guided anesthesia was able to reduce the dosage of volatile anesthetics and subsequently the cumulative time with electroencephalography suppression, but not the delirium incidence within the first 5 days after major surgery. The authors attributed the differences from the meta-analyses to, among other things, older patients and compared major surgical procedures in their study. While the studies in the referred metanalyses used bispectral-index (BIS) entropy parameters in our study were comparable between groups and in the lower target range of around 40, indicating adequate depth of anesthesia.

Although in the intervention group fluid and catecholamine management was tightly controlled by the hemodynamic optimization protocol, both groups received equivalent amounts of fluids and vasopressors. This resulted in comparable intraoperative hemodynamic parameters, like sufficient mean arterial pressure and cardiac output. As cardiac output was only measured in the intervention group, this resulted in higher amounts of inotropes and therefore an increased cardiac index in this group. In the control group MAP was minimally elevated without clinical relevance. As hemodynamics did not differ between groups, not surprisingly NIRS values as

TABLE 3 | Comparison of perioperative parameters.

	Control *N* = 87	Intervention *N* = 85	Effect size [95% CI]	*P*-value
Fluids and catecholamines during surgery				
Ringer's acetate (ml), median [IQR]	2400 [1850 to 3400]	3100 [1900 to 4500]	-700 [-1050 to 300]	0.08
Gelatine administered, n/total N (%)	4 (5%)	3 (4%)	-1.1% [-7 to 4.8%]	1.00
Albumin administered, n/total N (%)	13 (15%)	18 (21%)	6.2% [-5.2 to 17.7%]	0.39
Blood products administered, n/total N (%)	5 (6%)	12 (14%)	8.4% [-0.5 to 17.2%]	0.11
Mean inotropic ($\mu g\ kg^{-1}\ min^{-1}$), median [IQR]	0 [0 to 0]	0 [0 to 1.8]	0 [0 to 0]	<0.001
Mean vasopressors ($\mu g\ kg^{-1}\ min^{-1}$), median [IQR]	0.04 [0.03 to 0.06]	0.04 [0.02 to 0.07]	0 [-0.02 to 0]	0.67
Fluids in PACU				
Ringer's acetate (ml), median [IQR]	1500 [0 to 2700]	1850 [0 to 3200]	-350 [-2058.7 to 925.4]	0.15
Gelatine administered, n/total N (%)	2 (2%)	1 (1%)	-1.1% [-5 to 2.8%]	1.00
Albumin administered, n/total N (%)	10 (12%)	19 (23%)	10.9% [-0.2 to 22%]	0.10
Blood products administered, n/total N (%)	11 (13%)	6 (7%)	-5.6% [-14.4 to 3.3%]	0.32
Hemodynamics during surgery				
MAP (mmHg), median [IQR]	86 [78 to 96]	81 [75 to 88]	5.2 [-2 to 10.1]	0.02
Heartrate (bpm), median [IQR]	60 [54 to 68]	60 [56 to 70]	0.3 [-4.5 to 3.5]	0.34
Cardiac index ($l\ min\ m^{-2}$), median [IQR]	2.5 [2.2 to 3.0]	2.7 [2.6 to 3.1]	-0.2 [-0.4 to -0.1]	<0.001
Hemodynamics in PACU				
MAP (mmHg), median [IQR]	85 [77 to 94]	83 [79 to 95]	2.8 [-3.2 to 6.5]	0.86
Heartrate (bpm), median [IQR]	72 [65 to 79]	69 [62 to 80]	2.7 [-2.2 to 7]	0.61
Cardiac Index ($l\ min\ m^{-2}$), median [IQR]	3.1 [2.6 to 3.5]	3.3 [2.7 to 3.8]	-0.2 [-0.5 to 0.2]	0.15
NIRS and entropy during surgery				
NIRS total, median [IQR]	68 [63 to 72]	65 [59 to 70]	2.93 [-0.88 to 6.03]	0.09
NIRS left (%), median [IQR]	70 [63 to 74]	66 [60 to 71]	4.4 [-0.5 to 7.1]	0.05
NIRS right (%), median [IQR]	67 [62 to 72]	65 [60 to 70]	1.8 [-0.8 to 5.7]	0.16
Delta NIRS left (pre-induction and mean during surgery) (%), median [IQR]	-4 [-7 to 0]	-4 [-8 to -1]	-0.1 [-4.1 to 3.1]	0.84
Delta NIRS right (pre-induction and mean during surgery) (%), median [IQR]	-3 [-8 to 2]	-4 [-7 to 0]	-1.6 [-5.4 to 2.8]	0.50
SE during surgery, median [IQR]	40 [34 to 47]	42 [33 to 49]	-2 [-5.1 to 3.7]	0.68
NIRS in PACU				
NIRS left (%), median [IQR]	64 [59 to 70]	63 [60 to 69]	1 [-2.8 to 4.2]	0.68
NIRS right (%), median [IQR]	64 [58 to 69]	62 [58 to 68]	2.1 [-2.8 to 5.7]	0.40

Blood products include red blood cells, thrombocytes and fresh frozen plasma. All blood products including gelatine and albumin are presented as the number of the patients, who received therapy: n/total N (%).

CI, confidence interval; IQR, interquartile range; ICU, intensive care unit; MAP, Mean Arterial Pressure; PACU, Post-anaesthesia Care Unit; NIRS, Near-Infrared-Spectroscopy; SE, State Entropy.

surrogate parameters for cerebral perfusion and oxygenation were comparable between groups. Based on this no difference in post-operative delirium could be expected.

Although we did not see significant results in our primary endpoint, secondary analysis showed a difference in 1-year mortality between groups (P = 0.03). Since there was no influence on hemodynamics or cerebral oxygenation this result cannot be attributed to the intervention and we consider it as an epiphenomenon.

As a strength of our pilot study, using a screening tool for detection of patients with high risk for delirium made it possible to include a wide variety of patients with severe pre-existing conditions, extensive surgery, and an expected high risk of at least 30% for post-operative delirium. For identification of these high-risk patients, we used a modification of the risk-score published by Marcantonio (18). Several other scores have been introduced to stratify patients according to their individual risk for delirium. For example, Inouye identified five independent factors during hospitalization. However, these scores were mainly validated on general wards and the factors are not specific to surgical patients (17). In contrast, Marcantonio introduced a risk-score, that considers additional intraoperative and post-operative precipitating factors, like type of anesthesia and type of surgery. Daily post-operative visits for up to 7 days as well as inspection of the patient medical charts allowed for almost complete post-operative monitoring in order to detect all forms of delirium. The CAM-Score is the most reliable and validated score to detect delirium and is available in German. It has a sensitivity of 0.79 and a specificity of 0.97 (26).

However, there are limitations to our study: a single-center pilot trial only allows to assess the level-of-care provided in our hospital. This effect is emphasized by the already good standard hemodynamic management in the control group, that could not be further optimized by the algorithm. This lack of effect, especially in comparison with an already good control group, has already been shown, also in own work (36, 37). It might be explained by the fact that the algorithm used was based on absolute values of MAP and

TABLE 4 | Primary and secondary endpoints in the two groups.

	Control *N* = 87	Intervention *N* = 85	Effect size [95% CI]	*P*-value
Primary endpoint				
Occurrence of delirium, n/total N (%)	18 (21)	13 (15)	-5.4 [-16.8 to 6.1]	0.470
Occurrence of delirium by CAM, n/total N (%)	16 (18)	11 (13)	-5 [-16 to 5]	0.440
Occurrence of delirium by chart review, n/total N (%)	6 (7)	5 (6)	-1 [-8 to 6]	1.000
Occurrence of delirium (worst-case imputation), n/total N (%)	20 (23)	15 (18)	-5 [-17 to 7]	0.496
Length of delirium (days), median [IQR]	2 [1 to 3]	1 [1 to 2]	1 [-1 to 2]	0.265
Severity of Delirium (CAM-S), median [IQR]	0 [0 to 2]	0 [0 to 1]	0 [0 to 0]	0.120
Secondary endpoints				
NRS, median [IQR]	2.3 [1.1 to 3.3]	2.0 [0.9 to 3.0]	0.29 [-0.25 to 0.85]	0.173
Δ MMSE, median [IQR]	0 [-1 to 1]	0 [-1 to 1]	0 [-1 to -1]	0.948
Number of patients admitted to ICU, n/total N (%)	48 (55)	51 (61)	4.8 [-9.9 to 19.6]	0.501
LOS ICU (days), median [IQR]	1 [0 to 1]	1 [0 to 1]	0 [-1 to 0]	0.396
LOS Hospital (days), median [IQR]	11 [8 to 17]	10 [7 to 16]	1 [-2 to 4]	0.414
In-hospital mortality, n/total N (%)	6 (7)	3 (4)	-3.3 [-10.0 to 3.2]	0.529
Long term secondary outcome				
Lost-follow up, n/total N (%)	16 (18)	9 (11)	-7.8 [-18.2 to 2.6]	
One-year mortality, n/total N (%)	24 (34)	12 (16)	-13.5 [-25.4 to -1.5]	*0.028*

CAM, Confusion Assessment Method, CAM-S, Severity of the Confusion Assessment Method, NRS, Numeric Rating Scale, MMSE, Mini Mental State Examination, LOS, Length of Stay, ICU, Intensive Care Unit.

cardiac index. This may be a limitation of our study, as recent evidence suggests the use of individualized hemodynamic target parameters based on pre-operative measurements (38). In addition, the possibility of performance bias as reason for the missing effect of the intervention must also be considered. Above that, it must be further noted that the risk of delirium in our patient population may not have been severe enough in order for the intervention to achieve a difference.

Furthermore, hemodynamic variability must be taken into account, as it is possible that patients in the control group experienced periods of hypotension followed by periods of hypertension. However, the amount of time patients experienced intraoperative hypotension was not measured. Intervention was limited to the perioperative period as we did not provide guidelines for pre-operative optimization or therapy in the post-operative course. A further limitation is the missing information regarding post-operative inflammation as blood samples were not taken in a regular base.

Our intervention focused solely on hemodynamic optimization. In particular, no targeted intervention was provided for additional optimization of insufficient NIRS values. This is partly due to the fact that improved cardiac output was hypothesized to improve cerebral perfusion and subsequently oxygenation. Further research in this field should include management of pathological NIRS values in the algorithm, although there is only a weak association of low NIRS values and worse neurological outcome and the effect is most prominent in cardiac surgery (39, 40). An additional individualized, multi-component intervention strategy might have been more efficient in reducing delirium and should be investigated in a subsequent trial (4, 41). Lastly, the outcome-assessor was not blinded in this trial and outcome was assessed once daily, which can lead to bias. This effect might be somewhat mitigated by communicating with the team and assessing psychoactive medication utilization. However, the combination of assessment by a team member and chart review to a composite endpoint is also not ideal as it mixes different delirium screening methods. Nevertheless, because the incidences for both methods separately are comparable to the composite endpoint, the results are valid. There is a possibility that a significant amount of hypoactive delirium was missed and that the CAM-positive patients in the study had more severe delirium. Ideally, a more sensitive assessment method for delirium should be used in a follow-up trial and applied multiple times daily.

In conclusion, a goal-directed hemodynamic optimization protocol did not change hemodynamic interventions, did not improve the patients' hemodynamics, and did not enhance cerebral oxygenation in old high-risk patients. The algorithm applied had no effect on the incidence of post-operative delirium.

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 Ethikkommission der Technischen Universität München, Ismaninger Straße 22, 81675 München. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS was the principal investigator and developed the protocol. BU was the study statistician. SS, BJ, and KEF were involved in the ethical approval. KEF, BU, AS, BJ, MB, SJS, and SS were involved in the analysis and interpretation of the data. KEF, SS, AS, and BJ were involved in the data acquisition and quality assurance. All authors critically revised the manuscript and approved its final version.

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The hemodynamic stability of remimazolam compared with propofol in patients undergoing endoscopic submucosal dissection: A randomized trial

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Objective: Hypotension is common in propofol anesthesia. Whether remimazolam could reduce intraoperative hypotension remains unknown. We therefore tested the primary hypothesis that remimazolam reduces the incidence of intraoperative hypotension compared with propofol in adult patients undergoing endoscopic submucosal dissection (ESD) surgery.

Materials and methods: We conducted a prospective trial to compare patients who received either remimazolam or propofol bolus induction and thereafter intravenous infusion. The hemodynamic parameters were measured using CNAP® Monitor 500 system. Our primary analysis was to compare the incidence of hypotension defined as systolic blood pressure below 90 mmHg between remimazolam and propofol during the whole anesthesia period.

Results: The incidence of hypotension decreased by 50%, from 67.9% in propofol group to 32.1% in remimazolam group ($p < 0.01$). Patients received less amount of intraoperative phenylephrine in the remimazolam group than the propofol group (0 [0–40] μg vs. 80 [0–200] μg, $p < 0.01$). Time-weighted average and cumulative time of hypotension was lower in remimazolam group compared with propofol group ($p < 0.05$). Cardiac output continuously measured by CNAP was preserved much better in remimazolam group compared with propofol group ($p = 0.01$), while systemic vascular resistance did not differ between the groups. The median time from discontinuation until full alertness was 4 [3–11.8] min in the remimazolam group compared with 15 [12.0–19.8] min in the propofol group ($p < 0.01$).

Conclusion: Remimazolam has better hemodynamic stability than propofol in adult patients undergoing ESD surgery. The benefits of remimazolam on

hemodynamic stability and hypotension prevention may be partly contributed to its better preservation of cardiac output.

Clinical Trial Registration: [http://www.chictr.org.cn/com/25/showproj.aspx?proj=61104], identifier [ChiCTR2000037975].

KEYWORDS

gastrointestinal endoscopy, anesthesia, hypotension, enhanced recovery after surgery, hemodynamics

Highlights

- Remimazolam has better hemodynamic stability than propofol in adult patients undergoing ESD surgery.
- The benefits of remimazolam on hypotension prevention may be partly contributed to its better preservation of cardiac output.
- Remimazolam promotes faster recovery after surgery compared with propofol when antagonized with flumazenil.

Introduction

Owing to advances in endoscopic techniques and favorable outcomes, endoscopic submucosal dissection (ESD) has become an established treatment for early esophageal cancer or mucosal disease, especially in patients without lymph node metastasis (1–3). Esophageal ESD is a relatively complex procedure, requiring precise maneuvers. Previous studies recommended that ESD should be performed under general anesthesia, with the aim to minimize patient movement, improve patients' satisfaction, and reduce the occurrence of perforation or aspiration pneumonia. Therefore, general anesthesia is currently considered to be an optimal method for most ESD surgery (4).

Propofol, which has excellent sedative properties and a short terminal half-life, is commonly used in ESD surgery (5, 6). Nevertheless, propofol has some unfavorable adverse effects, including pain noted on intravenous injection and dose-related cardiovascular depression, especially when given in conjunction with opioids. Hypotension is the most frequent adverse events related to propofol use. It has been reported that the incidence of hypotension caused by propofol is as high as 31–50% in ESD surgery (7, 8). These side effects have led to the evaluation of new sedatives.

Remimazolam, an ultra-short-acting benzodiazepine hypnotic, has been used in the anesthesia of ESD (9). Remimazolam has a short half-life, which results in the quick onset and recovery. Most importantly, remimazolam has little depressive effect on cardiovascular system and can reduce the incidence of hypotension (10–12). At a dose of 1 mg/kg/h, remimazolam will provide anesthesia for operative surgery without major adverse effects. However, there is a scarcity of data to investigate the impact of remimazolam on occurrence of intraoperative hypotension compared with propofol.

In this study, we aimed to investigate the benefits of remimazolam on preventing hypotension compared with propofol during ESD surgery. Specifically, we tested the hypothesis that remimazolam reduces the incidence of hypotension compared with propofol using a continuous non-invasive arterial pressure monitor, CNAP® Monitor 500 system (CNSystems Medizintechnik AG, Graz, Austria).

Materials and methods

Ethics and registration

This study was a prospective, randomized, parallel trial comparing remimazolam (HengRui Medicine Co., Ltd., Lianyungang, China) to propofol (Fresenius-Kabi AG, Bad Homburg, Germany) in ESD. Ethical approval for this study [IRB No. KS(Y)20230] was provided by the Institutional Review Board (IRB) of Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China (Chairperson Ning Zheng) on 14 August 2020. Written informed consent was obtained from each patient before enrollment. The trial was registered before patients' enrollment at http://www.chictr.org.cn/com/25/showproj.aspx?proj=61104 (ChiCTR2000037975, principal investigator: Jingxiang Wu, date of registration: 08 September 2020). Recruitment was extended from December 2020 to July 2021.

Inclusion and exclusion criteria of patients

The inclusion criteria were as follows: (1) male and female subjects, aged 18–80 years; (2) ASA I–III; and (3) body mass

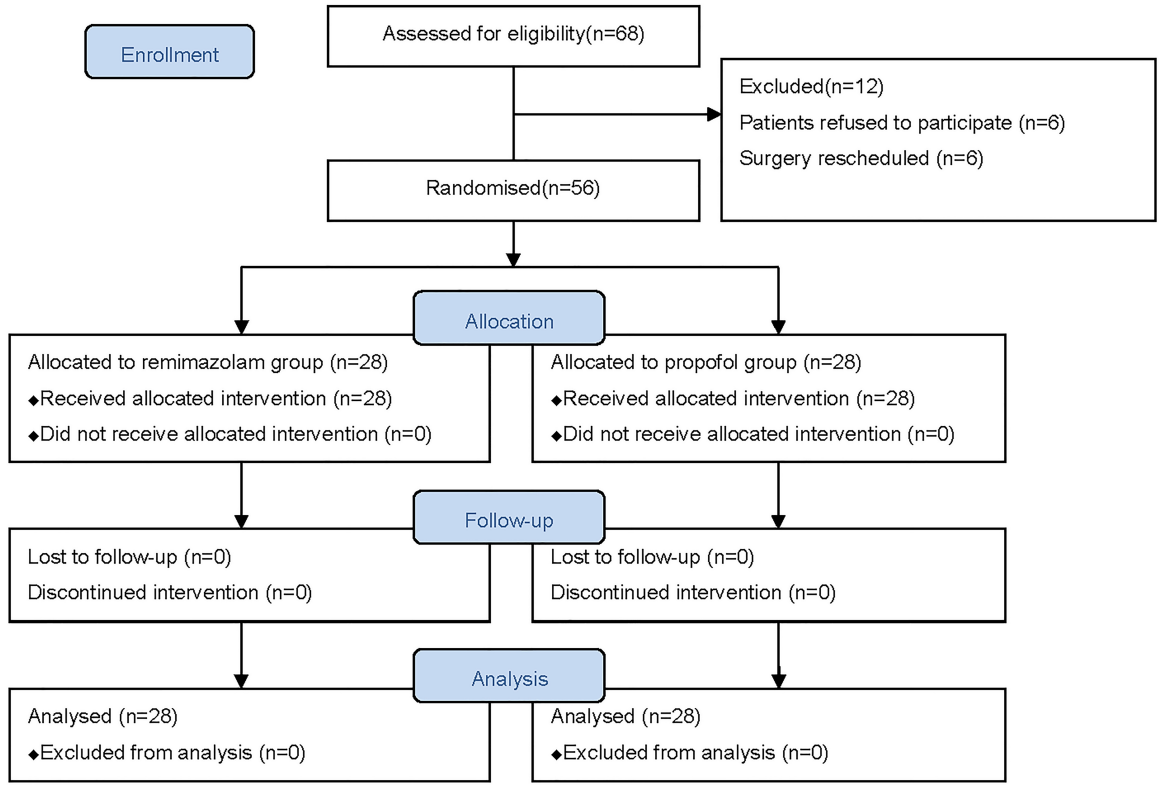

FIGURE 1
Flowchart of patients enrolled in the study.

index (BMI) between 18 and 30 kg/m^2. Patients were excluded if they had (1) uncontrolled hypertension or hypotension, or clinically important coronary atherosclerotic heart disease or heart failure; (2) severe respiratory disease; (3) severe sinus bradycardia, or heart block, or frequent ventricular arrhythmia, or atrial fibrillation; (4) clinically important coagulopathy; (5) end-stage hepatic dysfunction or renal disease requiring dialysis; (6) emergent surgeries; (7) peripheral artery disease with upper extremities dysfunction; and (8) other occasions when the investigators determined inappropriate, including patients unsuitable to rapid extubate when ESD was used for superficial pharyngeal carcinoma.

