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Peri-operative care in cardiac surgery

Edited by
Cristina Barbero, Marco Pocar, Luca Brazzi,
Pierre-Gregoire Guinot and Ludhmila Hajjar

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Peri-operative care in cardiac surgery

Topic editors

Cristina Barbero — 'Città della Salute e della Scienza' University Hospital, Italy
Marco Pocar — University of Milan, Italy
Luca Brazzi — University of Turin, Italy
Pierre-Gregoire Guinot — Centre Hospitalier Regional Universitaire De Dijon, France
Ludhmila Hajjar — University of São Paulo, Brazil

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EDITED AND REVIEWED BY
Hendrik Tevaearai Stahel,
University Hospital of Bern, Switzerland

*CORRESPONDENCE
Marco Pocar
marco.pocar@unito.it
Cristina Barbero
cristina.barbero@unito.it

†These authors have contributed equally to this work and share first authorship

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Editorial: Peri-operative care in cardiac surgery

Marco Pocar[1,2*†], Cristina Barbero[1*†], Andrea Costamagna[2,3], Mauro Rinaldi[1,2] and Luca Brazzi[2,3]

[1]Cardiovascular and Thoracic Department, 'Città della Salute e della Scienza' University Hospital, Turin, Italy, [2]Department of Surgical Sciences, University of Turin, Turin, Italy, [3]Department of Anesthesia, Intensive Care and Emergency, 'Città della Salute e della Scienza' University Hospital, Turin, Italy

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Editorial on the Research Topic
Peri-operative care in cardiac surgery

Rather than truly novel techniques, progress in cardiac surgery during the last two decades has greatly relied on patient-specific risk-to-benefit stratification and improved perioperative care (1). Conversely, less invasive surgical approaches and hybrid settings have progressively shifted the traditional definition of "(in)operability", thereby expanding therapeutic options to higher-risk candidates, most typically elderly individuals with multiple comorbidities (2). The growing interest in this field has promoted the development and implementation of protocols being proposed and aimed at the enhancement of perioperative outcomes. For instance, Enhanced Recovery After Surgery (ERAS) recommends indications for improved pre-, intra-, and postoperative outcomes, across various surgical specialties. More in particular, ERAS also includes pivotal advancements specifically referred to perioperative care in cardiac surgery (Figure 1). Patients undergoing minimally invasive cardiac surgery should represent an ideal cohort. Summarized in the Research Topic devoted to *Peri-operative Care in Cardiac Surgery* are several, albeit rather heterogeneous, efforts and their respective inferences to improve current outcomes in cardiac surgery.

An increasingly relevant topic relates to frail patients. Pozzi et al. reviewed the implications of offering intrinsically higher-risk cardiac operations to this population. They suggested a multidisciplinary approach with the objective of identifying the most vulnerable individuals in order to optimize preoperative conditions, stratify indications according to surgical invasiveness, and promote recovery. Importantly, their report confirms the well-known limitations of 30-day predicted mortality (and morbidity). The latter does not readily translate into a satisfactory medium-to-longer term outcome, and likely underscores overall risk at 3-to-6-months follow-up. Similarly, Gao et al. attempt to implement a home- and hospital-based prehabilitation program, ideally tailored on every single patient, and aimed at optimizing physical performance and alleviating psychological distress before and after cardiac surgery. This potentially promising field requires the contribution and strict collaboration between multiple professional figures, namely, physiotherapists, psychologists, nutritionists, nurses and physicians. The utmost importance of enhanced pain control, including minimally invasive operations, cannot be overemphasized (3).

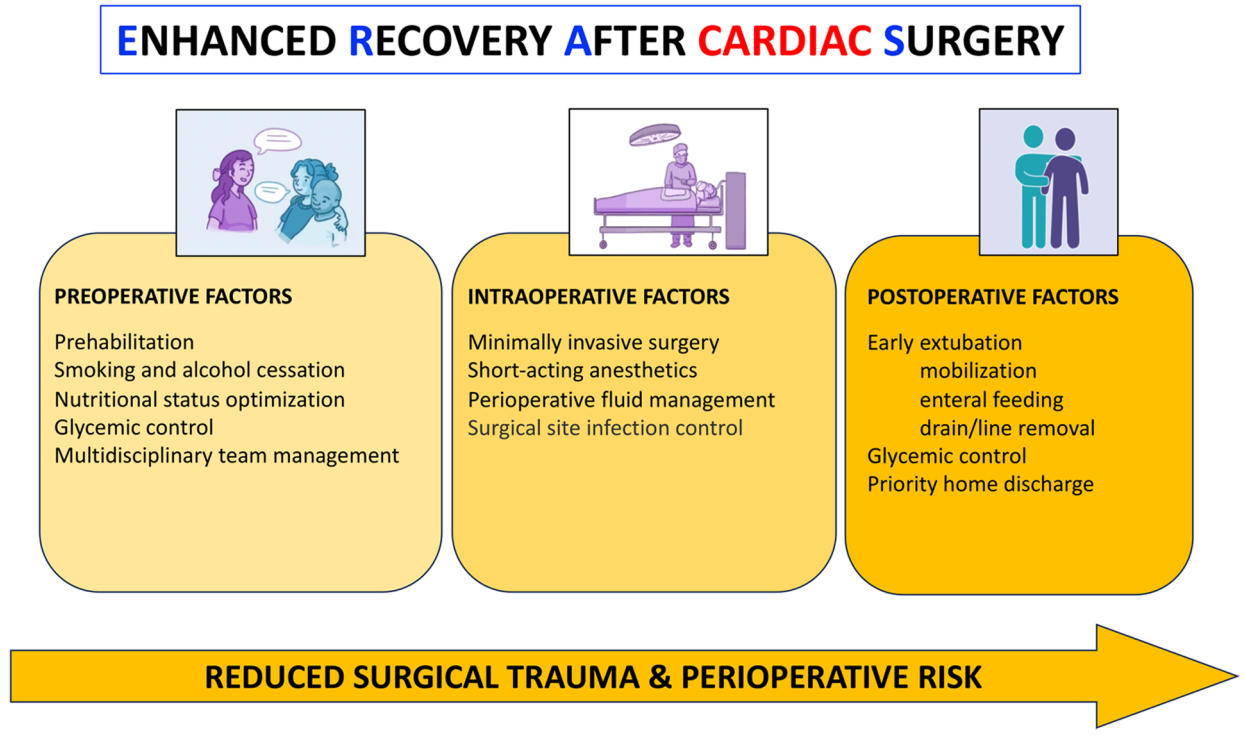

FIGURE 1
Key points of recent progress in cardiac surgery.

Renal dysfunction is among the best known and strongest determinants of operative outcome. Zhu et al. better defined the risk of perioperative acute kidney injury (AKI) in relation to longitudinal hemoglobin trajectories and red blood cell transfusion in 4,478 patients from the MIMIC-IV database, outlining the "highest, declining" and "medium, declining" trajectories at reduced risk compared to the "the lowest, rising, and then declining" subgroup. Noteworthily, hemoglobin levels >10 g/dl appear to correlate with a higher risk of AKI irrespective of hemoglobin trajectory, an apparently counterintuitive finding and "hot topic" with respect to liberal vs. restrictive transfusion policies included in more recent guidelines (4). In another retrospective study, Wang et al. also outlined mean platelet volume and cryoprecipitate administration as a risk factor for AKI in adults. Coupled with a significant overall incidence of AKI in recent years, this finding further stresses the importance of a proactive identification of high-risk individuals.

Infection remains a significant complication of the postoperative course following major surgery. The impact on early mortality, prolonged intensive care and hospital stay, and, ultimately, utilization of resources and costs, is particularly relevant in higher-risk patients. Wen et al. analyzed 1,460 patients, regarding the surgical subgroup randomized to coronary artery bypass grafting (CABG) alone (vs. medical therapy or associated ventricular restoration) in the STICH trial, i.e., with ischemic cardiomyopathy and ejection fraction ≤35%. They reported a non-negligible 10.2% incidence, indicating an increased susceptibility to postoperative infection in this scenario. Among other multivariable predictors, they also outlined body mass index, a finding inconsistent with the so-called obesity paradox concept, when extended to morbidity (5). They also identified associated mitral valve procedures as risk factor for postoperative infection. Unlike the well-defined benefits of open surgical repair vs. interventional procedures in degenerative disease with mitral prolapse etiology of regurgitation, the issues regarding when and how to treat ischemic and functional insufficiency remains largely undefined (6–8).

CABG is nowadays less prevalent to address coronary heart disease, primarily in relation to the tremendous achievements of percutaneous technologies and newer-generation stents. Diabetes, however, still portends disappointing results, particularly on the long term, and remains an Achille's heel of interventional cardiology, resulting in CABG being currently offered to patients with extensive and complex coronary anatomy, well reflected by the SYNTAX criteria (9). The identification of outcome predictors, aimed to mitigate the higher risk in CABG candidates with increasingly severe atherosclerotic burden and metabolic disorders, is pivotal. Accordingly, debate continues regarding the optimal choice between on- vs. off-pump, coupled with the increasing role of minimally invasive CABG and hybrid revascularization strategies (10). The report by Salikhanov et al. typically exemplifies this up-to-date scenario. With the routine use of pre- discharge control computed tomography angiography in 439 consecutive patients undergoing isolated on-pump or off-pump CABG, they found that the number of distal anastomoses and the duration of surgery tend to influence the risk of early

graft occlusion. This result is not too surprising and likely reflects the technical difficulties and the need for multiple more peripheral grafts on smaller target arteries to achieve complete revascularization in the presence of diffuse coronary atherosclerosis. Knochenhauer et al. outlined in 4,186 patients undergoing isolated CABG that a poor diabetic status, defined as baseline HbA1c >6.5%, anticipated a higher incidence of impaired wound healing, but not deep sternal wound infection The authors concluded that the contraindication for bilateral internal mammary artery on the basis of impaired glycemic control appears unjustified. Rather, further research should be directed to better identify special subgroups of patients at particular risk for deep sternal wound infection. In the conundrum of inflammatory biomarkers, Oh et al. demonstrated a strong relationship between C-reactive protein-to-albumin ratio and one-year mortality following off-pump CABG in 2,082 patients. Not confined to CABG only, Bello et al. characterized perioperative alterations of the acute phase plasma proteome to predict all-cause one-year mortality, hospital length of stay and periprocedural myocardial infarction and stroke in 192 adult patients undergoing on-pump cardiac operations. Among 402 quantified proteins, three were identified as hit-proteins for all endpoints, whereas insulin-like growth factor binding protein 2, IGFBP2, independently showed an over ten-fold association one-year death.

Finally, Li et al. evaluated the incidence and risk factors for gastrointestinal bleeding in a large pediatric population, comprising 21,893 patients who underwent cardiac operations on cardiopulmonary bypass during a 7-years span. This fearsome complication was most commonly encountered at the neonatal age, with an incidence of 23%, in patients with pre- and/or postoperative low cardiac output or hepatic dysfunction receiving complex reconstructive congenital heart surgery, and correlated with longer hospital stay and higher mortality rates. The occurrence of this complication steadily declined to 2% and 0.5% in infants and children, respectively. Baseline multivariable predictors included age and lower weight at time of surgery, likely associated with premature birth. The authors developed a promising prediction model with a sensitivity of 81% and specificity of 84%.

In summary, the Research Topic, which also illustrates some peculiar settings of extracorporeal life support technology (Daughtry and Richardson, Boskovic et al.), an expanding field with a growing role for the intensivist (11, 12), highlights a variegated scenario. More specifically, it touches different areas of current clinical research aimed at the continuing improvement of quality of care in cardiac surgery, largely dependent on optimized perioperative care.

Author contributions

MP: Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. CB: Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. AC: Formal Analysis, Methodology, Validation, Writing – review & editing. MR: Formal Analysis, Supervision, Validation, Writing – review & editing. LB: Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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EDITED BY
Pierre-Gregoire Guinot,
Centre Hospitalier Regional Universitaire De Dijon, France

REVIEWED BY
Philippe Gaudard,
Centre Hospitalier Universitaire de Montpellier, France
Pascal Colson,
Centre Hospitalier Universitaire de Montpellier, France

*CORRESPONDENCE
Yupei Wang
✉ wang_yupei_jade@163.com

†These authors have contributed equally to this work

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Longitudinal hemoglobin trajectories and acute kidney injury in patients undergoing cardiac surgery: a retrospective cohort study

Shouqiang Zhu[1†], Peng Lu[2†], Zhenran Liu[3,4,5†], Shaoyang Li[6], Peitong Li[7], Bingdi Wei[8], Jiayi Li[2] and Yupei Wang[9*]

[1]Department of Anesthesiology and Perioperative Medicine, Xijing Hospital, Fourth Military Medical University, Xi'an, China, [2]The First Clinical Medical College, Gansu University of Chinese Medicine, Lanzhou, China, [3]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Anhui Medical University, Hefei, China, [4]NHC Key Laboratory of Study on Abnormal Gametes and Reproductive Tract (Anhui Medical University), Hefei, China, [5]Key Laboratory of Population Health Across Life Cycle (Anhui Medical University), Ministry of Education of the People's Republic of China, Hefei, China, [6]The Second Clinical Medical College of Anhui Medical University, Hefei, China, [7]The Third Clinical Medical College of Zhejiang University of Traditional Chinese Medicine, Zhejiang, China, [8]School of Public Health, Gansu University of Chinese Medicine, Lanzhou, China, [9]The Center for Medical Genetics in Gansu Provincial Maternity and Child-Care Hospital, Gansu Provincial Clinical Research Center for Birth Defects and Rare Diseases, Lanzhou, China

Object: The purpose of this study was to describe the longitudinal dynamic hemoglobin trajectories in patients undergoing cardiac surgery and to explore whether they provide a broader perspective in predicting AKI compared to traditional threshold values. Additionally, the interaction of red blood cell transfusion was also investigated.

Methods: The MIMIC-IV database was searched to identify patients undergoing cardiac surgery with cardiopulmonary bypass. Group-based trajectory modeling (GBTM) was used to determine the hemoglobin trajectories in the first 72 h after ICU admission. The correlation between hemoglobin trajectories and AKI was evaluated using multivariable logistic regression and inverse probability of treatment weighting. Receiver operating characteristic (ROC) curves were created in the dataset to further validate previously reported thresholds.

Results: A total of 4,478 eligible patients were included in this study. Three hemoglobin trajectories were identified by GBTM, which were significantly different in the initial hemoglobin level and evolution pattern. Compared to the "the lowest, rising, and then declining" trajectory, patients in the "the highest, declining" and "medium, declining" trajectory groups had significantly lower AKI risk (OR 0.56; 95% CI 0.48, 0.67) and (OR 0.70; 95% CI 0.55, 0.90), respectively. ROC analysis yielded a disappointing result, with an AUC of 0.552, sensitivity of 0.25, and specificity of 0.86 when the hemoglobin threshold was set at 8 g/dl in the entire cohort. In the subgroup analysis of red blood cell transfusion, hemoglobin levels above 10 g/dl predicted higher AKI risk, and there was no correlation between hemoglobin trajectories and AKI in the non-red blood cell transfusion subgroup.

Conclusion: This study identified a hemoglobin trajectory that is associated with an increased risk of AKI after cardiac surgery. It is noteworthy that fixed hemoglobin thresholds should not be applied to all patient types. In patients receiving red blood cell transfusion, maintaining hemoglobin levels above 10 g/dl through transfusion was associated with an increased risk of AKI.

KEYWORDS

anemia, acute kidney injury, cardiopulmonary bypass, transfusion, trajectory

1. Introduction

Acute kidney injury (AKI) is a common complication after cardiac surgery, with a reported prevalence between 5% and 42% (1–3). Individuals with severe cardiac surgery-associated acute kidney injury (CS-AKI) were reported to have a three- to eightfold greater risk of mortality and morbidity, resulting in longer hospital and intensive care unit stays and higher healthcare costs (4). Even a mild elevation in creatinine levels (i.e., ≥0.3 mg/dl) can often signal poor outcomes (5). Moreover, patients who experience postoperative AKI and subsequently recover are at a heightened risk of developing long-term chronic kidney disease and end-stage renal disease compared to healthy individuals (6). Regrettably, effective interventions for CS-AKI remain elusive (7), underscoring the importance of identifying modifiable risk factors to mitigate the incidence of AKI among cardiac surgery patients.

Anemia is a common risk factor for acute kidney injury (AKI) in patients undergoing cardiac surgery (8–10). The underlying biological mechanism is complex and multifactorial. One major contributing factor is reduced oxygen delivery to the kidney due to decreased hemoglobin levels, which results in tissue hypoxia, including the kidney. This hypoxia triggers a cascade of events, including the release of vasoconstrictive and pro-inflammatory mediators, which cause renal vasoconstriction and decrease renal blood flow (11). Furthermore, anemia leads to an increase in cardiac output to compensate for reduced oxygen-carrying capacity, and this increased cardiac workload can exacerbate renal hypoperfusion by causing intravascular volume depletion and increasing renal oxygen demand (12, 13).

Perioperative anemia is a critical predictor of CS-AKI (14), and there is currently no established minimum acceptable hemoglobin level during cardiac surgery. While it has been presumed that a hematocrit level of ≥21% or higher during cardiac surgery reduces the incidence of AKI (15), the strength of this recommendation is questionable due to the heterogeneous and dynamic nature of AKI pathophysiology (16). Moreover, previous epidemiological studies examining the relationship between AKI and perioperative anemia have primarily focused on hemoglobin level at a specific time point (17), which may not accurately reflect the dynamic changes in hemoglobin levels during cardiac surgery. A better understanding of hemoglobin level dynamics could enable early identification of patients at risk for CS-AKI and facilitate personalized and targeted therapy.

To address this issue, Group-Based Trajectory Modeling (GBTM), also known as Semiparametric Mixture Model, can be utilized to analyze longitudinal data and explore population heterogeneity (18). GBTM enables the monitoring of changes in hemoglobin levels over time and the identification of different populations with similar longitudinal response patterns (19, 20). Therefore, the primary objective of this study is to describe the dynamic hemoglobin trajectories of patients undergoing cardiac surgery using GBTM and determine whether hemoglobin trajectories can serve as a novel and more valid diagnostic criterion for CS-AKI.

2. Method and materials

2.1. Sources of data and ethics compliance

Data were extracted from the MIMIC-IV database, which contains detailed information on 76,540 ICU admissions of 53,150 de-identified patients at the Beth Israel Deaconess Medical Center (BIDMC) from 2008 to 2019 (21). This information includes demographic data, laboratory test results, medications, vital signs, nursing notes, and radiology reports, which were obtained from digital electronic health records and hosted by the Laboratory for Computational Physiology at MIT. For privacy considerations, the patient information in this publicly accessible database has been de-identified. The use of the MIMIC database was granted approval by both the BIDMC institutional review board (2001-P-001699/15) and MIT (Approval ID: 10734458). The anonymization of the data permitted us to waive the requirement for informed consenting process. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (22).

2.2. Population selection criteria

We will include patients who have undergone cardiac surgery with the aid of cardiopulmonary bypass in our analysis. However, we will exclude patients who have been readmitted to the ICU after surgery and only retain their initial admission records. Additionally, patients without measurements of hemoglobin or creatinine will be excluded, as well as those with preoperative creatinine values >4 mg/dl or pre-existing end-stage renal disease.

2.3. Variable extraction

The main exposure factor of this study is the longitudinal trajectory pattern of hemoglobin within the first 72 h after cardiac surgery, with the primary outcome being the development of AKI (acute kidney injury) following cardiac surgery. The diagnosis of AKI relies on the KDIGO (Kidney Disease Improving Global Outcomes) diagnostic guidelines, which define AKI as an increase in serum creatinine by more than 0.3 mg/dl or 1.5 times the baseline value. The severity of AKI is also staged according to the KDIGO guidelines, with stage I defined as an increase in serum creatinine by 1.5 times the baseline value or an increase of more than 0.3 mg/dl, stage II as an increase in serum creatinine by 2 times the baseline value, and stage III as an increase in serum creatinine by 3 times the baseline value or serum creatinine greater than 4 mg/dl, or the need for renal replacement therapy after surgery (23). Covariates related to the study include demographic data (age, gender, race, and weight at admission), preoperative comorbidities (diabetes, hypertension, heart failure, and coronary artery disease), laboratory tests (measured within the first 24 h after ICU

admission, with the value that best reflects disease severity selected if multiple measurements are taken), treatment-related measures (red blood cell transfusion, surgical method, use of vasoactive drugs, and coronary angiography), and clinical assessments that reflect patient prognosis (length of hospital stay, initial SOFA score, cardiac output, and in-hospital mortality).

Variables with missing proportions exceeding 10% were excluded from our study. The missing values were replaced with the mean or median value (24). The details of the proportion of missing variables can be found in the supplementary material (**Supplementary Figure S1**).

2.4. Statistical methods

Continuous variables that follow a normal distribution are described as mean and standard deviation (SD) and compared between different hemoglobin trajectory patterns using analysis of variance (ANOVA). Non-normally distributed continuous variables are summarized as median and interquartile range (IQR) and compared between different patterns using Wilcoxon rank-sum test or Kruskal-Wallis test. Variable normality was assessed using the Kolmogorov-Smirnov test. Categorical variables were described in terms of frequency (*n*) and proportion (%), and tested using chi-square or Fisher's exact tests.

The longitudinal trajectory of hemoglobin was identified using group-based trajectory modeling (GBTM). The "traj" command in Stata 17 software was used to identify and determine the trajectory. The number and shape of trajectories were determined through a two-stage iterative model fitting process. First, the number of groups was determined by modeling each trajectory group as a high-order shape (i.e., a cube). Then, models with different numbers of groups were compared, starting from one group (no distinct trajectory) up to six groups. After determining the number of groups, the model was run to determine the shape of each trajectory. The Bayesian information criterion (BIC) and Akaike information criterion (AIC) values and Bayes factor were compared to determine the best-fit model. Bayes factor is approximately twice the difference between the Bayes information criterion of the more complex model and that of the simpler model [2 × (Bayes information criterion of more complex model—Bayes information criterion of simpler model)]. A Bayes factor greater than 2 indicates positive evidence in favor of a meaningful change in the Bayes information criterion in support of the more complex model, while a Bayes factor of 10 or greater provides very strong evidence. Additionally, each participant was assigned to a model with an average posterior probability of approximately 70% or higher, indicating a good fit, and models with a membership of greater than 5% in each trajectory group were selected (**Supplementary Table S1**).

Subsequently, a multivariable logistic regression model was used to estimate the association between the longitudinal trajectory of hemoglobin and the incidence of AKI following cardiac surgery. The model adjusted for variables, including covariates with imbalanced distribution between the AKI and non-AKI groups at baseline. In addition, the following principles were used for variable selection: variables that exhibited clinical or statistical collinearity (**Supplementary Table S2**) were removed; variables with a univariate p value <0.2 or those that showed a change in the effect estimate of >10% after multivariable adjustment were included; and variables with previous literature evidence supporting their association with CS-AKI were also included in the multivariable model. Inverse probability weighting regression adjustment was also used to control for confounding and obtain robust estimates (baseline and clinical characteristics before and after the inverse probability weighting was shown in **Supplementary Figure S2**). The hemoglobin trajectory allocation (propensity score) model included variables that were imbalanced in the hemoglobin trajectory. A sensitivity analysis according to AKI severity is required, we excluded patients with severe AKI, i.e., those with KDIGO stage III AKI, and subsequently re-modeled the sensitivity analysis cohort using the methods described above. We compared the crude incidence rates of AKI among different hemoglobin trajectory groups and explored whether the adjusted relationships were consistent with the original cohort. The diagnostic test was conducted to explore the utility of previously reported Hb level thresholds in predicting AKI occurrence in our dataset. Specifically, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) for each threshold using receiver operating characteristic (ROC) analysis. The diagnostic performance of each threshold was evaluated in comparison to our actual AKI diagnosis.

In this study, statistical analysis was performed using R software (version 4.1.2, www.r-project.org) and Stata version 17 (StataCorp LLC, College Station, TX, USA). The significance level was set at $p < 0.05$, indicating statistical significance.

3. Results

3.1. Study cohort

Initially, a total of 5,093 patients who underwent cardiac surgery with cardiopulmonary bypass were identified from the MIMIC-IV database. After applying exclusion criteria, 4,478 patients were ultimately included in the study cohort, among whom 794 (17.73%) were diagnosed with AKI (**Figure 1**). Overall, the AKI group was older than the non-AKI group (73.0 [65.0; 80.9] vs. 67.7 [60.0; 75.5], $p < 0.001$), and had a lower proportion of male patients (52.4% vs. 73.2%, $p < 0.001$). Compared to the non-AKI group, the AKI group had similar initial (9.30 [8.10; 10.7] vs. 9.90 [8.70; 11.2], $p < 0.001$) and maximum hemoglobin levels (11.4 [10.5; 12.3] vs. 11.5 [10.6; 12.6], $p < 0.007$), although there were statistical differences. A higher percentage of patients in the AKI group received red blood cell transfusion (69.9% vs. 37.6%, $p < 0.001$) and vasopressor support (89.2% vs. 81.6%, $p < 0.001$) (**Table 1**).

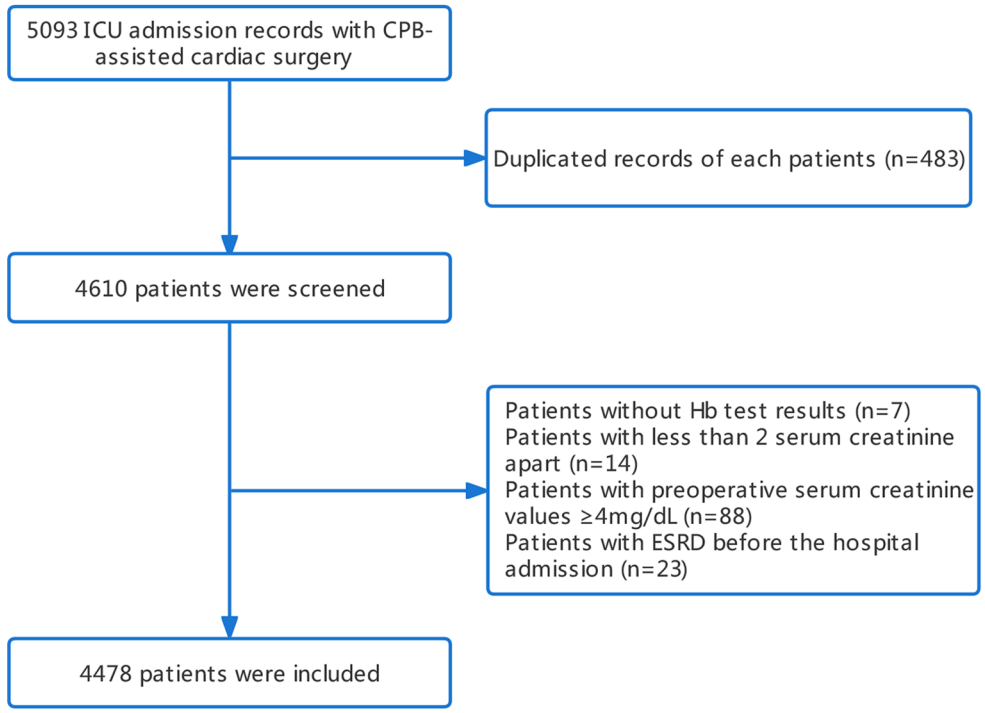

FIGURE 1
Study flow diagram for analytical sample.

3.2. Characterization of hemoglobin count trajectories

Our model identified three distinct longitudinal trajectories of hemoglobin levels in **Supplementary Table S1**, with average posterior probabilities (AvePP) greater than 0.8 for each group and population proportions greater than 5%. Traj-1 ($n = 1{,}986$, 44.35%) had the lowest initial hemoglobin levels (approximately 8.5 g/dl), slowly increasing to nearly 10 g/dl before gradually decreasing to 9 g/dl. Traj-3 had the highest initial hemoglobin levels, slowly decreasing to nearly 11.5 g/dl ($n = 538$, 12.01%). Traj-2 ($n = 1{,}954$, 43.64%) had initial hemoglobin levels between Traj-1 and Traj-3, slowly decreasing to nearly 9.5 g/dl (**Figure 3**). Traj-1 had a significantly higher proportion of patients receiving red blood cell transfusions compared to the other two groups (68.1% vs. 28.6%, 5.2%), and baseline characteristics differed among the trajectory groups as shown in **Table 2**.

3.3. Hemoglobin trajectories and CS-AKI

The overall incidence of AKI in Traj-1 group was higher than that in Traj-2 and Traj-3 groups, and the incidence rates of AKI stages I, II, and III were higher in Traj-1 group than those in Traj-2 group. The incidence rates of AKI stages I and II in Traj-1 group were also higher than those in Traj-3 group (**Figure 2**). After adjusting for the full model, the AKI risk in Traj-1 group was higher than that in Traj-2 group (OR = 0.61, 95% CI: 0.51–0.73, $p < 0.001$) and Traj-3 group (OR = 0.62, 95% CI: 0.45–0.85, $p = 0.004$). The results remained robust after inverse probability weighting, with the AKI risk in Traj-1 group being higher than that in Traj-2 group (OR = 0.56, 95% CI: 0.48–0.67, $p < 0.001$) and Traj-3 group (OR = 0.70, 95% CI: 0.55–0.90, $p = 0.007$) (**Table 3**). No heterogeneity was found in the subgroup analysis, and the results remained robust (**Figure 5**).

3.4. Hemoglobin trajectories, red blood cell (RBC) transfusion and CS-AKI

After cardiac surgery, red blood cell transfusion can cause an increase in hemoglobin levels. In our study, we found that the Traj-1 group had a significantly higher proportion of patients receiving red blood cell transfusions compared to the other two trajectory groups. Therefore, we conducted a subgroup analysis on red blood cell transfusions. In the non-red blood cell transfusion subgroup, all three hemoglobin trajectory groups showed a consistent decreasing trend, despite differences in initial hemoglobin levels (**Figure 4A**). In the red blood cell transfusion subgroup, the Traj-1 group had a low initial hemoglobin level (close to 9 g/dl), which increased to 11 mg/dl before decreasing to nearly 10 g/dl. The Traj-2 group had a low initial hemoglobin level (close to 8.5 g/dl), which slowly increased before decreasing to 9 mg/dl. The Traj-3 group had an initial hemoglobin level of 11 g/dl, which decreased to 9.5 g/dl (**Figure 4B**). After adjusting for the entire model and inverse probability of treatment weighting, we found that in the non-red blood cell transfusion subgroup, there was no correlation

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TABLE 1 Comparison of baseline characteristics of the group with and without acute kidney injury.