Randomization and masking

All eligible patients were randomized into one of the two groups, namely, remimazolam group and propofol group in a ratio of 1:1 by a computer-generated coding system. An opaque, sealed envelope was opened by a masked investigator to determine the group assignment after the patient had provided written informed consent. Outcome assessors and endoscopists were masked to the group assignment.

Protocol

Patients were randomized to receive an initial dose of either remimazolam (0.3 mg/kg) or propofol (2.0 mg/kg) for the induction of anesthesia. According to the "Chinese Experts' Consensus on the Diagnosis and Treatment of Sedation and Anesthesia in Digestive Endoscopy" (13), patients received their assigned treatment as intravenous push by a syringe in 1-min period. When the patient was sufficiently sedated [Modified Observer's Assessment of Alertness/Sedation (MOAA/S) = 0, **Supplementary Table 1**] (14), induction of anesthesia was accomplished. If sedation was deemed to be inadequate defined as MOAA/S > 0, supplemental doses were administered as intravenous push by a syringe in 1-min period (remimazolam 0.1–0.2 mg/kg or propofol 0.5 mg/kg) until MOAA/S = 0. Then, sufentanil 0.5 μg/kg and rocuronium 0.6 mg/kg were given to facilitate tracheal intubation. After tracheal intubation, the anesthesia machine was connected for mechanical ventilation and the volume control mode was used.

Remimazolam or propofol was intravenously infused according to bispectral index (BIS) between 40 and 60. Remimazolam was initially infused at 1 mg/kg/h, with the maximum infusion rate of 3 mg/kg/h. When BIS exceeded 60, a supplemental dose of 0.15 mg/kg of remimazolam was then

TABLE 1 Baseline characteristics of patients receiving remimazolam or propofol.

Variable	Remimazolam group (n = 28)	Propofol group (n = 28)	Standardized difference
Demographic factors			
Age (y)	62.8 ± 7.1	64.7 ± 8.9	0.24
Sex (male/female)	21/7	19/9	0.16
Body weight (kg)	65.1 ± 10.8	63.1 ± 8.5	0.20
Body mass index (kg/m^2)	23.2 ± 3.5	22.3 ± 2.9	0.27
History of hypertension, n (%)	7 (25)	13 (46.4)	0.54
History of diabetes mellitus	3 (10.7)	3 (10.7)	0
History of alcohol (none/former/current)	10/13/5	15/9/4	0.23
History of smoke (none/former/current)	10/17/1	16/11/1	0.30
ASA physical status			0.18
I	3 (10.7)	1 (3.6)	
II	21 (75)	24 (85.7)	
III	4 (14.3)	3 (10.7)	
Pre-operative fasting time, hours	23 [20, 24]	21.5 [20, 24]	0.25
Pre-operative lactate level, mmol/L	1.14 ± 0.31	1.17 ± 0.35	0.09
Pre-operative glucose level, mmol/L	5.71 ± 0.67	5.55 ± 0.64	0.24
Intraoperative factors			
Total amount of sufentanil	35 [31.3, 40]	35 [30, 45]	0
Total amount of rocuronium	50 [40, 60]	50 [42.5, 65]	0
Duration of surgery (min)	53 [27.5, 81]	55 [35.5, 77.3]	0.09
Duration of anesthesia (min)	92.5 [66.3, 120.8]	87 [71.5, 114.8]	0.07
Colloid (mL)	200 [0, 500]	225 [50.0, 450]	0.10
Crystalloid (mL)	500 [500, 950]	500 [500, 700]	0.32
Estimated urine output, ml	Not applicable	Not applicable	
Esophageal temperature at the end of surgery (°C)	36.4 ± 0.38	36.4 ± 0.39	0.06

Data are presented as either mean ± SD, median [quartile 1, quartile 3], or number (%). The absolute standardized difference measures the mean difference between the remimazolam and propofol groups.

TABLE 2 Summary of blood pressure outcomes.

Outcomes	Remimazolam group (n = 28)	Propofol group (n = 28)	P-value
Primary outcome			
SBP < 90 mmHg, n (%)	9/28 (32.1)	19/28 (67.9)	0.008**
Secondary outcomes			
Total amount of phenylephrine, μg	0 [0, 40]	80 [0, 200]	0.001**
Time-weighted average of SBP < 90 mmHg	23.6 [0, 135.0]	99.1 [29.6, 276.5]	0.015*
Cumulative time of SBP < 90 mmHg, min	4.2 [0, 17.5]	13.1 [6.1, 29.1]	0.035*
Time-weighted average of MAP > 100 mmHg	0 [0, 2.0]	0.1 [0, 2.4]	0.801
Number of patients with any MAP readings > 100 mmHg	14/28 (50%)	15/28 (53.6%)	0.791
Cumulative time of MAP > 100 mmHg, min	0.9 [0, 14.7]	1.6 [0, 10.9]	0.876

Data are presented as either median [quartile 1, quartile 3], or number (%). Denotes statistically significant (*$p < 0.05$ or **$p < 0.01$) differences among the two groups. Mann-Whitney U test was used to assess the difference between the two groups for non-normal distribution parameters, and Chi-square or Fisher Exact tests for binary outcomes. SBP, systolic blood pressure; MAP, mean arterial pressure.

intravenously added; when BIS was below 40, remimazolam was decreased at a rate of 0.2 mg/kg/h step by step. Propofol was initially infused at 5 mg/kg/h. When BIS exceeded 60, a supplemental dose of 0.5–1 mg/kg of propofol was then intravenously added over 30 s; or propofol was decreased at a rate of 1 mg/kg/h when BIS was below 40. The infusion of remimazolam or propofol stopped when the endoscopic probe was withdrawn.

All ESD procedures in this trial were accomplished by two experienced endoscopists who specialized in ESD at least

2 or 3 years. Typically, ESD was conducted in a sequential step, including marking the perimeter of the lesion with cautery, and then injecting a lifting agent into the submucosa around the lesion, thereafter cutting circumferentially around the lesion, dissecting the submucosa beneath the lesion, and finally managing intraprocedural bleeding that occurred during mucosal incision or submucosal dissection.

Immediately after discontinuation of remimazolam or propofol, flumazenil 0.5 mg was injected to reverse the sedatives, and muscle relaxants were routinely reversed with atropine/neostigmine. An anesthesiologist determined when to extubate and evaluate patients' recovery. When patients had an Aldrete score > 9 and felt warm-alert-comfortable, then they were allowed to discharge to the ward.

Measurements

Patient was positioned in left lateral decubitus for ESD surgery. We attached the CNAP® Monitor 500 system's finger cuff to the finger of left hand and started the measurement after calibration. CNAP® Monitor 500 system (CNSystems Medizintechnik, Graz, Austria) was a continuously non-invasive arterial blood pressure monitoring system with finger cuff-derived method, validated and utilized in various clinical settings (15). Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), and systemic vascular resistance (SVR) at specific time-points, including baseline, 1 and 3 min after tracheal intubation, start of operation, every 5 min during the operation, and the end of operation were obtained from CNAP. Electrocardiography, pulse oxygen saturation, radical arterial invasive blood pressure, and esophageal temperature were monitored using GE Carescape Monitor B850 (GE Healthcare, Chicago, IL, United States).

Outcome assessment

The primary outcome was the incidence of hypotension during the whole anesthesia period. Hypotension was defined as non-invasive systolic blood pressure (SBP) < 90 mmHg lasting at least 1 min. When hypotension occurred, phenylephrine 40 μg or more was intravenously administrated until SBP returned to the normal range (90–140 mmHg). The amount of phenylephrine was recorded.

The secondary outcome included the total amount of phenylephrine, time-weighted average and cumulative time of SBP < 90 mmHg, and time-weighted average and cumulative time of MAP > 100 mmHg. Time-weighted average of SBP under a threshold of 90 mmHg was calculated as the area between 90 mmHg threshold and the curve of the SBP measurements was divided by total continuous reading time (16). Time-weighted average of MAP > 100 mmHg was calculated by the same method. The time of first episode of hypotension was recorded.

We also recorded CO and SVR at the before-mentioned time points, as CO*SVR = (MAP-CVP) × 80; therefore, the product of CO and SVR could reflect the formation of MAP to some extent.

Emergence time was defined as the time from discontinuation of remimazolam or propofol to modified observer's assessment of alert/sedation (MOAA/S) = 5 measured repetitively three times (**Supplementary Table 1**) (17). Time to extubate was defined as the time from discontinuation of remimazolam or propofol to the removal of endotracheal tube. Recovery time was defined as the time from discontinuation of remimazolam or propofol to the modified Aldrete score returning to 9 (18).

Patients' demographics, surgical variables, anesthetic variables, pre-operative and post-operative arterial blood gases and electrolytes, and post-operative length of stay were measured and recorded.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± SD, while data showing a skewed distribution were expressed as median (interquartile range). Categorical data were presented as number or percentages.

For baseline analysis and primary outcome, quantitative data between the two groups were analyzed by the two-sample *t*-test or non-parametric test, and categorical data were analyzed by χ^2 test, or Fisher's exact test.

For secondary outcome analysis, we compared the time-weighted average of SBP < 90 mmHg, cumulative time of SBP < 90 mmHg, time-weighted average of MAP > 100 mmHg, and cumulative time between the two groups using two-sample *t*-test or non-parametric test. Mann-Whitney *U* test was used to assess the difference between the two groups for non-normal distribution parameters, and χ^2 test or Fisher's exact test for binary outcomes.

Two-way repeated-measures ANOVA was used to assess the difference of CO and SVR at the before-mentioned time-points between the two groups. For recovery time and complications, the between-group comparisons of continuous or categorical data were analyzed by two-sample *t*-test or, Mann-Whitney *U* test, or χ^2 test. $p < 0.05$ was considered statistically significant.

Our minimal sample size was determined as follows. The primary outcome of this study was the difference in the incidence of intraoperative hypotension between remimazolam and propofol. A previous study reported that the incidence of hypotension caused by propofol was as high as 31–50% in ESD surgery (7, 8). However, research was lacking regarding the incidence of hypotension following remimazolam treatment in

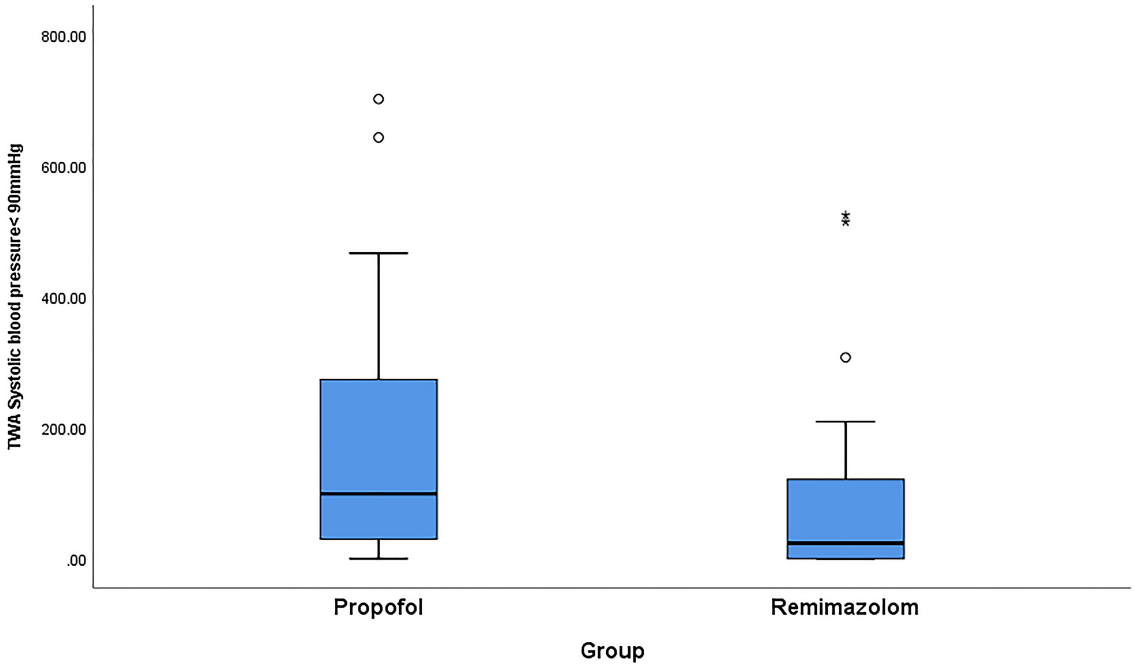

FIGURE 2
Comparison of propofol and remimazolam on time-weighted average of intraoperative hypotension. Boxplots are showed with the lines in the box represent median [Q1, Q3] of the observed TWA hypotension and the whiskers extended to the minimum at the bottom and the maximum on top. Abbreviation: TWA, time-weighted average. Intraoperative hypotension was defined as systolic blood pressure less than 90 mmHg. Q1 and Q3 represent 25th and 75th of the TWA hypotension.

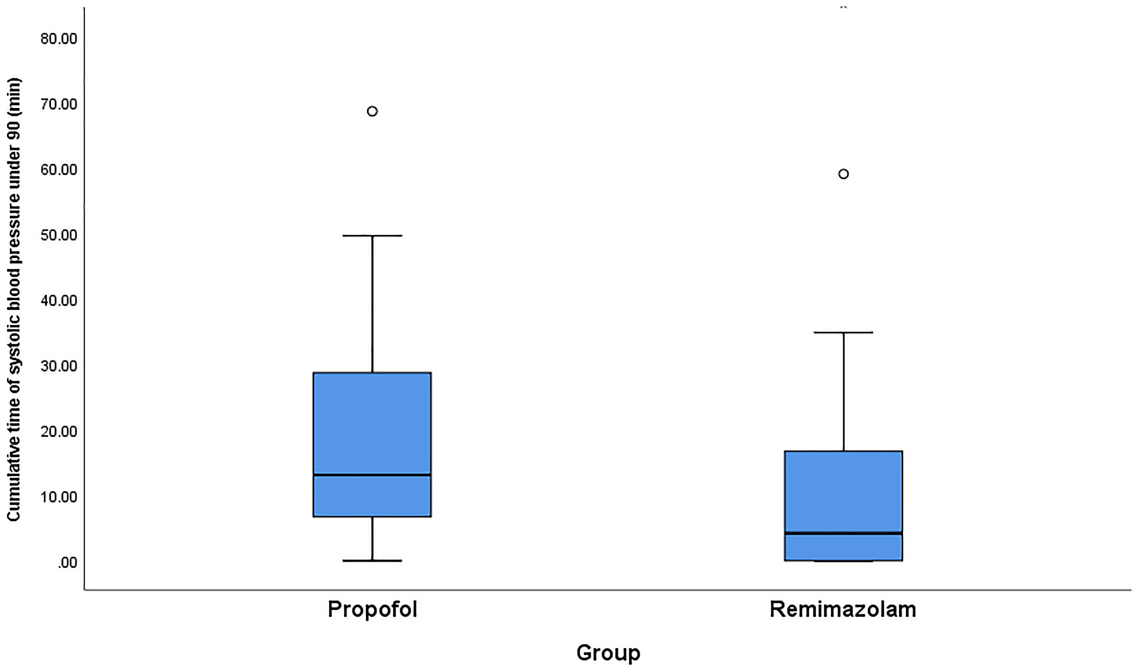

FIGURE 3
Comparison of propofol and remimazolam on cumulative time of intraoperative hypotension. Boxplots are shown with the lines in the box representing median [Q1, Q3] of the observed cumulative time and the whiskers extended to the minimum at the bottom and the maximum on top. Q1 and Q3 represent 25th and 75th of the cumulative time of intraoperative hypotension.

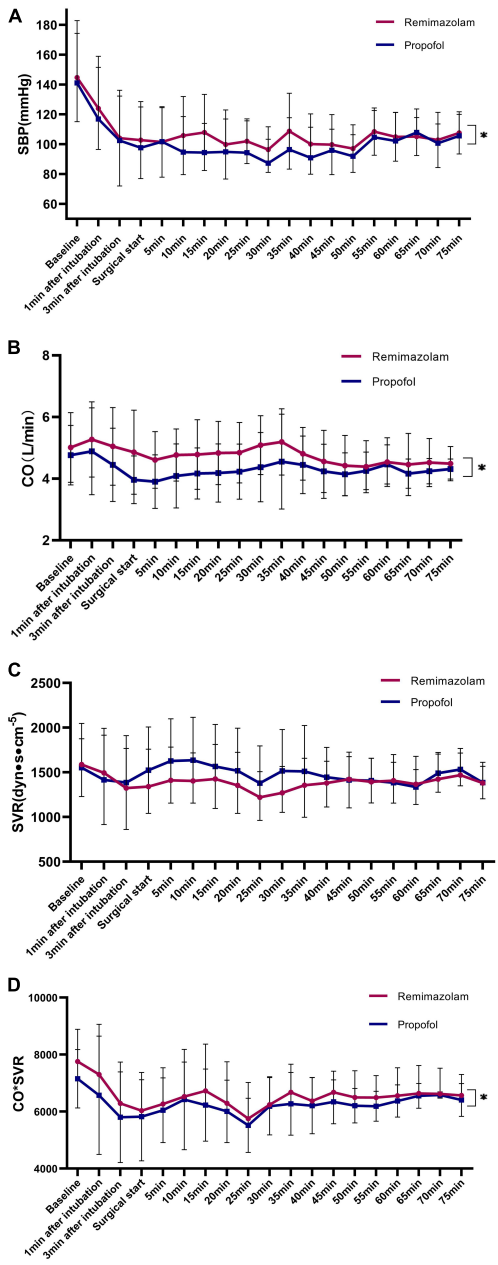

FIGURE 4
Trends of hemodynamic variables during surgery: **(A)** SBP; **(B)** CO; **(C)** SVR; **(D)** the product of CO and SVR. Data are presented as mean with error bars showing SD. Trends of SBP, CO, SVR, and the product of CO showing significant difference between groups (*$p < 0.05$). SBP, systolic blood pressure; CO, cardiac output; SVR, systolic vascular resistance; SD, standard deviation.

ESD surgery, and thus, we conducted a pilot study. The result of our pilot study showed that the incidence of hypotension was 67% (4/6) in the propofol group compared with 25% (2/8) in the remimazolam group. We predicted that remimazolam could reduce the incidence of intraoperative hypotension from 67 to 25% in ESD surgery. Based on the assumption, a sample size of 44 patients had 80% power to detect a one-tailed 5% level of significance by G*POWER3.1.9 (22 per group). We estimated lost-to-follow-up of 20% and therefore increased the sample size by 20% (to 28 subjects per group) to allow for dropouts.

Analyses were performed using SPSS 22.0 (IBM, Chicago, IL, United States) and Python (3.9.10), with statistical significance defined by a two-sided p value of <0.05.

Results

We initially assessed 68 patients for eligibility, and 56 patients were finally enrolled and randomized to receive either remimazolam (n = 28) or propofol (n = 28). All patients completed follow-up and were included in the final analysis (Figure 1). The estimated intraoperative blood loss was less than 100 ml in all patients. The patients in the two groups were similar at baseline and surgical variables in terms of age, sex, body mass index, ASA physical status, history of hypertension and diabetes mellitus, pre-operative fasting time, duration of anesthesia, duration of surgery, IV fluid administration, pre-operative blood glucose and lactate, and esophageal temperature at the end of surgery (Table 1).

The primary and secondary outcomes are reported in Table 2. For the primary outcome, the incidence of hypotension was 32.1% in remimazolam group and 67.9% in propofol group. Remimazolam significantly decreased the incidence of intraoperative hypotension by 50% ($p < 0.01$). From anesthesia induction until the start of surgery, one of 28 (3.5%) patients developed the first episode of hypotension in the remimazolam group, compared with 10 of 28 patients (35%) in the propofol group ($p = 0.002$).

For the secondary outcomes, the total dosage of phenylephrine in remimazolam group was significantly less than that in propofol group, with the median of phenylephrine 0 [0–40] μg in the remimazolam group and 80 [0–200] μg in propofol group ($p < 0.01$). Time-weighted average of hypotension and the cumulative time of hypotension were much lower in the remimazolam group compared with the propofol group (Table 2 and Figures 2, 3). Time-weighted average and cumulative time of MAP > 100 mmHg was not significantly different between the two groups ($p > 0.05$) (Table 2).