Variables	Non-AKI group (*N* = 3,684)	AKI group (*N* = 794)	*p*
Age (years, median [IQR])	67.7 [60.0; 75.5]	73.0 [65.0; 80.9]	<0.001
Male, *n* (%)	2,697 (73.2%)	416 (52.4%)	<0.001
Ethnicity, *n* (%)			0.358
African American	120 (3.26%)	33 (4.16%)	
Asian	69 (1.87%)	23 (2.90%)	
Caucasian	2,780 (75.5%)	590 (74.3%)	
Hispanic	122 (3.31%)	25 (3.15%)	
Native American	3 (0.08%)	0 (0.00%)	
Other/Unknown	590 (16.0%)	123 (15.5%)	
Initial weight (kg, median [IQR])	82.2 [72.5; 95.0]	78.8 [66.7; 92.0]	<0.001
Emergency, *n* (%)	1,861 (50.5%)	448 (56.4%)	0.003
Co-morbidities, *n* (%)			
Diabetes	1,110 (30.1%)	278 (35.0%)	0.008
Hypertension	2,346 (63.7%)	471 (59.3%)	0.023
HF	866 (23.5%)	297 (37.4%)	<0.001
CHD	2,694 (73.1%)	531 (66.9%)	<0.001
Biochemical indices, median (IQR)			
Initial WBC (10^9/L)	9.60 [7.40; 12.8]	10.1 [7.60; 13.3]	0.006
Maximal WBC (10^9/L)	15.5 [12.6; 19.3]	16.7 [13.5; 21.1]	<0.001
Initial Hb (g/dl)	9.90 [8.70; 11.2]	9.30 [8.10; 10.7]	<0.001
Maximal Hb (g/dl)	11.5 [10.6; 12.6]	11.4 [10.5; 12.3]	0.007
Initial platelet (10^9/L)	176 [136; 229]	177 [122; 246]	0.594
Minimal platelet (10^9/L)	120 [99.0; 150]	103 [75.0; 130]	<0.001
Initial creat (mg/dl)	0.90 [0.80; 1.10]	1.00 [0.80; 1.40]	<0.001
Maximal creat (mg/dl)	1.00 [0.90; 1.20]	1.50 [1.10; 2.10]	<0.001
Sodium (mmol/L)	138 [136; 139]	137 [135; 139]	<0.001
Potassium (mmol/L)	4.00 [3.80; 4.30]	4.10 [3.80; 4.30]	0.031
Calcium (mmol/L)	1.16 [1.13; 1.19]	1.15 [1.11; 1.19]	<0.001
Lactate (mmol/L)	1.30 [1.00; 1.70]	1.30 [1.00; 1.80]	0.328
Glucose (mmol/L)	107 [97.0; 126]	110 [97.0; 138]	0.005
Treatment measures			
RBC transfusion, *n* (%)	1,384 (37.6%)	555 (69.9%)	<0.001
Operation, *n* (%)			<0.001
Coronary artery bypass grafting	2,057 (55.8%)	296 (37.3%)	
Operation on valves	707 (19.2%)	212 (26.7%)	
Coronary bypass with valves	448 (12.2%)	171 (21.5%)	
Other	472 (12.8%)	115 (14.5%)	
Vasopressor use, *n* (%)[a]	3,005 (81.6%)	708 (89.2%)	<0.001
Coronary angiography, *n* (%)	1,175 (31.9%)	275 (34.6%)	0.146
Clinical evaluation			
Los hospital (day, median [IQR])	6.65 [5.06; 9.63]	9.26 [6.39; 14.8]	<0.001
LOS ICU (day, median [IQR])	1.40 [1.19; 2.49]	3.59 [2.23; 6.37]	<0.001
Initial SOFA (scores, median [IQR])	2.00 [1.00; 4.00]	3.00 [2.00; 5.00]	<0.001
Maximal SOFA (scores, median [IQR])	5.00 [4.00; 7.00]	7.00 [5.00; 10.0]	<0.001
Cardiac output (L/min, median [IQR])[b]	4.50 [3.60; 5.50] (*n* = 2,391)	3.90 [3.10; 4.97] (*n* = 633)	<0.001
Acute posthemorrhagic anemia, *n* (%)	469 (12.7%)	209 (26.3%)	<0.001
In-hospital death, *n* (%)	20 (0.54%)	47 (5.92%)	<0.001
AKI I, *n* (%)	0 (0.00%)	537 (67.6%)	
AKI II, *n* (%)	0 (0.00%)	169 (21.3%)	
AKI III, *n* (%)	0 (0.00%)	88 (11.1%)	

AKI, acute kidney injury; HF, heart failure; CHD, coronary heart disease; WBC, white blood cells; ICU, intensive care unit; Hb, hemoglobin; IQR, interquartile range; LOS, length of stay; RBC, red blood cell; SOFA, Sequential Organ Failure Assessment.
[a]Vasopressor use including dobutamine, dopamine, epinephrine, norepinephrine phenylephrine and asopressin.
[b]Data on cardiac output represented in the present study include only participants with no missing data.

between hemoglobin trajectory and the risk of AKI. However, in the red blood cell transfusion subgroup, the Traj-1 group still had a higher risk of AKI compared to the other two trajectory groups (Table 3).

3.5. Validation of previous hemoglobin level threshold

We conducted a diagnostic test for hemoglobin level thresholds on the original queue, red blood cell transfusion subgroup, and non-red blood cell transfusion subgroup. The ROC results showed that the AUC (area under the curve) was

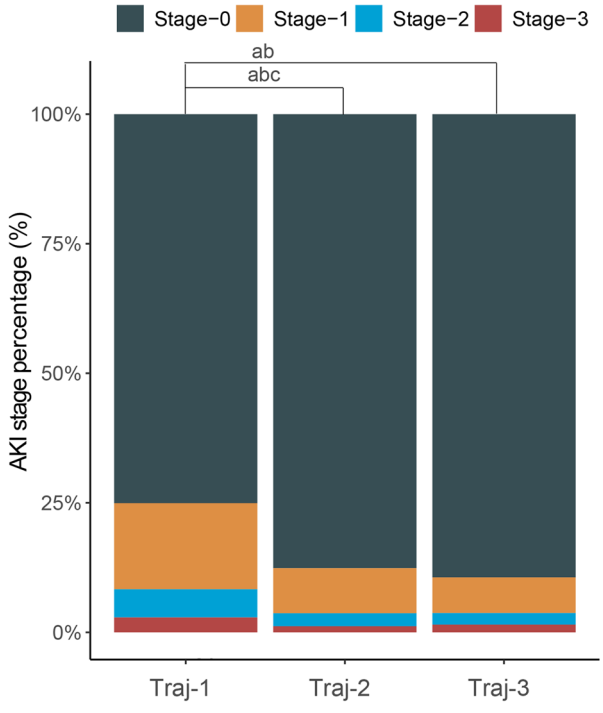

FIGURE 2
Stacked column chart with the percentage of AKI in stage 0–3 of each hemoglobin trajectories group. a: Significant statictical difference between the Traj-1 and Traj-2/3 in percentage of AKI stage-1; b: significant statictical difference between the Traj-1 and Traj-2/3 in percentage of AKI stage-2; c: significant statictical difference between the Traj-1 and Traj-2/3 in percentage of AKI stage-3.

TABLE 2 Crude comparison within hemgobin trajectories group.

	Traj-1 group ($N = 1,986$)	Traj-2 group ($N = 1,954$)	Traj-3 group ($N = 538$)	p
Initial Hb (g/dl)	8.50 [7.70; 9.40]	10.4 [9.60; 11.3]	12.3 [11.4; 13.5]	<0.001
Maximal Hb (g/dl)	10.5 [10.0; 11.1]	12.0 [11.3; 12.6]	13.6 [13.1; 14.3]	<0.001
Initial platelet (10^9/L)	178 [132; 239]	175 [135; 225]	176 [138; 227]	0.425
Minimal platelet (10^9/L)	112 [87.0; 143]	119 [97.0; 149]	124 [100; 153]	<0.001
Initial creat (mg/dl)	0.90 [0.80; 1.20]	0.90 [0.80; 1.10]	0.90 [0.80; 1.10]	0.002
Maximal creat (mg/dl)	1.10 [0.90; 1.50]	1.00 [0.90; 1.20]	1.00 [0.90; 1.30]	<0.001
RBC transfusion, *n* (%)	1,353 (68.1%)	558 (28.6%)	28 (5.20%)	<0.001
Operation, *n* (%)				<0.001
Coronary artery bypass grafting	904 (45.5%)	1,112 (56.9%)	337 (62.6%)	
Operation on valves	471 (23.7%)	360 (18.4%)	88 (16.4%)	
Coronary bypass with valves	347 (17.5%)	233 (11.9%)	39 (7.25%)	
Other	264 (13.3%)	249 (12.7%)	74 (13.8%)	
Vasopressor use, *n* (%)[a]	1,732 (87.2%)	1,614 (82.6%)	367 (68.2%)	<0.001
Coronary angiography, *n* (%)	627 (31.6%)	595 (30.5%)	228 (42.4%)	<0.001
Los hospital (day, median [IQR])	7.89 [5.34; 11.5]	6.27 [5.00; 8.89]	6.97 [5.14; 10.3]	<0.001
Los ICU (day, median [IQR])	2.18 [1.29; 3.54]	1.44 [1.19; 2.89]	1.43 [1.15; 2.79]	<0.001
Initial SOFA (scores, median [IQR])	3.00 [1.00; 5.00]	2.00 [1.00; 4.00]	2.00 [0.00; 4.00]	<0.001
Maximal SOFA (scores, median [IQR])	6.00 [4.00; 8.00]	5.00 [4.00; 7.00]	5.00 [3.00; 7.00]	<0.001
Cardiac output (L/min, median [IQR])[b]	4.12 [3.30; 5.10] ($n = 1,518$)	4.60 [3.60; 5.58] ($n = 1,249$)	5.28 [4.14; 6.01] ($n = 257$)	<0.001
Acute posthemorrhagic anemia, *n* (%)	398 (20.0%)	227 (11.6%)	53 (9.85%)	<0.001
In-hospital death, *n* (%)	43 (2.17%)	19 (0.97%)	5 (0.93%)	0.004
AKI Stage, *n* (%)				<0.001
I	330 (16.6%)	170 (8.70%)	37 (6.88%)	
II	108 (5.44%)	49 (2.51%)	12 (2.23%)	
III	57 (2.87%)	23 (1.18%)	8 (1.49%)	

AKI, acute kidney injury; ICU, intensive care unit; Hb, hemoglobin; IQR, interquartile range; LOS, length of stay; RBC, red blood cell; SOFA, Sequential Organ Failure Assessment.

[a]Vasopressor use including dobutamine, dopamine, epinephrine, norepinephrine phenylephrine and asopressin.

[b]Data on cardiac output represented in the present study include only participants with no missing data.

TABLE 3 Association of hemoglobin trajectories with risk of AKI in different regression models.

Model	Cluster	Original cohort ($n = 4,478$)			RBC transfusion subgroup ($n = 1,939$)			Non-RBC transfusion subgroup ($n = 2,539$)		
		OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Unadjusted Model	Traj-1	Reference			Reference			Reference		
	Traj-2	0.43	(0.36–0.50)	<0.001	0.46	(0.35–0.60)	<0.001	0.78	(0.59–1.03)	0.079
	Traj-3	0.36	(0.26–0.47)	<0.001	0.33	(0.24–0.45)	<0.001	0.84	(0.46–1.44)	0.551
$Model_1$	Traj-1	Reference			Reference			Reference		
	Traj-2	0.55	(0.46–0.66)	<0.001	0.48	(0.36–0.63)	<0.001	1.04	(0.77–1.40)	0.809
	Traj-3	0.55	(0.40–0.75)	<0.001	0.38	(0.27–0.54)	<0.001	1.21	(0.64–2.13)	0.535
$Model_2$	Traj-1	Reference			Reference			Reference		
	Traj-2	0.57	(0.48–0.68)	<0.001	0.49	(0.37–0.65)	<0.001	1.06	(0.79–1.43)	0.697
	Traj-3	0.56	(0.41–0.76)	<0.001	0.41	(0.29–0.58)	<0.001	1.12	(0.60–1.99)	0.705
$Model_3$	Traj-1	Reference			Reference			Reference		
	Traj-2	0.58	(0.48–0.69)	<0.001	0.51	(0.38–0.67)	<0.001	1.04	(0.77–1.40)	0.821
	Traj-3	0.54	(0.39–0.74)	<0.001	0.43	(0.30–0.61)	<0.001	1.04	(0.55–1.85)	0.906
$Model_4$	Traj-1	Reference			Reference			Reference		
	Traj-2	0.61	(0.51–0.73)	<0.001	0.51	(0.38–0.68)	<0.001	1.09	(0.80–1.48)	0.578
	Traj-3	0.62	(0.45–0.85)	0.004	0.44	(0.31–0.62)	<0.001	1.15	(0.60–2.08)	0.659
$Model_{IPW}$	Traj-1	Reference			Reference			Reference		
	Traj-2	0.56	(0.48–0.67)	<0.001	0.55	(0.41–0.73)	<0.001	1.09	(0.82–1.46)	0.545
	Traj-3	0.70	(0.55–0.90)	0.007	0.45	(0.33–0.63)	<0.001	1.69	(0.96–2.85)	0.570

AKI, acute kidney injury; RBC, red blood cell. IPW, inverse probability of treatment weighting. $Model_1$: adjusted for age, gender, initial weight and emergency. $Model_2$: additionally adjusted for diabetes, hypertension, hear failure and coronary hear disease upon $Model_1$. $Model_3$: additionally adjusted for initial white blood cells, serum sodium, serum potassium, serum calcium, serum lactate and serum glucose upon $Model_2$. $Model_4$: additionally adjusted for vasopressor use, coronary angiography and operation upon $Model_3$. $Model_{IPW}$: adjusted for all aforementioned covariates using the IPW method.

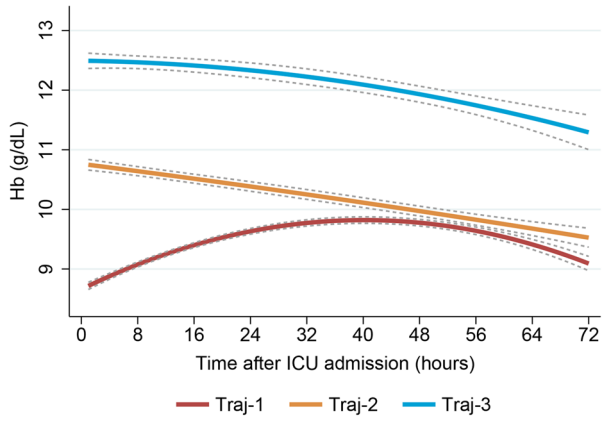

FIGURE 3
Trajectory plot of patients with three dynamic hemoglobin trajectory patterns.

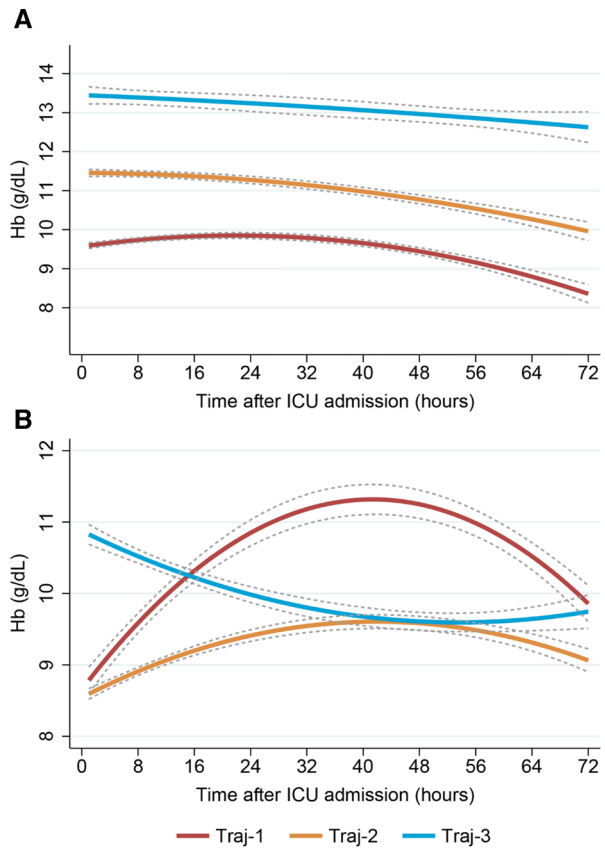

FIGURE 4
Dynamic hemoglobin trajectory patterns with and without RBC transfusion. (Plot A) Non-RBC transfusion group; (Plot B) RBC transfusion group. RBC, red blood cell.

not higher than 0.6, indicating that a "fixed and universal hemoglobin threshold" approach should be questioned when the thresholds were set at 8 g/dl, 10 dl, and 12 dl (**Supplementary Table S3**). Perhaps, focusing on the evolution trajectory of hemoglobin may be more appropriate than absolute values.

3.6. Sensitivity analysis

After excluding AKI-III patients, we re-modeled and identified a hemoglobin trajectory plot that closely matched the number and evolution pattern of the original queue trajectory (**Supplementary Figure S3**). We roughly compared three hemoglobin trajectory groups (**Supplementary Table S4**) and explored the adjusted relationships (**Supplementary Table S5**), which yielded results consistent with the original queue.

4. Discussion

Perioperative anemia has been reported as a risk predictor for postoperative acute kidney injury (AKI) in cardiac surgery. However, static and unchanging hemoglobin levels at a specific time point may not reflect the heterogeneity seen in real-world clinical practice. In our study, we identified three significantly different hemoglobin trajectory patterns using GBTM. The group with the trajectory pattern of "lowest, rising, and then declining" had a significantly higher risk of AKI compared to those in the "highest, declining" and "moderate, declining" trajectory groups. This relationship was validated in multivariable regression and inverse probability weighting models. Additionally, we found that red blood cell transfusion played an interactive role, with the AKI risk being higher in the subgroup with the trajectory pattern of "lowest, rising by more than 10 g/dl, and then declining" among those receiving red blood cell transfusions. However, among those not receiving red blood cell transfusions, three trajectory groups with different initial hemoglobin levels but similar declining trends did not show any correlation with the risk of AKI. Interestingly, our study showed that the previous threshold did not demonstrate good predictive performance in our dataset. Hemoglobin elevation is harmful to the kidneys, and correcting anemia and increasing hemoglobin levels may lead to kidney overcompensation, increasing glomerular filtration pressure and vasoconstriction, which can result in glomerular injury.

Perioperative anemia is common in cardiac surgery and multiple studies have shown a relationship between anemia or low hemoglobin levels and postoperative AKI in cardiac surgery. A retrospective analysis of 1,047 patients undergoing coronary artery bypass graft surgery by Luca and colleagues found that preoperative anemia was an independent risk factor for postoperative AKI and there was no dose-response relationship between the severity of anemia and acute kidney injury (25). However, in a cohort of 920 patients undergoing cardiac surgery with cardiopulmonary bypass, researchers found that the incidence of AKI increased significantly when hemoglobin levels were extremely low (less than 25th percentile) and receiving red blood cell transfusions when hemoglobin concentration was above 8 g/dl also increased the incidence of AKI (26). A study of

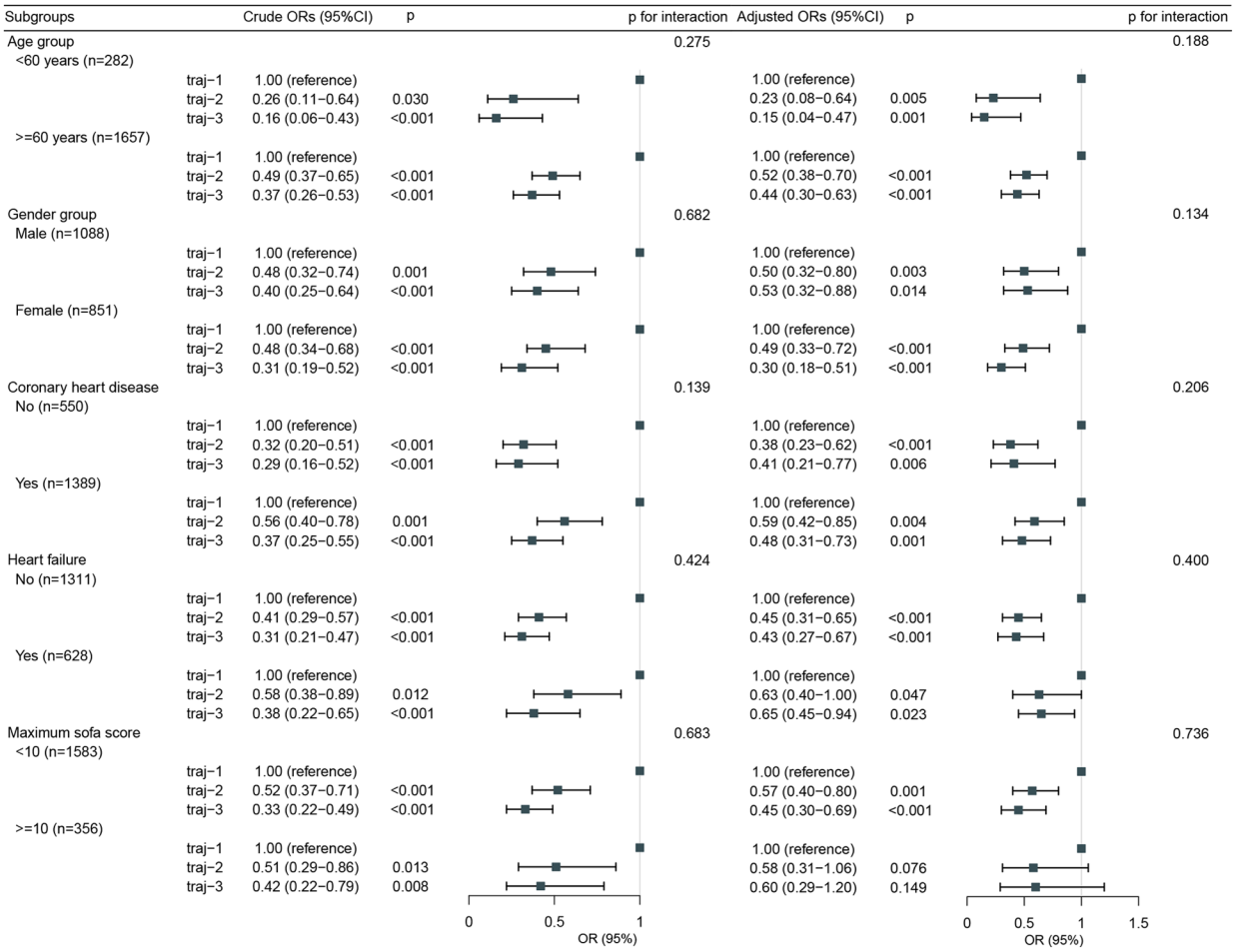

FIGURE 5
Subgroup analysis for the association of hemglobin trajectories with risk of acute kidney injury.

1,360 CPB patients found that the lowest hemoglobin level (rather than preoperative anemia) was an independent risk factor for adverse outcomes (27).

However, these studies have the following limitations. Firstly, previous studies have used different thresholds for defining anemia, which has led to inconsistency and difficulty in comparability of results. For example, a retrospective study involving 1,360 cardiac surgery patients defined anemia as preoperative hemoglobin levels below 8 g/dl (27), while a prospective cohort study involving 1,047 patients defined anemia as preoperative hemoglobin levels below 13 g/dl (male) or 12 g/dl (female) (25). These different definitions may have different impacts on the results. Secondly, most studies have used a single preoperative or postoperative measurement of hemoglobin to determine anemia, ignoring the temporal changes in anemia. Or only preoperative hemoglobin levels were used to determine anemia, without considering changes in postoperative hemoglobin levels. This may not reflect the impact of perioperative changes in hemoglobin levels on AKI. Finally, although some studies have explored the relationship between anemia and postoperative AKI in cardiac surgery, the sample sizes of these studies are insufficient, resulting in weak statistical power.

Using group-based trajectory modeling, we identified three distinct trajectories of hemoglobin levels, with the trajectory-1 (traj-1) group showing a significantly higher risk of AKI compared to the other two groups. The traj-1 group had lower initial hemoglobin levels, which reflected the severity of anemia, followed by an increase due to red blood cell transfusion. In our study, a significantly higher proportion of patients in the traj-1 group received red blood cell transfusions compared to the other two groups (68.1% vs. 28.6%, 5.2%). Red blood cell transfusion is known to play a significant role in the development of AKI after cardiac surgery. Transfusion can cause vasoconstriction, decreased oxygen delivery, and inadequate microcirculatory perfusion, leading to renal dysfunction (28, 29). Moreover, transfused blood may contain pathogenic agents such as bacteria and viruses, increasing the risk of postoperative infection and subsequent development of AKI (29, 30).

Therefore, in order to make our research more applicable to decision-making in real-world clinical settings, we performed a subgroup analysis on the use of blood transfusions. In the non-red blood cell transfusion subgroup, we identified three trajectories with consistent initial hemoglobin levels but subsequent decreases. Further analysis revealed that the incidence

of AKI did not differ significantly among the different hemoglobin trajectory groups. Even after adjusting for confounding factors and conducting IPW analysis, we did not find any correlation between hemoglobin trajectories and AKI, which contradicts previous conclusions that anemia is associated with an increased risk of AKI (27, 31, 32). This can be explained by several factors. First, previous studies have focused more on the correlation between preoperative anemia and postoperative AKI, and there is little literature on the correlation between postoperative anemia and AKI. A retrospective observational study including 6,130 patients who underwent coronary artery bypass surgery showed that preoperative anemia and preoperative anemia combined with postoperative anemia were associated with AKI and mortality rates after coronary artery bypass surgery, but no correlation was found between postoperative anemia and AKI (8). Second, most studies have not taken into account the impact of red blood cell transfusions on the results, especially postoperative red blood cell transfusions. Mixing patients who received red blood cell transfusions with those who did not can significantly bias the study results. Finally, in the non-red blood cell transfusion subgroup we studied, the lowest hemoglobin level was >8 g/dl, which provides sufficient oxygen to renal tissue. A higher hemoglobin level does not improve renal tissue oxygenation and therefore does not reduce the risk of AKI. A sub-study of a multicenter RCT exploring the hemoglobin threshold for receiving red blood cell transfusions showed that the incidence of AKI did not decrease when a restrictive transfusion strategy was implemented (limiting transfusions) and when the hemoglobin concentration was maintained above 8.5 g/dl compared to a strategy where transfusions were only performed when the hemoglobin threshold was below 7.5 g/dl (33).

In the subgroup of red blood cell transfusion, we also identified three distinct trajectories. The AKI risk in the traj-1 group, which showed a significant increase in hemoglobin levels followed by a subsequent decrease, was higher than that in the group with initially low hemoglobin levels that slowly increased and the group with initially normal hemoglobin levels that subsequently decreased. This suggests that the risk of AKI significantly

TABLE 4 Crude comparison within hemgobin trajectories group with or without RBC transfusion.

	Non-RBC transfusion subgroup				RBC transfusion subgroup			
	Traj-1 group	Traj-2 group	Traj-3 group	*p*	Traj-1 group	Traj-2 group	Traj-3 group	*p*
	N = 1,128	*N* = 1,245	*N* = 166		*N* = 280	*N* = 1,193	*N* = 466	
Initial Hb (g/dl)	11.2 [10.4; 12.1]	9.15 [8.40; 9.90]	13.5 [12.5; 14.7]	<0.001	8.70 [7.80; 10.4]	8.50 [7.60; 9.50]	10.4 [9.60; 11.4]	<0.001
Maximal Hb (g/dl)	12.6 [12.0; 13.2]	10.8 [10.2; 11.4]	14.6 [13.9; 15.2]	<0.001	11.9 [11.4; 12.5]	10.5 [10.0; 11.0]	12.0 [11.3; 12.8]	<0.001
Initial platelet (10^9/L)	177 [141; 223]	181 [141; 238]	178 [133; 246]	0.230	161 [119; 230]	175 [128; 239]	166 [125; 227]	0.054
Minimal platelet (10^9/L)	128 [103; 155]	125 [102; 155]	114 [96.2; 153]	0.025	94.0 [63.0; 121]	109 [85.0; 137]	104 [80.0; 127]	<0.001
Initial creat (mg/dl)	0.90 [0.80; 1.10]	0.90 [0.70; 1.10]	0.90 [0.80; 1.10]	0.210	0.90 [0.80; 1.30]	1.00 [0.80; 1.30]	0.90 [0.80; 1.10]	0.031
Maximal creat (mg/dl)	1.00 [0.90; 1.20]	1.00 [0.80; 1.30]	1.10 [0.90; 1.30]	0.043	1.20 [0.90; 1.70]	1.20 [0.90; 1.60]	1.10 [0.90; 1.40]	0.001
Operation, *n* (%)				<0.001				<0.001
Coronary artery bypass grafting	609 (54.0%)	779 (62.6%)	107 (64.5%)		95 (33.9%)	523 (43.8%)	240 (51.5%)	
Operation on valves	240 (21.3%)	213 (17.1%)	29 (17.5%)		80 (28.6%)	278 (23.3%)	79 (17.0%)	
Coronary bypass with valves	130 (11.5%)	95 (7.63%)	9 (5.42%)		63 (22.5%)	241 (20.2%)	81 (17.4%)	
Other	149 (13.2%)	158 (12.7%)	21 (12.7%)		42 (15.0%)	151 (12.7%)	66 (14.2%)	
Vasopressor use, *n* (%)[a]	904 (80.1%)	944 (75.8%)	94 (56.6%)	<0.001	255 (91.1%)	1,078 (90.4%)	438 (94.0%)	0.060
Coronary angiography, *n* (%)	329 (29.2%)	426 (34.2%)	68 (41.0%)	0.002	86 (30.7%)	389 (32.6%)	152 (32.6%)	0.081
Los hospital (day, median [IQR])	6.42 [4.93; 9.17]	6.06 [4.81; 8.31]	7.17 [5.31; 12.6]	<0.001	8.99 [6.35; 13.9]	8.23 [5.97; 11.9]	6.94 [5.31; 10.1]	<0.001
Los icu (day, median [IQR])	1.33 [1.17; 2.18]	1.29 [1.12; 2.20]	1.53 [1.21; 3.05]	<0.001	3.36 [2.21; 6.22]	2.35 [1.38; 4.19]	2.90 [2.00; 4.20]	<0.001
Initial sofa (scores, median [IQR])	2.00 [1.00; 4.00]	2.00 [1.00; 4.00]	1.00 [0.00; 3.00]	<0.001	3.00 [2.00; 6.00]	3.00 [1.00; 5.00]	2.00 [1.00; 4.00]	<0.001
Maximal sofa (scores, median [IQR])	5.00 [4.00; 7.00]	5.00 [4.00; 7.00]	5.00 [3.00; 7.00]	0.051	8.00 [6.00; 10.0]	6.00 [5.00; 8.00]	6.50 [5.00; 9.00]	<0.001
Cardiac output (L/min, median [IQR])[b]	4.60 [3.70; 5.40] (*n* = 713)	5.10 [4.14; 5.96] (*n* = 663)	5.55 [4.58; 6.36] (*n* = 75)	<0.001	3.40 [2.80; 4.30] (*n* = 253)	4.10 [3.30; 5.10] (*n* = 962)	4.20 [3.20; 5.09] (*n* = 358)	<0.001
In-hospital death, *n* (%)	8 (0.71%)	5 (0.40%)	3 (1.81%)	0.084	15 (5.36%)	27 (2.26%)	9 (1.93%)	0.008
AKI Stage, *n* (%)				0.221				<0.001
I	92 (8.16%)	79 (6.35%)	8 (4.82%)		83 (29.6%)	213 (17.9%)	62 (13.3%)	
II	22 (1.95%)	17 (1.37%)	5 (3.01%)		28 (10.0%)	74 (6.20%)	23 (4.94%)	
III	5 (0.44%)	9 (0.72%)	2 (1.20%)		16 (5.71%)	41 (3.44%)	15 (3.22%)	
RBC transfusion (ml, median [IQR])					1,088 [700; 1,750]	700 [350; 1,112]	700 [350; 1,050]	<0.001

AKI, acute kidney injury; ICU, intensive care unit; Hb, hemoglobin; IQR, interquartile range; LOS, length of stay; RBC, red blood cell; SOFA, Sequential Organ Failure Assessment.

[a]Vasopressor use including dobutamine, dopamine, epinephrine, norepinephrine phenylephrine and asopressin.

[b]Data on cardiac output represented in the present study include only participants with no missing data.

increases when hemoglobin levels rise to 10 g/dl after red blood cell transfusion. In our study, patients in the traj-1 group of the red blood cell transfusion subgroup received a greater volume of red blood cell transfusions than those in the other trajectory groups (**Table 4**).

The increase in hemoglobin levels after red blood cell transfusion is due to the large amount of hemoglobin contained in the transfused red blood cells. Transfusion of red blood cells and hemolysis caused by cardiopulmonary bypass can lead to an increase in the release of free hemoglobin. The free hemoglobin is filtered through the glomerulus and then reabsorbed and metabolized, with the resulting metabolites being excreted by the kidneys. Therefore, high concentrations of hemoglobin can increase the burden on the kidneys, leading to impaired kidney function (29). Additionally, red blood cell transfusion can cause inflammatory and oxidative stress reactions. The transfused blood may contain pathogenic substances such as bacteria and viruses, which can trigger an immune system response and generate a large amount of inflammatory mediators. These inflammatory mediators can promote kidney tissue inflammation and contribute to impaired kidney function (30). Furthermore, red blood cell transfusion may cause oxidative stress reactions, resulting in the production of large amounts of free radicals and oxidants within cells, which can damage kidney tissue and exacerbate the occurrence of acute kidney injury (34). Finally, red blood cell transfusion may lead to changes in hemodynamics. Transfusion of blood can cause vasoconstriction and inadequate microcirculation perfusion, affecting kidney perfusion and oxygen supply. These changes can impair kidney function and increase the risk of AKI.

This study has several limitations. Firstly, the data used in this study were obtained from the MIMIC-IV database, which only includes patients from medical institutions in the United States, and therefore may not fully represent populations from other countries or regions. Additionally, there may be selection bias among the patients included in this database, so caution is needed when extrapolating the study results. Secondly, this study used a retrospective cohort study design, which may suffer from information bias and omissions due to the pre-existing nature of the study subjects, which could potentially affect the accuracy of the results. Moreover, the definition of AKI in this study was based on changes in serum creatinine levels, rather than other biomarkers or clinical presentations. Thirdly, the sample size of patients in the subgroup who received red blood cell transfusion may be small, which could affect the reliability of statistical analyses and the feasibility of generalizing the study results. Therefore, larger-scale studies are needed to validate these findings. Fourthly, this study doesn't describe what happens during the surgery and CPB and is blinded about RBC transfusion and Hb trajectories during surgery. Furthermore, the use of Goal Directed Perfusion strategy during CPB may have a significant influence on postoperative AKI. Fifthly, the long time span (11 years) could pose several challenges. For example, changes in clinical practice, technology, or patient characteristics over time may introduce confounding factors that we cannot fully account for. Additionally, data collection methods and quality may have varied over the years, which could affect the accuracy and completeness of our results. Finally, hemoglobin elevation after RBC transfusion is harmful to the kidney, but we should be more cautious with a general relationship between hemoglobin elevation from other etiologies than transfusion (i.e., haemoconcentration, iron supply, erythropoietin stimulation) and AKI. Additionally, the threshold for RBC transfusion can be challenged by the metabolic tolerance of anemia assessed by SvO_2 (35, 36).

5. Conclusion

This study has identified a trajectory of hemoglobin levels that is associated with an increased risk of postoperative AKI following cardiac surgery. It should be noted that a fixed hemoglobin threshold should not be applied to all types of patients. Among patients receiving red blood cell transfusions, maintaining hemoglobin levels above 10 g/dl through red blood cell transfusions is associated with an increased risk of AKI.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Boards (IRB) of the Beth Israel Deaconess Medical Center (No. 2001-P-001699/15). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SZ contributed to drafting the article. SZ, PLu, ZL and YW contributed to the conception and design of the study. SZ, SL, PLi, BW and JL contributed to the analysis and interpretation of data. YW contributed to reviewing the final manuscript. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1181617/full#supplementary-material.

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EDITED BY
Cristina Barbero,
A.O.U. City of Health and Science of Turin, Italy

REVIEWED BY
Abimbola Faloye,
Emory University, United States
Paul Philipp Heinisch,
German Heart, Germany

*CORRESPONDENCE
Mao Zhang
z2jzk@zju.edu.cn
Jingfen Jin
zrjzkhl@zju.edu.cn

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Effectiveness of a short-term multimodal prehabilitation program in adult patients awaiting selective cardiac surgery: study protocol for an open-label, pilot, randomized controlled trial

Wen Gao[1,2], Hongyan Li[3], Yuaner Chen[4], Yuping Zhang[1], Mao Zhang[2,5]* and Jingfen Jin[1,5]*

[1]Nursing Department, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [2]Emergency Department, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [3]Department of Rehabilitation, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [4]Department of Cardiovascular Surgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [5]Key Laboratory of the Diagnosis and Treatment of Severe Trauma and Burn of Zhejiang Province, Zhejiang University, Hangzhou, China

Background: Prehabilitation has been demonstrated to positively impact postoperative recovery in patients undergoing selective cardiac surgery. However, the optimal modules included in prehabilitation programs are yet to be fully explored, as existing studies have primarily focused on exercise. This study will explore the effectiveness of a three-arm prehabilitation program among adult patients awaiting selective cardiac surgery.

Methods and analysis: A single-center, parallel-group randomized controlled trial will be conducted at the Second Affiliated Hospital of Zhejiang University School of Medicine (SAHZU). A total of 152 adult patients scheduled for elective cardiac surgery (coronary artery bypass grafting or valvular surgery) will be recruited from a tertiary teaching hospital. The patients will be randomly assigned to either the control group or the prehabilitation group. Patients assigned to the control group will receive standard care, which includes patient education and counseling as well as personal guidance on exercise, breathing, and coughing. Patients in the intervention group will be provided a multimodal prehabilitation program, including nutrition guidance, a diet journal, mindfulness training, and exercise guidance. The interventions will begin with home-based training and continue after hospital admission and before surgery. The primary outcome will be the perioperative 6-minute walk distance (6 MWD). The secondary outcomes will include preoperative readiness, postoperative recovery, and patient experience with the program.

Discussion: The purpose of the study is to examine whether a short-term multimodal prehabilitation program will be associated with improved preoperative readiness and postoperative outcomes. The findings of this study will provide evidence to support the development of a perioperative program aimed at enhancing patient recovery.

Clinical Trial Registration: www.ClinicalTrials.gov; identifier: NCT05503004.

KEYWORDS

prehabilitation, cardiac surgery, exercise, nutrition, mindfulness

1. Introduction

Valve surgery and coronary artery bypass grafting (CABG) are the most common types of cardiac surgery in China, accounting for 49.2% of all heart surgeries performed in 2021 (1). However, these surgeries can potentially lead to cognitive and functional decline (2, 3), resulting in reduced independence and a diminished health-related quality of life (HRQOL) (4). Therefore, it is of paramount importance to enhance the physical and psychological reserve of patients in order to improve their readiness for surgical stress, ultimately promoting patient recovery.

Prehabilitation refers to the process of enhancing an individual's functional capacity in preparation for upcoming surgery (5). The current guidelines of the Enhanced Recovery Association recommend that prehabilitation should be incorporated into perioperative care for cardiac surgery (6). As the first step in the enhanced recovery process, prehabilitation can mitigate sympathetic nervous overreaction and enhance patients' physical and psychological resilience (7, 8). Although studies have indicated that multimodal, multidisciplinary preoperative interventions are more effective than single-exercise interventions (9), the content of preoperative interventions prior to cardiac surgery has been primarily limited to exercises, such as respiratory muscle training and aerobic training (10). Another important consideration is the duration of prehabilitation, which has ranged from five days to ten weeks (11). Additionally, the suitability and scheduling of prehabilitation programs could significantly affect patient participation and adherence (12). Given the shortened waiting duration before hospital admission, there is a need for a short-term prehabilitation program to enhance preoperative recovery.

Recent research has provided evidence indicating the importance of preoperative nutritional evaluations and psychological interventions. It has been observed that between 12%–42% of patients undergoing cardiac surgery suffer from malnutrition before surgery, which can increase the inflammatory response and negatively impact postoperative recovery (13). Several standardized scoring systems have been developed to assess the preoperative nutritional status of patients (14), but routine risk screening for malnutrition is not currently incorporated into prehabilitation programs, and optimal methods for providing preoperative guidance are overlooked. In addition to physical and nutritional status, psychological distress can also initiate a stress response prior to surgery and dysregulate postoperative immune function, leading to worse outcomes (15). Mindfulness-based interventions have been found to have favorable effects on psychological outcomes. A study conducted on patients with heart disease found that mindfulness can decrease heart rate and improve exercise capacity (16). Furthermore, evidence indicates that mindfulness-based intervention can reduce preoperative emotional distress and lead to less emotional pain perception after surgery (17). Therefore, mindfulness may be a valuable addition to prehabilitation program, and further research exploring the use of mindfulness in this context is needed.

Additionally, it is important to note that the three prehabilitation modules – exercise, nutrition, and psychological support – can also have an interdependent relationship. Qualitative interviews with patients who underwent elective cardiac surgery revealed that physical factors such as reduced mobility and weakness can easily lead to negative emotions in patients, which may hinder their participation in rehabilitation programs (18). Psychological distress and malnutrition have also been identified as potential barriers to participation in rehabilitation (19). Conversely, exercise has been shown to improve emotional distress such as anxiety and depression in patients with heart disease by reducing stress and behavioral activation (20). This suggests that the modules in prehabilitation programs can interact with each other and may have a synergistic effect.

Therefore, the aim of this study is to implement a short-term multimodal prehabilitation program and investigate the effectiveness of such a program in improving physical function in patients receiving selective cardiac surgery. Additionally, secondary outcomes will be assessed, including preoperative readiness (preoperative anxiety, frailty, and preoperative nutritional risks), postoperative recovery (delirium, frailty, HRQOL, and length of stay), and patient experience with the program.

2. Methods

2.1. Trial design

This study is a single-center, prospective, parallel group, randomized clinical trial with an allocation ratio of 1:1, comparing a one-week prehabilitation program to usual care at the Second Affiliated Hospital of Zhejiang University (SAHZU), located in Hangzhou, China. The overall trial design is illustrated in **Figure 1**. The trial protocol was developed following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (21) and was pre-registered at clinicaltrials.gov (NCT05503004).

2.2. Study setting

This trial will be conducted at a tertiary academic hospital in Hangzhou, China (SAHZU). Patients will be assessed for eligibility at their initial visit to the cardiovascular clinic after receiving a clinical diagnosis requiring selective open-heart surgery. The one-week interventions will be performed at the patient's home while awaiting hospital admission and after hospital admission before surgery.

2.3. Eligibility criteria

Patients will be eligible for participation if they are 18 years or older and are referred for selective cardiac surgery with an expected

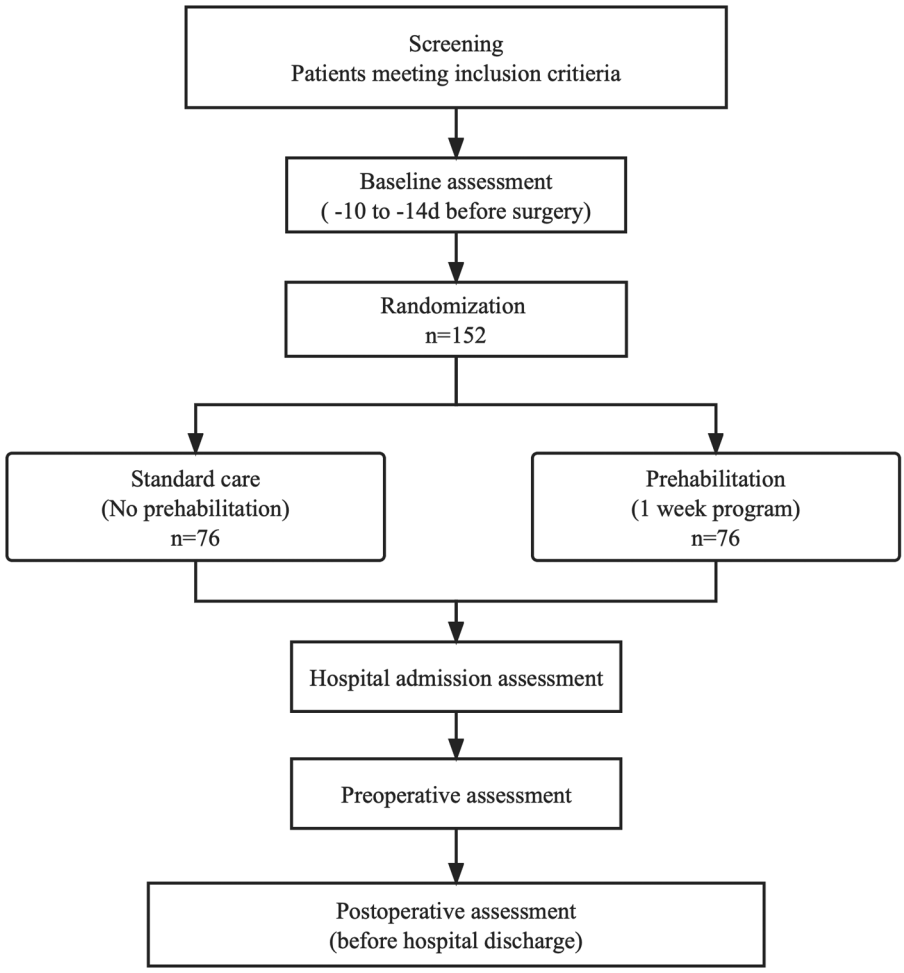

FIGURE 1
Study flowchart.

waiting time of 7 days prior to the surgical procedure. The exclusion criteria will be as follows: (1) comorbid medical, physical, and mental conditions that contraindicated exercise or mindfulness; (2) acute or unstable cardiac conditions (e.g., unstable angina or symptomatic severe aortic stenosis); (3) disabling orthopedic and neuromuscular disease; hearing disorder; (4) dementia; (5) cardiac failure (New York Heart Association functional classes III and IV); (6) hospitalization or mechanical ventilation in the past 30 days; and (7) previous history of cardiac surgery. Patients will be withdrawn from the trial if: (1) they request to do so without any reasons; (2) they develop adverse events due to prehabilitation (e.g., fall); (3) they are referred to the transcatheter cardiac surgery after hospital admission.

2.4. Interventions

2.4.1. Prehabilitation group

Patients assigned to the prehabilitation group will receive a prehabilitation program in conjunction with their usual preoperative care. The program will be provided by a multidisciplinary team consisting of physicians, rehabilitation therapists, nurses, and nutritionists. Patients will engage in a structured one-week prehabilitation program starting from their entry into the waiting list before selective surgery, both at home and after their hospital admission.

EXERCISE module will be composed of two sessions, namely aerobic exercise and resistance training. Aerobic exercise will require patients to walk or engage in stationary cycling for 30 min, which includes a 5-minute warm-up and cool-down activity at least three times per week. Resistance training, on the other hand, will use elastic bands for the upper and lower limbs, chest, and core muscles with ten repetitions per major muscle group for three days. Videos demonstrating the exercise routines will be sent to the mobile phones of patients and their accompanying family members during hospitalization. The intensity of each patient's exercise will be personalized based on their health status, exercise performance, and training response. The appropriate heart rate ranged will be within the range of (220 – age) × (50%–60%) and we will monitor the patient's heart rate and subjective perceived exertion [Borg rating of perceived exertion (RPE)] throughout the exercise using a wristband (Xiaomi Wristband 7, Xiaomi Technology Co., Ltd.).

NUTRITION interventions will consist of early screening for malnutrition and structured education to reduce fat-rich diets and increase high-quality protein uptake. Patients will be encouraged to consume healthy, high-protein diets including high-quality protein sources such as eggs, fish, lean meats, or dairy. The optimal suggested diet goals will be set at 1.5–2 g/kg/d of protein from routine food intake. To assess the daily protein intake, patients will be recommended to keep diet journals, record and take photos of their three daily meals, which will then be evaluated and guided by a nutritionist. Malnourished patients will be transferred to a face-to-face nutrition clinic, and high-protein oral nutritional supplement (ONS) servings will be provided daily.

PSYCHOLOGY intervention will involve a one-week brief mindfulness practice session, with 10 min of practice per day before sleep. This intervention will focus on breathing mindfulness and feelings, guided by an audio-mindfulness dialogue. Psychologists will introduce a short mindful breathing practice after patient allocation. Mindfulness guidance recordings will be sent to the patient's mobile phone, and the practice of mindfulness on breathing and feeling will be encouraged.

2.4.2. Control group

Patients assigned to the control group will not receive any additional prehabilitation intervention. Instead, they will receive usual care, which will include a thorough admission assessment, education on inspiratory muscle training, breath exercises, coughing, online health education, counselling, and nutrition risk assessment.

2.5. Outcomes

The timeline for this study will be one week. Prehabilitation will be implemented one week before the surgery, and the follow-up period will comprise of the perioperative period until the patient's discharge from the hospital. The outcomes will be assessed at four different time points: before the intervention (T0), upon admission to the hospital (T1), before surgery (T2), and after surgery (T3, before hospital discharge). Table 1 shows the complete assessment timeline.

The primary outcome was the change in functional capacity over time, measured as the difference in absolute change in 6-minute walk distance (6 MWD) between T0 and T2 (primary analysis), as well as between T0 and T3. In this regard, a change of 20 meters from the baseline was deemed significant, indicating either an improvement or deterioration. To conduct this evaluation, participants will be instructed to wear comfortable footwear and walk back and forth in a 20-meter stretch of hallway for 6 min, aiming to reach a point of exhaustion by the end of the exercise. The tests will be conducted under the supervision of a blinded assessor following a standardized procedure to minimize potential sources of error due to bias or different levels of encouragement.

Secondary outcomes will comprise preoperative readiness (preoperative anxiety, frailty, and preoperative nutritional risks), postoperative recovery (delirium, frailty, HRQOL, and length of hospital stay), and patient experience with the program. Preoperative anxiety will be evaluated based on the Amsterdam Preoperative Anxiety and Information Scale (APAIS), perioperative frailty will be assessed using the Fried Frailty Phenotype Criteria (FFPC), and preoperative nutritional risk will be screened using nutritional risk screening (NRS 2002). The Flow State Scale short version will be used to examine patient experience of prehabilitation. Delirium will be assessed using the Confusion Assessment Method of the Intensive Care Unit -7 (CAM-ICU-7) and the 4AT Rapid clinical test for delirium for every nurse shift. HRQOL will be assessed using the EuroQol 5 Dimension 5 Level (EQ-5D-5l). The postoperative lengths of ICU stay, hospital stay, and mechanical ventilation will be recorded.

2.6. Recruitment

Individuals who meet the eligibility criteria will be presented with a comprehensive overview of the study's aims and procedures by a cardiac rehabilitation therapist if they express an interest in participating. The initial appointment will be

TABLE 1 Overview of assessment.

Measurement	T0: baseline	T1: hospital admission	T2: 1 day before surgery	T3: after surgery (before hospital discharge)
6-minute walk distance (6MWD)	×	×	×	×
Preoperative anxiety (APAIS)	×	×	×	
Frailty (FFPC)	×		×	×
Nutrition risks (NRS2002)	×	×		
Prehabilitation experience (FSS)		×	×	
ICU delirium (CAM-ICU-7)				×
Postoperative delirium (4AT)				×
Health-related quality of life (EQ-5D-5l)	×	×	×	×
Length of ICU stay, days				×
Length of hospital stay, days				×
Length of mechanical ventilation, hours				×

scheduled 10–14 days before their hospital admission. Written informed consent will be collected from all participants at the hospital preparation center before the completion of the study assessments.

2.7. Randomization and blinding

Eligible patients will have an equal opportunity to be randomly assigned to either the prehabilitation group or the control group in a 1:1 ratio. Randomization will be performed via a computer-generated block scheme and the resulting group assignments will be placed in opaque envelopes with sequential numbering by an independent research assistant not involved in this study. The research assistant will open a concealed envelope to allocate patients to their respective group. The main interventionist, assessor, and statistician will remain unaware of the group assignments until the envelope is sealed. Due to the intervention's inherent nature, it will not be possible to mask the participants or healthcare professionals.

2.8. Data collection and management

At the baseline interview after randomization, demographic and clinical characteristics will be collected, including age, sex, BMI, ASA physical status class, comorbidities such as diabetes, hypertension, and hyperlipidemia, and Charlson Comorbidity index. Laboratory test results and assessment outcomes will be obtained from patients' electronic medical records, including serum hemoglobin, NRS 2002, HYHA, main diagnosis, and EuroScore. Additionally, data on daily exercise amount and intensity, diet details, and duration of mindfulness will be collected using a bracelet (Xiaomi Wristband 7, Xiaomi Technology Co., Ltd.). The 6 MWD test will be performed and recorded by trained researchers at our institution after providing standardized instructions and demonstrations of the tests. Patient-reported questionnaires will be administered, and the outcomes will be recorded by trained researchers. During the prehabilitation period, message interviews will be sent to patients every day, and feedback on their daily prehabilitation performance will be documented. After the surgery, information on the surgery, duration of ICU stay, and postoperative recovery will be obtained from electronic records. Patient identity and personal information will remain confidential unless consent is provided. All collected data will initially be recorded in a paper-based case report form and then entered into a digital database by an independent investigator.

2.9. Sample size

We determined that a difference of 20 meters in the change in 6-minute walk distance (6 MWD) between T0 and the T2 (primary analysis) in the prehabilitation group compared to the control group was a meaningful clinical outcome based on a previous study (22). Consequently, we conducted a sample size calculation using G*Power (version 3.1.) for the repeated-measures ANOVA with an alpha error of 5% and power of 0.95, with two groups and four measurements. The estimated sample size required was 132 patients. To account for a 15% attrition rate during the intervention period, the target sample size was increased to 152 participants (76 per group).

2.10. Statistical analysis

To compare baseline characteristics between groups, we will use an independent-samples t-test for continuous variables and a χ^2 Test for categorical variables. To analyze differences in primary outcomes, we will use repeated-measures analysis of variance. All statistical analyses will be conducted using SPSS (version 27.0; IBM) and R (version 4.0.5).

3. Discussion

Although enhanced recovery has been recommended and practiced for years in cardiac surgical patients, prehabilitation before surgery has not received sufficient attention. Due to impaired cardiopulmonary function and limited daily activities, patients are at risk of functional deterioration while waiting, which could lead to surgical delay and form a vicious circle (22). Another important consideration is the waiting time and duration of prehabilitation. A study reported that a delay of more than 7 days in patients requiring CABG was associated with worse in-hospital and long-term outcomes (23). Therefore, there is a need for short-term prehabilitation programs to quickly prepare patients for surgery. Further research is required in this field to better understand the clinical effectiveness of a short-term prehabilitation programs before surgery and to combine home and hospital prehabilitation as an effective bridge to achieve preoperative readiness.

The aim of this study is to investigate the impact of the prehabilitation on preoperative readiness and postoperative recovery. To date, while studies have mainly focused on postoperative functional performance and recovery (10), there is increasing evidence that preoperative readiness is essential for successful postoperative recovery. In particular, patient readiness for surgery has been associated with shorter mechanical intubation times and reduced length of stay after CABG (24). Preoperative frailty is also an important indicator in preoperative decision-making and can help predict patient recovery trajectory (25). It is also worth noting that patients undergoing cardiac surgery often experience high levels of preoperative anxiety (26), highlighting the importance of psychological interventions to improve patients' preoperative psychological readiness. In addition, malnutrition has been linked to a longer postoperative recovery time and higher risk of cardiovascular and infectious complications (13), indicating the need for a multimodal prehabilitation that includes elements to improve physical, psychological, and nutritional factors. To address these needs, we

have designed a three-arm program that incorporates exercise, nutritional optimization, and mindfulness.

This study will implement a comprehensive prehabilitation program that will be both home- and hospital-based, covering the entire waiting period before surgery. Our proposed prehabilitation program is designed to optimize preoperative and postoperative physical function performance and improve psychological well-being by enhancing physical function and alleviating psychological distress. This program was designed and will be supervised by physiotherapists, psychologists, nutritionists, cardiac rehabilitation nurse specialists, and cardiac surgical physicians, and the intensity of the program will be tailored to each patient's needs to ensure safety and effectiveness both practiced at home and in hospital. If this program is proven effective, it could provide significant benefits to patients on the waiting list by offering home-based prehabilitation and continuing care programs after hospital admission and postoperative recovery.

This study has some limitations. First, the study only includes patients awaiting for CABG and/or valve surgery. Second, this is a single-center study. Therefore, further multicenter studies including more patients with various diagnoses are needed. Third, due to the time window of 7 days, although the nutritional intervention may be beneficial for postoperative recovery, measurable changes in body composition or serum albumin concentrations may not be detectable.

Ethics statement

The studies involving human participants were reviewed and approved by Second affiliated hospital of Zhejiang University School of Medicine SAHZU Research Ethics Board (IR2022-0962). The patients/participants provided their written informed consent to participate in this study.

Author contributions

The protocol was jointly designed and written by WG, MZ and JJ, and was critically reviewed by HL, YC and YZ 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.

Publisher's note

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EDITED BY
Pierre-Gregoire Guinot,
Centre Hospitalier Regional Universitaire De Dijon, France

REVIEWED BY
Haiqing Li,
Shanghai Jiao Tong Universtity School of Medicine, China
Sebastian Rojas,
Heart and Diabetes Center North Rhine-Westphalia, Germany

*CORRESPONDENCE
Chao Liu
✉ liubeilun@me.com
Dashuai Wang
✉ wangdashuai@zzu.edu.cn

†These authors have contributed equally to this work

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Influence and risk factors of postoperative infection after surgery for ischemic cardiomyopathy

Bing Wen[1†], Yang Lu[2†], Xiaofan Huang[3], Xinling Du[3], Fuqiang Sun[1], Fei Xie[1], Chao Liu[1*] and Dashuai Wang[1*]

[1]Department of Cardiovascular Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [2]Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [3]Department of Cardiovascular Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Studies on postoperative infection (POI) after surgery for ischemic cardiomyopathy are still lacking. This study aimed to investigate the risk factors of POI and its influence on clinical outcomes in patients undergoing ischemic cardiomyopathy surgery.
Methods: The Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized patients with ischemic cardiomyopathy [coronary artery disease (CAD) with left ventricular ejection fraction ≤35%] to surgical and medical therapy. In this study, a *post hoc* analysis of the STICH trial was performed to assess the risk factors and clinical outcomes of POI in those undergoing coronary artery bypass graft (CABG). Patients were divided according to whether POI developed during hospitalization or within 30 days from operation.
Results: Of the 2,136 patients randomized, 1,460 patients undergoing CABG per-protocol was included, with a POI rate of 10.2% (149/1,460). By multivariable analysis, POI was significantly related to patients' age, body mass index, depression, chronic renal insufficiency, Duke CAD Index, and mitral valve procedure. Compared to patients without POI, patients with POI had significantly longer durations of intubation, CCU/ICU and hospital stay, and higher rates of re-operation, in-hospital death and failed discharge within 30 days postoperatively. In addition, these patients had significantly higher risks of all-cause death, cardiovascular death, heart failure death, and all-cause hospitalization during long-term follow-up. However, the influence of POI on all-cause death was mainly found during the first year after operation, and the influence was not significant for patients surviving for more than 1 year.
Conclusions: POI was prevalent after surgery for ischemic cardiomyopathy and was closely related to short-term and long-term clinical outcomes, and the effect of POI mainly occurred within the first postoperative year. This study first reported and clarified the relationship between POI and long-term prognosis and the predictors for POI after surgery for ischemic cardiomyopathy worldwide, which may have certain guiding significance for clinical practice.

Abbreviations
CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CCU, cardiac care unit; CI, confidence interval; CPB, cardiopulmonary bypass; EF, ejection fraction; HR, hazard ratio; ICU, intensive care unit; KM, Kapkan-Meier; LAD, left anterior descending artery; LV, left ventricular; NYHA, New York Heart Association; OR, odds ratio; PCI, percutaneous coronary intervention; POI, postoperative infection; STICH, Surgical Treatment for Ischemic Heart Failure; STICHES, STICH extension study; SVR, surgical ventricular reconstruction.

Clinical Trial Registration: https://www.clinicaltrials.gov, identifier (NCT00023595).

KEYWORDS

postoperative infection, heart failure, ischemic cardiomyopathy, coronary artery disease (CAD), coronary artery bypass graft (CABG)

Introduction

As a global pandemic with an increasing prevalence, heart failure (HF) remains a leading cause of mortality and morbidity (1–3). Ischemic cardiomyopathy, defined as severe coronary artery disease (CAD) with left ventricular (LV) dysfunction, is the most common cause of HF with reduced ejection fraction (EF) (3, 4). Despite advances in diagnosis and medical management these years, surgical revascularization for ischemic cardiomyopathy using coronary artery bypass graft (CABG) is still recommended as the preferred treatment strategy (4, 5). Nevertheless, the overall survival after surgery remains unsatisfied and the rates of various postoperative complications remain high (6).

Postoperative infection (POI) is one of the most prevalent complications after cardiac surgery, related to inferior outcomes and increased resource use (7–9). The incidence of POI varies widely in previous reports due to different definitions, specific types of infections, and surgical populations in different studies (9–12). Multiple types of infections have been reported in the literature, such as mediastinitis, surgical wound infection, pneumonia and sepsis (9–14). Regardless of the infectious type, the development of POI will increase mortality, prolong hospital stay, and increase total treatment costs to varying degrees. Compared to the majority of the common cardiac surgery, patients undergoing ischemic cardiomyopathy surgery had significantly higher perioperative risk due to the inherently more severe and complex nature of the condition. It is precisely due to the complexity and high risk of the ischemic cardiomyopathy surgery that has led to the fact that there were still few studies specifically conducted in this patient population. Notably, studies focused on POI conducted in patients undergoing surgery for ischemic cardiomyopathy are still lacking so far.