The trends of SBP, CO, SVR, and the product of CO and SVR at multiple measurement time points are shown in Figure 4. During the whole anesthesia period (around 75 min after surgery started), the trend of SBP was kept higher in remimazolam group compared with propofol group (p = 0.029, Figure 4A). CO preserved much better in remimazolam group compared with propofol group (p = 0.01, Figure 4B). In the remimazolam group, CO was kept stable at around 5 L, while in the propofol group, CO fluctuated continuously below 4.5 L, as shown in Figure 4B. SVR did

TABLE 3 Clinical recovery variables and complications.

Variables	Remimazolam group (n = 28)	Propofol group (n = 28)	P-value
Emergence time, min	4 [3, 11.8]	15 [12.0, 19.8]	0.001**
Time to extubate, min	5 [3.0, 13.8]	15 [12.3, 20.0]	0.001**
Recovery time, min	5 [3.3, 12.5]	15 [13.3, 20.8]	0.000**
Post-operative hospital stays (d)	2 [1, 3]	2 [1, 3]	0.800
Injection site pain, n (%)	0 (0)	6 (21.4)	0.030*
Intraoperative atropine use, n (%)	0 (0)	3 (10.7)	0.236
Blood lactate at the end of surgery (mmol/L)	0.81 ± 0.21	0.89 ± 0.36	0.388
Blood glucose at the end of surgery (mmol/L)	6.79 ± 1.38	6.01 ± 0.73	0.030*

Data are presented as mean ± SD, median [quartile 1, quartile 3] or n (percentages). Denotes statistically significant (*$p < 0.05$ or **$p < 0.01$) differences among the two groups. Emergence time was defined as the time from discontinuation of remimazolam or propofol to MOAA/S = 5 measured repetitively three times; Recovery time was defined as the time from discontinuation of remimazolam or propofol to modified Aldrete score returned to 9.

not differ between the two groups (p = 0.126, Figure 4C). Although SVR showed a reduction in the remimazolam group, the difference did not reach statistical significance compared with that in the propofol group (shown in Figure 4C). The product of CO and SVR during the whole anesthesia period demonstrated a higher value in the remimazolam group compared with the propofol group (p = 0.001, shown in Figure 4D).

The incidence of injection site pain was 0% in the remimazolam group and 21.4% in the propofol group ($p < 0.01$) (Table 3). At the end of surgery, the level of blood glucose was 6.79 ± 1.38 mmol/L in the remimazolam group, compared with 6.01 ± 0.73 mmol/L in the propofol group, p = 0.030 (Table 3). Blood lactate levels were similar between the groups (Table 3).

The emergence time was 4 [3.0–11.8] min in the remimazolam group, much shorter than that in the propofol group, i.e., 15 [12.0–19.8] min ($p < 0.01$). Time to extubate was 5 [3.0–13.8] min in the remimazolam group and 15 [12.3–20.0] min in the propofol group ($p < 0.01$). Recovery time in the remimazolam group was 5 [3.3–12.5] min, which was shorter than 15 [13.3–20.8] min in the propofol group ($P < 0.01$).

One patient had post-operative agitation in the propofol group and none of the patients had post-operative agitation in the remimazolam group. Re-sedation occurred in 14.3% (4/28) of patients compared with 7.1% in both the groups (2/28), p = 0.669. Post-operative hospital stay in the two groups was not different (p = 0.800).

Discussion

In this prospective, controlled study, we found that remimazolam had a clinically and statistically significant reduction of peri-anesthesia hypotension. Remimazolam decreased the hypotension by 50%, from 67.9% in the propofol group to 32.1% in adult patients undergoing ESD surgery, presenting a relatively stable cardiovascular profile. The total amount of intraoperative phenylephrine had a corresponding decrease. Our data showed that the benefits of remimazolam on hypotension prevention may be partly contributed to its better preservation of cardiac output during the whole period, without much reduction of systemic vascular resistance. Remimazolam also fastened recovery of patients after surgery compared with propofol.

Current anesthesia strategies recommend general anesthesia as a safer option for ESD (19). However, the fact which anesthetics or their combination is the better choice remains unclear in ESD. Although presenting acceptable sedative profile, propofol has a cardiovascular depression effect, resulting in a drop in blood pressure (20). Even a single shot of propofol during anesthesia induction can lead to the incidence of hypotension as high as 44% (21). Our study found that the incidence of peri-anesthesia hypotension caused by propofol was 67.9% during the 45 min to 1 h procedure. Previous trials mainly focused on the single-use of remimazolam on hypotension during induction (21–23). We continuously monitored the hypotension during the whole perioperative period and found that remimazolam decreased the hypotension by 50%, from 67.9% in propofol group to 32.1%. Remimazolam had the advantages of stable hemodynamics (24, 25), which may help explain why incidence of peri-anesthesia hypotension caused by remimazolam was much lower than propofol. Due to immediate treatment of hypotension, we had a corresponding increased amount of phenylephrine in remimazolam compared with propofol.

To find more information about hypotension, we also compared the TWA and cumulative time of SBP < 90 mmHg. We found that the severity and duration of hypotension was lower in remimazolam group compared with propofol group. Our data showed that remimazolam can reduce the

incidence of post-induction hypotension and extend the time to first episode of hypotension. From post-induction until the start of surgery (around 14 min), one of 28 (3.5%) patients developed the first episode of hypotension in the remimazolam group, compared with 10 of 28 (35%) in the propofol group. We also investigated the effect of remimazolam on peri-anesthesia hypertension compared with propofol during the surgery and we found that it did not differ between the groups.

Our study was the first to compare the hemodynamic stability between remimazolam and propofol using the CNAP® Monitor 500 system. Although previous studies found the stable profile of remimazolam in non-cardiac or cardiac surgery, the mechanism still remained uncertain. Interestingly, our data shed a light on the possible mechanism that how remimazolam benefited hypotension prevention and provided stable hemodynamics. Our result showed that remimazolam bolus injection and thereafter continuous infusion preserved better cardiac output than propofol. In the remimazolam group, we found that the cardiac output was kept stable above 5 L, while it fluctuated between 3 and 4.5 L in the propofol group. We also found that remimazolam had no significant reduction of systemic vascular resistance compared with propofol. While the product of cardiac output and systemic vascular resistance might greatly reflect the blood pressure, so, we made a plausible explanation that remimazolam prevented hypotension partly due to its better preservation of cardiac output as well as the product of cardiac output and systemic vascular resistance. As the median time of surgical duration was around 60 min, herein, we plotted the trend of cardiac output, systemic vascular resistance, and cardiac output*systemic vascular resistance in 75 min.

Remimazolam was metabolized rapidly into a non-active metabolite by non-specific esterase in the tissues (25, 26). A previous study showed that the full alertness was naturally regained 19 ± 7 min after stop of remimazolam infusion (27) without reversal. The hypnotic effect of remimazolam can be reversed by flumazenil, so remimazolam-treated patients had a quicker recovery from sedation after reversal by flumazenil. We found that the median time from discontinuation of remimazolam until full alertness was 5 min after reversal with flumazenil, which was similar to 3.5 min after one shot of remimazolam (22). No injection site pain was observed in the remimazolam group, compared with 21.4% that occurred in the propofol group, which was consistent with a previous study (28). Our data showed that patients given remimazolam infusion for 1 h had higher levels of blood glucose at the end of surgery compared with propofol. Our result was inconsistent with the finding of Liu (29), revealing that there was no significant difference in glucose values between propofol and remimazolam, following a one shot of 0.3 mg/kg (29). The change in blood glucose inadvertently found in our trial was perhaps an interesting finding. However, relevant literature about the effect of remimazolam on blood glucose was lacking, so we were not sure that this change of blood glucose was truly caused by the effect of remimazolam or just due to a small sample size. Large trials may be needed to address the question.

Our prospective, parallel control trial has some strengths to address our hypothesis. However, it still has some limitations. First, in this study, we used CNAP, the finger-application type, non-invasive hemodynamic monitors to detect hypotension and explore possible mechanism. The measurements of CNAP may be affected by exogenous vasoconstrictors. Second, we just included patients without severe cardiovascular diseases, so the conclusion cannot be generated to more elderly or fragile patients. Third, patients in both the groups had relatively long fasting time, which may exacerbate the occurrence of hypotension. Finally, our sample size was relatively small, so it may not exclude some potential confounders. The conclusion should be interpreted as conservative.

In summary, remimazolam has better hemodynamic stability and faster recovery than propofol in adult patients undergoing ESD surgery. Its efficacy in more generalized populations to prevent intraoperative hypotension remains to be further studied. The benefits of remimazolam on hypotension prevention may partly contribute to its better preservation of cardiac output during the whole period, without much reduction of systemic vascular resistance.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China [IRB No. KS(Y)20230] on August 14, 2020. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YQ contributed to the conceptualization, designing and writing the original draft, preparation, reviewing and editing, and statistical analysis. WG contributed to the collection

and assembly of data, writing – original draft preparation, and reviewing. MZ contributed to the data analysis and collection and manuscript writing. YZ contributed to the data collection and manuscript writing. JW contributed to the conceptualization, methodology, administrative support, manuscript writing, reviewing, and editing. All authors have finally approved the manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.938940/full#supplementary-material

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Prediction of low cardiac output syndrome in patients following cardiac surgery using machine learning

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Background: This study aimed to develop machine learning models to predict Low Cardiac Output Syndrome (LCOS) in patients following cardiac surgery using machine learning algorithms.

Methods: The clinical data of cardiac surgery patients in Nanjing First Hospital between June 2019 and November 2020 were retrospectively extracted from the electronic medical records. Six conventional machine learning algorithms, including logistic regression, support vector machine, decision tree, random forest, extreme gradient boosting and light gradient boosting machine, were employed to construct the LCOS predictive models with all predictive features (full models) and selected predictive features (reduced models). The discrimination of these models was evaluated by the area under the receiver operating characteristic curve (AUC) and the calibration of the models was assessed by the calibration curve. Shapley Additive explanation (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) were used to interpret the predictive models.

Results: Data from 1,585 patients [982 (62.0%) were male, aged 18 to 88, 212 (13.4%) with LCOS] were employed to train and validate the LCOS models. Among the full models, the RF model (AUC: 0.909, 95% CI: 0.875–0.943; Sensitivity: 0.849, 95% CI: 0.724–0.933; Specificity: 0.835, 95% CI: 0.796–0.869) and the XGB model (AUC: 0.897, 95% CI: 0.859–0.935; Sensitivity: 0.830, 95% CI: 0.702–0.919; Specificity: 0.809, 95% CI: 0.768–0.845) exhibited well predictive power for LCOS. Eleven predictive features including left ventricular ejection fraction (LVEF), first post-operative blood lactate (Lac), left ventricular diastolic diameter (LVDd), cumulative time of mean artery blood pressure (MABP) lower than 65 mmHg (MABP < 65 time), hypertension history, platelets level (PLT), age, blood creatinine (Cr), total area under curve above threshold central venous pressure (CVP) 12 mmHg and 16 mmHg, and blood loss during operation were used to build the reduced models. Among the

reduced models, RF model (AUC: 0.895, 95% CI: 0.857–0.933; Sensitivity: 0.830, 95% CI: 0.702–0.919; Specificity: 0.806, 95% CI: 0.765–0.843) revealed the best performance. SHAP and LIME plot showed that LVEF, Lac, LVDd and MABP < 65 time significantly contributed to the prediction model.

Conclusion: In this study, we successfully developed several machine learning models to predict LCOS after surgery, which may avail to risk stratification, early detection and management of LCOS after cardiac surgery.

KEYWORDS

cardiac surgery, low cardiac output syndrome, machine learning, predictive model, risk stratification

Introduction

Low Cardiac Output Syndrome (LCOS), a clinical manifestation of insufficient cardiac output and peripheral tissue perfusion, was first proposed by Rao et al. (1). Previous studies have shown that all-cause mortality in LCOS ranges from 14.8 to 62.5% in the short term (1 month post onset) and 21.4–36.6% in the long term (2 months to 1 year post onset) (2). LCOS following cardiac surgery not only leads to tissue malperfusion, but also multiple organ dysfunction of brain, lung, liver, kidney, and gastrointestinal tract, thereby increasing health care resource utilization and associated costs (3). More importantly, LCOS may be a state of reversible cardiac output (CO) reduction after cardiac surgery and early recognition and appropriate treatment of LCOS may avoid its progression to refractory cardiogenic shock and improve clinical outcomes, with early detection being of great significance (4–9).

The most common definition of LCOS (1) includes a decrease in the cardiac output index (CI) to < 2.2 L/min/m^2 and a systolic blood pressure of < 90 mmHg, in conjunction with signs of tissue malperfusion (cold periphery, clammy skin, confusion, oliguria, elevated lactate level) in the absence of hypovolemia. Accordingly, it is of necessity to monitor CO by the pulmonary artery catheter (PAC) or pulse indicator continuous cardiac output (PICCO). All these current monitoring technologies, however, are too costly to be routinely applied in the setting of patients undergoing cardiac surgery, which consequently increases the difficulty of early recognition and prevention. Studies showed that significant independent risk factors for LCOS include age, preoperative left ventricular ejection fraction (LVEF), emergency surgery, temperature during cardiopulmonary bypass (CPB), application of cardioprotective drugs and echocardiographic parameters (10–12). Nevertheless, there were few studies on prediction models for LCOS. Therefore, this study was aimed to apply machine learning to develop models for the precise prediction of LCOS following cardiac surgery using preoperative variables and intraoperative time-series data, with the potential to avail early recognition and management of LCOS.

Abbreviations: LCOS, low cardiac output syndrome; EMR, electronic medical records; LR, logistic regression; SVM, support vector machine; DT, decision tree; RF, random forest; XGB, extreme gradient boosting; LGB, light gradient boosting machine; AUC, area under the receiver operating characteristic curve; SHAP, shapley additive explanation; LIME, local interpretable model-agnostic explanations; LVEF, left ventricular ejection fraction; CO, cardiac output; CI, cardiac index; PAC, pulmonary artery catheter; PICCO, pulse indicator continuous cardiac output; CPB, cardiopulmonary bypass; CABG, coronary artery bypass graft; AD, aortic dissection; EMR, electronic medical record; LVDd, left ventricular diastolic diameter; LAD, left atrial diameter; IVSd, interventricular septum thickness in diastole; LVPWT, left ventricular posterior wall thickness; PASP, pulmonary artery systolic pressure; WBC, white blood cell count; NEU, neutrophil ratio; LYM, lymphocyte ratio; PLT, platelets level; Hb, Hemoglobin; Cr, blood creatinine; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; TB, total bilirubin; LDL, low density lipoprotein; CKMB, creatine kinase-MB; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; BNP, brain natriuretic peptide; Lac, blood lactate; AO, aortic occlusion; UO, urine output; MABP, mean arterial blood pressure; CVP, central venous pressure; MV, mechanical ventilation; AUC, area under curve; ROC, receiver operating characteristic; SABP, systolic artery blood pressure; KNN, k-nearest neighbors; LASSO, least absolute shrinkage and selection operator.

Materials and methods

Data sources and study population

This retrospective study was conducted on 1,681 consecutive patients admitted and received cardiac surgery at Nanjing First Hospital from June 2019 to November 2020. Patients who received cardiac surgery during the study period were recruited as the study objects, including but not limited to coronary artery bypass, heart valve surgery, aortic dissection (AD) repair surgery, etc. Exclusion criteria: (1) Patients under 18 years of age. (2) Patients who died or were discharged during or within 48 h after the operation. (3) Patients with incomplete clinical data, such as pre-operation echocardiographic measurements or intraoperative hemodynamic data. Data were collected from electronic medical records (EMR) database, and approval was

gained from the Ethics Committee of Nanjing First Hospital (KY20220518-KS-01).

Definition of low cardiac output syndrome

According to previous reports (10, 13), the criteria for LCOS in our study included: (1) Patients with a cardiac index (CI) reduced to < 2.2 L/min/m^2; (2) Patients with systolic blood pressure < 90 mmHg, in conjunction with signs of tissue hypoperfusion [oliguria (urine output < 1 ml/kg.h), elevated lactate level > 3.0 mmol/L]; (3) Patients requiring mechanical circulatory support or inotropic agents (dopamine or dobutamine at least 4 μg/kg.min for a minimum of 12 h and/or epinephrine at least 0.2 μg/kg.min and/or milrinone at least 0.02 μg/kg.min and/or levosimendan at least 0.05 μg/kg.min) to maintain hemodynamics after optimizing preload. Patients who received vasoconstricting medication to increase peripheral vascular resistance in the presence of normal cardiac output were not considered to have LCOS.

Data collection and preprocessing of data

Clinical variables extracted from electronic medical records (EMR) database included demographics: age, sex, height, weight; comorbidities: hypertension, diabetes, myocardial infarction, hyperlipidemia, cerebral vascular disease, atrial fibrillation, chronic obstructive pulmonary disease (COPD), congestive heart failure, renal disease, liver disease; preoperative echocardiographic parameters: left ventricular diastolic diameter (LVDd), left atrial diameter (LAD), interventricular septum thickness in diastole (IVSd), left ventricular posterior wall thickness (LVPWT), pulmonary artery systolic pressure (PASP), left ventricular ejection fraction (LVEF); preoperative laboratory results: white blood cell count (WBC), neutrophil ratio (NEU), lymphocyte ratio (LYM), platelets level (PLT), hemoglobin (Hb), blood creatinine (Cr), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein (TP), total bilirubin (TB), low density lipoprotein (LDL), creatine kinase-MB (CKMB), triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), brain natriuretic peptide (BNP); operation information: operation time, cardiopulmonary bypass (CPB) time, aortic occlusion (AO) time, Emergency surgery, urine output (UO) during operation, blood loss during operation, operation type; intraoperative hemodynamics: mean arterial blood pressure (MABP), central venous pressure (CVP); postoperative hemodynamics: cardiac output (via pulmonary artery catheter for some patients), systolic artery blood pressure (SABP), CVP, inotropes (dopamine, dobutamine, epinephrine, milrinone, and levosimendan) usage, urine output and first post-operative blood lactate levels (within 30 min post operation), prognosis variables: mechanical ventilation (MV) time, ICU stay time and hospital stay time. Renal disease was defined as preoperative glomerular filtration rate < 30 ml/min/1.73 m^2 (body surface area) (14). Hyperlipidemia was defined as total cholesterol > 200 mg/dl and/or triglyceridemic value > 150 mg/dl. Other comorbidities were identified from diagnosis before operation using the International Classification of Disease, Tenth edition (ICD-10). ICD-10 codes used for the identification of comorbidities are outlined in Supporting Information (**Supplementary Table 1**).

During operation, MABP and CVP were continuously monitored using invasive peripheral artery, central vein or pulmonary artery catheter and saved as time-series data. Artifactual data were removed according to previously published criteria (15). Thresholds for MABP (< 65, < 60, < 55, < 50 mmHg) and CVP (> 12, > 16, > 20 mmHg) were used to assess the site of hypotension and central venous congestion occurred during operation. To comprehensively assess the time-series data, cumulative time under or above thresholds, total area under curve under or above threshold (AUT) and time weighted average (TWA) of MABP and CVP for corresponding threshold were calculated based on a previous study (16).

Model construction and evaluating

The entire dataset was randomly stratified into the training and test sets (7:3), meaning that the ratio of patients with LCOS to those without LCOS was maintained consistent in both subsets. The training set was applied to train the model with 10-fold cross-validation and test set was used later to assess the models' performance. All variables with a missing rate > = 10% were excluded from the analysis (**Supplementary Figure 1**). Variables with a missing rate < 10% were imputed by the k-nearest neighbors (KNN) imputation procedure (17). The low incidence of LCOS and the large number of variables we included in this study made it typical unbalanced high dimension data, Synthetic Minority Oversampling Technique (SMOTE) was applied to overcome this imbalance.

Six conventional machine learning algorithms were employed to construct the LCOS prediction models will all variables (full models), including logistic regression (LR), support vector machine (SVM), decision tree (DT), random forest (RF), extreme gradient boosting (XGB), and light gradient boosting machine (LGB).

Boruta and the least absolute shrinkage and selection operator (LASSO) were used to select the optimal subset of variables. All variables confirmed as important by the Boruta algorithm were entered the LASSO regressing. Finally, variables

identified by LASSO regression were included for constructing reduced models using the same six machine learning algorithms.

Statistical analyses

Baseline characteristics of patients in the training and test sets were compared. Measurements conforming to a normal distribution were described as mean ± standard deviation. Student's *t*-test was employed for comparisons. Measurement data that did not conform to a normal distribution were denoted as median [lower quartile-upper quartile]. Wilcoxon rank-sum tests were performed to draw comparisons. The enumeration data were represented as frequency and percentage and compared by performing Pearson χ^2 test. Fisher's exact test was performed under the expected frequencies of one or more cells less than 5. The difference was considered with statistical significance at $P < 0.05$.

The discriminations of models were evaluated by the area under curve (AUC) of the receiver operating characteristic (ROC), accuracy, sensitivity, specificity and calibration of the models were assessed by the calibration curve and Brier score. Shapley Additive explanation (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) were used to provide consistent and locally accurate values for each variable within the prediction models. All analyses were conducted in R (version 3.6.3) and Python (version 3.7).

Results

Overall, the eligibility of 1,681 patients who underwent cardiac surgery and were admitted to the Cardiovascular ICU of Nanjing First Hospital, Nanjing Medical University, from June 2019 to November 2020 was assessed. The excluded cases were as follows: 35 cases were younger than 18 years old, 8 patients were dead or discharged within 48 h after surgery and 53 patients had uncompleted data. Finally, 1585 patients [982 (62.0%) male, 18 to 88 years old] were enrolled for analyses. Among them, 386 (24.4%) patients received PAC insertion during the surgery, and the proportion of PAC use varied by surgery types (**Supplementary Table 2**). Among patients with PAC, 61 (15.8%) were diagnosed with LCOS by CI criterion, and among the other 1,199 patients without PAC, 151 (12.6%) were diagnosed with LCOS by other criteria. Overall, 212 (13.4%) patients developed LCOS postoperatively. Compared to patients without LCOS, patients with LCOS had prolonged MV time (20.25 [13.08,40.38] vs. 9.50 [7.00,15.33] hours, $P < 0.001$), longer ICU stay time (3.0 [2.0,6.0] vs. 1.0 [1.0,2.0] days, $P < 0.001$) and hospital stay time (21.0 [16.0,27.0] vs. 17.0 [14.0,21.0] days, $P < 0.001$). There was no significant difference in morbidity between patients with LCOS diagnosed by CI criterion and other criteria (15.6 vs. 12.5%, $P = 0.127$), and patients with LCOS diagnosed by different criteria had similar prognoses (**Supplementary Figure 2**), indicating consistency between the different criteria.

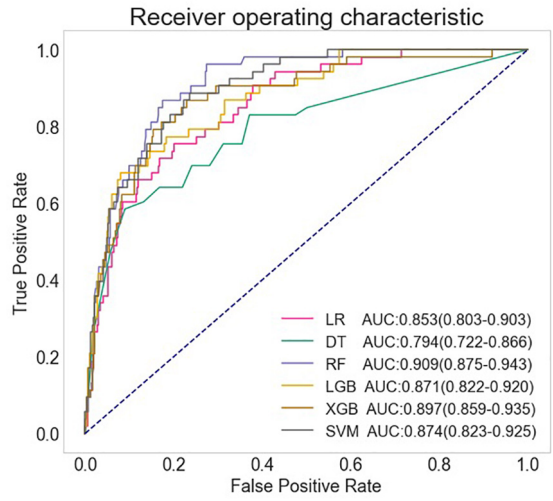

FIGURE 1
Comparison of AUCs among different machine learning models. LR, logistic regression; DT, decision tree; RF, random forest classifier; LGB, light gradient boosting machine; XGB, extreme gradient boosting machine; SVM, support vector machine.

We randomized 70% of these 1,585 patients into the training set and the remaining 30% into the test set. The clinical variables of patients in training and test set are listed in **Table 1**. There was no significant difference between patients in training and test sets for these variables.

The full models were conducted with all variables, using the six algorithms including LR, DT, SVM, RF, XGB, and LGB for LCOS predicting, and the AUC, accuracy, sensitivity, and specificity of each full model on test set were presented in **Figure 1** and **Table 2**. Among the full models, the RF model (AUC: 0.909, 95% CI: 0.875–0.943; Sensitivity: 0.849, 95% CI: 0.724–0.933; Specificity: 0.835, 95% CI: 0.796–0.869) and the XGB model (AUC: 0.897, 95% CI: 0.859–0.935; Sensitivity: 0.830, 95% CI: 0.702–0.919; Specificity: 0.809, 95% CI: 0.768–0.845) showed well predictive power for LCOS. The main parameters of the full RF model were set as follows: bootstrap = True, criterion = "gini," n_estimators = 500, max_depth = None, min_samples_leaf = 1, min_sample_split = 2. The main parameters of the full XBG model were set as follows: n_estimators = 200, learning_rate = 0.1, max_depth = 9, gamma = 0. The calibration plot and Brier score indicated all the full models have well calibration (**Figure 2**).

Feature selection was performed by the following two steps. First, Boruta algorithm was employed and 35

TABLE 1 Patient characteristics and clinical variables.

	Training set (N = 1,109)	Test set (N = 476)	P-value
Demographic data			
Age (years)	61.26 ± 12.02	60.98 ± 11.47	0.658
Male, n (%)	693 (62.5%)	289 (60.7%)	0.541
Height (cm)	165.38 ± 8.39	165.33 ± 8.64	0.920
Weight (kg)	65.83 ± 11.93	65.94 ± 11.68	0.860
Comorbidities			
Hypertension, n (%)	568 (51.2%)	227 (47.7%)	0.218
Diabetes, n (%)	256 (23.1%)	93 (19.5%)	0.135
Myocardial infarction, n (%)	62 (5.6%)	26 (5.5%)	1
Hyperlipidemia, n (%)	233 (21.0%)	87 (18.3%)	0.240
Cerebral vascular disease, n (%)	105 (9.5%)	33 (6.9%)	0.123
Atrial Fibrillation, n (%)	244 (22.0%)	100 (21.0%)	0.709
COPD, n (%)	39 (3.5%)	19 (4.0%)	0.752
Heart failure, n (%)	445 (40.1%)	206 (43.3%)	0.266
Kidney disease, n (%)	78 (7.0%)	29 (6.1%)	0.565
Liver disease, n (%)	39 (3.5%)	11 (2.3%)	0.270
Preoperative ECHO			
LVDd (mm)	53.98 ± 9.86	53.78 ± 9.09	0.695
LVPWT (mm)	9.85 ± 2.21	9.74 ± 1.40	0.218
LVEF (%)	59.11 ± 9.08	59.05 ± 8.42	0.906
Laboratory			
WBC (10^9/L)	6.76 ± 2.81	6.64 ± 2.45	0.393
NEU (%)	62.84 ± 10.71	62.13 ± 10.62	0.224
LYM (%)	25.42 ± 9.20	27.13 ± 9.52	0.170
PLT (10^9/L)	188.90 ± 66.07	183.33 ± 63.05	0.113
Hb (g/L)	131.07 ± 18.69	131.92 ± 19.13	0.413
Cr (mmol/L)	83.83 ± 77.54	80.54 ± 59.35	0.359
BUN (mmol/L)	6.67 ± 2.94	6.66 ± 3.17	0.981
AST (U/L)	22.00 [17.00, 30.00]	22.00 [17.00, 30.00]	0.810
Lac (mmol/L)	2.23 ± 1.80	2.26 ± 1.87	0.745
Operative variables			
Operation time (hour)	4.39 ± 1.37	4.38 ± 1.36	0.903
CPB time (min)	101.62 ± 66.24	100.45 ± 54.72	0.714
AO time (min)	69.85 ± 54.37	67.61 ± 38.54	0.351
Emergency surgery, n (%)	117 (10.6%)	41 (8.6%)	0.276
Urine output (ml/kg/h)	3.18 ± 1.99	3.16 ± 2.01	0.869
Blood loss (ml)	1165.90 ± 699.38	1155.65 ± 612.52	0.770
Operation type			
CABG only, n (%)	311 (28.0%)	130 (27.3%)	0.813
Valve surgery only, n (%)	420 (37.9%)	188 (39.5%)	0.58
CABG + valve surgery, n (%)	100 (9.0%)	53 (11.1%)	0.224
Congenital surgery, n (%)	70 (6.3%)	24 (5.0%)	0.387
Heart transplant, n (%)	14 (1.3%)	4 (0.8%)	0.640
Aortic dissection repair, n (%)	84 (7.6%)	23 (4.8%)	0.059
Other surgery, n (%)	110 (10.3%)	54 (11%)	0.437
Hemodynamic data			
MABP < 65 time (min)	129.87 ± 77.61	128.13 ± 72.32	0.667
MABP < 60 time (min)	94.73 ± 66.78	92.88 ± 60.96	0.592

(Continued)

TABLE 1 (Continued)

	Training set (N = 1,109)	Test set (N = 476)	P-value
MABP < 55 time (min)	65.72 ± 53.95	63.61 ± 48.11	0.441
MABP < 50 time (min)	41.72 ± 41.44	40.34 ± 35.95	0.503
MABP_AUT_65 (mmHg*min)	1583.54 ± 1235.09	1535.92 ± 1087.10	0.443
MABP_AUT_60 (mmHg*min)	1005.51 ± 899.36	966.54 ± 780.09	0.385
MABP_AUT_55 (mmHg*min)	592.29 ± 617.00	563.21 ± 524.40	0.338
MABP_AUT_50 (mmHg*min)	313.91 ± 393.54	292.96 ± 323.69	0.270
MABP_TWA_65 (mmHg)	11.30 ± 3.87	11.31 ± 3.72	0.938
MABP_TWA_60 (mmHg)	9.54 ± 3.78	9.54 ± 3.42	0.982
MABP_TWA_55 (mmHg)	7.79 ± 3.62	7.80 ± 3.41	0.969
MABP_TWA_50 (mmHg)	6.07 ± 3.39	6.07 ± 3.25	0.995
CVP > 12 time (min)	15.00 [0.00, 65.00]	20.00 [5.00, 60.00]	0.815
CVP > 16 time (min)	0.00 [0.00, 10.00]	0.00 [0.00, 10.00]	0.447
CVP > 20 time (min)	0.00 [0.00, 0.00]	0.00 [0.00, 5.00]	0.129
CVP_AUT_12 (mmHg*min)	50.00 [0.00, 225.00]	67.50 [5.00, 220.00]	0.373
CVP_AUT_16 (mmHg*min)	0.00 [0.00, 50.00]	0.00 [0.00, 60.00]	0.231
CVP_AUT_20 (mmHg*min)	0.00 [0.00, 0.00]	0.00 [0.00, 10.00]	0.081
CVP_TWA_12 (mmHg)	2.22 [0.00, 4.00]	2.27 [1.00, 4.57]	0.122
CVP_TWA _16 (mmHg)	0.00 [0.00, 2.86]	0.00 [0.00, 4.00]	0.081
CVP_TWA _20 (mmHg)	0.00 [0.00, 0.00]	0.00 [0.00, 2.00]	0.053
LCOS			
Yes, n (%)	148 (13.3%)	64 (13.4%)	1

ECHO, echocardiography; LVDd, left ventricular diastolic diameter; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; WBC, white blood cell count; NEU, neutrophil properties; Cr, blood creatinine; BUN, blood urea nitrogen; AST, aspartate aminotransferase; Lac, blood lactate; CPB, cardiopulmonary bypass; AO, aortic occlusion; CABG, coronary artery bypass graft; MABP < 65 time, cumulative time of mean artery blood pressure lower than 65 mmHg; MABP < 60 time, cumulative time of mean artery blood pressure lower than 60 mmHg; MABP < 55 time, cumulative time of mean artery blood pressure lower than 55 mmHg; MABP < 50 time, cumulative time of mean artery blood pressure lower than 50 mmHg; MABP_AUT_65, total area under curve below threshold mean artery blood pressure 65 mmHg; MABP_AUT_60, total area under curve below threshold mean artery blood pressure 60 mmHg; MABP_AUT_55, total area under curve below threshold mean artery blood pressure 55 mmHg; MABP_AUT_50, total area under curve below threshold mean artery blood pressure 50 mmHg; MABP_TWA_65, time weighted average mean artery blood pressure below threshold 65 mmHg; MABP_TWA_60, time weighted average mean artery blood pressure below threshold 60 mmHg; MABP_TWA_55, time weighted average mean artery blood pressure below threshold 55 mmHg; MABP_TWA_50, time weighted average mean artery blood pressure below threshold 50 mmHg; CVP > 12 time, cumulative time of central venous pressure upper than 12 mmHg; CVP > 16 time, cumulative time of central venous pressure upper than 16 mmHg; CVP > 20 time, cumulative time of central venous pressure upper than 20 mmHg; CVP_AUT_12, total area under curve above threshold central venous pressure 12 mmHg; CVP_AUT_16, total area under curve above threshold central venous pressure 16 mmHg; CVP_AUT_20, total area under curve above threshold central venous pressure 20 mmHg; CVP_TWA_12, time weighted average central venous pressure above threshold 12 mmHg; CVP_TWA_16, time weighted average central venous pressure above threshold 16 mmHg; CVP_TWA_20, time weighted average central venous pressure above threshold 20 mmHg; LCOS, low cardiac output syndrome.

features were confirmed important to the prediction of LCOS (Supplementary Figure 3). Then, Lasso regression was applied to select the best subset features from the 35 confirmed important features (Supplementary Figure 4). Eleven variables were finally selected by Boruta and LASSO features selection procedure, including LVEF, lactate (Lac), LVDd, cumulative time of mean artery blood pressure (MABP) lower than 65 mmHg (MABP < 65 time), hypertension history, PLT, age, blood Cr, AST, total area under curve above CVP 12 mmHg (CVP_AUT_12), total area under curve above threshold CVP 16 mmHg (CVP_AUT_16) and blood loss during operation. Six reduced models with these eleven variables and the same six algorithms were then developed. Among the reduced models, among which, RF model (AUC:0.895, 95% CI: 0.857–0.933; Sensitivity:0.830, 95% CI: 0.702–0.919; Specificity: 0.806, 95% CI: 0.765–0.843) revealed the best performance. The main parameters of the reduced RF model were set as follows: bootstrap = True, criterion = "gini," n_estimators = 700, max_depth = None, min_samples_leaf = 1, min_sample_split = 2. The AUC, accuracy, sensitivity and specificity of the full and reduced models are presented in Table 2.

The SHAP summary plot (Figure 3) and dependence plot (Figure 4) represented the contributions of these eleven variables to the prediction of the RF model, with SHAP values above zero indicating an increased risk of developing LCOS and SHAP values below zero indicating a decreased risk of LCOS. For example, SHAP values for high LVEF (red) were usually less than zero, indicating a decreased risk of LCOS in patients with higher LVEF. In addition, Figure 3A displays the ranking of the features based on the average absolute SHAP value. Among the eleven variables, LVEF, Lac, LVDd and MABP < 65 time were the four variables with the greatest influence on prediction power. Lower LVEF, higher Lac, larger LVDd and longer MABP < 65 time indicated

TABLE 2 The performance of each model.

	Model	AUC	Accuracy	Sensitivity	Specificity
Full models	LR	0.853 (0.803–0.903)	0.761 (0.72–0.798)	0.755 (0.617–0.862)	0.761 (0.718–0.801)
	DT	0.794 (0.722–0.866)	0.716 (0.674–0.756)	0.698 (0.557–0.817)	0.719 (0.673–0.761)
	RF	0.909 (0.875–0.943)	0.836 (0.800–0.868)	0.849 (0.724–0.933)	0.835 (0.796–0.869)
	LGB	0.871 (0.822–0.920)	0.813 (0.775–0.847)	0.755 (0.617–0.862)	0.820 (0.780–0.856)
	XGB	0.897 (0.859–0.935)	0.811 (0.773–0.845)	0.830 (0.702–0.919)	0.809 (0.768–0.845)
	SVM	0.874 (0.823–0.925)	0.813 (0.775–0.847)	0.774 (0.638–0.877)	0.818 (0.778–0.854)
Reduced models	LR	0.815 (0.754–0.877)	0.708 (0.665–0.748)	0.717 (0.577–0.832)	0.707 (0.661–0.75)
	DT	0.740 (0.661–0.818)	0.580 (0.534–0.625)	0.774 (0.638–0.877)	0.556 (0.507–0.604)
	RF	0.895 (0.857–0.933)	0.809 (0.771–0.843)	0.830 (0.702–0.919)	0.806 (0.765–0.843)
	LGB	0.853 (0.800–0.906)	0.767 (0.726–0.804)	0.792 (0.659–0.892)	0.764 (0.72–0.803)
	XGB	0.854 (0.803–0.905)	0.752 (0.711–0.790)	0.792 (0.659–0.892)	0.747 (0.703–0.788)
	SVM	0.853 (0.800–0.905)	0.775 (0.735–0.812)	0.774 (0.638–0.877)	0.775 (0.733–0.814)

AUC, area under curve of receiver operating characteristic; LR, logistic regression; DT, decision tree; RF, random forest classifier; LGB, light gradient boosting machine; XGB, extreme gradient boosting machine; SVM, support vector machine.

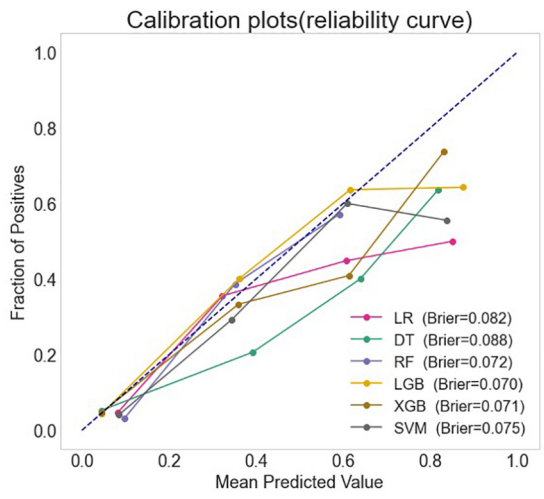

FIGURE 2
The calibration curves and the Brier score of different machine learning models. LR, logistic regression; DT, decision tree; RF, random forest classifier; LGB, light gradient boosting machine; XGB, extreme gradient boosting machine; SVM, support vector machine.

an increased possibility of the onset of LCOS. We randomly selected two patients with LCOS (Figure 5A) and without LCOS (Figure 5B) and used LIME algorithm to interpret how they were predicted to be have a 68% possibility of LCOS and 92% possibility without LCOS. The first patient (Figure 5A) was predicted to be with possibility of prospective LCOS due to low LVEF (38%), high Lac (2.9 mmol/L), large LVDd (84 mm), long MABP < 65 time (185 min) and advanced age (76 years). The second patient (Figure 5B) was predicted to be without prospective LCOS due to relatively normal variables: Lac (1.0 mmol/L), LVDd (52 mm), hypertension, CVP_AUT_16 (0 min), Blood loss (700 ml), CVP_AUT_12 (15 min), age (64 years), MAPB < 65 time (125 min), PLT (256 * 10^9/L).

Discussion

Big data and machine learning are enabling the shift from conventional to customized treatment, which could soon result in the birth of a new health system (18, 19). To the best of our knowledge, no machine learning prediction model has been established to predict the occurrence of LCOS following cardiac surgery. In the present study, in the cooperation of clinicians and information technology engineers, we successfully developed several machine learning models to predict LCOS following cardiac surgery. Six conventional machine learning algorithms were employed to construct the LCOS prediction models, including LR, SVM, DT, RF, XGB, and LGB, indicating that RF and XGB models exhibited the best performance. RF is a homologous ensemble algorithm that constructs a great number of decision trees during training, which helps to build robust prediction models with able to deal with non-linear data. XGB is a distributed algorithm with fast operation speed and high fault tolerance, which could accurately predicts the outcome of multiple diseases in ICU (20–22). Commendably, our study demonstrated that the performance of machine learning models was significantly superior to the traditional logistic regression models in the prediction of LCOS following cardiac surgery.