The Surgical Treatment for Ischemic Heart Failure (STICH) study was a large-scale, multicenter, randomized controlled trial that enrolled 2,136 patients with coronary artery disease (CAD) amenable to CABG and left ventricular ejection fraction (LVEF) ≤35% (15). Using data from the STICH study and the STICH extension study (STICHES), we aimed to (1) identify the risk factors of POI after CABG for ischemic cardiomyopathy, (2) assess the influence of POI on short-term (in-hospital or within 30 postoperative days) clinical outcomes, and (3) assess the influence of POI on long-term follow-up outcomes.

Methods

This study is a *post hoc* analysis of the STICH/STICHES study (15, 16) using data from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Centre (BioLINCC). This study complies with the Declaration of Helsinki and an exemption from the institutional review board oversight was granted due to the deidentified nature of the data. Written informed consent was obtained from each included participant and the study protocols were approved by the institutional review board at each site.

Study population

Study details with regard to the rationale, design, enrolment, and main findings of the STICH/STICHES trial have been published previously (15–17). Briefly, a total of 2,136 patients with ischemic cardiomyopathy from 127 clinical sites in 4 continents and 26 countries between 2002 and 2007 were enrolled to test two hypotheses. In hypothesis 1, 1,212 patients were enrolled and randomized to either medical therapy + CABG ($n = 610$) or medical therapy alone ($n = 602$). In hypothesis 2, 1,000 patients were included and randomized to undergo CABG + surgical ventricular reconstruction (SVR) ($n = 501$) or CABG alone ($n = 499$). Among the 2,136 patients enrolled in the STICH/STICHES trial, the following criteria were used to exclude participants from this study: (1) patients were randomized to the medical therapy group ($n = 602$); (2) patients were randomized to but did not receive surgical treatment actually in both hypothesis 1 and 2 ($n = 74$). Patients randomized to medical therapy but received CABG during the follow-up period ($n = 65$) were also excluded for this study due to the fact that detailed perioperative and postoperative data were not available in these patients. The remaining 1,460 patients met the inclusion criteria and were included for further analysis in this study.

Endpoints, variables, and outcome events

In this study, the primary endpoint was POI within 30 days after surgery for ischemic cardiomyopathy. POI was defined as the development of any type of major postoperative infections, such as mediastinitis, pneumonia, pyelonephritis, septicemia, and infections at the vein-harvest site, just as defined in previously published literature (6). Mediastinitis was defined as any wound disruption exposing the sternum or requiring a secondary operation or stabilization of the sternum; pneumonia was defined as infection of the lung often accompanied by inflammation; pyelonephritis was defined as inflammation of the kidney involving the renal parenchyma; septicemia was defined as systemic inflammatory response syndrome with a proven or suspected infectious etiology. Patients were divided into two groups according to whether POI developed and pre-, intra- and post-operative variables and outcomes were compared between the two groups.

After selection, preoperative variables analyzed in this study included sex, age, race, body mass index, body surface area, current smoker, depression, hypertension, diabetes, hyperlipidemia, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation/flutter, chronic renal insufficiency, previous percutaneous coronary intervention (PCI), previous CABG, Canadian Cardiovascular Society (CCS) angina class, New York Heart Association (NYHA) class, LVEF, number of diseased vessels, left main stenosis, proximal left anterior descending artery (LAD) stenosis, Duke CAD Index, hemoglobin, serum creatinine and mitral regurgitation. Intraoperative variables included off/on-pump bypass, concomitant SVR, mitral valve procedure, cardiopulmonary bypass (CPB) time, and aortic cross clamp time. Postoperative variables before discharge or within 30 days after surgery included the durations of intubation, cardiac or intensive care unit (CCU/ICU) and hospital stay, and the incidence rates of re-operation, in-hospital death and failed discharge within 30 days. All postoperative events and complications has been prespecified and defined in previous reports (6).

All the enrolled patients was followed up at the time of hospital discharge, 30 days after surgery, at 4-month intervals for the first year, and at 6-month intervals over the remainder of the follow-up period thereafter. In this study, the follow-up outcomes included all-cause death, cardiovascular death, heart failure (HF) death, all-cause hospitalization, cardiovascular hospitalization, HF hospitalization, and the composite of all-cause death and all-cause, cardiovascular and HF hospitalization.

Statistical analysis

Continuous variables were biased and were expressed as median (25th, 75th percentile), and were compared by Mann–Whitney *U*-test. Categorical variables were expressed as count (percentage) and compared by chi-square test or Fisher's exact test. Independent risk factors for POI were identified by multivariable logistic regression analysis with a forward stepwise procedure. The Cox proportional hazards regression model was used to assess the influence of POI on long-term outcomes in both univariable and multivariable analyses. The multivariable model was adjusted for sex, age, race, body mass index, current smoking, depression, hypertension, diabetes, hyperlipidemia, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation/flutter, chronic renal insufficiency, previous PCI, previous CABG, CCS angina class, NYHA class, left ventricular ejection fraction, Duke CAD Index, hemoglobin, mitral regurgitation, surgical treatment and CPB time. The results were presented as odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI). Cumulative event rates were calculated by the Kaplan-Meier (KM) method and the log-rank test was used for comparison between groups.

Two-tailed *P*-values of less than 0.05 were considered statistically significant. All analyses were performed under the per-protocol principle using R software (version 4.0.5) and SPSS (IBM SPSS Statistics 26.0, SPSS Inc., Chicago, IL).

Results

Characteristics

After screening, a total of 1,460 patients undergoing CABG per-protocol were included in this study, with a POI rate of 10.2% (149/1,460) within 30 days postoperatively. The median age of these patients was 61.2 (54.0, 68.3) years, 13.7% were female. Compared to patients with POI, patients without POI had younger age, lower depression rate, better renal function, better cardiac function, fewer diseased vessels, higher Duke CAD Index, less on-pump bypass and mitral valve procedure, as well as shorter CPB and aortic cross clamp time. The details of comparison of baseline characteristics and intraoperative variables in patients with and without POI are summarized in **Table 1**.

Independent risk factors for POI

Variables with a *P*-value of less than 0.1 in the univariable analysis or considered clinically significant were further analyzed by a multivariable logistic regression procedure to identify independent risk factors for POI. Six factors were identified to be significantly associated with the development of POI by multivariable analysis, including age, body mass index, depression, chronic renal insufficiency, Duke CAD Index, and mitral valve procedure (**Table 2**).

In-hospital or 30-day postoperative outcomes

Clinical outcomes in hospital or within the first 30 days postoperatively are compared and summarized in **Table 3**. The overall 30-day mortality after surgery was 5.1% (74/1,460), with a rate of 9.4% in patients with POI vs. 4.6% in those without POI ($P = 0.011$). A total of 77 patients (5.3%) had a hospital stay of longer than 30 days, while the rate was significantly higher in patients with POI (1.8% vs. 35.6%, $P < 0.001$). Higher rate of re-operation was also observed in patients with POI (5.0% vs. 24.2%, $P < 0.001$). In addition, the durations of total intubation time, CCU/ICU and hospital stay were also significantly prolonged in patients with POI (**Table 3**).

Long-term follow-up outcomes

The median follow-up time of this study population was 4.7 (3.3, 9.4) years, with a maximum follow-up period of 13.3 years. Compared to patients without POI, patients with POI had significantly higher risk of all-cause death throughout the follow-up period (HR: 1.966, 95% CI: 1.555–2.486, $P < 0.001$; **Figure 1**). This difference remained significant even after adjusting for confounding factors by multivariable Cox proportional hazards regression model (HR: 1.472, 95% CI: 1.148–1.886, $P = 0.002$;

TABLE 1 Preoperative baseline characteristics and operative variables in patients with or without POI.

Variable	Without POI, $n = 1,311$ (%)	With POI, $n = 149$ (%)	*P*-value
Female	178 (13.6)	22 (14.8)	0.689
Age (years)	61 (54, 68)	64 (55, 71)	0.007
Ethnic minority	282 (21.5)	30 (20.1)	0.698
Body mass index (kg/m2)	26.9 (24.3, 30.1)	27.3 (24.2, 30.6)	0.080
Body surface area (m2)	1.9 (1.8, 2.1)	1.9 (1.8, 2.1)	0.578
Current smoker	271 (20.7)	33 (22.1)	0.674
Depression	81 (6.2)	16 (10.7)	0.034
Hypertension	775 (59.1)	94 (63.1)	0.349
Diabetes	473 (36.1)	61 (40.9)	0.243
Hyperlipidemia	887 (67.7)	98 (65.8)	0.641
Myocardial infarction	1,088 (83.0)	124 (83.2)	0.943
Stroke	86 (6.6)	11 (7.4)	0.702
Peripheral vascular disease	187 (14.3)	28 (18.8)	0.139
Atrial fibrillation/flutter	146 (11.1)	24 (16.1)	0.073
Chronic renal insufficiency	94 (7.2)	24 (16.1)	<0.001
Previous PCI	214 (16.3)	28 (18.8)	0.443
Previous CABG	32 (2.4)	6 (4.0)	0.249
CCS angina class			0.227
0	370 (28.2)	51 (34.2)	
I	129 (9.8)	15 (10.1)	
II	359 (27.4)	28 (18.8)	
III	375 (28.6)	45 (30.2)	
IV	78 (5.9)	10 (6.7)	
NYHA class			0.002
I	127 (9.7)	9 (6.0)	
II	620 (47.3)	57 (38.3)	
III	511 (39.0)	69 (46.3)	
IV	53 (4.0)	14 (9.4)	
Left ventricular ejection fraction (%)	27.5 (21.8, 33.1)	26.3 (21.7, 30.6)	0.056
Number of diseased vessels (stenosis ≥75%)			0.001
0	28 (2.1)	1 (0.7)	
1	255 (19.5)	23 (15.4)	
2	541 (41.3)	45 (30.2)	
3	487 (37.1)	80 (53.7)	
Left main stenosis ≥50%	179 (13.7)	26 (17.4)	0.206
Proximal LAD stenosis ≥75%	947 (72.2)	111 (74.5)	0.558
Duke CAD Index	65 (39, 77)	71 (52, 91)	<0.001
Hemoglobin (g/dl)	13.7 (12.7, 14.8)	13.8 (12.5, 15.0)	0.958
Serum creatinine (mg/dl)	1.1 (0.9, 1.2)	1.2 (1.0, 1.4)	<0.001
Mitral regurgitation			0.017
None or trace	491 (37.5)	44 (29.5)	
Mild	608 (46.4)	69 (46.3)	
Moderate	175 (13.3)	26 (17.4)	
Severe	37 (2.8)	10 (6.7)	
Off-pump bypass	150 (11.4)	7 (4.7)	0.012
Concomitant SVR	446 (34.0)	49 (32.9)	0.782
Mitral valve procedure	183 (14.0)	43 (28.9)	<0.001
CPB time (minutes)	97 (65, 130)	115 (80, 168)	<0.001
Aortic cross clamp time (minutes)	60 (38, 85)	73 (50, 107)	<0.001

CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CPB, cardiopulmonary bypass; LAD, left anterior descending artery; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; POI, postoperative infection; SVR, surgical ventricular reconstruction.

Table 4). The KM estimates of survival probabilities of 1-, 5-, and 10-year in patients without POI were respectively 88.9%, 68.2%, and 44.9%; however, the survival probabilities were significantly reduced in patients with POI, with corresponding values of 67.8%, 48.6%, and 19.3%, respectively. To further clarify the impact of POI on postoperative survival, a temporal analysis were performed. The results showed that the effect of POI on the increased risk of postoperative death was mainly reflected in the first postoperative year (HR: 3.257, 95% CI: 2.350–4.516, $P < 0.001$; Figure 2A). However, the effect of POI on the risk of all-cause death was not significant during follow-up one year later ($P > 0.05$; Figures 2B–G).

The risks of cardiovascular death and HF death were also significantly increased in patients with POI by log-rank test, with HR values of 2.078 (95% CI: 1.588–2.720, $P < 0.001$) and 1.888 (95% CI: 1.114–3.200, $P = 0.018$), respectively (Figure 3). After adjusting for confounding factors, the difference for cardiovascular death between groups remained significant (HR: 1.547, 95% CI: 1.165–2.054, $P = 0.003$), but the difference for HF death disappeared ($P = 0.488$; Table 4). Similarly, patients with POI had higher risk of all-cause hospitalization by log-rank test (HR: 1.272, 95% CI: 1.006–1.610, $P = 0.045$; Figure 4A), but the difference disappeared in multivariable analysis ($P = 0.757$; Table 4). The difference for cardiovascular hospitalization and HF hospitalization was not significant between patients with and without POI by both log-rank test (Figures 4B,C) and multivariable analysis (Table 4).

The impact of POI on the composite endpoint events of all-cause death and all-cause/cardiovascular/HF hospitalization was also evaluated by both log-rank test and multivariable analysis. The results indicated that patients with POI had higher risks of all the three composites by log-rank test (Figures 4D–F), and the difference remained significant for the composites of all-cause death and all-cause/HF hospitalization by multivariable analysis (Table 4).

Discussion

Infections after cardiac surgery are common and closely associated with higher risks of poor clinical outcomes (7–9), which was confirmed again by our results. In this study, the POI rate after surgery for ischemic cardiomyopathy within the first 30 postoperative days was 10.2%, and the 30-day mortality rate was 5.1%. Six independent risk factors for POI was identified, including age, body mass index, depression, chronic renal insufficiency, Duke CAD Index, and mitral valve procedure. Compared to patients without POI, patients with POI had significantly higher risks of re-operation and postoperative death, and significantly longer durations of total intubation, CCU/ICU, and hospital stay. The risks of all-cause death, cardiovascular death, HF death and all-cause hospitalization were significantly increased in patients with POI, as well as the risks of the composites of all-cause death and all-cause/cardiovascular/HF hospitalization. However, the effect of POI on postoperative death was mainly reflected in the

TABLE 2 Multivariate analysis of significant risk factors for POI.

Characteristic	Coefficient	Standard error	OR (95% CI)	*P*–value
Age (years)	0.024	0.010	1.024 (1.005–1.044)	0.014
Body mass index (kg/m2)	0.042	0.019	1.043 (1.006–1.083)	0.024
Depression	0.621	0.299	1.860 (1.036–3.342)	0.038
Chronic renal insufficiency	0.703	0.257	2.019 (1.220–3.340)	0.006
Duke CAD Index	0.012	0.004	1.012 (1.004–1.021)	0.003
Mitral valve procedure	0.924	0.203	2.519 (1.692–3.750)	<0.001
Intercept	−5.960	0.908	0.003	<0.001

CAD, coronary artery disease; CI, confidence interval; OR, odds ratio; POI, postoperative infection.

first postoperative year, and was no longer significant during follow-up one year later.

Infections following cardiac surgery is a broad concept that encompasses many different types of infection, such as mediastinitis and pneumonia. Numerous studies focused on both POI and each type of infection have been conducted and reported due to the high prevalence since the introduction of cardiac surgery (9–12, 18). Although considerable progress has been made in drug research and postoperative care in recent years, the incidence of kinds of POI remains high (7, 10, 19–22). A recent multicenter retrospective cohort study conducted by Joseph and colleagues reported that POI developed in 8.0% of the adults undergoing elective CABG, valve surgery or a combination, in which the most common infection was pulmonary, followed by urinary tract, sepsis/bacteremia, wound and gastrointestinal infections (7). The incidence of POI varies dramatically across studies, even for the same type of infection (11). Previous studies indicated that the incidence of POI varies widely in different types of cardiac surgery, with rates of pneumonia 2%–15%, deep sternal wound infection 0.2%–8.0%, and sepsis up to 9.5% (11, 13, 23, 24). The overall incidence of POI in this study was 10.2%, falling within previously reported ranges in the literature.

The six independent risk factors for POI identified in this study was consistent with clinical perception and previous reports. A higher Duke CAD Index represents a higher severity of the lesion and concomitant mitral valve procedure indicates more complex procedures and injuries, which may both increase the risks of various adverse outcomes (25). Advanced age has been widely identified to be associated with the development of various infections after kinds of surgeries, such as pneumonia after acute aortic dissection, heart valve, and redo cardiac surgery (25). This may be due to the fact that with the increase of age, patients may have more comorbidities, declined organ function, weakened defense mechanism and immune function, which may together lead to a higher risk of POI and other complications (11). Body mass index has also been previously reported to relate to the development of POI after cardiac surgery, including pneumonia, wound infection and mediastinal infection, which strengthens the significance of a scientific diet and proper exercise to maintain a fine body and consequently good health (9, 10, 22, 25). Another significant risk factors for POI identified in this study was chronic renal insufficiency, which was consistent with previous reports (9, 10). Louis and colleagues conducted a prospective multi-institutional cohort study to explore risk factors for mediastinal infection after cardiac operations, finding that higher body mass index and creatinine was significantly associated with the development of mediastinal infection by multivariable analysis (10). A recent review conducted in patients undergoing cardiovascular surgery concluded that advanced age, chronic kidney disease and body mass index were significantly associated with the occurrence of pneumonia (11). In addition, depression was identified as one of the independent risk factors for POI by multivariable analysis in this study, indicating that mental state can also significantly affect the prognosis of the disease. Some other risk factors for POI after cardiac surgery have also been previously reported in the literature but was not identified as independent predictors in our analysis, such as smoking and CPB time (11). This may be caused by the difference in study populations and thus partially reflected the significance and necessity of this study.

TABLE 3 Comparison of in-hospital or 30-day postoperative outcomes in patients with or without POI.

Outcome	Without POI, *n* = 1,311 (%)	With POI, *n* = 149 (%)	*P*-value
Total intubation time (hours)	15.5 (11.2, 22.5)	22.0 (13.9, 48.1)	<0.001
Time in CCU/ICU (hours)	51.2 (38.5, 96.0)	137.3 (65.3, 285.8)	<0.001
Hospital stay (days)	8 (7, 12)	21 (12, 41)	<0.001
Re-operation	65 (5.0)	36 (24.2)	<0.001
Hospital stay longer than 30 days	24 (1.8)	53 (35.6)	<0.001
Postoperative death	60 (4.6)	14 (9.4)	0.011
Death or not discharged within 30 days	84 (6.4)	67 (45.0)	<0.001

CCU, cardiac care unit; ICU, intensive care unit; POI, postoperative infection.

The relationship between various infections and short-term outcomes after cardiac surgery has been widely reported in the literature and well recognized in clinical practice (7–9). Joseph and colleagues reported that POI was independently associated with higher risks of mortality, non-home discharge, 90-day readmission and cost increase, and they found that the greatest incremental impact on patient-level and annual cohort costs was due to pulmonary infections (7). Nicolas and colleagues conducted a retrospective analysis of prospectively collected data to study the mortality fraction due to POI in patients undergoing cardiac surgery, finding that patients with POI had significantly

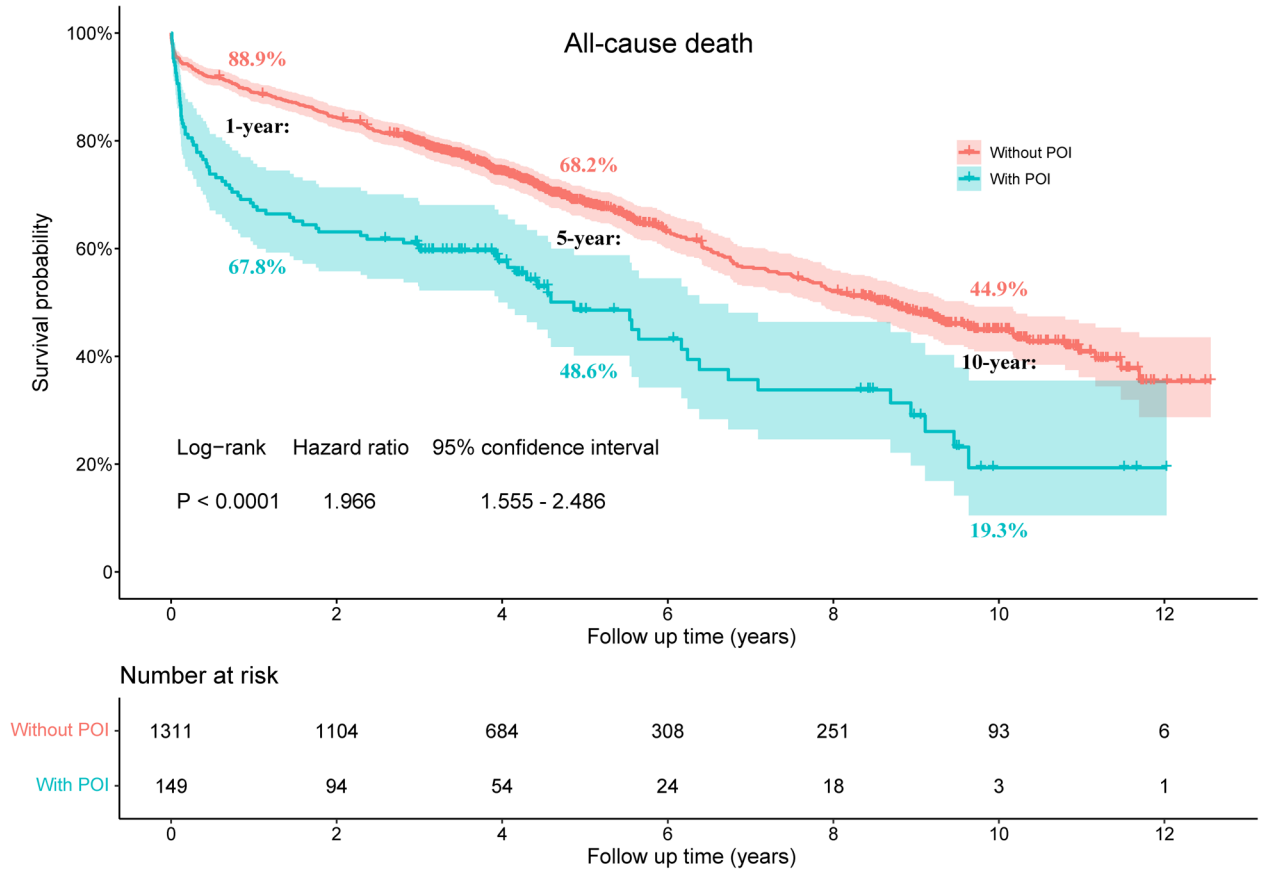

FIGURE 1
Kaplan-Meier estimated survival probabilities in patients with and without POI. POI, postoperative infection.

higher in-hospital mortality than patients without POI, and pneumonia, bloodstream infection and Pseudomonas aeruginosa infection were each independently associated with increased in-hospital mortality (8). Tamayo and colleagues conducted a prospective observational study in patients undergoing cardiac surgery to identify the impact of POI on patient mortality, finding that the ICU stay was significantly longer and the 90-day survival rate was significantly lower in patients with POI and POI constituted the main independent risk factor for death after the first postoperative week, with 6.23-fold increased risk (9).

Studies focused on a single type of infection have yielded similar results (10, 13, 26, 27). Likosky and colleagues conducted a large-scale multicenter study to examine the relationship between pneumonia and 90-day episode payments and outcomes

TABLE 4 Hazard ratios of POI for long-term outcomes by univariable and multivariable Cox regression analysis.

Event	No. of events (KM 10-year rate)		Unadjusted, HR (95% CI)	*P*-value	Adjusted[a], HR (95% CI)	*P*-value
	Without POI	With POI				
All-cause death	479 (55.1%)	82 (80.7%)	1.966 (1.555–2.486)	<0.001	1.472 (1.148–1.886)	0.002
Cardiovascular death	339 (39.2%)	63 (65.1%)	2.078 (1.588–2.720)	<0.001	1.547 (1.165–2.054)	0.003
Heart failure death	101 (15.8%)	16 (30.3%)	1.888 (1.114–3.200)	0.018	1.225 (0.690–2.175)	0.488
All-cause hospitalization	735 (76.0%)	77 (86.8%)	1.272 (1.006–1.610)	0.045	0.962 (0.753–1.230)	0.757
Cardiovascular hospitalization	570 (63.7%)	59 (75.1%)	1.192 (0.912–1.559)	0.199	0.879 (0.663–1.164)	0.367
Heart failure hospitalization	292 (34.8%)	30 (39.0%)	1.188 (0.816–1.730)	0.369	0.797 (0.536–1.185)	0.261
All-cause death or all-cause hospitalization	933 (85.0%)	125 (95.9%)	1.620 (1.343–1.953)	<0.001	1.232 (1.012–1.500)	0.037
All-cause death or cardiovascular hospitalization	826 (78.6%)	115 (93.4%)	1.568 (1.290–1.907)	<0.001	1.168 (0.950–1.437)	0.140
All-cause death or heart failure hospitalization	620 (64.0%)	96 (86.3%)	1.796 (1.448–2.227)	<0.001	1.332 (1.060–1.675)	0.014

CI, confidence interval; HR, hazard ratio; KM, Kapkan-Meier; POI, postoperative infection.
[a]Adjusted for sex, age, race, body mass index, current smoking, depression, hypertension, diabetes, hyperlipidemia, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation/flutter, chronic renal insufficiency, previous PCI, previous CABG, CCS angina class, NYHA class, left ventricular ejection fraction, Duke CAD Index, hemoglobin, mitral regurgitation, surgical treatment and CPB time.

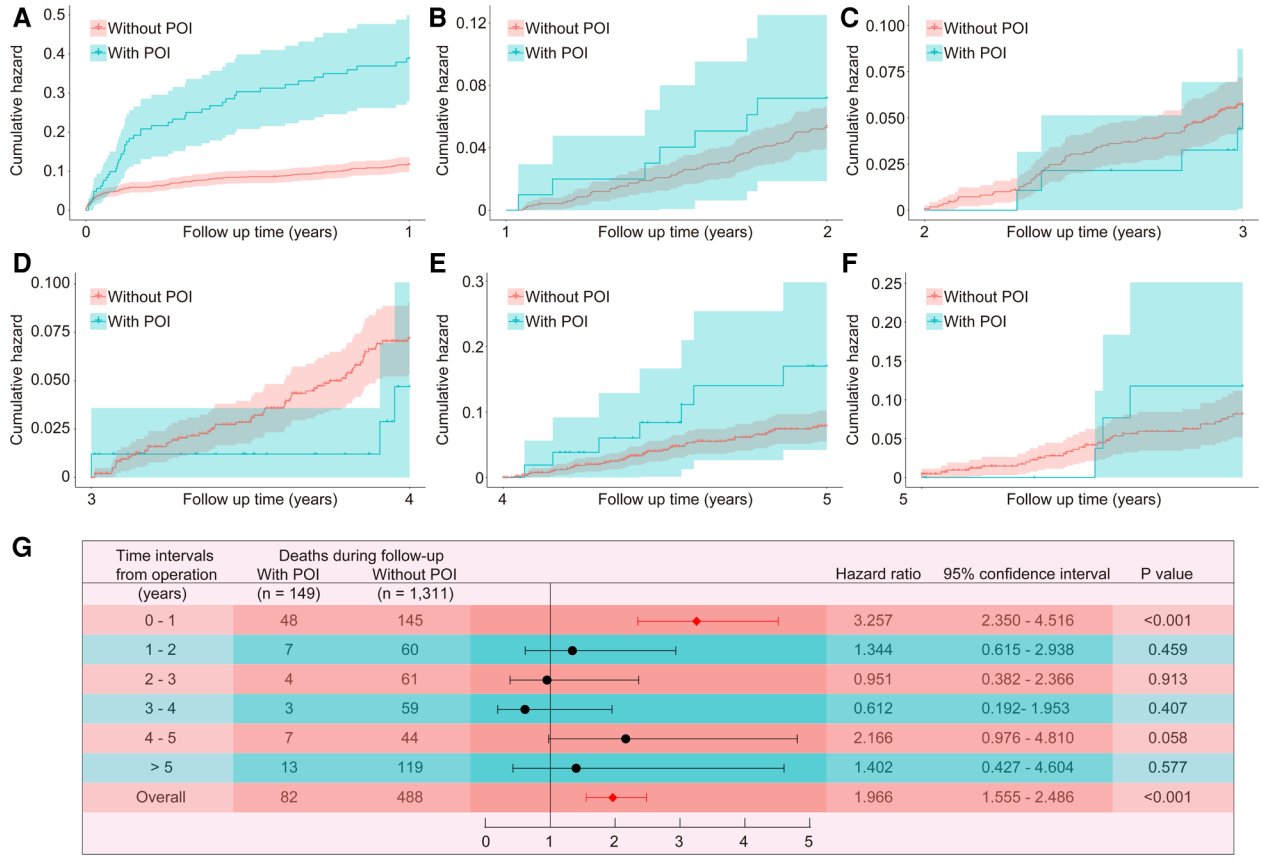

FIGURE 2
Temporal analysis of the effect of POI on all-cause death. The Kaplan-Meier estimated cumulative incidence of all-cause death during the follow-up year 0–1 (A), 1–2 (B), 2–3 (C), 3–4 (D), 4–5 (E), >5 (F), and time-varying hazard ratios (G) in patients with and without POI. POI, postoperative infection.

in patients undergoing CABG and valve surgery, finding that pneumonia was significantly associated with higher 90-day episode payments, longer postoperative length of stay, more frequent discharge to postacute care, and higher rates of 30-day mortality and 90-day readmission (26). Howitt and colleagues conducted a prospective study to assess the incidence and outcomes of sepsis in patients in a cardiac ICU after cardiac surgery, finding that sepsis with both suspected infection and proven infection were associated with increased length of ICU stay and higher 30-day mortality risk, and patients meeting the criteria for septic shock had significantly longer ICU stay, higher 30-day mortality and lower 2-year survival rate than those who suffered sepsis without septic shock (13). Kobayashi and colleagues conducted a multicenter retrospective case-controlled

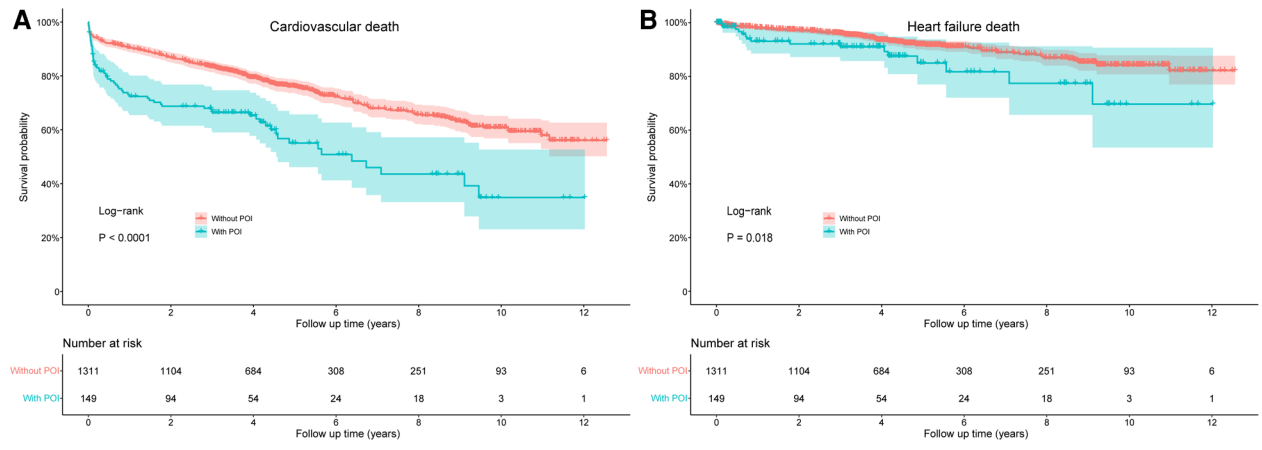

FIGURE 3
Comparison of cardiovascular death (A) and heart failure death (B) between patients with and without POI during follow-up. POI, postoperative infection.