We adopted a dual definition of LCOS, similar to the prior studies (10, 13), with the CI criterion requiring perioperative PAC monitoring. However, even in the field of cardiothoracic surgery, the usage of the PAC has declined over the years. The most accurate way to evaluate the pulmonary artery and cardiac output in patients with pulmonary hypertension and heart failure, however, is through the use of PAC. The

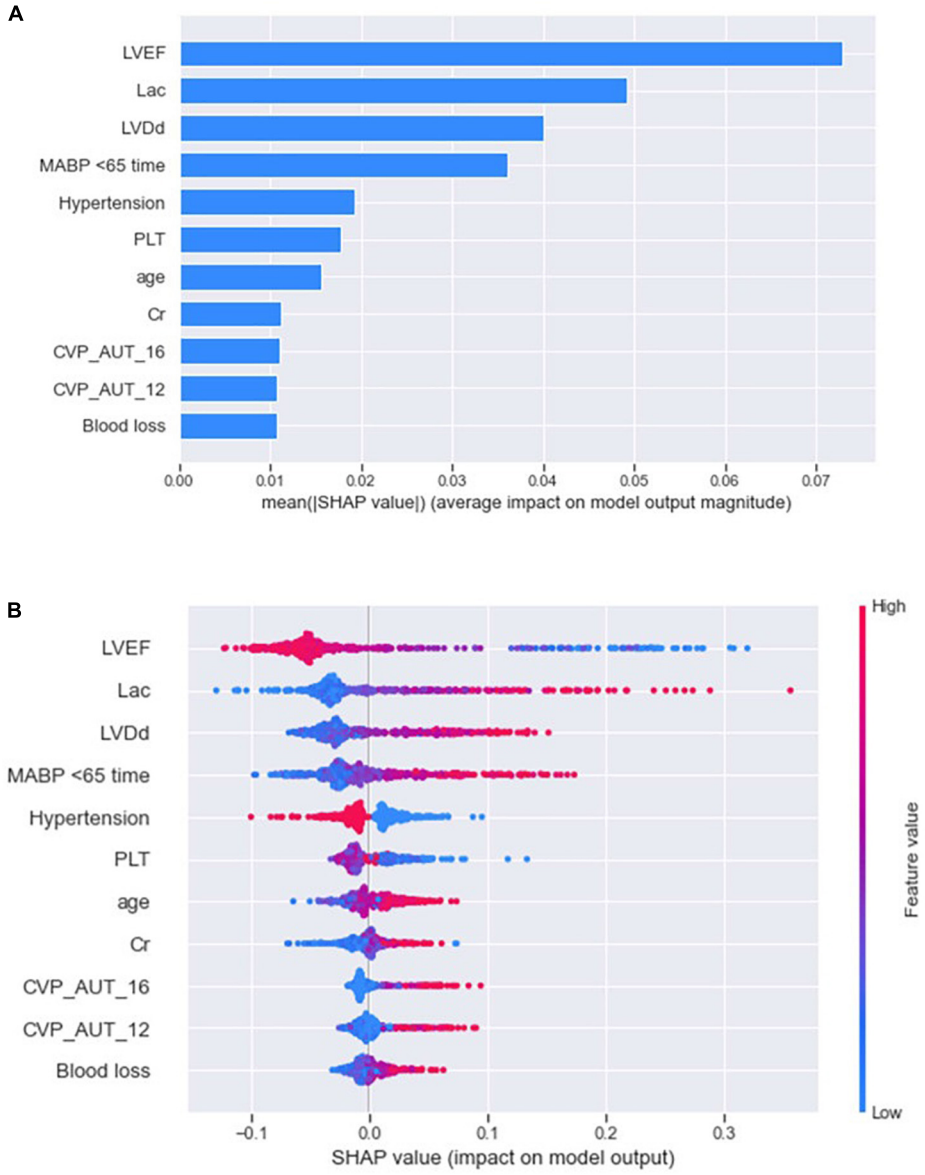

FIGURE 3
SHAP summary plot of the reduced RF model. The plot showed the importance of each variable **(A)** and the specific distribution between variables and Shapely value **(B)** using SHAP algorithm.

large proportion of PAC usage in various procedures, such as heart transplant, adult congenital surgery, and challenging combination CABG + valve surgery, can be attributed to its potential benefit in patients with a high risk of RV failure (8, 23) (**Supplementary Table 2**). PAC could continually provide important hemodynamic measurements like pulmonary circulation resistance, right heart afterload, cardiac output, etc. Those measurements are imperative in perioperative management of critically ill patients after those types of surgery. However, PAC use was reported to be associated with a poorer outcome in patients receiving cardiac surgical. As an invasive hemodynamic monitoring method, the difficulty of placement and consequent side effects may contribute to iatrogenic adverse outcomes for patients (24). The similar prognosis outcome between LCOS patients diagnosed by CI criterion and other criteria indicated consistency across different criteria. Importantly, our prediction models could provide a non-invasive, precious, interpretable way to predict LCOS, perhaps reducing the need for intrusive monitoring techniques like PAC.

Low Cardiac Output Syndrome could be corrected by timely and effective intervention and a variety of therapeutic

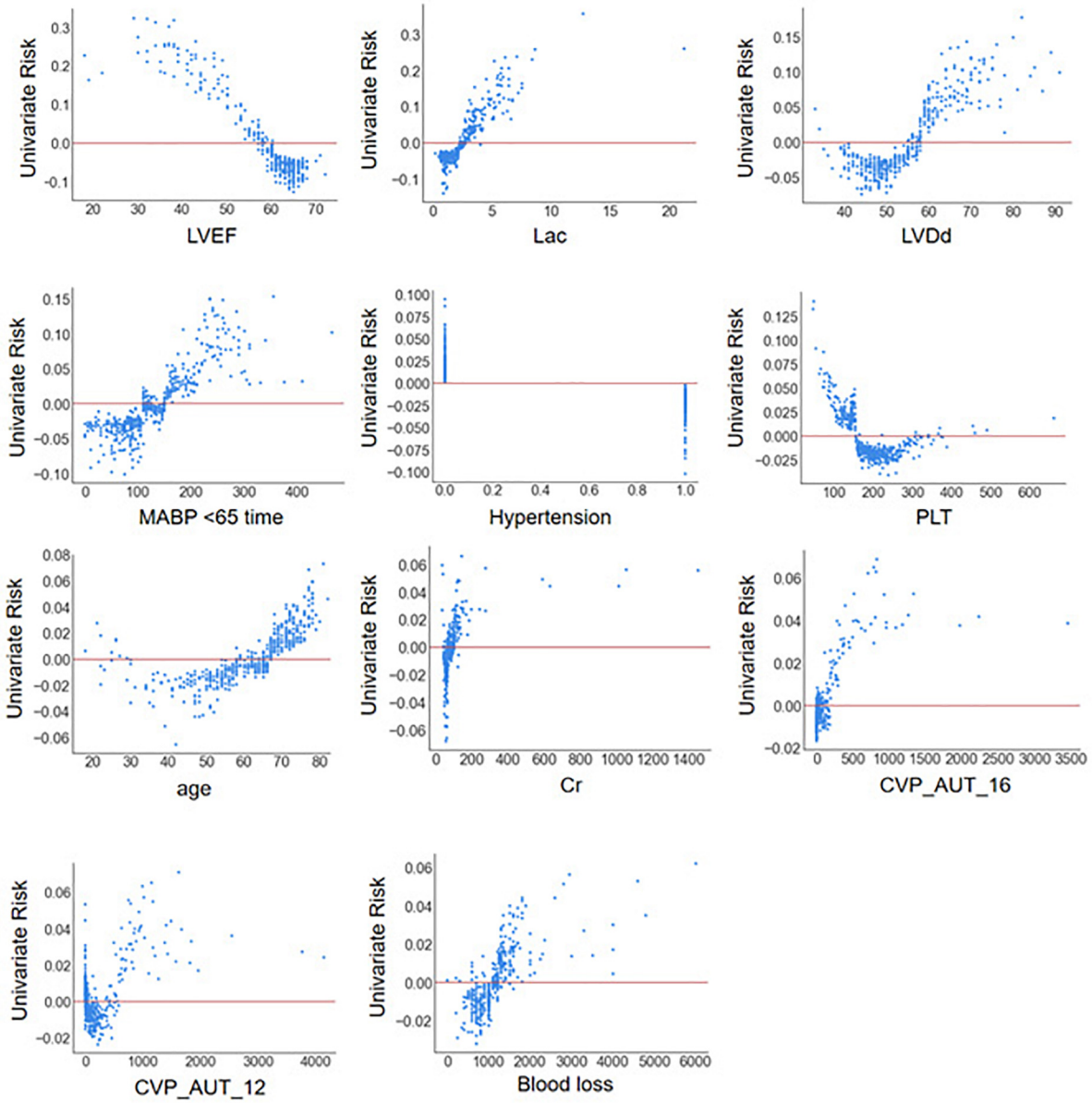

FIGURE 4
SHAP dependence plot of the reduced RF model. ECHO, echocardiography; LVDd, left ventricular diastolic diameter; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; WBC, white blood cell count; NEU, neutrophil properties; Cr, blood creatinine; BUN, blood urea nitrogen; AST, aspartate aminotransferase; Lac, blood lactate; CPB, cardiopulmonary bypass; AO, aortic occlusion; CABG, coronary artery bypass graft; MABP < 65 time, cumulative time of mean artery blood pressure lower than 65 mmHg; MABP < 60 time, cumulative time of mean artery blood pressure lower than 60 mmHg; MABP < 55 time, cumulative time of mean artery blood pressure lower than 55 mmHg; MABP < 50 time, cumulative time of mean artery blood pressure lower than 50 mmHg; MABP_AUT_65, total area under curve below threshold mean artery blood pressure 65 mmHg; MABP_AUT_60, total area under curve below threshold mean artery blood pressure 60 mmHg; MABP_AUT_55, total area under curve below threshold mean artery blood pressure 55 mmHg; MABP_AUT_50, total area under curve below threshold mean artery blood pressure 50 mmHg; MABP_TWA_65, time weighted average mean artery blood pressure below threshold 65 mmHg; MABP_TWA_60, time weighted average mean artery blood pressure below threshold 60 mmHg; MABP_TWA_55, time weighted average mean artery blood pressure below threshold 55 mmHg; MABP_TWA_50, time weighted average mean artery blood pressure below threshold 50 mmHg; CVP > 12 time, cumulative time of central venous pressure upper than 12 mmHg; CVP > 16 time, cumulative time of central venous pressure upper than 16 mmHg; CVP > 20 time, cumulative time of central venous pressure upper than 20 mmHg; CVP_AUT_12, total area under curve above threshold central venous pressure 12 mmHg; CVP_AUT_16, total area under curve above threshold central venous pressure 16 mmHg; CVP_AUT_20, total area under curve above threshold central venous pressure 20 mmHg; CVP_TWA_12, time weighted average central venous pressure above threshold 12 mmHg; CVP_TWA_16, time weighted average central venous pressure above threshold 16 mmHg; CVP_TWA_20, time weighted average central venous pressure above threshold 20 mmHg; LCOS, low cardiac output syndrome.

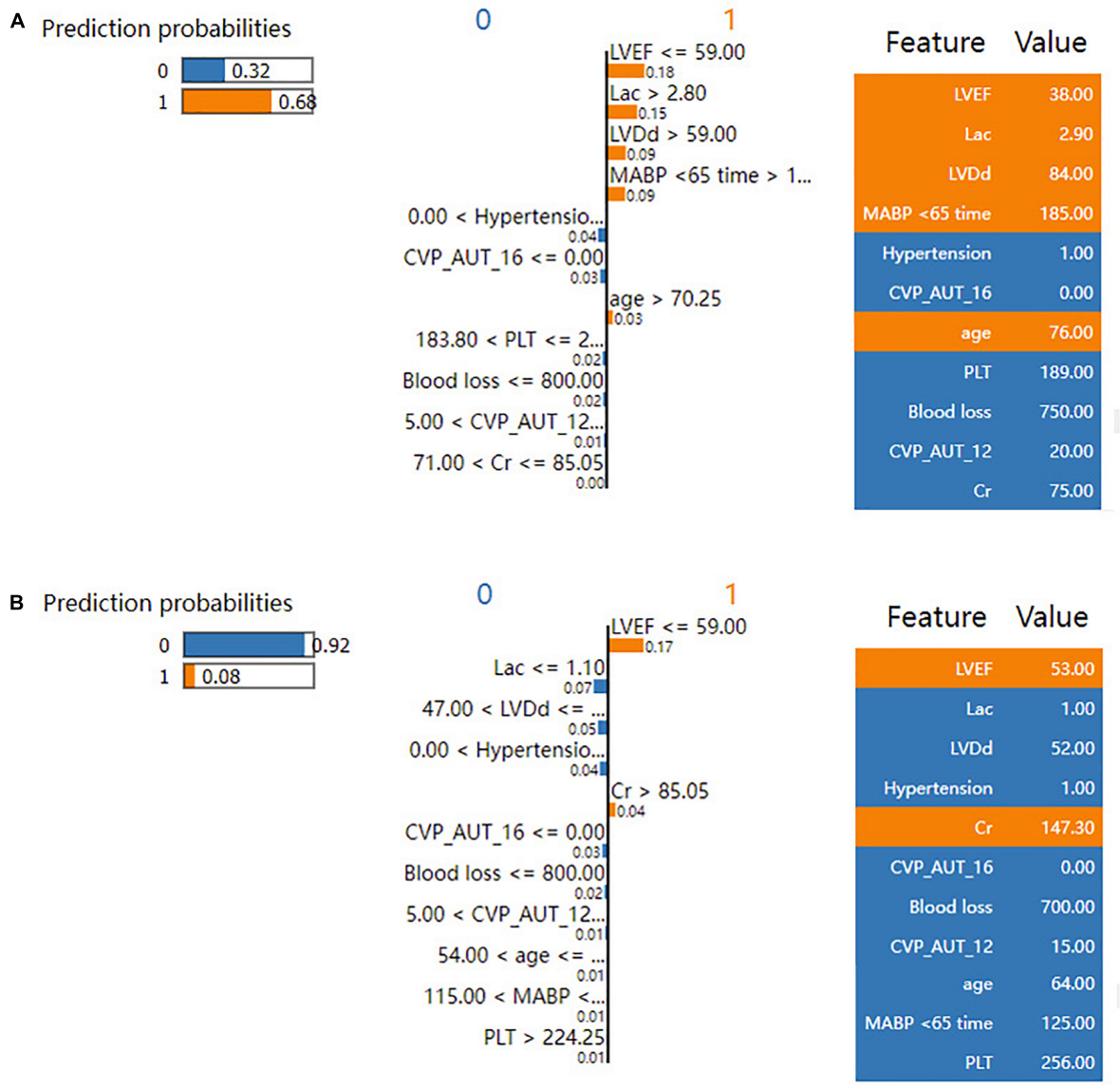

FIGURE 5
LIME plot for individual case explanation on two random patients for the test set of the reduced RF model. LIME plot included one patient with LCOS **(A)** and one patient without LCOS **(B)**, explained by LIME algorithm. ECHO, echocardiography; LVDd, left ventricular diastolic diameter; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; WBC, white blood cell count; NEU, neutrophil properties; Cr, blood creatinine; BUN, blood urea nitrogen; AST, aspartate aminotransferase; Lac, blood lactate; CPB, cardiopulmonary bypass; AO, aortic occlusion; CABG, coronary artery bypass graft; MABP < 65 time, cumulative time of mean artery blood pressure lower than 65 mmHg; MABP < 60 time, cumulative time of mean artery blood pressure lower than 60 mmHg; MABP < 55 time, cumulative time of mean artery blood pressure lower than 55 mmHg; MABP < 50 time, cumulative time of mean artery blood pressure lower than 50 mmHg; MABP_AUT_65, total area under curve below threshold mean artery blood pressure 65 mmHg; MABP_AUT_60, total area under curve below threshold mean artery blood pressure 60 mmHg; MABP_AUT_55, total area under curve below threshold mean artery blood pressure 55 mmHg; MABP_AUT_50, total area under curve below threshold mean artery blood pressure 50 mmHg; MABP_TWA_65, time weighted average mean artery blood pressure below threshold 65 mmHg; MABP_TWA_60, time weighted average mean artery blood pressure below threshold 60 mmHg; MABP_TWA_55, time weighted average mean artery blood pressure below threshold 55 mmHg; MABP_TWA_50, time weighted average mean artery blood pressure below threshold 50 mmHg; CVP > 12 time, cumulative time of central venous pressure upper than 12 mmHg; CVP > 16 time, cumulative time of central venous pressure upper than 16 mmHg; CVP > 20 time, cumulative time of central venous pressure upper than 20 mmHg; CVP_AUT_12, total area under curve above threshold central venous pressure 12 mmHg; CVP_AUT_16, total area under curve above threshold central venous pressure 16 mmHg; CVP_AUT_20, total area under curve above threshold central venous pressure 20 mmHg; CVP_TWA_12, time weighted average central venous pressure above threshold 12 mmHg; CVP_TWA_16, time weighted average central venous pressure above threshold 16 mmHg; CVP_TWA_20, time weighted average central venous pressure above threshold 20 mmHg; LCOS, low cardiac output syndrome.

strategies can be applied to the treatment of LCOS, when it is early recognized, including optimization of ventricular preload and afterload; inotropic agents; positive pressure ventilation; heart rhythm and rate control; metabolic and hormonal disorders correction; and in extreme circumstances mechanical circulatory support (8, 9, 25, 26). Most features we included in the full and reduced models were preoperative clinical and intraoperative hemodynamic variables. Our prediction model could be integrated into the EMR system for use in everyday practice, and the HER database could automatically provide the model with the data it needs. In the very early phase after surgery, LCOS models could provide LCOS risk prediction and shed a light on further strategies for postoperative management and initiation of individualized therapy.

The present study showed that LVEF, Lac, LVDd, MABP < 65 time, hypertension, PLT, age, Cr, CVP_AUT_16, CVP_AUT_12, and blood loss significantly contributed to the prediction. The reduced RF model using these features also showed little discrimination loss in the prediction of LCOS (AUC:0.895 vs. 0.909) but it could significantly increase the efficiency and convenience, which may contribute to risk stratification and short-term decision making for LCOS.

Traditionally, machine learning models have been less interpretable when compared to traditional regression models. This black-box behavior has hindered their application in clinical settings. To enhance the interpretability of machine learning, we utilized SHAP and LIME interpreter techniques to visualize how features affect the prediction of LCOS, both globally and individually accordingly. SHAP summary plot revealed that LVEF, Lac, LVDd and MABP < 65 time were the most significant predictors of LCOS, with lower LVEF, higher Lac, larger LVDd and longer MABP < 65 time indicating increased possibility of the prospective onset of LCOS. LVEF is the most widely used estimate of left ventricular systolic function and a decreased LVEF is an independent risk factor for LCOS (27, 28). Serum lac is a well-recognized biomarker of tissue perfusion, and elevated lac can serve as a sensitive indicator of LCOS. Ventricular dilatation is a common compensatory response to decreased myocardial contractility (29), which can explain the association between enlarged LVDd and the risk of LCOS. MABP < 65 time also serves as a surrogate for a hypotension state subsequent to reduced cardiac output. We tried multiple thresholds of MABP (< 65, < 60, < 55, < 50 mmHg) and MABP < 65 mmHg showed a better predictive value than other thresholds, suggesting 65 mmHg was a good MABP threshold regarding maintenance of tissue perfusion (30). In our study, patients with a history of hypertension were less likely to develop LCOS after cardiac surgery, which is consistent with a previous study (3). Hypertension is usually associated with myocardial hypertrophy and is accompanied by enhanced myocardial contractility. Notably, hypertension patients were also reported to have higher mortality after the onset of LCOS, because myocardial hypertrophy would exacerbate the deficiency of oxygen supply subsequent to LCOS (31).

Our study had several advantages when compared to previous studies. Firstly, our study included comprehensive variables including demographics, commodities, echocardiographic and laboratory measurements and operation related information including intraoperative hemodynamic data, which could reflect the patient's profile in multiple dimensions. Secondly, we incorporated various hemodynamic time-series features that were considered difficult to incorporate in prediction models (32–34). In our previous study, we demonstrated an association between hemodynamic time-series data and postoperative organ dysfunction (35). It is well known that intraoperative hypotension and venous congestion may be a reflection of LCOS. We examined cumulative time, total area under curve and time weighted average under or above pre-specified thresholds other than using static measures as in other studies (36). In this way, we could assess both the duration and severity of hypotension and venous congestion, so as to better contribute to the prediction of LCOS.

Thirdly, we analyzed the predictive value of all features and selected features for LCOS prediction. Some studies made feature selection only based on linear regression or stepwise logistic regression, which may exclude features that were not statistically significant but have causal effects on the output variable due to non-linear relationships or interactions between the variables and outcomes (37). As a wrapper built around the random forest classification algorithm, Boruta performed classification by voting on multiple unbiased weak decision trees (38), which could deal with non-linear and complex relationships between the features and the outcome. Thus, our approach reduced the possibility of missing important or previously unreported features.

This study was subject to some limitations. First, we did not compare the performance of our models with previous LCOS risk scores because some of the variables required in the risk scores were not available. Second, the models have not been verified in the external validation queue. Third, this is a single center retrospective study. Further multi-center studies with external validation are needed to further verify our findings and prospective studies could be of more importance in assessing the performance of our predictive models.

Conclusion

In the present study, we successfully developed several machine learning models to predict LCOS following cardiac surgery, which may avail to risk stratification, early detection and management of LCOS following cardiac surgery.

Data availability statement

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

Ethics statement

The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Nanjing First Hospital, Nanjing Medical University (KY20220518-KS-01). Informed consent was not obtained due to the observational and anonymous nature of data collection.

Author contributions

LH, HX, CG, DG, and CZ conceived the conception of the study. LH, HX, CG, HT, and XSh acquired the data. XSo, DG, and CZ participated in data analyses. CG and DG constructed the predictive model. LH, HX, CG, and HT prepared the first draft of the manuscript. CZ and DG led the project and supervised the study. All authors were involved in writing or editing the manuscript, read, and approved the final version of the manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.973147/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Missing value in the study.

SUPPLEMENTARY FIGURE 2
Prognosis variables in patients with LCOS diagnosed by CI criterion and other criteria and patients without LCOS, including mechanical ventilation time **(A)**, ICU stay time **(B)** and hospital stay time **(C)**.

SUPPLEMENTARY FIGURE 3
Feature importance determined through Boruta algorithm.

SUPPLEMENTARY FIGURE 4
Subset feature selection through Lasso regression.

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Weaning from venous-arterial extracorporeal membrane oxygenation: The hemodynamic and clinical aspects of flow challenge test

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The cardiac function reserve is crucial for the successful weaning of V-A ECMO. During the V-A ECMO weaning phase, the gradual reduction in pump flow converts the blood flow originally driven by the pump to native cardiac output and also transforms afterload (caused by retrograde flow) into ventricular preload, thus introducing a "flow challenge" to the native heart. In this perspective, we propose to use this flow challenge as a test to simulate the preload-to-afterload conversion to assess cardiac functional reserve quantitatively. With this short article we offer the hemodynamic and clinical aspects regarding the flow challenge test.

KEYWORDS

flow challenge test, weaning evaluation, V-A ECMO, cardiogenic shock, cardiac function reserve

Introduction

Venous-arterial extracorporeal membrane oxygenation (V-A ECMO) is an important circulatory support to rescue patients with refractory cardiogenic shock (1, 2). However, the use of V-A ECMO can also lead to various complications (3, 4), such as infection, hemorrhage, lung injury and skeletal muscle atrophy (5). Besides, prolonged V-A ECMO support was also associated with higher mortality (6), therefore, early weaning should be considered to maximize its benefits. Before removing V-A ECMO, an accurate evaluation of the recovery of cardiac function is of crucial importance. On one hand, some patients, who failed to meet institutional criteria for weaning consistently, might have sufficient cardiac function reserve to tolerate the increased cardiac load after removal of V-A ECMO. This "unnecessary" V-A ECMO support exposed them to increased risk of subsequent complications. On the other hand, nearly one third of

deceased patients had once been weaned from ECMO (7). Of note, one of the major contributors for the death after weaning was heart failure (5).

Previously, studies have proposed several cardiac systolic function parameters to predict the successful weaning of V-A ECMO, such as aortic velocity-time integral (VTI), left and right ventricular ejection fraction, lateral mitral annulus peak systolic velocity and pulse pressure (8, 9). However, these parameters may not be good predictors for successful V-A ECMO weaning, as they fail to directly reflect the native heart's ability to cope with drastic hemodynamic changes after weaning. A more essential indicator to evaluate cardiac function reserve, that is, the ability to transfer excess blood volume (originally delivered by V-A ECMO) into the native cardiac output (CO) to maintain adequate systemic perfusion is necessary.

Downgrading venous-arterial extracorporeal membrane oxygenation flow brings a hemodynamic challenge to the native heart

With V-A ECMO support, the global blood flow is contributed by both the V-A ECMO device and the native heart. Thus, blood flow is distributed in two systems. Peripheral V-A ECMO draws blood from the right atrium, which is collected from the tissue by the venous return system, *via* a centrifugal pump (which generates a negative pressure), delivers it to a membrane oxygenator, and then returns it to the femoral artery. The residual blood volume in the right atrium goes through the left heart and is ejected into the systemic circulation (10).

The "flow challenge" is a process in which the downgrading of V-A ECMO flow is carried out to evaluate if the native heart can cope with the increased burden. During the V-A ECMO weaning phase, the speed of pump rotation is gradually reduced (8). This process of downgrading the device flow decreases the *trans*-pump pressure (suction power) leading to lower blood flow through the pump, increases the blood volume reaching the left heart (**Figure 1A**) (10), and therefore posing a remarkable but reversible hemodynamic challenge, which could be potentially used to evaluate the cardiac function reserve.

From fluid challenge test to flow challenge test

The assessment of fluid responsiveness in patients with V-A ECMO could not only help to optimize the preload but also guide the decision to wean from ECMO support. In the TEMPLE study (11), a change of preload was induced either by the Trendelenburg maneuver or fluid challenge, while the pump was maintained at the same rotation speed. Ventilation support, sedation and vasopressors remained unchanged as well. This study has demonstrated that an increase in VTI of at least 10%, induced by the Trendelenburg maneuver is reliable in predicting fluid responsiveness in patients with V-A ECMO while keeping the pump flow unchanged.

Adjusting the flow of V-A ECMO centrifugal pump is a routine to simulate different loading conditions to assess the performance of ventricles during the weaning phase (8). Different from fluid challenge, reducing V-A ECMO flow (flow challenge) will increase preload but decrease afterload (12). In other words, it is a conversion of afterload to preload. Patient's functional cardiac reserve, which was used to overcome afterload, is now converted to cope with the increased preload. Therefore, it has two main effects: (1) blood flow reaching the left heart will increase accordingly and move the operating point along the Frank-Starling curve to the right; (2) decreased retrograde device flow reduces afterload and thus shifts the Frank-Starling curve upward (**Figure 1B**). The combined effect is a shift of the heart's operating point to the upper right. This maneuver could be called flow challenge test (FCT).

Using flow challenge test maneuver to depict the relationship between venous-arterial extracorporeal membrane oxygenation flow and native CO

The speed of the pump could be gradually decreased when decisions are made to start the weaning evaluation process. Two types of flow reduction protocol are widely used in clinical studies, a proportional approach where a certain percentage of rotating speed is withdrawn (13), or an equidistant approach where a certain number of rotating speed is deducted (14). In our center, reducing the pump rotation speed involves two steps, each at 500 rpm (0.5 L/min equivalently). After reducing the pump rotation speed, the V-A ECMO flow will decrease, which in turn increases the blood flow back to the native heart. On a scatter plot, using V-A ECMO flow as the horizontal axis and the native CO as the vertical axis, the regression line corresponding to the three points can thus be obtained (**Figure 2A**). The intercept of the vertical axis represents the predicted immediate CO after ECMO weaning, and the slope indicates the **conversion ratio** between reduced ECMO flow and increased CO.

Prediction of CO after weaning by flow challenge test maneuver

Here we present two detailed cases underwent FCT before V-A ECMO weaning. Both patients received V-A

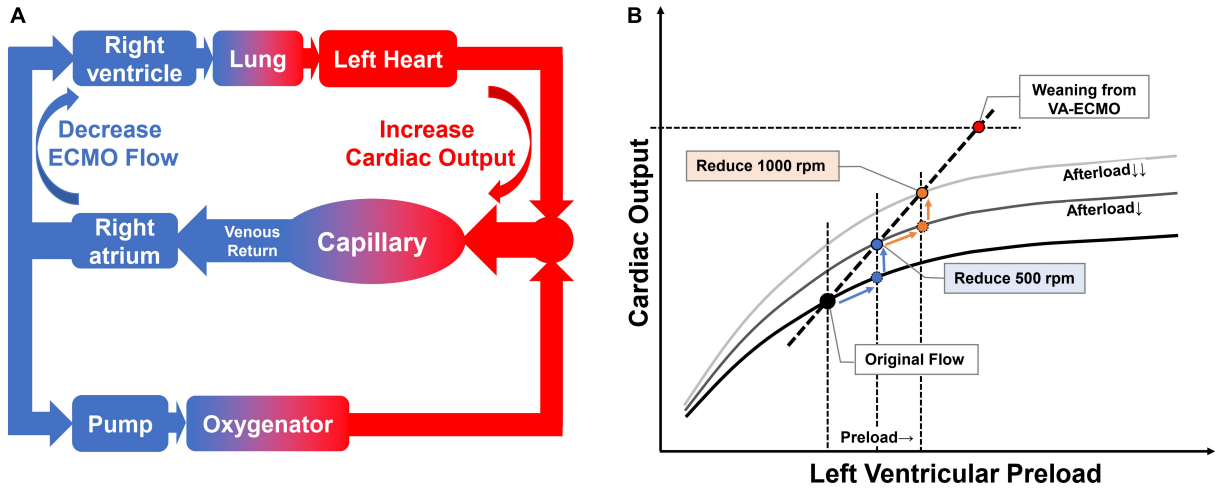

FIGURE 1
Effect of flow challenge test (FCT) on blood flow re-distribution and ventricular performance. Panel **(A)** the effect of reduced pump rotation speed on native cardiac output. When we reduce the V-A ECMO flow, the excess blood goes to the native heart and is then ejected into the systemic circulation. Panel **(B)** the flow challenge test shifts the cardiac operating points to the upper right on Frank-Starling curve. By stepping down the rotation speed of the V-A ECMO pump, the operating point shifts to the right along the Frank-Starling curve. In addition, the Frank-Starling curve itself shifts upward as afterload is reduced due to a decrease in retrograde blood flow. The combined effect is a shift of the heart's operating point to the upper right.

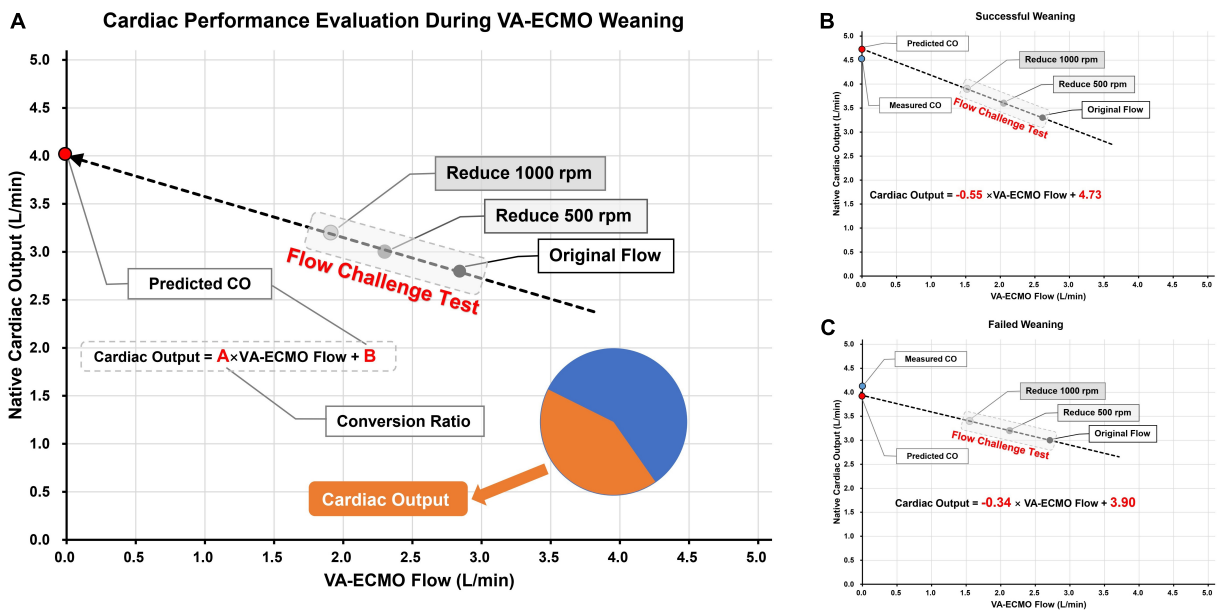

FIGURE 2
Schematic diagram of using flow challenge test (FCT) to predict cardiac output (CO) performance after V-A ECMO weaning. Panel **(A)** the picture on the left is the schematic diagram of FCT; The pump speed was reduced on two stages, each time by 500 rpm. CO were measured at the corresponding three points and the actual ECMO flow rates were also recorded. The CO after weaning was then predicted by linear regression and the conversion ratio between ECMO blood flow and CO was calculated. Panels **(B,C)** two cases of successful and failed weaning, respectively. The predicted and actual values of CO are very close to each other. The weaning successful patient shown higher predicted CO and conversion ratio than the weaning failure patient.

ECMO support for cardiogenic shock. Cardiac function was gradually recovered in both patients, and V-A ECMO blood flow rate was reduced to around 2.5 L/min. During the weaning process, transthoracic echocardiography was used to measure VTI (at the level of the left ventricular outflow tract) to calculate the CO. After pump speed reduction,

V-A ECMO flow and CO were recorded after a 10-min stabilization. In the first case (**Figure 2B**), during the FCT process, the V-A ECMO flow decreased from 2.61 to 2.05 and 1.53 L/min while CO increased from 3.3 to 3.6 to 3.9 L/min, sequentially. The linear regression formula is Cardiac Output = −0.55 × V-A ECMO flow + 4.73, with a vertical axis intercept of 4.73 (the predicted CO value immediately after V-A ECMO weaning), which is extremely close to the actual measurement (4.5 L/min). In the second case (**Figure 2C**), the FCT also induced a well-fitted regression line (Cardiac Output = −0.34 × V-A ECMO flow + 3.90). The predicted and measured values of CO were also very close (3.9 vs. 4.1 L/min).

Assessment of cardiac functional reserve by flow challenge test maneuver

In the aforementioned two cases, changes in the central venous pressure (CVP) were observed after weaning from V-A ECMO. During the FCT maneuver, CVP almost remained the same. We assumed it was because reflecting the subtle changes in cardiac preload under right atrial V-A ECMO drainage was difficult. After removal of V-A ECMO, the CVP of the two cases increased from 13 to 15 mmHg, and 14 to 19 mmHg, respectively, suggesting that more blood was retained in the venous and right heart system after weaning from V-A ECMO. This also means that the blood flow that was originally supplied by the device was not fully compensated by the native heart. Instead, the recovering heart could only convert part of the ECMO flow into native CO, while the unconverted part was transferred into stressed volume, achieving a new balance.

The concept of conversion ratio was then investigated. As we have previously defined, the conversion ratio indicates the ability of the heart to convert the reduced V-A ECMO flow into native CO. In the first case, the conversion ratio was 0.55, which meant every 1 L/min reduction in V-A ECMO flow could lead to 0.55 L/min increment in CO. However, in the second case, the conversion ratio was only 0.34. The two cases also had different outcomes, with the first case weaned successfully while the second one failed. Therefore, the conversion ratio has the potential to become a quantitative parameter for assessing cardiac functional reserve.

Enriching evidence for clinical application

Before formal clinical application can be made, several studies should be performed to provide more evidence. (1) *in vitro* simulation tests: digital cardiovascular system models (15) or the mock circulatory loops (16) could be used to simulate the conversion ratios corresponding to FCT performed with different cardiac function reserves. (2) Animal models: In the animal V-A ECMO model, we can place a variety of pressure and flow transducers and perform detailed transesophageal echocardiographic monitoring to assess whether the cardiovascular response, when performing FCT under different cardiac functions, is consistent with that predicted by the *in vitro* model. (3) Clinical observational study: In a larger cohort of population, evaluate the associations between conversion ratio or predicted CO and cardiac functional parameters or clinical outcomes, and then calculate their best cutoff values for weaning. (4) Interventional study: Use the conversion ratio and predicted CO at FCT to guide weaning and assess whether this tool could improve prognosis.

Summary

Flow challenge test is easy to implement during the V-A ECMO weaning phase and can provide quantifiable measures in guiding V-A ECMO management. During FCT, afterload is converted into preload. This process can introduce a hemodynamic challenge and be used to predict the CO value after weaning, which is an important determinant of systemic oxygen delivery and tissue perfusion. In addition, the proposed "conversion ratio" as a parameter of cardiac functional reserve measured during the process of FCT, has the potential to be used as a dynamic parameter to improve the accuracy of conventional static ones in the field of hemodynamic monitoring. The dynamic process of FCT could allow us to make more rational predictions about the instant cardiac consequences of V-A ECMO weaning.

Data availability statement

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

Ethics statement

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

Author contributions

J-CL, Y-JZ, and J-YH: development, authoring, editing, and final version approval of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

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

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Optimization of the target strategy of perioperative infusion therapy based on monitoring data of central hemodynamics in order to prevent complications

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Enhanced Recovery After Surgery (ERAS) protocols are increasingly used in the perioperative period around the world. The concept of goal-directed fluid therapy (GDT) is a key element of the ERAS protocols. Inadequate perioperative infusion therapy can lead to a number of complications, including the development of an infectious process, namely surgical site infections, pneumonia, urinary tract infections. Optimal infusion therapy is difficult to achieve with standard parameters (e.g., heart rate, blood pressure, central venous pressure), so there are various methods of monitoring central hemodynamics – from invasive, minimally invasive to non-invasive. The latter are increasingly used in clinical practice. The current evidence base shows that perioperative management, specifically the use of GDT guided by real-time, continuous hemodynamic monitoring, helps clinicians maintain a patient's optimal fluid balance. The manuscript presents the analytical data, which describe the benefits and basic principles of perioperative targeted infusion therapy based on central hemodynamic parameters to reduce the risk of complications.

KEYWORDS

ERAS (Enhanced Recovery After Surgery), GDT, infusion therapy, hemodynamic monitoring, central hemodynamics, cardiac output, esCCO, complications of infusion therapy

Introduction. Modern aspects of perioperative infusion therapy

Enhanced Recovery After Surgery (ERAS) protocols are increasingly used in the perioperative period around the world (1, 2). The introduction of ERAS protocols has reduced the hospital stay period by 30–50%, decreased the risk of complications and significantly reduced the frequency of re-hospitalizations (1–3). Goal-directed fluid therapy (GDT) is a key element of the ERAS protocols (4).

Monitoring of hemodynamics, volemia, blood loss, hemocoagulation and metabolism is the basis for selecting adequate methods to restore and maintain proper tissue perfusion. The value of monitoring lies in the use of the obtained data to determine the goals of therapeutic effects (5).

There is a list of clinical indications for circulatory optimization, the ultimate goal of which is the balance between delivery (DO_2) and oxygen consumption (VO_2). Indications may be due to the patient's condition and the cause of circulatory failure (6):

- severe disease or damage to the cardiovascular and respiratory systems with severe functional disorders;
- age-related functional disorders of one or more organ systems;
- acute massive blood loss of traumatic and surgical origin (> 2.5l);
- severe sepsis;
- shock or severe hypovolemia of any origin;
- respiratory failure (PaO_2 < 60 mm Hg, SaO_2 < 90% in a patient on spontaneous breathing or PaO_2/FiO_2 < 300 mm Hg in a patient on mechanical ventilation);
- acute enteropathy (abdominal compartment syndrome, pancreatitis, perforation of internal organs, gastrointestinal bleeding);
- acute renal failure (urea > 20 mmol/l, creatinine > 200 μ mol/l).