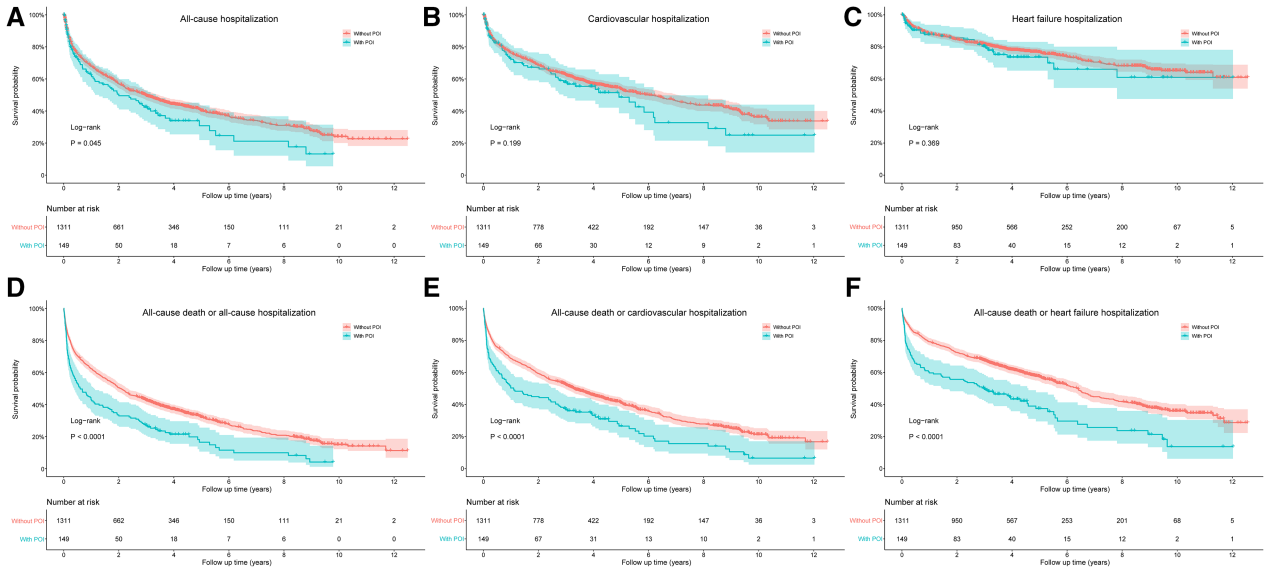

FIGURE 4
Comparison of all-cause hospitalization (**A**), cardiovascular hospitalization (**B**), heart failure hospitalization (**C**), all-cause death or all-cause hospitalization (**D**), all-cause death or cardiovascular hospitalization (**E**), and all-cause death or heart failure hospitalization (**F**) between patients with and without POI during follow-up. POI, postoperative infection.

study to examine the socioeconomic effects of surgical site infection after cardiovascular surgery, finding that patients with surgical site infection had significantly longer postoperative hospital stay and higher health care expenditure (13). Louis and colleagues also reported that mediastinal infection after cardiac operations was associated with substantial increases in length of stay, readmission and mortality (10).

Although the relationship between POI and short-term outcomes have been widely examined and reported, studies on the relationship between POI and long-term outcomes after cardiac surgery remains limited. In this study, we found that patients had significantly higher risks of all-cause death, cardiovascular death, HF death, all-cause hospitalization and composite endpoints in patients with POI during follow-up, which was consistent with the limited current literature (24). Roberto and colleagues recently conducted a study-level meta-analysis including 407,829 patients to evaluate the impact of deep sternal wound infection on short- and long-term clinical outcomes, finding that deep sternal wound infection was associated with longer postoperative hospitalization, higher risks of stroke, myocardial infarction, respiratory failure, renal failure, overall mortality, in-hospital mortality, and follow-up mortality during a mean follow-up of 3.5 years.

Another important finding in this study was that although the all-cause mortality was significantly increased in patients with POI during the whole follow-up, the impact of POI on the increased risk of death was mainly reflected in the first postoperative year and the impact was no longer significant during follow-up after the first year. This was similar to the results reported in previous studies (13). In the findings of Howitt and colleagues, although the overall 2-year survival rate was lower in patients with sepsis, the greatest difference in mortality was observed in the first 12 months after surgery and the difference between patients with and without sepsis was no longer statistically significant when only patients surviving more than a year were included in the analysis (13). This relatively short-term effect on risk was consistent with what has been observed in clinical practice, which may be due to the fact that the organ dysfunction that led to severe POI often progressed to organ failure in those had already been physiologically stressed by their operations and patients may recover from these critical complications or die within a relatively short period.

Although there have been many previous studies on POI after cardiac surgery, the current study was still unique and the findings may have potential implications for clinical practice and future research. To the best our knowledge, this was the first multicenter large-scale study that focused on POI after ischemic cardiomyopathy surgery worldwide, which identified the risk factors of POI and clarified its influence on short-term and long-term clinical outcomes. These findings may be helpful for individualized risk estimations, perioperative management and clinical decision-making, which may have certain guiding significance for clinical practice.

Limitations

Several limitations existed in the present study. First, as a *post hoc* analysis of the STICH/STICHES trial, only patients assigned to surgical treatment and undergoing surgical operations actually were included and analyzed in this study. Patients assigned to medical treatment but undergoing CABG eventually were not included, which may cause some information loss and influence the final analysis results. Second, some factors that may

significantly influence the development of POI were not collected and analyzed, such as blood transfusion and medication usage. Third, the 10-year follow-up was completed only in patients assigned to hypothesis 1, and the follow-up was not extended and ended at year 5 in patients assigned to hypothesis 2, which may produce a great deal of censored values and thus influence the analysis results. Fourth, the primary endpoint of this study was POI, which included all types of major infections after surgery; however, further classification of these infections and separate analysis of each type was not performed. Fifth, there has been some progress in medical technology and life support equipment these years, therefore, the impact of POI on prognosis may be different from what it is now due to the fact that the STICH/STICHES trial was conducted more than a decade ago. Sixth, the STICH/STICHES trial was conducted in multiple countries and centers and some centers may only perform very few surgeries, which may lead to significant heterogeneity among different centers, thereby affecting the generalizability of the study findings. Seventh, due to the *post hoc* nature of the analysis, this study cannot avoid the inherent limitations of this type of research and the influence of unknown potential confounding factors.

Conclusions

POI was prevalent after surgery for ischemic cardiomyopathy, closely associated with higher risks of poor short-term and long-term outcomes. The effect of POI on all-cause death was mainly reflected in the first postoperative year, and was no longer significant during follow-up one year later. Six significant predictors for POI was identified, including age, body mass index, depression, chronic renal insufficiency, Duke CAD Index, and mitral valve procedure. To our knowledge, this was the first report that clarified the relationship between POI and long-term prognosis and the predictors for POI after surgery for ischemic cardiomyopathy worldwide, which may have certain guiding significance for clinical practice.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://biolincc.nhlbi.nih.gov/.

Ethics statement

The studies involving humans were approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CL, BW and DW: conception and design. FX, FS and XD: administrative support, provision of study materials or patients. DW, YL and XH: collection and assembly of data. BW, DW and YL: data analysis and interpretation. 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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EDITED BY
Pierre-Gregoire Guinot,
Centre Hospitalier Regional Universitaire De Dijon, France

REVIEWED BY
Ömer Faruk Çiçek,
Selcuk University, Türkiye
Sirine Baltagi,
University of Texas Southwestern Medical Center, United States

*CORRESPONDENCE
M. Velten
markus.velten@ukbonn.de

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Case report: Perioperative management of a patient with shapiro syndrome during on-pump cardiac surgery

S. Boskovic[1], V. Ciobanu[2], N. Theuerkauf[1], F. Bakhtiary[2] and M. Velten[1]*

[1]Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany, [2]Department of Cardiac Surgery, University Hospital Bonn, Bonn, Germany

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Introduction

In 1969 Shapiro et al. described a specific triad, consisting of episodic hypothermia, hyperhidrosis, and corpus callosum agenesis (1). Less than 80 cases have been reported till today and the pathophysiological mechanism of this rare disorder remains to be elucidated. Hypothermic episodes differ in duration, frequency, and most important severity between patients. Current expert opinions on the topic involve a dysregulation of the hypothalamic body "thermostat". The initial drop from base line of 37°C (98.6°F) to a lower degree results in hyperhidrosis. Commonly, patients experience chills as the body temperature rises during recovery to regular body temperature (2). Other than the typical triad, a wide variety of different symptoms including headaches, hypoglycemia, or changes in blood counts have been reported (3–5).

Core body temperature is one of patient's vital signs that is closely monitored during anesthesia. Hypothermia, being defined as a core body temperature below 36°C (96.8°F), occurs in 20%–70% of all patients during surgical procedures, potentially leading to arrhythmias, blood clotting disturbances, changes in pharmacokinetics of drugs, and many more complications (6).

Herein, we report a case of a patient with known Shapiro syndrome, undergoing endoscopic aortic valve replacement for aortic stenosis.

Case report

A 59-year-old woman (59 kg, 163 cm) with severe aortic stenosis presented to the authors' institution for elective minimally invasive, endoscopic aortic valve replacement surgery. Cardiac assessment revealed a sclerotic aortic valve with a high-grade stenosis, a valve area of 0.55 cm^2, and peak velocity of 3.85 m/s, without regurgitation or dilatation of the ascendence aorta. Left ventricular function was preserved with an ejection fraction of 64% and a minimal mitral valve regurgitation was observed.

The Shapiro syndrome was diagnosed two years prior to the scheduled cardiac surgery as the patient experienced an episode of hypothermia with a reported body core temperature of 30.7°C (87.26°F) resulting in ventricular fibrillation and cardiac arrest that was treated by cardiopulmonary resuscitation (CPR). After recovery, the patient received an implantable

cardioverter-defibrillator (ICD Medtronic Miro VR) and a drug therapy with 200 mg clonidine daily was initiated as a prophylactic measure to which the patient responded well with no further occurrences of hypothermia since then. Going through detailed patients' medical history it was revealed that she had so called episodes of low body temperature all her life, sometimes as low as 29°C (84.2°F) with profuse sweating, vomiting, and diarrhea, followed by chills as the body temperature rose back to 37°C (98.6°F). She personally had contributed these episodes to psychological disturbances and did not seek medical advice. The diagnostic following CPR revealed an aortic valve stenosis of 1.1 cm^2. Neither the electrocardiogram (ECG), nor cardiac magnetic resonance imaging (MRI) revealed further pathologies. There were signs of a mild coronary artery disease, hypoplasia of the left vertebral artery, essential hypertension, and fibromyalgia. The brain MRI revealed a pathological contact between the acoustic nerve and a small blood vessel on the left side with no clinical correlation and no further pathological changes. Prior to surgery her body mass index was 22.2 with a body surface area of 1.63 m^2. There were no abnormalities in laboratory findings. The patient is a smoker and married.

She had progression of her aortic valve stenosis through regular close follow ups. Two years after the initial diagnosis the indication for an aortic valve replacement and decision for a minimally invasive surgery procedure were made.

As a precautionary measure the patient was placed on a full underbody air warming blanket (Mock) upon arrival in the operating room (OR) for potential perioperative temperature control if needed. Prior to induction of general anesthesia, the patients' body temperature was 37°C (98.6°F) and an arterial line (Vygon) was introduced for invasive blood pressure monitoring. Following general anesthesia induction with 100 µg remifentanil, 70 mg propofol, and 50 mg rocuronium the patient was intubated using a 7.5 mm [ID] endotracheal tube. Ultrasound guided internal jugular vein cannulated was performed, a four-lumen central venous line (Arrow) and a 9Fr sheath introducer (Arrow) were introduced, a urinary catheter with a temperature sensor (Resch) and a second rectal temperature probe (Resch TeleFlex) were placed for a more comprehensive temperature monitoring. Anesthesia was maintained using sevoflurane and a continuous infusion of remifentanil. Further monitoring consisted of ECG, capnography, peripheral oxygen saturation, central venous pressure, near-infrared spectroscopy (Medtronic), bispectrality index (Medtronic), and transesophageal echocardiography (GE Healthcare). The operating theater thermostat was set at 22°C (71.6°F), preventing temperature loss.

The procedure was started after pre-surgical TEE confirming of the diagnosis. Peripheral canulation was performed through the right femoral artery and vein. Bypass was initiated after TEE confirmation of venous canula positioning in the superior vena cava. Surgical approach to the aortic valve was through an anterolateral thoracotomy 6 cm in length. Before initiating CPB the patient's body temperature gradually reduced from 37°C (98.6°F) at the beginning of anesthesia induction to 36.8°C (98.24°F) over the course of 87 min and therefore no active warming was initiated. During CPB the patient was actively warmed through the by-pass machine (Stocking S5) to a body temperature of 37.0°C (98.96°F). During CPB the patient required high vasopressors dosages (up to 1.7 µg/kg/min noradrenalin and 4 U/h vasopressin) to establish a perfusion pressure above 65 mmHg. As prophylactic measure due to an anticipated strong systemic inflammatory response syndrome the patient received 100 mg of hydrocortisone and to shorten the ischemic and reperfusion time a biological, sutureless, self-expanding Percival Plus M size replacement aortic valve was implanted. The left atrial auricule was closed with a 35 mm AtriClip. Overall CBP time was 104 min with 59 min cross-clamp and 11 min reperfusion duration (Figure 1).

After the patient was weaned from cardiopulmonary bypass her hemodynamic state was gradually recovering, while she slightly cooled down and over the course of 45 min reached a body temperature of 36.7°C (98.06°F). Prior to the end of the surgery, the patient received 7 mg piritramide, 1,000 mg metamizole as postoperative analgesia, 50 µg clonidine and 4 mg ondansetron as postoperative nausea and vomiting prophylaxis, according to institutional standards. Following uncomplicated extubation, 17 min after suturing, the patient was transferred to the intensive care unit (ICU) on low dose noradrenalin (0.05 µg/kg/min) (Figure 1).

On the first evening after the surgery the patient started experiencing fevers peaking at 38.5°C (101.3°F) and therefore remained on ICU observation. Elevated body temperature continued on the second postoperative day and the patient experienced an asthma attack from which she quickly recovered. Other than flatulence the patient had no other complaints during the postoperative course and as her vital signs stabilized with body temperature normalizing, she was transferred to the ward on the fourth postoperative day. On the sixth postoperative day the patient was discharged to further outpatient care with a body temperature of 36.5°C (96.8°F) and without any complications. During her entire hospital stay the patient had no episodes of hypothermia (Figure 2).

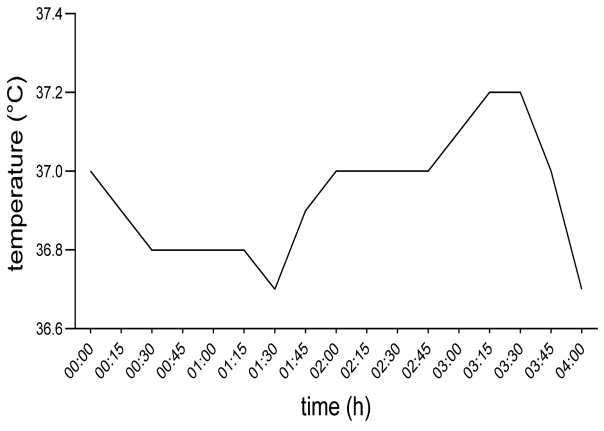

FIGURE 1
Body core temperature of the patient during surgery. 00:00 timestamp indicating the first measurement before inducing general anesthesia.

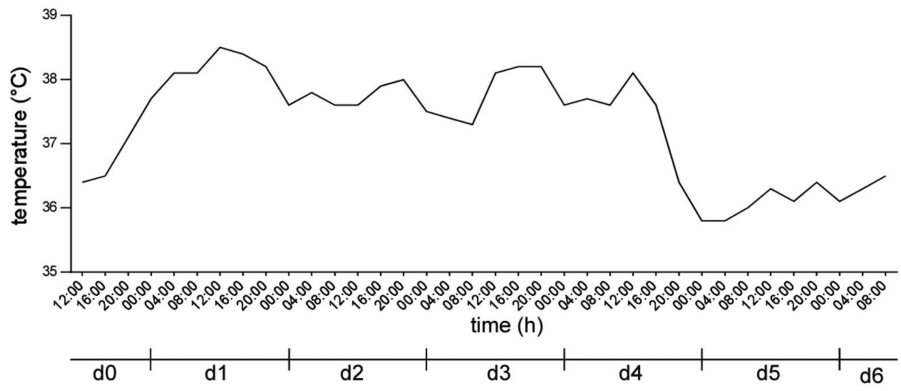

FIGURE 2
Body core temperature of the patient after surgery. d0 indicating the day of surgery, d1 to d6 indicating the first to sixth postoperative day.

At her scheduled 1 month and 3 months post-op follow-up the patient was feeling well and had no occurrences of hypothermia. Echocardiography showed a preserved ejection fraction of 64.1%, no evidence of paravalvular leakage and a good quality function of the implanted aortic valve with Vmax. of 2.3 m/s.

Discussion

Shapiro Syndrome is an extremely rare medical condition and through our extensive research of the available literature up until our case report there have only been 78 cases reported with just one during general anesthesia and none during cardiac surgery.

Our patient was diagnosed with Shapiro Syndrome after an incident of ventricular fibrillation and CPR. Atrial and ventricular dysrhythmias are a common life-threatening complication of hypothermia. In approximately 20,000 cases in the UK and 25,000 cases in the USA hypothermia was either the leading or an attributing cause of death annually (7, 8).

The typical triad of Shapiro Syndrome is episodic hypothermia, hyperhidrosis, and agenesis of corpus callosum. In the extensive diagnostics post cardiac arrest, our patient lacked the absence of corpus callosum agenesis, but 50% of all patients with Shapiro syndrome have no corpus callosum abnormalities, 40% have a complete agenesis, and 10% have other anatomical changes in the region. Her episodes of hypothermia were followed by gastrointestinal disturbances which occurs in around 14% of patients with Shapiro Syndrome (9).

Body temperature drops in Shapiro Syndrome patients are related to an disbalance between the anterior and posterior hypothalamus centers. The first being heat-dissipating and the second being heat conserving. There are various theories for this disbalance (degenerating, irritating, neurochemical, epileptical) but none are conclusive as to why the hypothalamus temperature set point is altered (10). General anesthesia damps thermoregulatory responses such as shivering or vasoconstriction caused by hypothermia and with non-shivering thermogenesis having little role in adults, patients become somewhat poikilothermic during surgery (11). Our case report showed that general anesthesia for cardiac surgery and CBP does not trigger hypothermic episodes in a Shapiro Syndrome patient.

An inflammatory response to CPB is well documented and increases in interleukin-6 have been reported (12). It is believed that this activation of the immune system is being generated as a result of its' contact with the artificial surface of the CPB machine, as well as genetic factors, which also play a major role (13, 14). Clinically, our high vasopressor dosage requirement during CPB potentially resulted from a strong inflammatory response during CPB and our patient was given glucocorticoids, with a good outcome and a fast reversal of vasoplegia, although their role in preventing or damping the inflammatory response during CBP remains questionable (15).

The anterolateral thoracotomy approach was chosen for our patient as newer studies have shown that the inflammatory response to CBP is lower in using this approach rather than median sternotomy (16). This approach is also linked to a shorter ICU and hospital stay, reduced infection rate and less blood loss (17). The cross-clamp time was shortened using a sutureless self-expanding prosthesis. Although self-expanding prosthesis are linked to a higher incident of postoperative permanent pace maker implantation, our patient already had an implanted ICD (18). Minimal invasive endoscopic aortic valve replacement is very suitable for middle-aged patients with preserved ejection fraction, which is the case regarding our patient (19).

Postoperative hyperthermia after surgery occurs in more than 25% of patients after major surgery which peaks at approximately 12 h after surgery and is associated with elevated levels of interleukin-6, which through inflammatory responses sets a new value of the thalamic thermostat set-point (20, 21). Our case report showed that patients suffering from Shapiro Syndrome react to inflammatory interleukins similar to what is described in the literature (20, 21) and that although the thalamic thermostat episodically sets to a new low point it is possible to be set to a new high point through inflammation.

Clonidine medication was not paused preoperatively, with the patient taking her medication as per usual on the morning of

surgery and continued immediately after surgery as well as the patient receiving a small dose of 50 µg clonidine prior to extubation. With such a rare disorder as Shapiro Syndrome there is an obvious lack of guidelines for treatment. Most commonly, patients are treated with cyproheptadine, clonidine, or carbamazepine. Patients treated with clonidine show either a full recovery with no new episodes of hypothermia or a drastic reduction of instances and duration of symptoms (2).

Up until our case report, to the best of our knowledge, there has been only one case of a patient with Shapiro Syndrome undergoing surgery and general anesthesia. The patients' body temperature regulation reacted similar to other patients undergoing the same surgical procedure (22).

Conclusion

This case report shows that Shapiro syndrome patients need to be closely monitored during the peri operative period, and investigate all the options to support the temperature homeostasis. Our case demonstrates this is doable and successful through close monitoring. More studies are needed though to understand temperature homeostasis.

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

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

Author contributions

VC, FB, and MV were in charge of the peri- operative strategy, discussed it with the patient, and obtained informed consent. SB, VC, and MV managed the intraoperative period. NT, FB, and VC managed the ICU treatment. SB collected all clinical data. SB, FB, and MV drafted the manuscript. SB, VC, NT, FB, and MV read, corrected, and approved the final version. All authors contributed to the article and approved the submitted version.

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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EDITED BY
Cristina Barbero,
A.O.U. City of Health and Science of Turin, Italy

REVIEWED BY
Paul Philipp Heinisch,
German Heart, Germany
Heidi J. Dalton,
Inova Health System, United States

*CORRESPONDENCE
Wei Wang
wangwei@scmc.com.cn

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Risk factors of gastrointestinal bleeding after cardiopulmonary bypass in children: a retrospective study

Zheng-Qing Li, Wei Zhang, Zheng Guo, Xin-Wei Du and Wei Wang*

Department of Cardiothoracic Surgery, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: During cardiac surgery that involved cardiopulmonary bypass (CPB) procedure, gastrointestinal (GI) system was known to be vulnerable to complications such as GI bleeding. Our study aimed to determine the incidence and risk factors associated with GI bleeding in children who received CPB as part of cardiac surgery.
Methods: This retrospective study enrolled patients aged <18 years who underwent cardiac surgery with CPB from 2013 to 2019 at Shanghai Children's Medical Center. The primary outcome was the incidence of postoperative GI bleeding in children, and the associated risk factors with postoperative GI bleeding episodes were evaluated.
Results: A total of 21,893 children who underwent cardiac surgery with CPB from 2013 to 2019 were included in this study. For age distribution, 636 (2.9%) were neonates, 10,984 (50.2%) were infants, and 10,273 (46.9%) were children. Among the 410 (1.9%) patients with GI bleeding, 345 (84.2%) survived to hospital discharge. Incidence of GI bleeding in neonates, infants and children were 22.6% (144/636), 2.0% (217/10,984) and 0.5% (49/10,273), respectively. The neonates (22.6%) group was associated with highest risk of GI bleeding. Patients with GI bleeding showed longer length of hospital stays (25.8 ± 15.9 vs. 12.5 ± 8.9, $P < 0.001$) and higher mortality (15.9% vs. 1.8%, $P < 0.001$). Multivariate logistic regression analysis showed that age, weight, complicated surgery, operation time, use of extracorporeal membrane oxygenation (ECMO), low cardiac output syndrome (LCOS), hepatic injury, artery lactate level, and postoperative platelet counts were significantly associated with increased risk of GI bleeding in children with congenital heart disease (CHD) pediatric patients that underwent CPB procedure during cardiac surgery.
Conclusion: The study results suggest that young age, low weight, long operation time, complicated surgery, use of ECMO, LCOS, hepatic injury, high arterial lactate level, and low postoperative platelet counts are independently associated with GI bleeding after CPB in children.

KEYWORDS

congenital heart disease, cardiopulmonary bypass, children, gastrointestinal bleeding, risk factors

1. Introduction

In data from previous studies, 6–9 of every 1,000 newborns were diagnosed with different forms of congenital heart disease (CHD), in which majority require surgical correction during childhood (1, 2). The gastrointestinal (GI) system is most vulnerable to complications (i.e., GI bleeding) after cardiac surgery due to low abdominal perfusion

after prolonged ischemia (3, 4). Despite advanced improvements in CPB techniques, anesthesia procedure, and intensive care support, GI bleeding remains a serious complication after cardiopulmonary bypass (CPB), with incident rate ranging from 0.2% to 2%, with a significantly high mortality rate observed between 8.8% and 19.0% (3–13). Despite the apparent association in between postoperative GI bleeding with length of intensive care unit stays and increased morbidity, risk factors associated with GI bleeding after CPB in children remains unclear (14–17).

Our study aimed to determine risk factors of GI bleeding after CPB in children aged <18 years. We extensively collected potential preexisted factors and variables during whole course of hospitalization. By identifying potential risk factors, this might help surgeons to deploy preventive measures for high-risk patients and enhance early recognition of postoperative GI bleeding, thus improving prognostic outcomes in this cardiovascular surgical population.

2. Methods

2.1. Patient and study design

This retrospective study was carried out and approved by the Ethical Committee of Shanghai Children's Medical Center. Medical files of all patients who underwent cardiac surgery with CPB from January 2013 to December 2019 were collected from database and analyzed. Inclusion criteria refers to patients <18 years of age who underwent cardiac surgery with CPB. Condition such as cardiac surgery without CPB procedures, incomplete medical records or GI bleeding occurs within 30 days prior to cardiac surgery were excluded. Variables investigated in the study include the preexisted demographic data, laboratory test data, and surgical related variables. All these study data were obtained from electronic medical record system of Shanghai Children's Medical Center. This study was approved by the Ethical Committee of Shanghai Children's Medical Center.

2.2. Definition and variables

We retrospectively reviewed 21,893 consecutive cardiac surgery patients. Cardiac surgical procedure refers to any cardiac or intrathoracic great vessel procedure. GI bleeding refers to hemorrhage from the upper or lower GI tract. The clinical presentation of GI bleeding varies according to severity and localization of bleeding. Definition of GI bleeding refers to a positive occult blood test (OB) results in specimen including feces or gastric juice.

The following data were recorded for each cardiac surgical procedure: patient demographics [age, gender, premature birth (birth <37 weeks)], operative procedure, CPB time (minutes), temperature of CPB, perfusion mode of CPB, and postoperative factors [(length of hospital stay, length of mechanical ventilation, use of renal replacement therapy, and use of ECMO, postoperative ejection fraction, postoperative dialysis, postoperative lactate, postoperative hepatic function (ALT and AST), postoperative platelet, and survival to hospital discharge (%)]. Patients' age was classified into three categories: neonates (<28 days), infants (29 days to 1 year), and children (1–18 years). Operative procedure risk stratification was categorized using the Risk Adjusted Classification for Congenital Heart Surgery (RACHS-1), and RACHS-1 scoring 3–6 was defined as complicated surgery. In our study, hepatic injury was defined as detection of ALT $\geq$ 80 U/L and/or AST $\geq$ 80 U/L in 30 days after surgery. Low cardiac output syndrome (LCOS) refers to a decrease in cardiac output that is due to myocardial dysfunction. Diagnostic criteria for LCOS: Cardiac output index (CI) <2.5 $L{\cdot}min^{-1}{\cdot}m^{-2}$.

2.3. Statistical analysis

All statistical analyses were performed using SPSS 22.0. The measurement data were expressed by mean ± standard deviation ($\bar{x} \pm s$), the mean between the two groups was compared by Mann-Whitney *U*-test, the count data were expressed by the number of cases (constituent ratio), and the comparison between groups was expressed by the χ^2 test. Logistic regression analysis was applied to assess the association between potential risk factors and GI bleeding after cardiopulmonary bypass. A *P* value of 0.05 was considered statistical significant. Based on the risk factors obtained from the multivariate logistic analysis, the Receiver Operating Characteristic Curve (ROC) were plotted for each risk factor to predict GI bleeding after CPB in Children. Risk prediction models were developed, column line plots were generated using R software package. The discriminative ability of nomograms was evaluated by ROC curve and Area under the Curve (AUC).

3. Results

3.1. Patient characteristics

A total of 21,893 children who underwent cardiac surgery with cardiac pulmonary bypass from January 1 2013 to December 31 2019 were included in this study. At the time of operation, 636 (2.9%) were neonates, 10,984 (50.2%) were infants, and 10,273 (46.9%) were children. Of 21,893 children, 410 (1.9%) developed GI bleeding as a post-operative complication. Regarding outcomes of patients with GI bleeding, 65 patients (15.9%) died during their hospital stay, while 345 patients (84.1%) survived to hospital discharge. The incidence of GI bleeding in neonates, infants and children were 22.6% (144/636), 2.0% (217/10,984) and 0.5% (49/10,273), respectively. As shown in **Table 1**, in the non-GI bleeding group, the top 5 congenital heart diseases were ventricular septal defect (44%), atrial septal defect (10.5%), tetralogy of Fallot (8.3%), double outlet of right ventricle (3.6%) and atrioventricular septal defect (3.3%). While in the GI bleeding group, the top 5 congenital heart diseases were

TABLE 1 Preoperative diagnosis of congenital heart diseases in patients with GI bleeding or without GI bleeding.