In addition, there are indications associated with surgery:

- major non-cardiac surgery (pneumonectomy, resection of the liver, intestines, complex trauma and orthopedic interventions);
- major (combined) interventions on the heart and blood vessels (aortic aneurysm, combined prosthetic heart valves, coronary artery bypass grafting and carotid endarterectomy);
- long-term surgical interventions (for example, in neurosurgery, gastrointestinal surgery);
- urgent cavitary surgery (7).

Until recently, only invasive hemodynamic monitoring was possible to assess key indicators used in GDT protocols. However, in recent decades there have been restrictions on the use of pulmonary artery catheters (PAC) in the perioperative period. Routine use of a PAC is not recommended in patients with surgical pathology, except for heart surgery (8–10).

The need for monitoring and its volume change over time, taking into account the patient's condition, risk of complications, stage of the disease and intensive care (**Figure 1**) (11).

Perioperative infusion therapy plays an important role in reducing the risk of surgical infections. Both fluid overload and hypovolemia can impair tissue oxygenation, which adversely affects wound healing as well as the development of surgical infections (12, 13). Optimal infusion therapy is difficult to achieve with standard parameters [e.g., heart rate (HR), blood pressure (BP), central venous pressure (CVP)] (14). Surgical infections remain an important cause of morbidity and mortality in patients, ranking third in the incidence of healthcare associated infections. Surgical infections prolong the length of hospital stays, increase the cost of treatment and become a key indicator of the quality of care (15–17).

In recent years, various non-invasive hemodynamic monitoring technologies have been proposed (18). Innovative technologies for continuous non-invasive hemodynamic monitoring significantly expand the possibilities of improving the strategy of infusion therapy and personalization of hemodynamic management (19).

Among modern technologies of non-invasive monitoring, the pulse wave transit time (PWTT) is one of the newest ways to determine the main indicators of hemodynamics. The wide possibilities of this method is little studied. The strong correlation between stroke volume (SV) and PWTT discovered by Japanese scientists at Nihon Kohden was the basis of a formula that allows continuous monitoring of the most important volumetric parameters of the heart (stroke and heart indices). The results of a limited number of clinical trials of this non-invasive and convenient technique are available in the literature. An unequivocal opinion on this method has not yet been formed, but its accuracy and reliability for trend monitoring are considered quite satisfactory (20).

Fluid management within Enhanced Recovery After Surgery protocols

One critical element of all ERAS programs is a protocol known as perioperative goal-directed therapy (PGDT), which helps ensure adequate hydration and maintain euvolemia while avoiding hypervolemia or hypovolemia that can contribute to postoperative complications (**Figure 2**) (21, 22).

Fluid management within ERAS protocols should be viewed as a continuum through the preoperative, intraoperative, and postoperative period (1). The goal of preoperative fluid

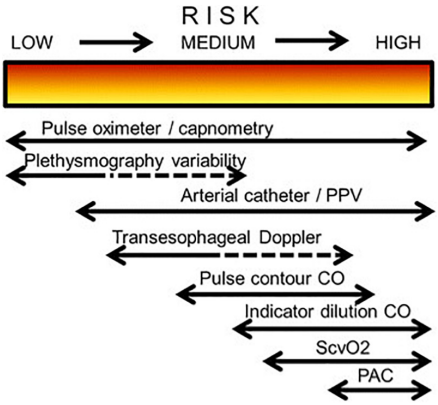

FIGURE 1
Possible choice of monitoring system in relation to a patient's degree of perioperative risk (CO, cardiac output; PAC, pulmonary artery catheter; PPV, pulse pressure variation; $ScvO_2$, central venous oxygen saturation).

management is for the patient to be in a hydrated and euvolemic state when arriving in the operating room. This is usually achieved by avoidance of prolonged fasting and mechanical bowel preparation and encouraging patients to ingest a clear carbohydrate drink approximately 2 h prior to surgery. The goals of intraoperative fluid management are to avoid excess salt and water and to maintain central euvolemia. As such, patients undergoing surgery within an ERAS protocol should have an individualized fluid management plan. Maintenance of intravascular euvolemia throughout the perioperative period is ideal (23).

To achieve optimal fluid balance for the surgical patient, PGDT relies on continuous monitoring of a variety of hemodynamic targets, including cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume variation (SVV), and pulse pressure variation (PPV).

Routine hemodynamic measurements, such as HR and mean arterial pressure (MAP), remain relatively unchanged despite reduced blood flow and are considered insensitive indicators of hypovolemia or changes in CI (24, 25). As a result, conventional fluid management is based on clinical assessment, vital signs, CVP monitoring, or a combination of these. However, recent studies have shown that CVP is not able to predict fluid responsiveness nor can changes in BP be used to approximate changes in SV or CO (26, 27).

Modern monitoring of perioperative infusion therapy is a personalized correction of hemodynamics, rather than on the basis of generally accepted schemes and rules. Some of the important requirements for monitoring methods are given in Table 1. The advanced hemodynamic monitoring equipment used to guide clinical decision-making intraoperatively be selected based on a combination of surgical patient and institutional factors (4).

Methods of central hemodynamic monitoring of perioperative infusion therapy

Cardiac output monitoring is considered the gold standard for assessing central hemodynamic parameters and infusion response. There are many ways to measure CO, which differ in the degree of invasiveness and continuous or periodic research method (28–30). The various methods classification of monitoring central hemodynamics is presented in Figure 3.

Invasive methods of hemodynamic monitoring

The classic invasive method is catheterization of the right heart with a Swan-Ganz catheter (Edwards Life Sciences,

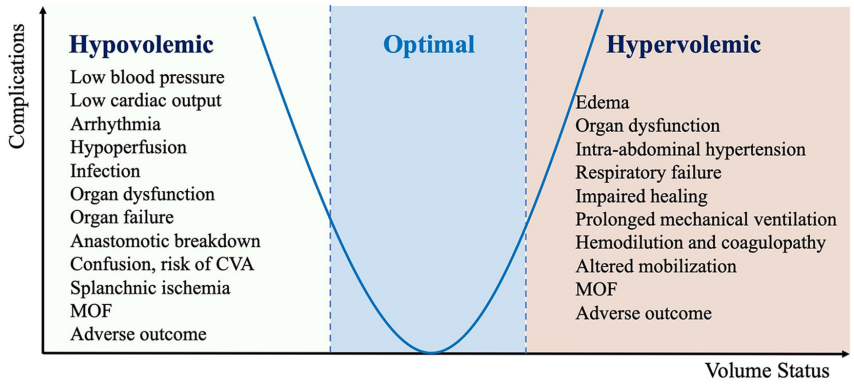

FIGURE 2
Complication associated with inadequate perioperative fluid management (CVA, cerebrovascular accident; MOF, multiple organ failure).

TABLE 1 Requirements for the "ideal" method of monitoring.

Ensuring the measurement of the required indicators
Ensuring the accuracy and reproducibility of measurements
Obtaining data to be interpreted
Availability in clinical practice
Independence of results from operator skills
Fast response time
No risk of complications
Profitability
Providing the necessary information for the correction of treatment

Irvine, CA, USA). Swan-Ganz advanced technology pulmonary artery catheters enable continuous assessment of flow, pressure, and oxygen delivery and consumption. Pulmonary artery catheterization or transpulmonary thermodilution is indicated for the most difficult patients to determine the type of shock. Swan-Ganz catheter allows continuous monitoring of the balance of oxygen delivery and consumption with the following advanced hemodynamic parameters: mixed venous oxygen saturation (SvO_2), CO, SV, systemic vascular resistance (SVR), right ventricular ejection fraction (RVEF), right ventricular end diastolic volume (RVEDV), pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP) (31).

This technique requires technical skills. Risks of a PAC procedure include arrhythmias, pneumothorax, heart block, lung infarction, perforation of the balloon, thrombosis, air embolism, knotting of the catheter, valvular damage, or infection (32). In less than 0.2% of cases Swan-Ganz catheterization results in serious vascular damage – pulmonary artery rupture (33).

To date, routine use of these methods is not recommended (34). Specific indications for PAC are cases of inconsistency of right ventricular and left ventricular (LV) contractility, pulmonary arterial hypertension, for example in cardiac surgery, lung and liver transplantation or severe ARDS (35–37). At the same time the CVP ceases to adequately reflect a preload of LV therefore for this purpose it is necessary to carry out monitoring of PAOP (38).

Minimally invasive methods of hemodynamic monitoring

Minimally invasive methods based on usage transpulmonary dilution of the indicator (CeVOX, $PiCCO_2$, LIDCOplus) and analysis of arterial pulse wave (ProAQT technology, MostCare®, Edwards Vigileo™ and Acumen IQ Sensor system).

The most established commercially available complete CeVOX and $PiCCO_2$ sets are produced by Pulsion Medical Systems, Germany. The sensor for venous oximetry is installed through one of the lumens of the central venous catheter. CeVOX or $PiCCO_2$ central units equipped with an optical module and a disposable fiber optic sensor are required for continuous measurement of venous saturation. There are studies that prove validity and clinical usefulness of the CeVOX (39–43). The $PiCCO_2$ system allows continuous monitoring of blood oxygen supply and consumption values (44). Lithium dilution cardiac output (LiDCO™; LiDCO, London, UK) is a minimally invasive indicator dilution technique for the measurement of CO. The technique is quick and simple, requiring only an arterial line and central or peripheral venous access. A small dose of lithium chloride is injected as an intravenous bolus, and CO is derived from the dilution curve generated by a lithium-sensitive electrode attached to the arterial line.

ProAQT technology (Pulsion Medical Systems, Germany) is implemented as follows. The ProAQT sensor is an instantaneous pressure sensor and is inserted into a standard arterial catheter. A continuous blood pressure signal is supplied from the ProAQT sensor to a special monitor. Based on this signal, a number of hemodynamic parameters are determined. The most important thing in shock is the trend of minute blood volume (MBV). Initial calibration, which is calculated on the basis of basic anthropometric indicators (45), is required for continuous assessment of the MBV trend. There are other indicators that are determined by the ProAQT method, such as SVR and SVV.

MostCare® (Vytech Health, Padua, Italy) is a method developed for continuous CO monitoring based on BP parameters. This technique does not require initial calibration and does not require central venous access. MostCare® requires access to one of the peripheral arteries. The technology is based on the principle that a change in pressure changes the diameter of the vessel and, as a result, changes the volume of blood passing through its cross section. Variables such as LV contractility, pulse wave parameters, arterial wall elasticity, flexibility and peripheral resistance of small arterioles are closely interrelated and evaluated by the system. Thus, the flow gives the area under the curve, and then the formula is calculated by CO (46).

Edwards Vigileo™ system consists of a sensor (FloTrac, Edwards LLC) and a processing/display unit (Vigileo, Edwards LLC). The sensor is a transducer that preprocesses and sends a signal to both a cardiovascular monitor (for real time waveform display) and the Vigileo monitor. The processing unit applies a proprietary algorithm to the digitized wave, and reports CO, CI, SV, stroke volume index (SVI) and SVV. If a central venous pressure catheter has been placed, its signal can be interfaced with the Vigileo, allowing for the calculation of SVR and SVR index (SVRI). When used with a central venous oximetry catheter, the Vigileo also provides continuous central venous oxygen saturation (ScvO2).

Potential weaknesses of the system include possible inaccuracy in the presence of arterial wave artifact, compromise

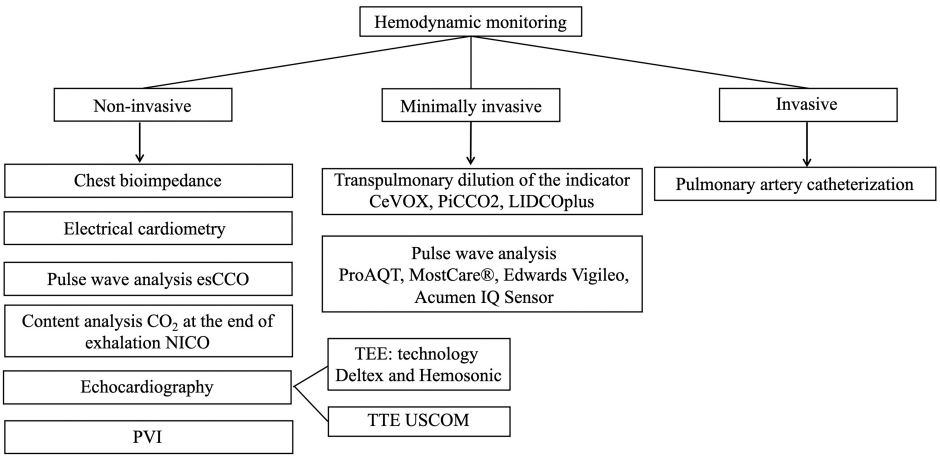

FIGURE 3
Methods of monitoring central hemodynamic (esCCO, estimated continuous cardiac output; NICO, non-invasive cardiac output partial CO_2 rebreathing technique; PVI, pleth variability index; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography, USCOM, ultrasonic cardiac output monitor; CeVOX, continuous central venous oxygenation measurement; PiCCO, pulse index continuous cardiac output; LiDCO, lithium dilution cardiac output).

of the arterial catheter, aortic regurgitation, intense peripheral vasoconstriction and irregular pulse.

The Acumen IQ Sensor with Acumen hypotension prediction index (HPI) software (Edwards Lifesciences Ltd) is designed to predict the chance of an individual having a hypotensive event in surgical and non-surgical settings. A hypotensive event is defined as MAP of less than 65 mmHg, that exceeds a cumulative length of 15 min. The sensor attaches to any existing radial arterial line and is used to automatically calculate key parameters every 20 s. The parameters include HPI, contractility (systolic slope; dP/dt), afterload (dynamic arterial elastance), CO, pulse rate, SV, SVV, MAP, CI, PPV and SVR. HPI requires a good-quality arterial line waveform. To the extent that the waveform is damped or varies consequent to changes in patient position or other mechanical issues, predictions may be compromised.

Non-invasive types of hemodynamic monitoring

Non-invasive monitoring is increasingly used in routine practice compared to invasive techniques, due to the lack of complications and the need for special technical skills, technical support (47).

Pleth variability index (PVi – volemia index; Masimo, Irvine, California, USA) – variations in the perfusion index during the respiratory cycle (Masimo Rainbow Pulse CO-Oximetry technology) (48). A number of independent objective studies have shown that Masimo SET technology provides the most reliable readings of oxygen saturation and HR measured in difficult clinical settings, including patient movements and low peripheral perfusion (49). PVi values are informative in predicting the response to fluid infusion in ventilated patients. However, changes in vasomotor tone, the appointment of vasopressors, hypothermia have a direct effect on plethysmographic signal and are potential limitations of the method.

The Non-invasive Cardiac Output partial CO_2 rebreathing technique technology (NICO) introduced by Novametrix allows the measurement of CO by analyzing the CO_2 content at the end of exhalation. The accuracy of NICO technology is lower compared to invasive techniques, also there is a dependence on ventilation and gas exchange. Partially reversible breathing is used to implement this technology. The monitor processor analyzes 4 parameters: the amount of carbon dioxide released during normal and reversible breathing and the content of carbon dioxide in the arterial blood during normal and reversible breathing (50). Specially conducted comparative studies of the results of CO registration by the NICO monitor and reference methods (Fick's Principle, thermodilution) under critical conditions registered reliable correlation coefficients. Thus, it can be stated that this non-invasive method of CO registration is quite accurate (50).

ClearSight system finger cuff (Edwards Lifesciences) is a non-invasive device that is fixed on the patient's finger. It allows continuous measurement of blood pressure. In addition, the device is able to calculate such parameters as CO, SVR, stroke volume, MAP.

The device has a so-called Heart Reference Sensor (HRS), which automatically compensates for changes in hydrostatic pressure due to differences in height between the finger and the heart. HRS compensates for changes in the

patient's arm position during any procedure or during patient movement (51).

Impedance cardiography (ICG) is a non-invasive method that uses changes in impedance of the chest to assess hemodynamic parameters, including CO. Studies of ICG have reported conflicting results and are difficult to compare, since they have been performed using devices of different generations in patients with different characteristics, while also using different equations (52). The technology is non-invasive, but the method is sensitive to electrical interference, patient movements, largely depending on the correct placement of electrodes. The accuracy of bioimpedance methods is questionable in a number of critical conditions (pulmonary edema, pleurisy, volume load, ventilation, arrhythmias, valve pathology) (50).

Electrical Cardiometry (EC) is a monitor for non-invasive method of measuring continuous CO monitoring based on measurement of thoracic electrical bioimpedance. Bioimpedance CO is based on the principle that cyclical increases in blood volume in the great vessels, as well as alignment of red blood cells (RBCs) in the thoracic aorta resulting from increased velocity, cause concomitant decreases in the electrical impedance in the chest. An alternating current of low amplitude is introduced and simultaneously sensed by electrodes placed around the neck, and laterally on the thorax to measure thoracic electrical bioimpedance. Changes in thoracic bioimpedance are induced by ventilation and pulsatile blood flow. EC is often confused with the traditional bioimpedance technology most commonly known as ICG. Though both methods use sensors placed on the thorax, traditional bioimpedance or ICG methods rely on the assumption of periodical volumetric changes in the aorta to determine SV and CO. ICG attributes the steep increase in the conductivity waveform to a volumetric expansion of the aorta during systole, while EC contributes the increase in conductivity to the orientation change of the RBCs to determine the velocity of the blood flow. EC method may be used for measuring cardiac output in a wide spectrum of diseases and patient populations including neonates and children, while ICG is limited to relatively healthy adults. The disadvantage associated with electric cardiometry is that the parameters are not available during electrical interference (electric cautery) (53).

The EC technology is utilized on the Aesculon and ICON device (Osypka Medical, Berlin, Germany/Cardiotronic, San Diego, CA, USA).

Monitoring of hemodynamics by echocardiography

Echocardiography, as a non-invasive or semi-invasive method for the assessment of cardiac anatomy and function, is favored in clinical practice. The methods commonly used for echocardiography include transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and ultrasonic CO monitor (USCOM). TEE or TTE echocardiography can provide immediate point-of-care assessment of acute hemodynamic changes in selected patients. Indications for TEE include the evaluation of cardiac and aortic structure and function in situations in which the findings will alter management and the results of TTE are non-diagnostic or TTE is deferred because there is a high probability that results will be non-diagnostic. Situations in which TTE may be non-diagnostic include, but are not limited to, detailed evaluation of the abnormalities in structures that are typically in the far field, such as the aorta and the left atrial (LA) appendage; evaluation of prosthetic heart valves; evaluation of native valve masses; evaluation of paravalvular abscesses (both native and prosthetic valves); and various uses in critically ill patients. Transthoracic echocardiographic image quality may be compromised in patients on ventilators, those with chest wall injuries, obese patients, and those unable to move into the left lateral decubitus position.

Contraindications include esophageal disease with known stricture, diverticuli, varices or tumor, prior esophageal or stomach surgery, perforated viscus, or an uncooperative patient. Relative contraindications include cervical spine disease, hiatal hernia, coagulopathy, prior chest radiation, or facial or airway trauma. In addition to the estimation of CO (usually easier with TEE than with TTE), Doppler echocardiographic examination can provide an indication of cardiac function because it allows visualization of the cardiac chambers, valves, and pericardium (54). Doppler imaging can be used to calculate important indicators such as CO, CI, MBV, SVR, PAOP and a number of other indicators (55).

The USCOM ultrasonic cardiac output monitor (USCOMPty Ltd., Coffs Harbour, NSW, Australia) provides non-invasive transcutaneous measurement of CO. The flow profile is obtained by using a transducer (2.0 or 3.3 MHz) placed on the chest in either the left parasternal position to measure transpulmonary blood flow or the suprasternal position to measure transaortic blood flow. This flow profile is presented as a time–velocity spectral display showing variations of blood flow velocity with time. The CO is then calculated from the equation (56):

$$CO = \text{heart rate} \times \text{stroke volume}$$

where the SV is the product of the velocity time integral (VTI) and the cross-sectional area (CSA) of the chosen valve.

The USCOM monitor is limited to cardiac output measurement and gives no indication of other hemodynamic variables, such as pressure measurements, vascular resistance or stroke work calculations. In addition, it does not provide the means to measure mixed venous oxygenation.

Ultrasonic transesophageal Doppler (Deltex, HemoSonic technologies) provide continuous assessment of CO by measuring the linear velocity of blood flow in the aorta. Doppler

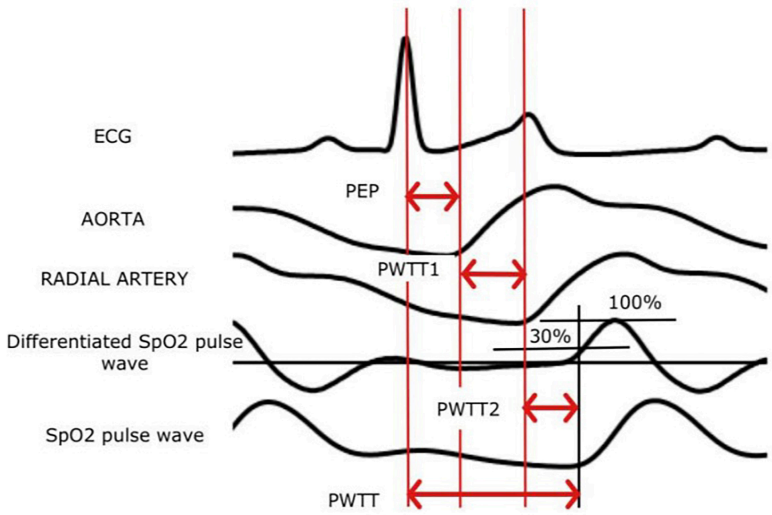

FIGURE 4
The principle of measuring esCCO (ECG, an electrocardiogram; PWTT, pulse wave transit time).

techniques are non-invasive and relative simple in application, but the results are approximate and depend on the position of the esophageal sensor and dysphagia may occur. Unstable hemodynamics and a narrow ultrasound window increase the measurement error. In addition, ultrasound techniques require a specially trained specialist (50).

CardioQ and CardioQ-ODM use Doppler ultrasound to monitor HR and intravascular fluid volume. CardioQ and CardioQ-ODM monitors are designed for use with a number of Doppler esophageal probes for Deltex Medical.

Recently, a non-invasive method of CO monitoring – estimated continuous cardiac output (esCCO), based on the assessment of pulse wave transit time (PWTT), has become available in clinical practice. The esCCO system defines PWTT as the time interval between the moment of appearance of the R wave on the electrocardiogram (ECG) and the beginning of the pulse wave on the plethysmogram of the pulse oximeter. This interval includes three points of measurement of time intervals (**Figure 4**): PEP – from R to ventricular contraction, T1 – the passage of a pulse wave from the aortic valve to the radial artery, T2 – from the radial artery to peripheral blood vessels. An inverse correlation was found between PWTT and SV (57–59).

Measured PWTT, BP and HR are used to calculate CO according to the following formula (60):

$$CO = K \times (\alpha \times PWTT + \beta) \times HR,$$

where CO – cardiac output; α is a constant that has been determined in previous clinical trials of esCCO technology; β is a variable that is a derivative of pulse pressure; K – calibration factor based on the biometric characteristics of the patient (height, weight, sex, and age); PWTT – pulse wave transit time; HR – heart rate.

Estimated continuous cardiac output technology is effective because it does not require to use of any additional sensors or specially trained personnel (61). EsCCO technology allows you continuously obtain indicators of central hemodynamics (CO, CI, SV, stroke index). Existing studies show that CO measured by esCCO and thermodilution (61, 62), showed a good correlation, with a small deviation (from 0.04 to 0.13 l/min). When comparing esCCO with TTE, the correlation was observed in cardiac patients with a range of −0.60 to 0.68 l/min (63), as well as in patients of intensive care unit with a deviation of −1.6 l/min (64).

However, the expressed disturbances of peripheral microcirculation, the presence of clinically significant cardiac arrhythmias, significant damage to peripheral arteries, severe heart valve dysfunction are the limitations of the method (65).

All monitoring systems have unique characteristics in terms of accuracy, reliability, measurement accuracy, stability and reliability (66). Physicians should take into account the technical limitations of each monitoring system and the potential compromise between more invasive but highly accurate CO measurements and less invasive but less accurate methods (**Figure 5**).

Indications for different methods of cardiac output assessment during perioperative hemodynamic management

Indications for the different methods of CO assessment during the perioperative hemodynamic management of surgical

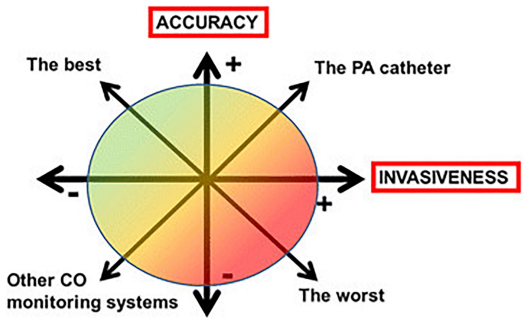

FIGURE 5
The compromise between accuracy and invasiveness of monitoring systems (CO, cardiac output; PA, pulmonary artery).

patients are shown in **Figure 6**. In non-cardiac surgery patients, indications for CO monitoring depend on the presence of various patient-related and surgery-related risk factors for perioperative complications. The routine use of PAC to assess CO is not recommended (10). In addition, TEE is only recommended in patients with acute sustained severe hemodynamic instability in the perioperative period (10). Low-risk non-cardiac surgical patients can be monitored using basic hemodynamic monitoring (i.e., HR and rhythm, non-invasive arterial pressure, and peripheral oxygen saturation). In high-risk non-cardiac patients, monitoring of CO is indicated (11) as goal-directed hemodynamic management using fluids and inotropes to optimize CO (and oxygen delivery) has been shown to improve outcome (67–71). In high-risk non-cardiac surgical patients without marked alterations in vascular tone, invasive uncalibrated pulse wave analysis or esophageal Doppler can be used to guide CO optimization (71). Whether non-invasive uncalibrated pulse wave analysis can also be used for the assessment of CO in this category of patients is a subject of current research (72). In high-risk non-cardiac surgical patients with marked alterations in vascular tone (e.g., patients with liver failure or sepsis), CO can be assessed using invasive calibrated pulse wave analysis or esophageal Doppler (71). In patients undergoing open-heart and thoracic aortic surgery, TEE is indicated (73, 74). TEE may also be considered in coronary artery bypass graft surgery (73, 74). In selected cardiac surgery patients, advanced hemodynamic assessment and monitoring using a PAC may be considered.

Traditional and modern assessment of response to infusion therapy

To assess the susceptibility to infusion, the simplest method is considered to be the test with passive raising of the legs by 30–45° to assess the response of CO and BP (75). Ventilation mode, type of fluid injected, starting position and measurement method do not affect the diagnostic efficiency of passive leg lift. It is considered the best test for fluid infusion response for patients with hypotension who do not require vasopressor therapy. Echocardiographic assessment of cardiac function is considered to be the best choice for more severe patients undergoing mechanical ventilation and vasopressor support. For patients in consciousness, spontaneous breathing, and with vasopressor support, a passive leg lift test is also recommended to assess the dynamics of changes in cardiac output (76).

The response to infusion therapy using esCCO method can be assessed as follows. If infusion bolus of 500–1,000 ml caused a significant increase in cardiac output (4–6 l/min) and stroke volume (60–100 ml), the patient was considered susceptible to volemic therapy and continued to fill the circulating volume (77). In the absence of a positive hemodynamic response, the need for vasopressor and inotropic drugs was considered. It is available a GDT protocol recommended for the ultrasound method of hemodynamic monitoring (78), the modification of which can be used in other non-invasive monitoring techniques (**Figure 7**) (79).

Complications with inadequate perioperative infusion therapy

Inadequate perioperative infusion therapy may lead to a decrease of CO and DO_2 in damaged tissues, which is associated with an increased incidence of perioperative complications (**Figure 2**). In addition, the systemic inflammatory response associated with tissue damage leads to systemic capillary leakage syndrome and tissue edema. Limiting fluid intake and reducing diuresis may reduce edema in patients with reduced ventricular function, but increase the incidence of acute renal failure. There is increasing evidence from large databases that even short durations of hypotension with MAP $<$ 65 mm Hg are associated with myocardial and kidney injury (80, 81).

Excessive infusion therapy can lead to a number of side effects, including coagulopathy and edema of the lungs, intestines, and peripheral tissues (11). Sodium and water retention after surgery may reduce the need for infusion. After stabilization of the patient's condition, infusion therapy should be calculated only to restore the deficit and pathological losses.

The authors of multicenter observational study about clinical potential of an optimized perioperative fluid strategy in patients undergoing emergency gastrointestinal surgery (82) registered the postoperative complications as follows: wound-related complications included superficial wound rupture, rupture of the fascia, or anastomotic leakage. Cardiopulmonary complications included cardiac arrhythmia, acute myocardial infarction, cardiac arrest, pleural effusion,

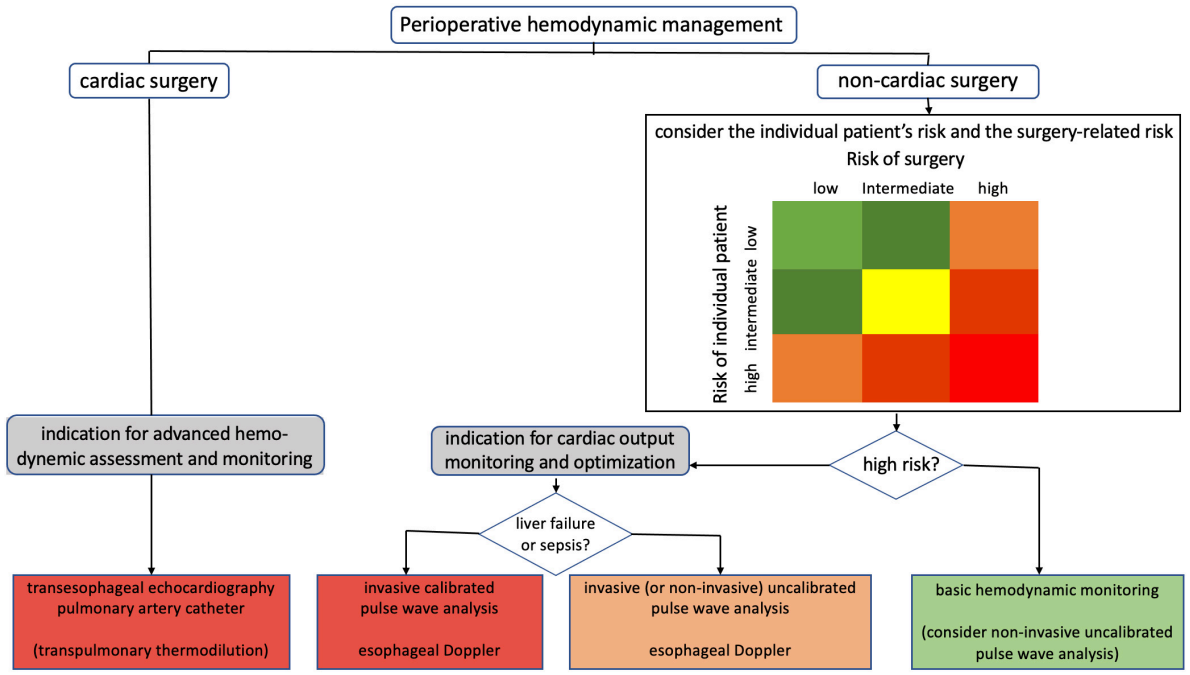

FIGURE 6
Indications for different methods of perioperative cardiac output assessment.

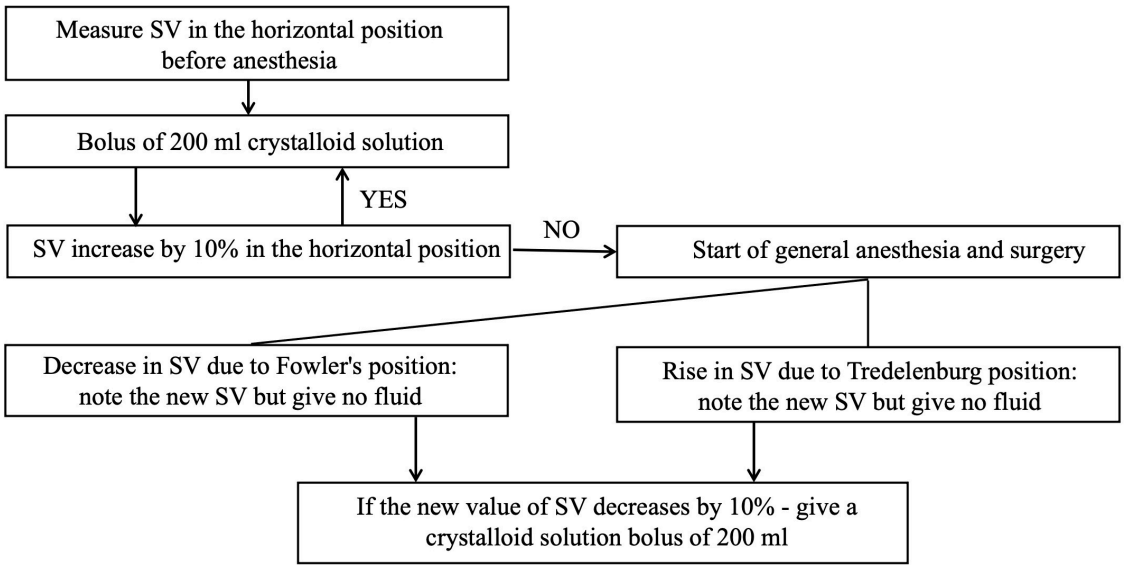

FIGURE 7
GDT protocol based on non-invasive monitoring of central hemodynamic (SV, stroke volume).

pulmonary congestion, pulmonary edema, congestive heart failure, or respiratory failure (failure to wean > 48 h, requiring continuous positive airway pressure after the day of extubating, or reintubation of any cause). Renal complications included the need for dialysis or other renal complications (nephritis or hydronephrosis treated with a nephrostomy catheter). Infectious complications included superficial wound infection, pneumonia, urinary tract infection, or cutaneous infection.

By improving cardiovascular function and balancing fluid intake, PGDT helps clinicians maintain adequate oxygen supply perioperatively. The implementation of PGDT protocols guided by continuous hemodynamic monitoring has also been shown

to help decrease nausea, vomiting, and incidence of ileus (intestinal obstruction) while allowing patients to take solid food earlier, become more alert, and start walking sooner after surgery, ultimately reducing hospital LOS (21, 22).

The goal of targeted perioperative infusion therapy is to optimize the balance between delivery and oxygen consumption. Tissue hypoxia may occur with normal hemodynamic values such as MAP, CVP, and HR. Tissue hypoperfusion contributes to postoperative complications and increases the incidence of mortality, which requires adequate methods of enhanced hemodynamic monitoring and implementation of algorithms for targeted infusion therapy.

It is known that surgical patients following the principles of targeted infusion therapy during the perioperative period had a low risk of developing infectious complications, namely surgical site infections (SSIs), pneumonia and urinary tract infections (UTIs). There were no convincing data on catheter-related bloodstream infections (83).

Surgical patients carry a high overall risk of hospital-acquired infections (HAIs), mainly because SSIs occur in addition to non-surgery-specific infections (84). Despite existing prevention schemes, SSI remains one of the most common preventable surgical complications. SSIs occur in up to 20% of all abdominal surgeries and significantly contributing to morbidity, risk of death and increased treatment costs (85, 86). Surgical patients who did not receive surgical treatment also had a higher risk of infectious complications, including pneumonia and UTIs (84).

In surgical patients, the risk of infection is determined by the interaction between the microbes (degree of contamination and virulence), the patient (immune status) and the nature of the surgery (duration of the operation and the volume of damaged tissue). The infectious process occurs due to an unbalanced relationship between bacterial load and patient resistance. During the operation, the patient's susceptibility to infection increases, the risk of infection increases due to damage to the integrity of the skin and mucous membranes, impaired microbicidal activity of immune cells (87). In this case, the perioperative delivery of oxygen DO_2 plays an important role. It is known that a sufficient level of oxygen in the tissues promotes wound healing and increases resistance to infections (12, 88–90). This is because the oxidative function of neutrophils and the destruction of bacteria by alveolar macrophages (91) depend on adequate levels of oxygen in the tissue (88, 92). It is proved that low oxygen saturation in tissues is one of the prognostic factors in the development of SSIs (93). Therefore, maintaining adequate oxygen delivery to tissues is an important element in promoting a positive immune response to infection, especially in the context of surgery, which in itself leads to increased oxygen demand. Intraoperative increase in the ratio of oxygen in the inhaled air has not been shown to affect the postoperative wound and the risk of lung infections (94).

Oxygen delivery DO_2 can be improved with GDT, which reduces the incidence of postoperative infectious complications. In the perioperative period, hypovolemia and decreased CO cause musculoskeletal and splanchnic vasoconstriction, which causes hypoperfusion and tissue hypoxia (95–97). This weakens the immune response of the mucous membrane and disrupts the intestinal barrier. Insufficiency of the intestinal barrier can lead to sepsis due to bacterial translocation and the release of cytokines into the blood, damaging other tissues and altering the body's immune environment (98). In addition, ischemic reperfusion trauma of the intestine markedly disrupts intestinal lymphoid tissue (GALT), further weakens the immunity of the extraintestinal mucosa and contributes to the increased susceptibility of the patient to infections (98, 99).

Goal-directed fluid therapy aims to optimize DO_2 by maintaining or increasing cardiac output. This preserves the microbicidal function of immune cells and the protection of organs that are particularly sensitive to perioperative hypoperfusion (21), avoiding intestinal barrier failure and GALT disorders. Adequate perioperative infusion therapy increases the oxygen content of tissues and increases the amount of collagen in wound healing (100).

Pathophysiological mechanisms of postoperative pneumonia are complex (101–103). Intestinal barrier failure and bacterial translocation through the lymphatic and thoracic ducts (104) with impaired airway mucosal immunity due to decreased DO_2 have a potential pathogenetic role (105–107).

In surgical patients, GDT optimizes DO_2 and prevents HAIs. Therefore, hemodynamically controlled principles of infusion therapy should be followed, especially in high-risk surgical patients (108–110) with a high probability of such complications.

The current evidence base shows that perioperative management, specifically the use of PGDT guided by real-time, continuous hemodynamic monitoring, helps clinicians maintain a patient's optimal fluid balance. Meta-analyses of published studies focused on major abdominal surgery show that applying ERAS practice guidelines reduces postoperative complications by up to 50% and hospital LOS by 2.5 days (111, 112).

Conclusion

Goal-directed fluid therapy is a key element of the ERAS protocols, which can only be achieved through high-quality monitoring. Among many techniques non-invasive hemodynamic monitoring is now evolving rapidly and is a highly accurate tool for clinical use. The use and further study of this method of hemodynamic monitoring can improve the

understanding of the mechanisms underlying the systemic capillary leakage syndrome in critical conditions, and serve as a basis for developing new algorithms for GDT. Modern non-invasive technologies, like esCCO, allow to assess the heart failure as a component of circulatory failure and its targeted correction by optimizing the preload, postload and inotropic function of the heart, which meets most of the requirements for adequate continuous hemodynamic monitoring (7, 113).

Infusion therapy improves hemodynamic status by increasing SV and CO. CO changes of at least 10–15% are used to determine a positive response to fluid resuscitation after 250 to 500 ml of fluid infusion (33, 114, 115). If SV or CO increases, further fluids can be given in a controlled manner, repeating the fluid challenge so long as there is a positive response (SV maximization). This approach avoids fluid overload, as the only excess fluids are equivalent to one fluid challenge (116). Beyond immediate response to fluid infusion, the efficacy of a fluid bolus over time is affected by various parameters such as blood volume status, cardiac function, type of infused fluid, and capillary leak severity (96).

Goal-directed fluid therapy provides adequate systemic oxygenation, protects against ischemic-reperfusion injury and reduces the incidence of SSIs, respiratory infections and UTIs after surgery. Hemodynamically based perioperative optimization of infusion therapy reduces postoperative mortality and morbidity in surgical patients at high risk of infectious complications (67, 69, 70).

Therefore, it is necessary to continue research on aspects of perioperative GDT based on methods of monitoring central hemodynamics to reduce the risk of complications and improve the treatment outcomes of surgical patients.

Author contributions

DD, ON, MM, and BL: investigation and resources. DD and MM: writing – original draft preparation. DD, ON, and MM: writing – review and editing. DD and ON: supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

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

Publisher's note

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