	GI bleeding ($n = 410$)	NO GI bleeding ($n = 21,483$)
VSD	41 (10.0%)	9,453 (44.0%)
ASD	0 (0.0%)	2,246 (10.5%)
TOF	19 (4.6%)	1,790 (8.3%)
DORV	22 (5.4%)	763 (3.6%)
AVSD	11 (2.7%)	713 (3.3%)
APVC	34 (8.3%)	667 (3.1%)
CoA	104 (25.4%)	575 (2.7%)
TGA	61 (14.9%)	577 (2.7%)
PA	25 (6.1%)	610 (2.8%)
PS	14 (3.4%)	433 (2%)
TVD	2 (0.5%)	446 (2.1%)
MVD	11 (2.7%)	432 (2.0%)
SV	13 (3.2%)	332 (1.5%)
CAD	13 (3.2%)	188 (0.9%)
SRVOT	1 (0.2%)	157 (0.7%)
SLVOT	2 (0.5%)	124 (0.6%)
PTA	11 (2.7%)	75 (0.3%)
CT	2 (0.5%)	69 (0.3%)
PVS	7 (1.7%)	52 (0.2%)
PAS	1 (0.2%)	57 (0.3%)
HLHS	2 (0.5%)	4 (0.0%)
Others	14 (3.4%)	1,720 (8%)

Abbreviations related to the diagnosis of congenital heart diseases are shown in Supplementary Table S1.

coarctation of aorta (25.4%), transposition of great arteries (14.9%), ventricular septal defect (10.0%), anomalous pulmonary venous connection (8.3%) and pulmonary atresia (6.1%). There are statistical differences in length of hospital stay and discharge status between different age groups with GI bleeding or no GI bleeding (Table 2). Patients with GI bleeding after CPB was associated with higher mortality (15.9% vs. 1.8%) compared to non-GI bleeding patients. The overall 30-day mortality rate was 2.0% (443/21,893).

TABLE 2 Hospital stay and discharge status comparison between GI bleeding or without GI bleeding in different age group.

	GI bleeding	NO GI bleeding	*P* value
Neonate			
Number	144 (22.6%)	492 (77.4%)	
Hospital stay (days)	26.0 ± 16.1	18.5 ± 10.2	<0.001
Discharge status			0.165
Death	14 (9.7%)	71 (14.4%)	
Live	130 (90.3%)	421 (85.6%)	
Infant			
Number	217 (2.0%)	10,767 (98.0%)	
Hospital stay (days)	24.2 ± 15.1	13.3 ± 8.3	<0.001
Discharge status			<0.001
Death	42 (19.4%)	193 (1.8%)	
Live	175 (80.6%)	10,574 (98.2%)	
Child/adolescent			
Number	49 (0.5%)	10,224 (99.5%)	
Hospital stay (days)	32.0 ± 17.7	11.4 ± 9.3	<0.001
Discharge status			<0.001
Death	9 (18.4%)	113 (1.1%)	
Live	40 (81.6%)	10,111 (98.9%)	

3.2. Univariate analysis for GI bleeding

To analysis independent variables and features associated with GI bleeding after CPB, all enrolled patients were categorized into GI bleeding group ($n = 410$) and non-GI bleeding group ($n = 21,483$) based on the post-operative occult blood test results. In consideration of pathophysiology of GI bleeding, types of surgical procedures and findings interpreted from preexisted studies, a series of preoperative, intraoperative and postoperative variables were compared between the two groups.

Results of univariate analysis for GI bleeding after CPB were shown in Table 3. In this CPB cohort (21,893 children), 410 (1.9%) had postoperative GI bleeding. In regards of demographic and clinical variables, patients with GI bleeding were of younger age (278.6 ± 712.1 vs. 720.0 ± 931.6 days, $P < 0.001$) and lower weight. Incidence of preterm birth was more prevalent in the GI-bleeding group, nearly five times (5.4% vs. 1.1% $P < 0.001$) higher than non-GI-bleeding group. Pre-operative assessment such as surgical options (radical or palliative) and RACHS-1 category that largely depends on CHD diagnosis, were significantly different between the two groups. During operation, patients with GI bleeding has longer CPB time (131.8 ± 87.2 vs. 68.8 ± 46.4, $P < 0.001$), aortic cross-clamp time (73.9 ± 40.3 vs. 39.5 ± 38.6 $P < 0.001$) and operation time (252.9 ± 110.9 vs. 151.8 ± 65.0 $P < 0.001$).

As to postoperative platelet counts, patients with GI bleeding had lower level of platelet counts (87.5 ± 64.1 vs. 187.2 ± 73.2, $P = 0.012$). Postoperative artery lactate level was higher in patients with GI bleeding compared with those who did not develop GI bleeding (2.72 ± 2.4 vs. 1.2 ± 2.8, $P < 0.001$).

Overall, patients with GI bleeding had longer hospital stays (25.8 ± 15.9 vs. 12.5 ± 8.9, $P < 0.001$) and intensive care unit (ICU) stays (11.8 ± 13.3 vs. 6.4 ± 63.0, $P < 0.001$). Mortality rate was significantly higher among patients with GI bleeding compared with those who did not develop GI bleeding (15.9% vs. 1.8%, $P < 0.001$).

3.3. Multivariate logistic regression analysis of risk factors

The results of multivariate analysis of risk factors for GI bleeding after CPB in children were shown in Table 4 Multivariate analysis showed that the operation time [95% confidence interval (CI): 1–1.004; $P = 0.01$], age (95% CI: 0.999–1.000; $P < 0.001$), complicated surgery (95% CI: 2.304–5.211; $P < 0.001$), weight (95% CI: 0.912–0.988; $P = 0.011$), low cardiac output syndrome (LCOS) (95% CI: 2.203–3.945 $P < 0.001$), use of ECMO (95% CI: 2.736–9.508; $P < 0.001$), hepatic injury (95% CI: 1.05–2.257 $P = 0.027$), artery lactate level (95% CI: 1.194–1.426; $P < 0.001$), and postoperative platelet counts (95% CI: 0.989–0.994; $P < 0.001$) were associated with GI bleeding in CHD children with CPB.

TABLE 3 Univariate analysis for gastrointestinal bleeding after cardiopulmonary bypass in children.

	GI bleeding ($n = 410$)	NO GI bleeding ($n = 21,483$)	*P* value
Pre-operative variables			
Age (days)	278.6 ± 712.1	720.0 ± 931.6	<0.001
Age group			
Neonate	144 (35.1%)	492 (2.3%)	<0.001
Infant	217 (52.9%)	10,767 (50.1%)	
Child/adolescent	49 (12.0%)	10,224 (47.6%)	
Gender			0.002
Male	258 (62.9%)	11,887 (55.3%)	
Female	152 (37.1%)	9,596 (44.7%)	
Premature birth (<37 weeks)			<0.001
Yes	22 (5.4%)	227 (1.1%)	
No	388 (94.6%)	21,256 (98.9%)	
Weight (kg)	5.1 ± 6.1	9.5 ± 8.1	<0.001
Pre-operative SpO_2	88.5 ± 11.5	95.3 ± 18.7	<0.001
Intra-operative variables			
Surgical options			<0.001
Radical surgery	331 (80.7%)	19,519 (90.9%)	
Palliative surgery	79 (19.3%)	1,964 (9.1%)	
RACHS-1 category			<0.001
1–2	57 (13.9%)	6,808 (31.7%)	
3–6	353 (86.1%)	14,675 (68.3%)	
Operation time (min)	252.9 ± 110.9	151.8 ± 65.0	<0.001
CPB mode			<0.001
Parallel	24 (5.9%)	1,008 (4.7%)	
Circulatory arrest	39 (9.5%)	193 (0.9%)	
Selective cerebral perfusion	55 (13.4%)	393 (1.8%)	
Full-flow extracorporeal circulation	292 (71.2%)	19,889 (91.1%)	
CPB temperature			<0.001
Normothermic	72 (17.6%)	11,106 (51.7%)	
Mild hypothermia	152 (37.1%)	8,250 (37.8%)	
Moderate hypothermia	137 (33.4%)	1,838 (8.6%)	
Deep hypothermia	49 (12.0%)	289 (1.3%)	
CPB time (min)	131.8 ± 87.2	68.8 ± 46.4	<0.001
Aortic cross-clamp time (min)	73.9 ± 40.3	39.5 ± 38.6	<0.001
Postoperative variables			
Hepatic injury			<0.001
Yes	73 (17.8%)	366 (1.7%)	
No	337 (82.2%)	21,117 (98.3%)	
Post-operative ECMO			<0.001
Yes	42 (10.3%)	36 (0.2%)	
No	368 (89.7%)	21,447 (99.8%)	
LCOS			<0.001
Yes	230 (56.1%)	1,927 (9.0%)	
No	180 (43.9%)	19,556 (91.0%)	
Ventilation time (min)	278.8 ± 233.0	83.3 ± 154.0	<0.001
Postoperative platelet (10^9/L)	87.5 ± 64.1	187.2 ± 73.2	0.012
Artery lactate level (mmol/L)	2.72 ± 2.4	1.2 ± 2.8	<0.001
ICU stay (days)	11.8 ± 13.3	6.4 ± 63.0	<0.001
Hospital stay (days)	25.8 ± 15.9	12.5 ± 8.9	<0.001
Discharge status			<0.001
Death	65 (15.9%)	378 (1.8%)	
Live	345 (84.1%)	21,105 (98.2%)	

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; ICU, intensive care unit; LCOS, low cardiac output syndrome; RACHS-1, risk adjustment for congenital heart surgery-1.

TABLE 4 Multivariate logistic regression analysis of risk factors for gastrointestinal bleeding after cardiopulmonary bypass in children.

	P value	Odds ratio	95% CI
Operation time (min)	0.01	1.002	1.000–1.004
Age (days)	<0.001	0.999	0.999–1.000
RACHS-1 category	<0.001	3.465	2.304–5.211
Weight (kg)	0.011	0.95	0.912–0.988
LCOS	<0.001	2.948	2.203–3.945
Hepatic injury	0.027	1.54	1.05–2.257
Artery lactate level (mmol/L)	<0.001	1.305	1.194–1.426
Postoperative platelet (10^9/L)	<0.001	0.992	0.989–0.994
Postoperative ECMO	<0.001	5.1	2.736–9.508

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; LCOS, low cardiac output syndrome; RACHS-1, risk adjustment for congenital heart surgery-1.

3.4. ROC curve of independent risk factor predicting GI bleeding

The independent risk factors obtained from the multivariate logistic analysis are further visually presented through ROC curves (Figure 1). Incidence prediction of gastrointestinal bleeding based on ROC analysis of age, operation time, RACHS-1 category, weight, LCOS, hepatic injury, artery lactate level, postoperative platelet and postoperative ECMO. The area under the curve of ROC predicting GI bleeding risk after cardiopulmonary bypass in children. Table 5 displays the specific details of each ROC curve.

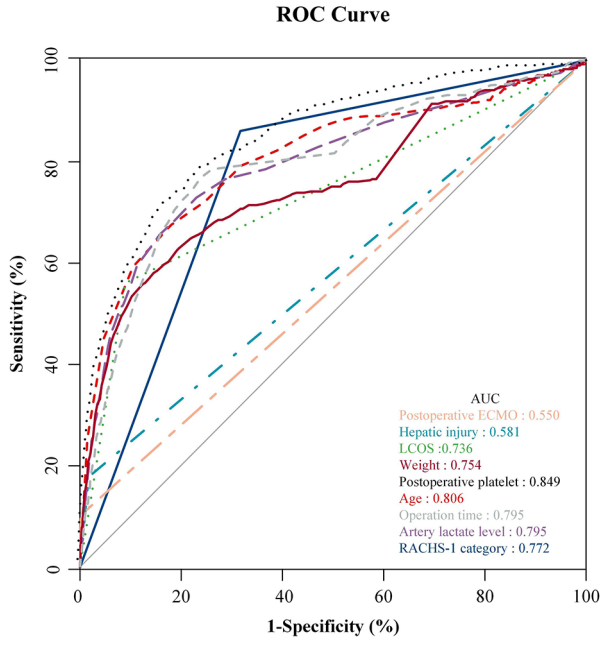

FIGURE 1
Incidence prediction of GI bleeding based on ROC analysis of age, operation time, RACHS-1 category, weight, LCOS, hepatic injury, artery lactate level, postoperative platelet and postoperative ECMO. The area under the curve of ROC predicting GI bleeding risk after CPB in children.

TABLE 5 Details of the ROC curves analysis.

	Area under the curve	Sensitivity (%)	Specificity (%)	Youden index (%)	*P* value	95% CI		Best cut-off value
Postoperative ECMO	0.55	10.2	99.8	10.1	<0.001	0.52	0.581	/
Hepatic injury	0.581	17.8	98.3	16.1	<0.001	0.549	0.612	/
LCOS	0.736	56.1	91.0	47.1	<0.001	0.706	0.765	/
Weight (kg)	0.754	58.0	85.5	43.5	<0.001	0.726	0.782	5.35
RACHS-1 category	0.772	86.1	68.3	54.4	<0.001	0.752	0.792	/
Artery lactate level (mmol/L)	0.795	72.9	77.0	49.9	<0.001	0.769	0.821	1.35
Operation time (min)	0.795	76.8	76.2	53.0	<0.001	0.77	0.82	164
Age (years)	0.808	67.6	82.0	49.5	<0.001	0.782	0.834	0.35
Postoperative platelet (10^9/L)	0.849	72.0	83.2	55.1	<0.001	0.829	0.868	111.5

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; LCOS, low cardiac output syndrome; RACHS-1, risk adjustment for congenital heart surgery-1.

3.5. Nomograms predicting GI bleeding risk after cardiopulmonary bypass in children

Probability of GI bleeding after CPB in children can be estimated with the nomograms (Figure 2). In order to predict GI bleeding risk after CPB in children with congenital heart disease, each parameter has a corresponding score on the point axis, and the sum of the scores is plotted on the "total point" axis. The probability of GI bleeding risk after cardiopulmonary bypass in children is the value at a vertical line from corresponding total points. As shown in Figure 3, the area under the ROC curve of the nomograms prediction model for GI bleeding was 0.898 (95% CI: 0.884–0.914, $P < 0.001$), with a sensitivity of 80.9% and specificity of 84.2%.

4. Discussion

CHD has gradually turned into the most common congenital defect, in which majority situation require cardiac surgery correction with cardiopulmonary bypass. The ultimate goal of CPB is to maintain sufficient tissue perfusion of all organs and tissues, but it is difficult to fully simulate normal blood circulation and pulsation processes. During this period, due to the redistribution of blood perfusion, blood flow is redistributed and its pathophysiological changes are similar to those observed in shock patients (18–21). Cardiopulmonary bypass give priority to guarantee effective blood supply to the brain and other important organs, which in turn leading to progressive reduction in gastrointestinal mucosa blood flow. GI bleeding after CPB is an unusual fatal event. GI bleeding was found to occur after 0.2%–2% of cardiac surgery cases with CPB and was associated with high mortality rates (8.8%–19.0%) (3–13). In our study, the observed GI bleeding incidence rate was 1.9% (410/21,893), which was similar to that reported in preexisted literature. The mortality rate in this series, 15.9%, well agreed with those previously reported (3–13). We observed a nine-fold increase in mortality risk (15.9% vs. 1.8%, $P < 0.001$) and a significantly longer hospital stay (26.0 ± 15.9 vs. 12.5 ± 8.9, $P < 0.001$) in

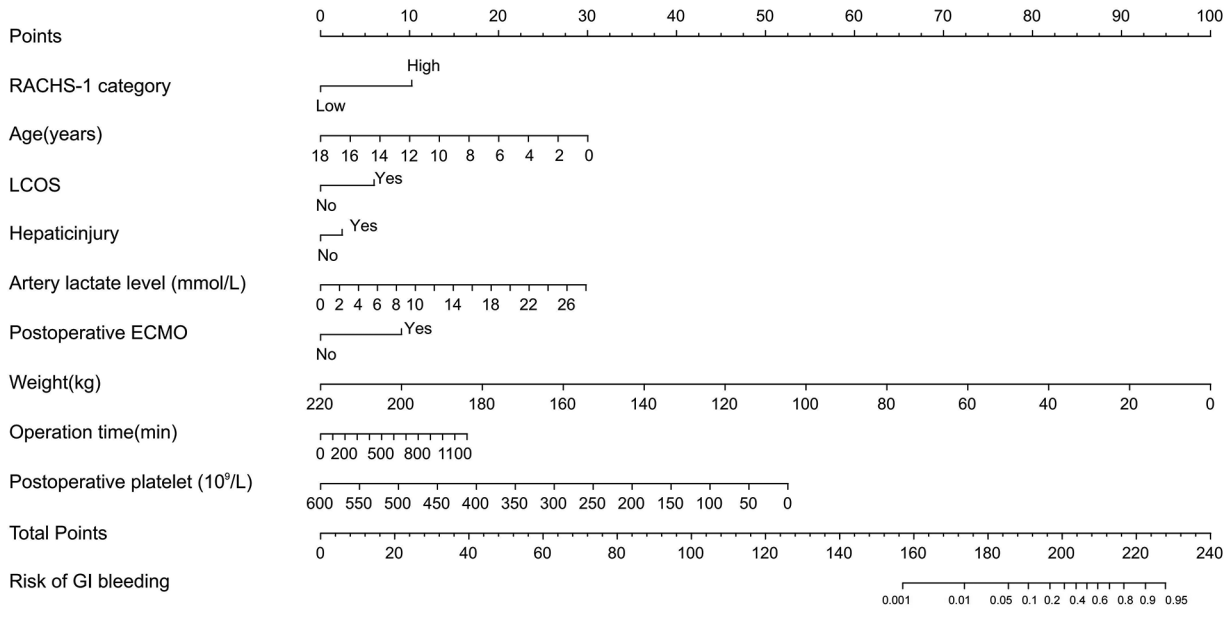

FIGURE 2
Nomograms predicting GI bleeding risk after cardiopulmonary bypass in children.

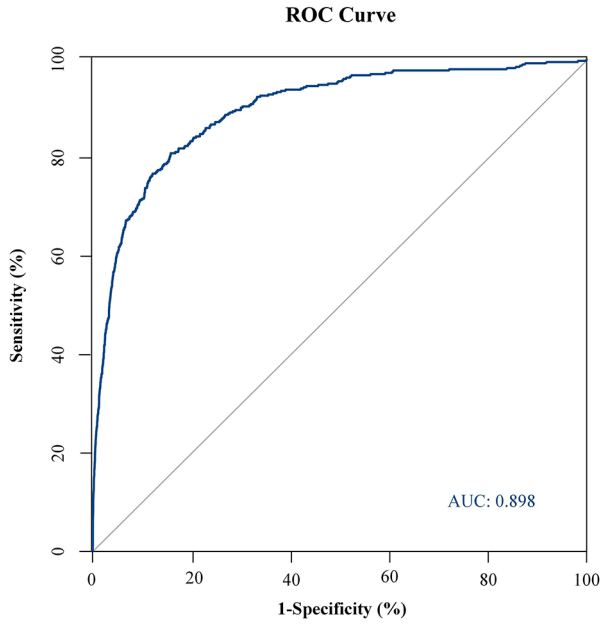

FIGURE 3
ROC curve of GI bleeding risk prediction model. The area under the ROC curve of the nomogram prediction model for GI bleeding was 0.898 (95% CI: 0.884–0.914, $P < 0.001$), with a sensitivity of 80.9% and specificity of 84.2%.

patients with postoperative GI bleeding. Generally, children undergoing congenital heart surgery were confronted with increased risk of GI complications than adults (22, 23). Frequent monitoring for symptoms and related clinical indicators in these high-risk patients are necessary. Due to the absence of typical clinical signs or masking by signs of other more common complications, GI bleeding demands early clinical recognition so to secure favorable outcomes.

In this large cohort study, we aimed to identify potential risk factor of GI bleeding after CPB by multivariate logistic regression model. Clinical, laboratory and surgical variables during perioperative period were considered. Increased surgical complexity (OR = 3.465, $P < 0.001$) was one of the independent risk factor for GI bleeding. We also observed significant longer CPB time and aortic cross-clamp time in the GI-bleeding group, however multivariate analysis failed to prove its association with GI complication (not shown in table). In earlier studies, CPB time and aortic cross-clamp durations were widely suggested as influential factors of abdominal perfusion. Some evidences pointed out that splanchnic perfusion during CPB procedure might led to inadequate metabolic supply that further enhance GI complications. As reported by Andersson et al. (24), CPB procedure exceeding 150 min was one of the independent factors for predicting GI complications after cardiac surgery. In another prospective study, patients who received CPB longer than 100 min showed significant increase in gut permeability and gut impairment (25). Others conclude the associated risk of cardiopulmonary bypass time on intestinal ischemia damage by measuring biomarkers (26). Though ample evidences mentioned longer CPB time as risk factor of GI complication. However, most of these evidences focus on outcomes such as intestinal ischemic damages but not solely gastrointestinal bleeding. In other words, we cannot fully agree the independent role of extracorporeal circulation variables (such as CPB and aortic cross-clamp duration) in GI bleeding.

In our circulation system, GI system account to 20%–25% of the body's cardiac output and provide 20% of the oxygen supply in adult. Pathogenesis of GI complication could be multifactorial, while major contributing mechanisms during cardiac surgery is reduced systemic blood flow, which leads to insufficient oxygen delivery and energy deficit. Our study findings suggest that a LCOS (95% CI: 2.203–3.945, $P < 0.001$) after surgery is associated with GI bleeding. LCOS was a common postoperative complication, occurring in 9.9% (2,157/21,893) of the patients in this study in the first 24 h after surgery and we observed increased mortality of 6.4% (139/2,157) in this particular subgroup (not shown in table).

In our results, there was a statistical difference in pre-operative SpO_2 between the bleeding and non-bleeding groups (88.5 ± 11.5 vs. 95.3 ± 18.7, $P < 0.001$), but SpO_2 was not a risk factor after multivariate analysis. In our analysis of preoperative diagnosis (**Table 1**), the proportion of TOF in the bleeding group and the non-pulmonary bleeding group was (4.6% vs. 8.3%), respectively. Most congenital heart conditions in cyanotic CHD are complex congenital heart conditions. There are few studies of hypoxia tolerance between cyanotic and acyanotic CHD, and we need to further explore the relationship between them (27, 28). Recently, it has been suggested that cyanotic patients with CHD are characterized by increased arterial stiffness, expressed as a worse vasodilator response (29).

Among all organs, the gut is extremely vulnerable to ischemic injuries during postoperative LCOS because the splanchnic circulation is susceptible to endogenous and exogenous catecholamines. Immobilization, administration of high doses of opioid drugs, and delayed or absent enteral alimentation can aggravate the adverse effects of intraoperative mucosal damage caused by on pump surgery (30, 31). More importantly, prolonged and severe hypoperfusion might result in insufficient splanchnic blood flow. Pathophysiological events include uneven blood flow distribution, oxygen supply abnormalities, oxygen demand imbalance, and systemic inflammation (25, 32). Consequently, impairment of intestinal barrier integrity gradually results in translocation of bacteria and toxins, systemic inflammatory response syndrome and finally remote organ injury. We showed that the GI bleeding following cardiac surgery was common in neonates but rare in children. This may cause by neonates likelier to have LCOS and the sensitivity of neonatal gastrointestinal (33). In our study, we found patients with GI bleeding were younger than non-GI bleeding cases (278.6 ± 712.1 vs. 712.0 ± 931.6). Multivariate logistic regression analysis suggested that a younger age is closely associated with a higher incidence of GI bleeding. Our present series showed an incidence of postoperative GI bleeding of 22.6% (144/636) in neonates, 2.0% (217/10,984) in infants, and 0.5% (49/10,273) in children, which are similar to results reported in earlier literature. As in neonates, low body weight possess increased risk in development

of GI bleeding, particularly necrotizing enterocolitis (NEC) (33, 34). Low body weight usually indicates preterm with organ immaturity. Poor visceral regulation to hypoperfusion changes might be the underlined mechanism.

The splanchnic circulation plays an important role during hypovolemia and possess several regulation mechanisms. For instance, splanchnic vasoconstriction stimulated by catecholamine and renin-angiotensin help compensate systemic circulation by increasing total systemic vascular resistance and auto-transfusion (35). Splanchnic hypoperfusion also ensure vital organ perfusion. In this situation, splanchnic flow respond slow to reperfusion even when systemic flow was restored. In more vulnerable patients, persistent hypoperfusion might result to splanchnic ischemia and visceral organ injuries such as GI bleeding. Physically, intestinal villous structure is highly sensitive to ischemia. During perfusion, arterial inflow enters from the base of intestinal villous which result in lower oxygen partial pressure at the tip. However, the high metabolic rate and oxygen demand observed at the tip make it incompatible to ischemia (35, 36).

Another important mechanism is the negative consequences of nonpulsatile blood flow during ischemia (32, 37). Earlier study pointed out that nonpulsatile blood flow as a determinant for renin release, activation of the renin–angiotensin–aldosterone axis and secretion of angiotensin II (38). Hypothermia is also associated with vasoconstriction and altered regional blood flow and distribution. Routine post-operative vasoactive drugs such as noradrenaline and vasopressin are also associated with splanchnic hypoperfusion.

Spotnitz et al. (39) first mentioned the importance of prolonged mechanical ventilation as an indeterminate risk factor for GI complications following cardiac surgery. D'Ancona et al. (7) reemphasized the significance of prolonged postoperative mechanical ventilation on GI bleeding and confirmed as an independent predictor based on multivariate analysis. Other studies have also observed prolonged ventilation as a risk factor during CPB surgery (8, 9, 13, 40, 41). Patients receiving mechanical ventilation often present signs of sympathetic nervous system activation and decreased cardiac output (42), which further contribute to splanchnic hypoperfusion and the injury of gastrointestinal mucosa. Elizalde et al. (43) have clarified the relationship of gastric mucosal ischemia and mechanically ventilated patients in the ICU. Nevertheless, it is reasonable to speculate that mechanical ventilation may enhance the adverse effects of critical illness on GI pathology. Similarly, our study showed a statistical difference in the length of mechanical ventilation between the GI-bleeding group and the non-GI bleeding group (278.8 ± 233.0 vs. 83.3 ± 154.0). However, multivariate analysis verified that long-term mechanical ventilation is not an independent risk factor for GI bleeding ($P = 0.438$).

The application of ECMO has saved the lives of many patients with cardiopulmonary insufficiency, but ECMO-related complications have also become thorny problems in clinical practice. The most common complications are bleeding and thrombus events. To a large extent, the occurrence of such complications is related to anticoagulation management during ECMO. At present, heparin is widely used in clinic, which mediates anticoagulation through its interaction with anti-thrombin (44–46). The results of our study suggest that post-operative use of ECMO ($P < 0.001$) may be a risk factor GI bleeding after CPB in children. This reminds us to pay attention to the effects of heparin during ECMO use and closely monitor relevant indicators such as APTT (activated partial thromboplastin time). At present, there is a shortage of specific anticoagulant preparations for children. Heparin has many disadvantages, such as binding to other plasma proteins and endothelial cells in addition to anti-thrombin, causing unpredictable reactions, difficulties in monitoring, and the risk of heparin-induced thrombocytopenia (HIT). HIT is a life-threatening complication of heparin exposure. HIT is a life-threatening complication of heparin exposure. It is initiated by immunoglobulin G (IgG) against the PF4–heparin complex (47, 48). Currently, a few studies confirm that direct thrombin inhibitors (DTIs), such as bivalirudin, may be a good option for anticoagulation (47–52). High-quality randomized controlled studies are needed to confirm the superiority of bivalirudin to provide a better option for future ECMO anticoagulation.

In order to minimize GI complications, high-risk patients must be identified to ensure optimal splanchnic perfusion. Intraoperative monitoring of gastrointestinal mucosal blood perfusion is essential to avoid gastrointestinal complications. However, splanchnic perfusion is currently difficult to monitor and optimal splanchnic perfusion was not well-defined. Although methods for detecting gastrointestinal mucosal blood flow have been proposed, their effectiveness will be difficult to prove due to the relatively low incidence of gastrointestinal complications. Further research on the early diagnosis and treatment of GI bleeding interventions is critical so that interventions can be taken before GI bleeding progresses to more severe conditions.

Recent research has shown that we must be cautious about the effects of vasoactive drug therapies on the splanchnic circulation because the effects of vasoactive agents on pHi (gastric intramucosal pH) are unpredictable (53). For example, the administration of a high dose of vasopressin may reduce rectosigmoidal mucosal perfusion and increase the risk for rectosigmoidal ischemia during and after CPB (54). Animal studies have shown that the supply of oxygen to the gastrointestinal system decreases obviously when the blood is diluted (18). Moreover, clinical outcome studies have shown an inverse relationship between mortality and the lowest hematocrit on bypass, suggesting that excessive hemodilution should be avoided (55, 56). Monitoring indicators that can be considered, such as inflammatory mediators, arterial lactic acid levels, gastrointestinal mucosal pH. In recent years, near infrared spectroscopy has been widely used in continuous monitoring of regional tissue oxygenation during perioperative and postoperative cardiopulmonary bypass in children and some pediatric studies have been conducted to determine near-infrared spectroscopy usage, safety, and efficacy (57–59). Several strategies have been proposed for improvement of CPB, such as maintaining adequate perfusion, avoiding hemodilution and severe anemia, using pulsatile blood flow, and using filters to

reduce emboli. The role of pulsatile and non-pulsatile blood flow in cardiopulmonary bypass has been widely debated. Pulsating flow has improved gastrointestinal mucosal oxygenation and perfusion in some previous studies (60–62). Goal-directed therapy has been applied in a variety of perioperative and postoperative areas of medicine with promising results, usually including rigorous oxygen perfusion and monitoring and active management to improve clinical outcomes (63, 64).

The use of proton pump inhibitors to suppress gastric acid is currently recommended to reduce the risk of gastrointestinal bleeding and has been shown to be superior to non-prevention and the use of histamine receptor antagonists to prevent GI bleeding (65). The European Association of Cardiothoracic Surgery has recommended that proton pump inhibitors should be considered in all patients following heart surgery (class IIa recommendation). The improvement in prophylactic use of proton pump inhibitors was statistically significant in reducing GI bleeding after cardiac surgery (66). More cohorts are needed to further evaluate its significance.

Combined with the statistically significant correlation of these risk factors after multivariate logistic regression analysis, we can use the nomograms (**Figure 2**) to assess the risk of gastrointestinal bleeding after CPB in children with congenital heart disease. In our study, the area under the ROC curve of the nomograms prediction model for GI bleeding was 0.898 (95% CI: 0.884–0.914, $P < 0.001$), with a sensitivity of 80.9% and specificity of 84.2%. As a result, the nomogram has a good ability to distinguish the risk of GI bleeding after CPB in children. The risk prediction model established in this study has good sensitivity and specificity. The nomograms prediction model we developed can score patients more intuitively and quickly to predict the probability of gastrointestinal bleeding after CPB in children, which can provide certain support for clinical work.

4.1. Limitations

Several limitations should be considered in this study. First, this is a retrospective single-center study. Second, this study is an observational study, which can only demonstrate correlation, and further prospective studies are needed to make causal inference. Third, we noted that there may be a big difference in morbidity and mortality between asymptomatic positive fecal occult blood and a hemodynamically significant GI bleed, but the severity of GI bleeding was not measured in this observational study. The nomograms model we constructed to predict GI bleeding after CPB in children requires further external validation.

5. Conclusion

In this study, we identified several independent risk factors of GI bleeding post-cardiac surgery, including young age, low weight, long operation time, surgical complexity, use of ECMO, LCOS, hepatic function damage, high arterial lactate level, and low postoperative platelet counts. In particular, neonates and patients with low weight have a higher risk of developing GI bleeding. The nomograms prediction model established in this study can evaluate patients more intuitively and quickly, and predict the probability of GI bleeding after CPB operation in children, thus providing support for clinical work.

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 research project is in accordance with the ethical principles of "Declaration of Helsinki" and "International Ethical Guidelines for Biomedical Research Involving Human Subjects" promulgated by the Council for International Organization of Medical Sciences. The research was reviewed and approved by the Ethical Committee of Shanghai Children's Medical Center. The need for informed consent was waived by the Ethical Committee of Shanghai Children's Medical Center, because of the retrospective nature of the study.

Author contributions

Z-QL: responsible for research implementation, data collection and drafting the manuscript. WZ: responsible for supervision of project execution and drafting the article. ZG: responsible for the statistics and analysis of research data. X-WD: responsible for retrieval and screening literature, final approval of the version to be published. WW: responsible for the determination of the research direction, the design of the research program, and the summary of the research questions. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1224872/full#supplementary-material

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EDITED BY
Cristina Barbero,
A.O.U. City of Health and Science of Turin, Italy

REVIEWED BY
Marco Moscarelli,
Imperial College London, United Kingdom
Michele Gallo,
University of Louisville, United States

*CORRESPONDENCE
Matteo Pozzi
matteo.pozzi1@unimib.it

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The frail patient undergoing cardiac surgery: lessons learned and future perspectives

Matteo Pozzi[1]*, Silvia Mariani[2,3], Margherita Scanziani[1], Davide Passolunghi[3], Adriana Bruni[4], Alberto Finazzi[4,5], Maddalena Lettino[6], Giuseppe Foti[1,5], Giuseppe Bellelli[4,5] and Giovanni Marchetto[3]

[1]Department of Emergency and Intensive Care, IRCCS San Gerardo dei Tintori Foundation, Monza, Italy, [2]Cardiovascular Research Institute Maastricht (CARIM), Maastricht, Netherlands, [3]Division of Cardiac Surgery, IRCCS San Gerardo dei Tintori Foundation, Monza, Italy, [4]Acute Geriatrics Unit, IRCCS San Gerardo dei Tintori Foundation, Monza, Italy, [5]School of Medicine, University of Milan Bicocca, Monza, Italy, [6]Department of Cardiovascular Medicine, IRCCS San Gerardo dei Tintori Foundation, Monza, Italy

Frailty is a geriatric condition characterized by the reduction of the individual's homeostatic reserves. It determines an increased vulnerability to endogenous and exogenous stressors and can lead to poor outcomes. It is an emerging concept in perioperative medicine, since an increasing number of patients undergoing surgical interventions are older and the traditional models of care seem to be inadequate to satisfy these patients' emerging clinical needs. Nowadays, the progressive technical and clinical improvements allow to offer cardiac operations to an older, sicker and frail population. For these reasons, a multidisciplinary team involving cardiac surgeons, clinical cardiologists, anesthesiologists, and geriatricians, is often needed to assess, select and provide tailored care to these high-risk frail patients to optimize clinical outcomes. There is unanimous agreement that frailty assessment may capture the individual's biological decline and the heterogeneity in risk profile for poor health-related outcomes among people of the same age. However, since commonly used preoperative scores for cardiac surgery fail to capture frailty, a specific preoperative assessment with dedicated tools is warranted to correctly recognize, measure and quantify frailty in these patients. On the contrary, pre-operative and post-operative interventions can reduce the risk of complications and support patient recovery promoting surgical resilience. Minimally invasive cardiac procedures aim to reduce surgical trauma and may be associated with better clinical outcome in this specific sub-group of high-risk patients. Among postoperative adverse events, the occurrence of delirium represents a risk factor for several unfavorable outcomes including mortality and subsequent cognitive decline. Its presence should be carefully recognized, triggering an adequate, evidence based, treatment. There is evidence, from several cross-section and longitudinal studies, that frailty and delirium may frequently overlap, with frailty serving both as a predisposing factor and as an outcome of delirium and delirium being a marker of a latent condition of frailty. In conclusion, frail patients are at increased risk to experience poor outcome after cardiac surgery. A multidisciplinary approach aimed to recognize more vulnerable individuals, optimize pre-operative conditions, reduce surgical invasivity and improve post-operative recovery is required to obtain optimal long-term outcome.

KEYWORDS

frailty, cardiac surgery, minimally invasive cardiac surgery, ERAS, comprehensive geriatric assessment

1. Clinical frailty: definition and pathophysiology

From the latin "fragilis" meaning "easily broken", frailty is a geriatric syndrome defined as a form of vulnerability to stress due to decline of physiologic reserve (1). In particular, frailty is a multidimensional condition involving many organ systems, general health status, physical and cognitive functions, nutritional state, skeletal muscle mass, strength and mobility, mood, social support and relations (2). Although aging is closely linked to frailty, and frailty is often seen in older adults, frailty can be present also in younger people (3). This condition is clinically characterized by the presence of some key signs, such as weakness, slow gait speed, poor mobility, fatigue and unintentional weight loss (2).

From a pathophysiological point of view, a two-way relationship between cardiovascular diseases (CVD) and frailty has been proposed (4). According to the current hypothesis, a proinflammatory state occurring with aging represents the key factor of the phenotypic modifications observed in frail subjects, leading to cellular damage, catabolic muscles modifications, impaired homeostasis and ultimately vulnerability to external stressors (5). As CVD shares a common etiological pathway, these two conditions are clinically and epidemiologically closely linked with a significant amount of frail persons among CVD patients (6, 7).

2. Frailty and surgery

Surgery can be considered a major stressor able to unveil a silent frailty condition or to dramatically decompensate an overtly frail patient. Since frail subjects are increasingly represented among surgical patients, their identification in the perioperative phase has become crucial. This has prompted careful preoperative selection of cases, appropriate management of pre-operative and post-operative conditions, and adequate estimation of long-term outcomes (8).

The association between frailty and adverse postoperative outcome in adult non-cardiac surgery patients has been extensively described. In particular, frail patients are at higher risk to develop postoperative delirium (9), cardiovascular events (10), and procedural complications (10–13). They are characterized by a slower recovery (14, 15), prolonged intensive care unit (ICU) and in-hospital stay (14, 16) and ultimately morbidity and mortality (10, 17), with a huge increase in global medical costs (16, 18). Moreover, this association between frailty and postoperative adverse outcomes seems independent from patients' age, comorbidities and the procedural-related surgical risk. A recent analysis of a large US database revealed that among patients undergoing non-cardiac surgery, those with higher frailty risk score (19) have higher risk for perioperative cardiovascular events and mortality. They require more frequent discharge to short–term acute care or intermediate care facilities compared to those with lower frailty, in all age groups and independently from patients comorbidities (20). Moreover, in a large longitudinal cohort study, the independent association of frailty with an increased postoperative mortality was retained not only in high risk procedures but also in low-risk procedures from low-intensity surgical specialties (21).

The increasing number of aging patients living with more comorbidities, together with the improvement of surgical outcome in the older population, led to a large proportion of frail patients in cardiac surgery. However, cardiac surgery is associated with a high degree of invasiveness and iatrogenic stress that can compromise postoperative outcomes in frail patients with reduced ability to face such distress. As the aim of each cardiac operation is to restore biological integrity and functional capacity so as to improve the patient's quality of life (QoL), the inability to face the surgical stress may ultimately compromise the net result of a surgical procedure. Indeed, frailty was reported to be an independent predictor of in-hospital and mid-term mortality in a large Canadian cardiac surgery population (22). These data were confirmed by a meta-analysis including more than 60,000 patients (23). As in non-cardiac surgery patients, this association is maintained independently of age (24) or surgical risk score (25) and is proportional to the degree of frailty (23, 24). Moreover, pre-operative vulnerability is not only associated with major postoperative complications and prolonged hospitalization (25), but also with worse post-discharge QoL up to one year after surgery (26).

For the above mentioned reasons, it can be postulated that the active pre-operative recognition of frail patients may help to ameliorate their own outcome and impact patient management in different moments of the clinical course from risk stratification to pre-habilitation programs and surgical choices (**Figure 1**). The first step to improve outcomes in frail patients is the recognition of their condition at the moment of surgical indication. Indeed, its recognition allows clinicians to formulate a more precise risk estimation (27) based on a precise and commonly accepted definition of frailty. This issue has important consequences on the communication with patients and families, as it involves the shared definition of the goals of care, ensures a patient-centered treatment and avoids disproportionate treatments or futility. The second step implies the reduction of patients' vulnerability by means of a "pre-habilitation" program (28) involving physical, respiratory and nutritional preoperative optimization. Last, identification of more vulnerable patients could promote the tailoring of the best perioperative pathway for each patient, in particular in terms of minimally invasive surgical options and postoperative care bundles.

Such a holistic clinical approach matches up well with the already conceptualized organizational model of the "Heart Team" (28), which includes the participation of physicians from different disciplines (e.g., cardiac anesthesiologists, geriatricians, internal medicine physicians) in addition to cardiologists and cardiac surgeons to provide the best comprehensive management of cardiac conditions in frail patients. The following paragraphs will systematically investigate the available tools to optimize the clinical course of frail patients in cardiac surgery.

3. Pre-operative assessment of frail patients

3.1. Predictive scores in cardiac surgery

Estimation of surgical risk relies upon the use of scoring systems to predict patients' risk of adverse outcomes. Traditionally, two main

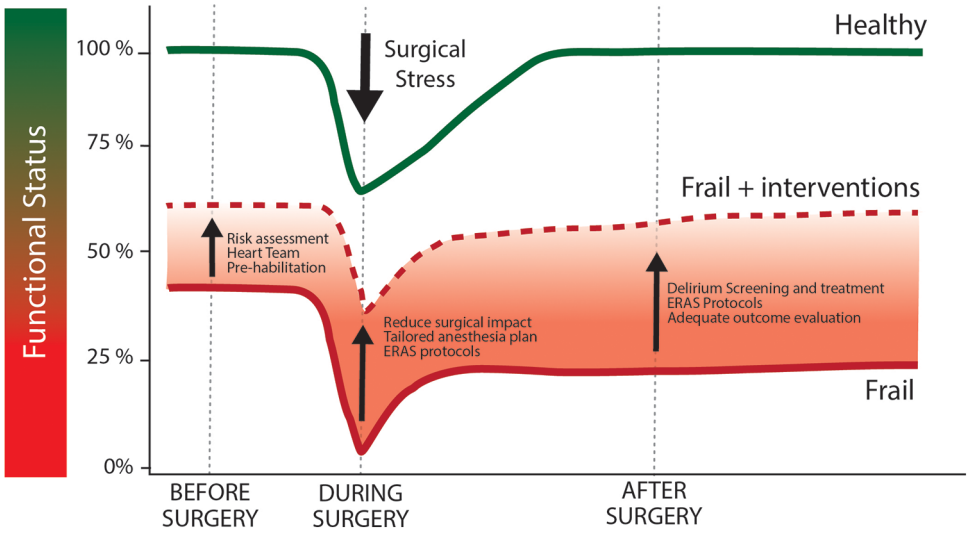

FIGURE 1
Effect of surgical stress and optimization measures above functional status trajectories in healthy and frail patients. Following the stress of cardiac surgery healthy individuals (green line) suffer from a acute worsening of functional status, that promptly return to baseline during post-operative period. Frail individuals (red line) are characterized by a compromised baseline functional capacity. Similarly to healthy individuals, functional capacity is further reduced after surgery. As frail patients are not able to face such stressing factor, they could not be able to return to baseline functional capacity during post-operative period. This circumstance can compromise long-term outcome and ultimately the net result of the surgical procedure. Functional capacity trajectory could be modified by pre-operative, intra-operative and post-operative specific intervention (dashed red line), whose aim is to improve baseline conditions and to reduce the stressful burden of cardiac surgery.

risk scoring systems have been available in cardiac surgery: the Society of Thoracic Surgery (STS) Predicted Risk of Mortality or Major Morbidity (29) and the EuroSCORE (30).

Both these scores incorporate age, major comorbidities and traditional physiological variables, but they do not consider variables such as liver cirrhosis, right ventricle function and frailty (31) which are becoming frequent among cardiac patients. Consequently, these scores lost their predictive performance. If STS Score tends to underestimate the risk in more vulnerable patients (32), the old versions of EuroSCORE were burdened by a systematic overestimation of perioperative risk. Although they have been recalibrated (30, 33) high-risk patients remain excluded from accurate risk predictions. In particular the new EuroSCORE II partially reduces the overprediction of the previous versions, at the cost of a tendency toward miscalibration in high-risk groups (31, 32, 34).

Moreover, the inclusion of risk factors for mortality that are very rare in surgical population but with a dramatic impact on the outcome poses some unresolved statistical issues. As an example, advanced liver cirrhosis in extremely rare in surgical population (<0.5%), but mortality associated with this condition is probably more than 70% (35).

Already in 2010, it has been described that slow gait speed, a clinical marker for frailty, confers a 2- to 3- fold increase in risk for any given level of STS predicted mortality and major morbidity (27). Based on the growing evidence that the addition of variables related to frailty could improve the predictive power of these scoring systems (27), frailty was partially incorporated into the available scores. Consequently, STS score version 2.73 included gait speed as a marker of patient frailty, while in the revised version of EuroSCORE II the variable "neurologic dysfunction" was replaced by "poor mobility", as a generic component of frailty phenotype (30). Although this can be considered a first important step, these scores will continue to underestimate the impact of frailty on patient's outcomes. Moreover, gait speed evaluation is often not performed in the daily routine of cardiac surgery patients (36).

3.2. Beyond eyeball evaluation: how to measure frailty using the comprehensive geriatric assessment

Besides the traditional risk scores for cardiac surgery patients, specific tools have been designed to test frailty. In 2001, Fried and colleagues introduced the concept of a physical phenotype model to clinically characterize frailty (2). According to this model, older adults can be diagnosed with frailty if they exhibit three or more out of five criteria: unintentional weight loss of ≥10 pounds in the last year, weakness (determined by grip-strength), exhaustion, low physical activity, and slowed walking speed (2). Similarly, Rockwood and Mitnitski proposed a frailty index (FI), based on an accumulation of age-related deficits model (37). In their model, frailty is quantified as a continuous score that sums up signs, symptoms, disabilities, and diseases (37).

Frailty leads to various clinical consequences and manifestations, including cognitive impairment, loss of independence in daily activities, reduced mobility, and even mortality. Regardless of the specific tool employed, the diagnosis of frailty can be attained by gathering information about an individual's physical performance, mobility, cognitive and nutritional status. In this context, the

TABLE 1 Domains of the comprehensive geriatric Assessment and corresponding instrument for clinical assessment.

Domain	Topic investigated	Clinical Assessment instruments
Health status	Chronic diseases, multimorbidity and polypharmacy	• Charlson Index • Cumulative Illness Rating Scale • Number of medications
Nutritional status and sarcopenia	Malnutrition	• Mini Nutritional Assessment • Geriatric Nutritional Risk Index • Serum albumin levels • Anthropometric measures handgrip strength • Bioelectrical impedance analysis
Cognition and mood	Cognitive status and affective disorders	• Mini Mental State Examination • Montreal Cognitive Assessment • Geriatric Depression Scale
Functional status	Basal and instrumental activities of daily living	• Activities of Daily Living • Instrumental Activities of Daily Living
Mobility	Gait and balance	• Gait speed • Chair Stand Test • Short Physical Performance Battery
Socioeconomic status and quality of life	Home care, long term care service, nursing homes, income	• Cohabitation status • Short Form Health Survey 36

comprehensive geriatric assessment (CGA) emerges as a robust method to capture frailty's essence (38). CGA involves administering specific scales to assess comorbidities and number of medications, functional ability, nutritional status, mobility, cognition and mood, physical activity and risk of falls, and socioeconomic status (**Table 1**). Hereafter the most significant domains for frailty assessment are presented.

3.2.1. Health status

Health status encompasses medical history, multimorbidity and polypharmacy. The Cumulative Illness Rating Scale (CIRS) is a comprehensive tool used to assess an individual's overall health status by evaluating the presence and severity of various medical conditions across different body systems. The CIRS aims to provide a holistic picture of an individual's health by considering the cumulative impact of multiple medical conditions on the well-being. The scale is widely used in clinical and research settings to assess the overall health and functional capacity of individuals, particularly in the context of aging and chronic diseases (39). The Charlson Comorbidity Index (CCI) is a widely used scoring system that quantifies the burden of comorbidities or underlying medical conditions in a patient and their potential impact on mortality (40). Each condition is assigned a weight, and these weights are summed to calculate an overall score for an individual patient. The higher the score, the greater the burden of comorbidities. The CCI is commonly used in clinical research and healthcare settings to assess the overall health status and to predict the risk of mortality or other adverse outcomes. It provides a standardized way to account for the presence and severity of comorbidities. The index has been validated and adapted for various medical conditions and populations.

3.2.2. Functional status

Functional status refers to an individual's ability to perform daily activities necessary for independent living and self-care. Functional status is often categorized into two main components: Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs). The ADLs encompass the fundamental self-care activities that are essential for maintaining one's personal well-being and functioning daily, including bathing, dressing, toileting, transferring, continence and eating (41). The Instrumental Activities of Daily Living (IADLs) include 8 complex activities related to the ability to live independently in the community, such as managing finances and medications, meal preparation, housekeeping, laundry, transportation, communication, and shopping (42).

3.2.3. Mobility impairment

Mobility impairment in older individuals can have a significant impact on their health status. The ability to move and navigate one's environment is crucial for maintaining independence, participating in daily activities, and enjoying a high QoL. Gait speed is a simple test to assess mobility in older adults. This single-item test involves timing individuals while they walk at a steady pace for a set distance, usually 4 meters. Generally, a gait speed greater than 5 s for 4 meters (<0.85 m/s) is associated with an increased risk of having frailty (43). The Short Physical Performance Battery (SPPB) (44) is a tool designed to evaluate the physical functioning and mobility of older adults. It is helpful in identifying age-related declines in physical performance and predicting functional limitations. The SPPB consists of a series of three tests (balance tests, gait speed test and chair stand test) that together provide a comprehensive picture of an individual's lower extremity function and overall physical capacity. The tests are simple, quick to administer, and require minimal equipment.

3.2.4. Cognitive functions and mood disorders

The assessment of cognitive function is a crucial component of CGA. Utilizing validated screening tools like the Mini-Mental State Examination (MMSE) (45) and Montreal Cognitive Assessment (MOCA) (46), physicians can quickly evaluate an individual's cognitive abilities, including memory, attention, language, and executive function. Identification of cognitive deficits enables timely intervention, such as cognitive rehabilitation and targeted support, to mitigate functional decline and enhance overall QoL.

Moreover, the Geriatric Depression Scale (GDS) aids in detecting depressive symptoms (47), which can intersect with cognitive impairment. By addressing cognitive well-being, the CGA contributes to a holistic understanding of a frail person's health and guides tailored care strategies.

3.2.5. Nutritional status

Adequate nutritional status is essential for maintaining physical health, supporting immune function, and preventing chronic diseases. Measuring nutritional status involves assessing various factors related to an individual's diet, body composition, and overall health. The Mini Nutritional Assessment (MNA) (48) and the Geriatric Nutritional Risk Index (GNRI) (49) are instruments to explore nutritional status of the elderly. The MNA is composed of simple measurements and brief questions that can be completed in about 10 min. The sum of the MNA score distinguishes between older people with adequate nutritional status, protein-calorie malnutrition or at risk of malnutrition. The Geriatric Nutritional Risk Index (GNRI) (49) is an objective and easy screening method based on height, weight, and serum albumin level. Additional evaluations to assess nutritional status include anthropometric measurements, such as Body Mass Index (BMI), blood biomarkers, such as albumin serum levels and body composition analysis, such as bioelectrical impedance analysis (BIA).

3.2.6. Hand grip strength

Hand Grip Strength (HGS) measurement assess muscle function and overall health in older adults (50). It provides a reliable measure of muscle strength, an indirect measure of functional independence and can predict the risk of fall and other adverse outcomes. HGS can be measured using a handheld dynamometer. Three trials for each hand are performed, and the highest value of the strongest hand is recorded. BMI-adjusted values are used to identify low muscle strength in females and males.

3.2.7. Polypharmacy

Polypharmacy refers to the simultaneous use of multiple medications by an individual, typically involving the use of five or more different medications. These medications can include prescription drugs, over-the-counter medications, and even herbal or complementary remedies. Polypharmacy becomes particularly relevant in older adults with multiple chronic diseases and various medications to manage their health (51). Polypharmacy is a significant issue due to its potential to cause adverse drug reactions, decrease medication adherence, and negatively impact the overall health and well-being of older adults. As a result, healthcare professionals specializing in geriatrics must carefully assess and manage medication regimens to ensure that the benefits of each medication outweigh the risks, and to promote optimal health outcomes for their older frail patients.

3.2.8. Socioeconomic status and quality of life

Socio-Economic Status (SES) plays an important role since a high SES provides older adults with material resources, helps them develop healthy lifestyles, and confers psychological benefits. Consequently, older adults with a higher SES tend to have a lower likelihood of mortality than their lower SES counterparts (52). The Short Form Health Survey 36 (SF-36) is validated for the assessment of QoL, the questionnaire consists of 36 questions covering 8 domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health), scaled from 0 to 100, a higher score indicates a better QoL. The domains are summarized into physical and mental health scores (53).

In summary, CGA is the most reliable approach to identifying the frail patient and to making a personalized care plan. However, it is not always possible to take a complete evaluation given the different settings and available resources. Therefore, health care professionals need a frailty assessment that is simple, not time-consuming, and helpful in making decisions about interventions and care allocation. The Essential Frailty Toolset (EFT), for example, has shown to be easy to use and predictive of adverse events in patients undergoing aortic valve replacement procedures (54) and coronary artery bypass grafting in older adults (55). The EFT is scored 0 (least frail) to 5 (most frail) based on the following 4 items: pre-procedural anemia, hypoalbuminemia, lower-extremity muscle weakness defined as a time of $\geq$15 s or inability to complete five sit-to-stand repetitions without using arms, and cognitive impairment defined as a score of <24 on the Mini-Mental State Examination. Although the EFT is not all-encompassing, it is a well-rooted starting point to test for frailty, and to identify patients in whom further geriatric assessment should be considered to confirm the diagnosis of sarcopenia, malnutrition, dementia, depression, or disability.

3.3. Incorporating frailty evaluation into clinical practice: the Heart Team model

Starting from the belief that a multidisciplinary approach is frequently required to manage and ensure better care for patients, international recommendations progressively emphasized the importance of the Heart Team (HT) in all fields of cardiology and cardiac surgery. Indeed, current guidelines strongly recommend HT implementation for optimal management of valvular disease (56), heart failure (57) and myocardial revascularization (58). Nowadays, in addition to cardiologists and cardiac surgeons, HT includes heart imaging specialists, anesthesiologists, ICU physicians and other specialists (e.g., neurologist, nephrologist, geriatrician) whose contribution is required by the specific patient condition. As comprehensive frailty evaluation improves perioperative risk prediction (27), and since a huge amount of patients with CVD are deemed to be frail (6, 7), geriatricians play an increasingly important role in this multidisciplinary patients management.

HT physicians are committed to a unique purpose: to provide a precise risk stratification of the patient and then to identify the best treatment strategy. Such a treatment plan cannot disregard patients' own wishes as shared decision-making improves surgical outcomes and QoL. In this way, the role of HT is to holistically put the patients' complexity at the center of medical decision-making.

Besides perioperative risk quantification and frailty evaluation, treatment decisions should take into account life expectancy.

Statistical estimation of the averaged remaining years of life at a single patient level is not a simple task, in particular in elderly patients with multiple associate conditions, but different scores have been developed for this purpose (59). In this perspective, this evaluation can help to balance perioperative short term mortality and morbidity risk with long term survival expectancy (60).

According to the guidelines of the European Society of Cardiology (ESC) and the European Society of Cardio-Thoracic Surgery for the management of valve diseases, frailty assessment should always precede the final decision concerning the type of chosen intervention and its timing, particularly in elderly patients (56). For example, in the flowchart that outlines the management of patients with severe aortic stenosis comorbidity and frailty assessments are mandatory to decide whether any kind of intervention is likely to be of benefit and should be considered during the HT decision process. Similarly to the ESC recommendation also The American College of Cardiology and American Heart Association emphasize shared decision-making in cardiac surgery, taking into account patients' values, preferences, and frailty status (61). Both suggest the use of validated frailty scores such as the Katz index (41) to grade the level of frailty and take operative decisions accordingly.

Despite preoperative frailty assessment and prehabilitation practices have been recommended by both the aforementioned guidelines and several consensus documents, such as the ones issued by the Society of Perioperative Assessment and Quality Improvement (SPAQI) (62) and the Enhanced Recovery After Surgery (ERAS) Society (63), frailty is so far not being routinely assessed before surgery for many different reasons. First of all, neither a comprehensive geriatric assessment nor any intervention to optimize the patient's condition and reduce complications are feasible under acute conditions. In addition, many clinical tools to assess frailty require patient's active participation and this is not always the case for patients with a poor clinical, social or educational status (64). Finally, there is still a lack of consensus among different frailty instruments that might affect anesthesiologists' and surgeons' behavior, suggesting the opportunity to develop a more practicable and validated workflow in this specific context.

4. Pre-operative optimization: *is frailty a modifiable factor?*

As previously mentioned, the preoperative identification of frail patients can trigger the development of dedicated programs to improve the preoperative patients' condition. In this context, the Enhanced Recovery After Surgery (ERAS) guidelines has gained popularity and are increasingly applied (63). ERAS is a multimodal, multidisciplinary care improvement initiative to promote recovery of patients undergoing surgery throughout their entire perioperative journey (65). Modifiable factors addressed by the ERAS recommendations include an optimal perioperative glycaemic control, defined by a hemoglobinA1c level less than 7% (66), and an evaluation of hypoalbuminemia (63). For patients who are malnourished or have a serum albumin level less than 3.0 g/dl, nutritional supplementation for 7 to 10 days before surgery may improve outcomes (63, 67). Carbohydrate loading shortly before surgery might be considered to improve postoperative glucose control and gut function but evidence to support the routine application of this strategy are still lacking (63). Intake of clear liquids until 2 to 4 h preoperatively may be considered before general anesthesia but further studies are required to investigate the risk of aspiration pneumonitis in cardiac surgery patients undergoing intraoperative transoesophageal echocardiography or characterized by delayed gastric emptying due to diabetes mellitus (63). Screening for excessive alcohol use and cigarette smoking should be performed (68) and consumption should be stopped 4 weeks before elective surgery (69).

4.1. Patient engagement and prehabilitation

Pre-operative assessment of fragile patients leads to the application of preventive interventions (prehabilitation) including inspiratory muscle training, functional exercise training, psychological support (anxiety and depression reduction), nutritional support, and smoking cessation (63, 70). It has been demonstrated that such strategies, together with the optimization of modifiable factors, may reduce the length of hospital stay, decrease the postoperative morbidity (especially in terms of pulmonary complications) and mortality, and improve the transition from the hospital to the community (71–73). **Table 2** provides a summary of the previous randomized studies evaluating the effect of prehabilitation protocols on different perioperative outcomes.

Patient education and counseling prior to surgery can be completed in person, through printed material, or through application-based approaches (63). As telemedicine has become widely adopted, especially during the COVID-19 pandemic (77, 78), personalized prehabilitation programs may also be delivered using this technology, as already described in the field of cardiac rehabilitation (79, 80).

5. Intraoperative choices for frail patients: the right strategy for the right patient

Besides the preoperative targeting of modifiable factors and prehabilitation programs, much can be done intraoperatively to optimize patients' outcomes. A multidisciplinary approach should guide the intraoperative management in terms of surgical technique and anaesthesiologic strategies, with careful preoperative planning. It has been demonstrated that with a proper preoperative patient assessment in terms of past medical history, comorbidities, and anatomy and with an adequate allocation to the most appropriate surgical and anaesthesiologic approach, the overall rate of early mortality and main complications remain low (81). Indeed, the era of the "one size fits all" approach in cardiac surgery has now been overtaken by precision medicine and tailored surgery. New technologies such as virtual reality (82) and 3D printing (83) can further assist in surgical planning. Hereafter the different options for surgical approach according to different cardiac conditions are presented (**Table 3**).

TABLE 2 Available randomized trials evaluating prehabilitation.

Paper	Study design	Sample Size	Type of Surgery	Intervention	Main Results
Arthur et al. (74)	RCT	246	CABG	Multimodal prehabilitation before planned cardiac surgery. Outpatient setting	Reduction of postoperative ICU LOS (by 2.1 h, 95% CI -1.2–16 h, $p = 0.001$) and Hospital LOS (by 1 day, 95% CI 0–1, $p = 0.002$). Better preoperative and postoperative quality of life. No differences in mortality.
Herdy et al. (75)	RCT	56	CABG	Multimodal Prehabilitation before planned cardiac surgery. Hospitalized patients.	Shorter duration of mechanical ventilation. Reduction of pleural effusion (RR = 0.2; 95% CI: 0.5–0.8), atelectasis (RR = 0.15; 95% CI: 0.03–0.8), and AF (RR = 0.2; 95% CI: 0.05–0.8). Reduction of in-hospital LOS (5.9 ±/−1.1 vs. 10.3 ±/−4.6 days, $p < 0.001$).
Rosenfeldt et al. (76)	RCT	117	CABG, valve surgery	Multimodal Prehabilitation before planned cardiac surgery. Outpatients setting	No differences in quality of life, LOS and Atrial Fibrillation.

RCT, Randomized Clinical Trial; CABG, Coronary Artery Bypass Graft; ICU, Intensive Care Unit; LOS, Length of Stay; CI, Confidence Interval; AF, Atrial Fibrillation; RR, Relative Risk.

TABLE 3 Surgical approaches in frail patients.

Disease	Surgical principles in frail patients	Available techniques
Coronary artery disease	Reduce aortic manipulation Minimize surgical incision Consider LITA-LAD + PCI of other vessels	Anaortic coronary artery bypass: off-pump + no touch Left thoracotomy: MIDCAB, MICS CABG Robotic surgery: TECAB Hybrid revascularization
Aortic valve disease	Minimize surgical incision Reduce CPB time	Mini-sternotomy / Mini-thoracotomy /Right Mini-thoracotomy Sutureless and rapid deployment valves
Mitral valve disease	Minimize surgical incision Consider trans-apical off-pump approaches	Right Mini-thoracotomy NeoChord Trans-catheter valves
Tricuspid valve disease	Minimize surgical incision Reduce CPB time	Right Mini-thoracotomy Beating heart right heart surgery
Ascending aorta and aortic arch	Minimize surgical incision Reduce cardiac ischemic time Consider debranching of supra-aortic vessels + EVAR Consider total endoscopic approach	Mini-sternotomy Beating heart aortic surgery Hybrid arch repair Fenestrated/branched arch endografts
Heart failure	Minimize surgical incision	LVAD implantation with right thoracotomy + mini-sternotomy

CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass time; EVAR, endovascular aneurysm repair; LAD, left anterior descending artery; LITA, left internal thoracic artery; LVAD, left ventricular assist device; MICS, minimally invasive cardiac surgery; MIDCAB, minimally invasive direct coronary artery bypass; PCI, percutaneous coronary intervention; TECAB, total endoscopic coronary artery bypass.

5.1. Coronary artery bypass graft (CABG)

CABG surgery remains the most frequently performed operation in adults. Nevertheless, cardiopulmonary bypass and aortic cross-clamping may be related to complications in fragile patients with porcelain ascending aorta and/or atheroma in the ascending aorta or arch. These patients might suffer from embolization due to the aortic cross-clamp, the jet from the aortic cannula inflow and, in the case of a porcelain aorta, aortic rupture and or dissection from a cross-clamp injury. A simple preoperative screening with a non-contrast computed tomography or an intraoperative epiaortic scan helps in the triage of these patients (Class IIa indication in the EACTS/ECC 2018 Coronary Revascularization Guidelines) to the appropriate surgical technique including no-touch approaches or hybrid minimally invasive approaches (58).

Anaortic CABG is a technique of off-pump coronary artery revascularization that avoids aortic manipulation by often using all arterial grafts. Typically, the mammary arteries are used for in-flow and the radial artery as a composite graft (84). This technique is particularly indicated for patients with a diseased ascending aorta (Class I indication in the EACTS/ECC 2018 Coronary Revascularization Guidelines and Class 2a indication in the most recent AHA coronary guidelines) (58, 85).

Where expertise exists, minimally invasive direct CABG (MIDCAB) through limited thoracic access should be considered in patients with isolated lesions on the left anterior descending artery (LAD) or in the context of hybrid revascularization strategies (Class IIa indication in the EACTS/ECC 2018 Coronary Revascularization Guidelines) (58). The MIDCAB operation is characterized by LAD grafting with the left internal thoracic artery through a left anterior small thoracotomy. It can be combined with percutaneous coronary intervention (PCI) of non-LAD coronary stenoses in a sequential or concomitant way. This latter approach is defined as hybrid revascularization where stents become substituted for saphenous vein grafts for non-LAD lesions (86).

Minimally invasive coronary surgery (MICS CABG) was developed as an extension of the MIDCAB operation and implies multivessel grafting through a limited left anterior thoracotomy (86, 87). A further development of this approach is the robotic total endoscopic coronary artery bypass (TECAB) technique which provides multivessel revascularization without an open incision through port access (86). Aim of these less invasive

approaches is to reduce the post-operative complications, reduce the surgical trauma and accelerate discharge timing (88).

5.2. Aortic valve surgery

Aortic valve (AV) surgery has evolved towards less invasive approaches including mini-sternotomy or right thoracotomy (89). Several studies have shown that patients undergoing less invasive AV surgery have a shorter hospital stay, less pain, shorter duration of ventilation, less blood loss, and less blood transfusion than patients undergoing conventional full sternotomy (90). Postoperatively, patients can be mobilized earlier, and the respiratory function may be better, making this approach particularly suitable for fragile and elderly patients (91).

Less invasive surgical approaches can be implemented with the use of sutureless or rapid deployment valve bio-prostheses. By avoiding placement and tying of sutures after annular decalcification, the use of these valves minimizes cross-clamp and cardiopulmonary bypass times, reduce post-operative morbidity and mortality and improve cost-effectiveness, particularly in high-risk patients as well as in those undergoing complex or concomitant procedures (92–94). Sutureless or rapid deployment aortic valves should be considered for isolated AV replacement in patients with comorbidities, old age, small aortic annulus, delicate aortic wall and conditions such as calcified root (95).

5.3. Mitral valve surgery

Similarly to AV surgery, mitral valve (MV) interventions can be performed with techniques to reduce the surgical stress. Right mini-thoracotomy has become the preferred approach for MV surgery at many institutions but it might be burdened by perioperative stroke. Previous cardiac surgery and the severity of aortic and ileo-femoral arterial disease should guide the choice toward an antegrade arterial flow when indicated, and the optimal technique of aortic occlusion and myocardial protection to reduce neurological events (96).

Primary MV regurgitation can also be addressed through off-pump techniques with trans-apical access to the left ventricle through left thoracotomy. This approach is used for the implantation of NeoChord. These artificial chordae tendinae are inserted in the left ventricle, tensioned under echocardiographic guidance, and secured to the left ventricular epicardium using Teflon pledgets (97). This technique has proven effective also in reinterventions and high-risk patients (98). Catheter-based trans-apical mitral valve prosthesis implantation is a potential therapeutic option in high-risk patients but its effect in reducing post-operative morbidity and mortality in frail patients still needs to be demonstrated (99, 100).

5.4. Tricuspid valve surgery, right heart failure and atrial fibrillation

MV diseases might be associated with tricuspid valve (TV) regurgitation, pulmonary hypertension, right heart failure and atrial fibrillation (AF). Even though TV disease and AF can be indications for isolated surgical procedures they are often associated with MV surgery in frail patients, increasing the surgical complexity and the risk of postoperative complications. Less invasive approaches through a right mini-thoracotomy and beating heart techniques have been described to address both TV surgery (101, 102) and AF ablation (102). Right mini-thoracotomy has proven to be safe and feasible even in the presence of pulmonary hypertension (103) but its postulated protective role in case of right heart failure is still under discussion.

5.5. Ascending aorta and arch surgery

Surgical complexity reaches high levels in case of ascending aorta and aortic arch surgeries where prolonged cardiopulmonary bypass and circulatory arrest are required with potential detrimental effects in frail patients. Moreover, up to 25% of aortic patients fall into the frailty definition (104). Also in this case, less invasive approaches through mini-sternotomy (105) and beating heart techniques to reduce the myocardial ischemic time (106) have been described. Besides the open repair techniques, hybrid arch repair combining vascular and endovascular treatment has gained popularity (107). This approach implies the endovascular exclusion of the pathologic aortic segments following the creation of an adequate proximal landing zone (in zones 0, 1 and 2) by means of supra-aortic transposition (debranching) of one or more arch vessels (107). Finally, a total endovascular aortic arch repair has become possible with the introduction of fenestrated and branched arch endografts (107).

5.6. Heart failure surgery

Many heart failure patients fall into the group of frail patients due to their catabolic state, end-organ damage and comorbidities (108). Some of them are candidates for left ventricular assist device (LVAD) implantation but they might suffer from longer time to extubation, longer hospital length of stay, and increased long-term mortality compared to non-frail patients (108). Among the options to reduce their surgical stress, less invasive strategies to implant LVADs have been developed (109). A left anterolateral thoracotomy for pump implant and a mini-sternotomy or a right anterior thoracotomy for the outflow graft anastomosis can be used to implant an LVAD (109, 110), exchange a pump (111) or explant a pump after myocardial recovery (112).

5.7. Other intraoperative strategy that could improve outcomes

Literature and clinical practices are lacking specific anesthesiology approaches for frail patients (47, 113). Nevertheless, geriatric principles of anesthesia management can be applied to frail patients (113). This implies the use of lung protective strategies and the reduction of medications potentially

inappropriate for older adults, such as long-acting benzodiazepines, diphenhydramine, scopolamine, and promethazine (114). Temperature management during cardiopulmonary bypass should avoid an excessively fast rewarming phase which has been associated with postoperative neurological complications (113). The use of intraoperative anesthesia depth monitoring has been advocated to decrease the amount of medications required and therefore allow for more hemodynamic stability and reduced postoperative delirium and 30-day mortality. Nevertheless, evidence supporting the routine use of electroencephalography-guided anesthesia protocols are still lacking (115).

6. Outcome evaluation in frail patients

6.1. Postoperative delirium and cognitive impairment

Delirium is a severe neuropsychiatric syndrome characterized by an acute disorder of cognition (mainly but not exclusively attention and awareness), that develops over a short period of time (usually hours to a few days) and represents a change from baseline attention and awareness (116). Delirium tends to fluctuate in severity during the day, and it is almost always caused by underlying medical issues. Risk factors for delirium include age, pre-existing cognitive impairment and dementia, multimorbidity, depression, other psychiatric illnesses, alcohol consumption, poor nutritional status, visual and auditory impairments and frailty (9). The relationship between delirium and frailty is particularly intriguing as these two conditions share similar underlying pathophysiological mechanisms and act as predisposing factors for each other (117, 118). Delirium, in fact, arises from an interplay between predisposing and precipitating factors (9). According to this view, delirium can thus be regarded as a clinical consequence of frailty in older persons experiencing stressful events (118). At least three psychomotor subtypes of delirium can be distinguished: hyperactive (characterized primarily by agitation), hypoactive (characterized mainly by lethargy and drowsiness), and mixed (fluctuation between hyperactive and hypoactive subtypes) (119).

Delirium is a common yet neglected complication after cardiac surgery, affecting about 25%–50% of all patients (120–122). Postoperative delirium (POD) usually occurs within the first four days after surgery (123) and is associated with increased rates of intubation (124) and longer length of hospital stays (121). Delirium has been described by patients as something that affects their emotions and interactions with others and by caregivers as a frightening experience (125). Patients who experience post-operative POD also face an elevated risk of mortality at 30 days and six months after surgery (126, 127), with patients experiencing the hypoactive subtype carrying the worst prognosis (119).

Notably, delirium is also associated with subsequent decline of cognitive functions and risk of dementia (127–129), significantly affecting both individual's and family QoL, and determining increased costs for the society and healthcare systems. Several studies have prospectively assessed cognitive states in medical patients before, during and after delirium, finding a prospective association of delirium with cognitive decline over 2 years and incident dementia (128, 130, 131). A prospective cohort study examined the patterns and pace of cognitive decline during a period of 72 months in 560 community-dwelling older adults who underwent major elective surgery and developed POD. This study demonstrated that patients experiencing POD showed accelerated cognitive decline in comparison to those who either did not develop delirium or did not undergo surgery (128). Globally, these studies demonstrate that delirium is associated with significant cognitive decline in the medium- and long-term.

The mechanisms through which cognitive deficits can develop because of delirium are not entirely understood. However, Davis and colleagues have shown that the pathophysiological mechanisms that contribute to accelerating the progression of cognitive deficits following delirium differ from those implicated in the pathogenesis of dementia (particularly Alzheimer's) which may act independently and additively to the classical pathological processes of dementia (132).

6.2. Early recognition, prevention and treatment of postoperative delirium

The initial step for an effective POD treatment is its early recognition. Terms like "acute confusional state," "toxic-metabolic encephalopathy," or "psychomotor agitation" should be avoided, while "suspected delirium" should be used for suggestive symptoms (133). However, a proactive strategy to detect the first signs and symptoms of POD is advised. All patients undergoing major surgery (9) should be screened for POD during the first three days after the operation and until resolution of the clinical situation. For this purpose, validated scales such as the 4AT (134) and CAM-ICU (135) scales could be used.

Besides early recognition, it is necessary to reduce precipitating factors that can trigger the onset of POD. A systematic review including 315 articles and 101,144 patients identified 112 precipitating factors associated with the onset of delirium. These factors can be divided into 8 main categories based on pathophysiology: surgical factors, systemic illness or organ dysfunction, metabolic abnormalities, drugs, iatrogenic and environmental factors, trauma, biomarkers, and neurotransmitters (9). Such a complex list of precipitating factors indicates how addressing POD requires a multimodal approach and the contribution of several medical specialists as well as nurses, physiotherapists, psychologists, and other healthcare professionals. Indeed, the currently best approach to POD is non-pharmacological, multicomponent, and interdisciplinary (136–138). The Hospital Elder Life Program (HELP) exemplifies this approach, including interventions like spatial-temporal reorientation (e.g., the use of calendars), limited use of psychoactive drugs, early mobilization, proper sleep hygiene, hydration, nutrition, and sensory aids (139, 140). This program has been shown to be effective in preventing delirium in both medical and surgical patients, potentially reducing cases by 40% (138, 141, 142). Notwithstanding, application of all these measures might be complex and healthcare professionals might experience difficulties in adopting these approaches, often due to staff shortages and different routines (143).

Even when all the above mentioned measures are correctly implemented, POD may still occur. In this case, clinicians should pay attention to POD aetiological treatment (144). All precipitating factors and potential medical causes underlying delirium should be excluded and/or addressed (9). The acronym DELIRIUM, which stands for Drugs, Electrolyte disturbances, Low Oxygen, Infection, Restraints or Reduced sensory input, Intracranial disorders, Urinary and fecal retention, Myocardial and pulmonary disorders (ischemia, heart failure, hypoxia) may aid remembering the most common medical causes of POD (145).

When a patient develop POD, simultaneous supportive care, complications prevention, and behavioral symptoms management are also required (133). Cognitive stimulation and clear communication with patients are essential alongside with family involvement, mobilization, reduction of restraint and devices (bladder catheter, venous access), sensory deficits mitigation (adequate lighting, glasses, hearing aids), and noise reduction (146).

When delirium is severe, causing significant distress to the patient and/or endangering the continuation of life-saving treatments, pharmacological interventions might be necessary (146). It is recommended to start with a single medication at a low dosage (133, 146). The first-line choice is usually haloperidol (0.5/1 mg i.m., repeatable up to a maximum of 5 mg/day) with avoidance of medications with heavy anticholinergic burden (e.g., promazine, chlorpromazine, promethazine) (147). The use of benzodiazepines should be considered only in selected cases, such as Lewy body dementia (marked sensitivity to antipsychotics) and alcohol withdrawal forms (133). Physical restraint should not be routinely used, and it might be considered only if other non-pharmacological and pharmacological approaches have shown to be ineffective (133, 146). In case of physical restraint, monitoring of agitation should be provided regularly to check if restraint measures can be removed (133).

The approach described above underscores the need for comprehensive and coordinated care, emphasizing that managing such a complex syndrome requires a multidisciplinary team dedicated to delirium prevention and management.

6.3. Quality of life and functional recovery

Frailty is synonymous with diminished QoL, and its exacerbation by adverse events significantly compounds the distress in these patient cohorts (148). Cardiac surgery aims to enhance QoL and ameliorate patients' prognosis. However, the

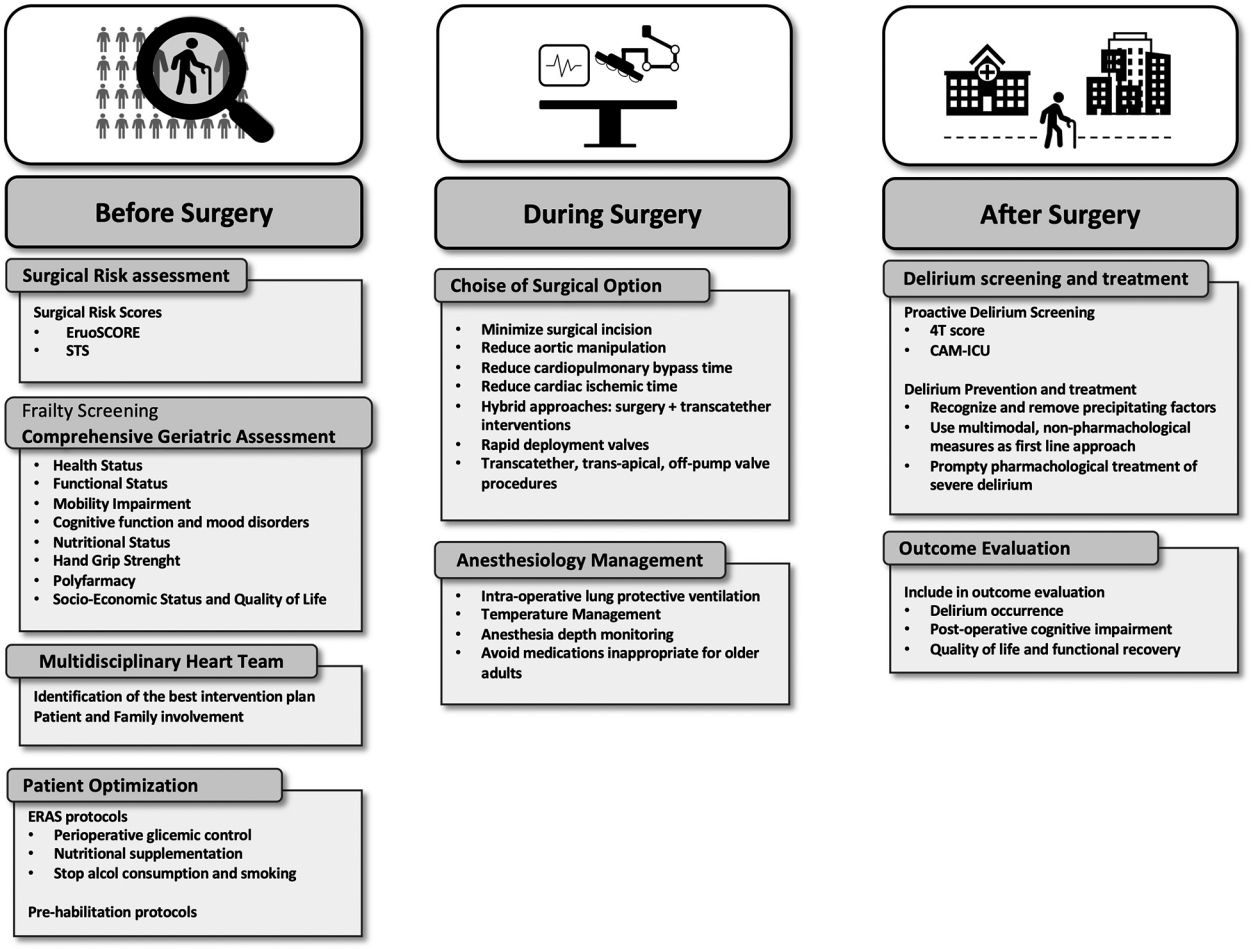

FIGURE 2
Suggested pathways for pre-operative assessment, intropeative optimization and post-operative outcome improvement for frail patients.

latter wanes in significance as age advances. Indeed, for older individuals, the preservation of cognitive and functional capacities, along with the sustenance of a high QoL, usually outwits mere life extension (149). While preoperative risk calculators are useful for predicting the risk of mortality in cardiac operations (150), scant guidance is available to anticipate the potential improvement in postoperative QoL. A systematic review conducted in 2015 showed that QoL tends to improve in most octogenarians following cardiac surgery (151). Nonetheless, 8%–19% of them experience a deterioration of QoL, subsequently regretting their decision to proceed with heart surgery. Given the burgeoning population of geriatric patients, identifying those who will not benefit from an improvement of their QoL is pivotal. Therefore, the development of predictive models for postoperative QoL is warranted to improve the quality of informed consent and ameliorate resources allocation (151).

QoL is closely related to the patient's functional status (152) and functional recovery in the postoperative course (153). Notably, functional decline is closely associated with prolonged length of hospital stay, greater use of healthcare resources, increased likelihood of long-term care admission and high mortality risk (154). Pre-operative impairments in ADLs and disability should be assessed to screen those patients who might benefit from post-operative strategizing, especially concerning aid with self-care during the first 4–6 weeks following cardiac surgery (155). It has been demonstrated that >20% of those aged 70 years and above experience functional decline 3 months post hospital admission in comparison to their preadmission functional status (156), with delirium influencing the association between frailty and variation in the IADL score at 1-month (157). This post-hospitalization functional decline could be predicted using a four-variable model at a threshold of $\geq$1. The contributing factors encompass preadmission daily reliance on assistance in IADL (1 point), use of a walking device (2 point), dependence on assistance for travel (1 point) and no education beyond age 14 (1 point) (156).

In summary, pre-operative assessment of functional and cognitive status might significantly impact care in the post-operative trajectories for frail adults. Further research is warranted to elucidate the role of this potentially powerful tool into routine clinical practice.

7. Conclusions

Frail individuals are characterized by an increased vulnerability to surgical stress due to the decline of their physiological reserve. Indeed, they are at increased risk for complications and poor outcomes after cardiac surgery. Pre-operative assessment of these patients should incorporate a multidimensional frailty evaluation by CGA. An accurate quantification of surgical risk is the first step to identify vulnerable patients suitable for pre-operative optimization programs. Moreover, it allows a shared decision making process which involves patients and family to ensure a patient-centered definition of goals of care and avoid treatment futility. Patients who are deemed suitable for surgery may benefit from a tailored intraoperative strategy aimed to minimize surgical invasiveness e to enhance postoperative recovery. Finally, an early recognition of possible postoperative complications, such as delirium, may enhance patients' recovery toward a better postoperative quality of life (**Figure 2**).

Author contributions

MP: Conceptualization, Writing – original draft, Writing – review & editing. SM: Writing – original draft, Writing – review & editing. MS: Writing – original draft, Writing – review & editing. DP: Writing – review & editing. AB: Writing – original draft, Writing – review & editing. AF: Writing – original draft, Writing – review & editing. ML: Writing – original draft, Writing – review & editing. GF: Supervision, Writing – review & editing. GB: Conceptualization, Supervision, Writing – review & editing. GM: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

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EDITED BY
Pierre-Gregoire Guinot,
Centre Hospitalier Regional Universitaire De Dijon, France

REVIEWED BY
Lei Du,
Sichuan University, China
Maja-Theresa Dieterlen,
Leipzig Heart Center, Germany

*CORRESPONDENCE
Mark G. Filipovic
✉ mark.filipovic@insel.ch

†These authors have contributed equally to this work and share first authorship

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Discovery of plasma proteome markers associated with clinical outcome and immunological stress after cardiac surgery

Corina Bello[1†], Mark G. Filipovic[1*†], Markus Huber[1], Sarah Flannery[2], Beatrice Kobel[3], Roman Fischer[2], Benedikt M. Kessler[2], Lorenz Räber[4], Frank Stueber[1] and Markus M. Luedi[1]

[1]Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [2]Nuffield Department of Medicine, Target Discovery Institute, Centre for Medicines Discovery, University of Oxford, Oxford, United Kingdom, [3]Department for BioMedical Research (DBMR), University of Bern, Bern, Switzerland, [4]Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland

Background: Molecular mechanisms underlying perioperative acute phase reactions in cardiac surgery are largely unknown. We aimed to characterise perioperative alterations of the acute phase plasma proteome in a cohort of adult patients undergoing on-pump cardiac surgery using high-throughput mass spectrometry and to identify candidate proteins potentially relevant to postoperative clinical outcome through a novel, multi-step approach.

Methods: This study is an analysis of the Bern Perioperative Biobank, a prospective cohort of adults who underwent cardiac surgery with the use of cardiopulmonary bypass (CPB) at Bern University Hospital between January and December 2019. Blood samples were taken before induction of anaesthesia and on postoperative day one. Proteomic analyses were performed by mass spectrometry. Through a multi-step, exploratory approach, hit-proteins were first identified according to their perioperative prevalence and dynamics. The set of hit-proteins were associated with predefined clinical outcome measures (all-cause one-year mortality, length of hospital stay, postoperative myocardial infarction and stroke until hospital discharge).

Results: 192 patients [75.5% male, median age 67.0 (IQR 60.0–73.0)] undergoing cardiac surgery with the use of CPB were included in this analysis. In total, we identified and quantified 402 proteins across all samples, whereof 30/402 (7%) proteins were identified as hit-proteins. Three hit-proteins—LDHB, VCAM1 and IGFBP2—demonstrated the strongest associations with clinical outcomes. After adjustment both for age, sex, BMI and for multiple comparisons, the scaled preoperative levels of IGFBP2 were associated with 1-year all-cause mortality (OR 10.63; 95% CI: 2.93–64.00; $p = 0.046$). Additionally, scaled preoperative levels of LDHB (OR 5.58; 95% CI: 2.58–8.57; $p = 0.009$) and VCAM1 (OR 2.32; 95% CI: 0.88–3.77; $p = 0.05$) were found to be associated with length of hospital stay.

Conclusions: We identified a subset of promising candidate plasma proteins relevant to outcome after on-pump cardiac surgery. IGFBP2 showed a strong association with clinical outcome measures and a significant association of preoperative levels with 1-year all-cause mortality. Other proteins strongly associated with outcome were LDHB and VCAM1, reflecting the dynamics in the

Abbreviations
CPB, cardiopulmonary bypass; IGFBP2, insulin-like growth factor binding protein 2; LDHB, lactate dehydrogenase B; SERPIN, serin-protease inhibitor; VCAM1, vascular cellular adhesion molecule-1.

acute phase response, inflammation and myocardial injury. We recommend further investigation of these proteins as potential outcome markers after cardiac surgery.

Clinical Trial Registration: ClinicalTrials.gov; NCT04767685, data are available via ProteomeXchange with identifier PXD046496.

KEYWORDS

cardiopulmonary bypass, acute phase, proteomics, proteome, outcome, cardiovascular surgery, cardiac surgery

1. Introduction

Invasive procedures resulting in an altered tissue integrity or contact with foreign materials, such as surgery or the use of cardiopulmonary bypass (CPB), are a source of trauma that induce a variety of inflammatory reactions (1). Such alterations of the immunological homeostasis have a critical impact on patient outcome (1, 2). In cardiac surgery, suspected contributing factors range from effects of the blood contacting the extracorporeal circuit, the sheer stress, the surgical trauma *per se* or lung reperfusion injury upon discontinuation of bypass (3). Nevertheless, despite decades of research, the exact mechanisms behind the systemic inflammatory response, damages of ischemia-reperfusion and subsequent high risk of organ injury and postoperative morbidity in patients undergoing CPB are not well understood (4). Moreover, we are currently unable to reliably identify patients at risk of a pronounced inflammatory response and thus complicated postoperative course.

At least in part, this gap of knowledge can be attributed to the complexity of inflammatory mechanisms, which typically involve a wide array of interrelated pathways, metabolites and interactions. Changes in functional immunity cannot be adequately assessed by routine inflammatory biomarkers such as C-reactive protein, procalcitonin, or numerical analysis of leukocyte (sub)-counts (2). In this context, proteomic analysis includes ideal means to analyse underlying mechanisms of diseases, medical treatments or complex critical conditions such as inflammatory responses to CPB through time-dependent analysis of activated proteins (5). Previous plasma proteomics studies revealed acute phase and inflammatory responses in response to surgical trauma (6), representing a part of complex immunological alterations following surgical stress (7–9), which are highly relevant to clinical outcome: Perioperative hyperinflammation may not only lead to organ dysfunction and death through a massive liberation of pro-inflammatory mediators (10) but can also induce a state of immunosuppression predisposing the individual to post-operative septic complications and infections (11). Identifying those at risk and seeking to attenuate or modulate the response to surgical trauma has the potential to reduce postoperative mortality and morbidity and save billions of dollars in healthcare costs (12).

However, the vast amount of data generated by proteomic analyses presents a challenge to both clinicians and statisticians (13). Tackling this challenge requires innovative methodologic approaches, but might offer the possibility to improve our understanding of underlying mechanisms in perioperative inflammation and may help to identify new prognostic markers and therapeutic targets, which could ultimately improve perioperative care of the individual patient.

Therefore, we aimed to characterise the perioperative acute phase response through mass-spectrometric analysis of the acute phase proteome in a cohort of adult patients undergoing on-pump cardiac surgery. Through application of a novel, multi-step approach including the association with clinical endpoints, we wanted to identify a subset of hit-proteins among the list of proteins detected by mass-spectrometry, which are likely to play a key role in the perioperative acute phase reaction in cardiac surgery patients and which are potentially relevant to postoperative clinical outcome.

2. Materials and methods

2.1. Study design and study population

This study is an analysis of the Bern Perioperative Biobank (ClinicalTrials.gov; NCT04767685; Submitted: December 16, 2020; principal investigator: Markus M Luedi), a prospective cohort of 192 adult patients undergoing non-emergency cardiac surgery at the Bern University Hospital between January 2019 and December 2019, described elsewhere (14, 15). In brief, all patients underwent elective cardiac surgery (coronary artery bypass grafting, replacement or repair of aortic, mitral or tricuspid valves, surgery of the ascending aorta or aortic arch) with the use of conventional extracorporeal circulation circuits or minimally invasive extracorporeal circulation circuits (16). Emergency surgery or the presence of (suspected) pregnancy were exclusion criteria. Written informed consent was obtained from all participants and the local ethics committee approved the study (Cantonal Ethics Commission of Bern, Bern, CH—KEK Nr. 2018-01272 for sampling and KEK Nr. 2019–2000 for data analysis). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed throughout the manuscript.

2.2. Blood sampling and acute phase proteome analysis

The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the PRIDE (17) partner repository with the dataset identifier PXD046496. Blood samples (EDTA) were

collected before induction of general anaesthesia (preoperative) and 24 h after surgery (postoperative) and stored at the Bern Liquid Biobank as described before (14, 15). Samples were diluted 10-fold in 5% sodium dodecyl sulphate, 100 mM triethylammonium bicarbonate pH 7.5 then centrifuged at 2,500 rcf for 15 min at ambient temperature. The supernatant was taken and subjected to cysteine reduction and alkylation for 30 min at ambient temperature with 10 mM tris(2-carboxyethyl) phosphine and 50 mM iodoacetamide, respectively. Samples were then processed by S-trap 96-well plate protocol (Protifi) according to the manufacturer's instructions. Digestion was performed overnight at 37°C with 5 µg trypsin (TPCK-treated, Worthington) per 3 μl processed plasma. The resulting peptide samples were dried by vacuum centrifugation then reconstituted in 3% acetonitrile, 0.1% formic acid prior to MS analysis. Peptide samples were loaded onto Evotips (Evosep) according to the manufacturer's instructions and analysed by LC-MS/MS using an Evosep One liquid chromatography system coupled to a TimsTOF Pro mass spectrometer (Bruker). Peptides were chromatographically separated using the 60 samples per day standard Evosep method. The mass spectrometer was operated in diaPASEF mode using 8 diaPASEF scans per TIMS-MS scan. The ion mobility range was set to 0.85–1.3 Vs/cm^2. Each mass window isolated was 25 m/z wide, ranging from 475 to 1,000 m/z with an ion mobility-dependent collision energy that increased linearly from 20 eV to 59 eV between 0.6–1.6 Vs/cm^2. Raw MS data were searched in DIA-NN v1.8 against the UniProt human proteome database (UP000000589, downloaded 30th May 2022) plus common contaminants. Identified peptides were permitted a maximum of 1 missed cleavage and cysteine carbamidomethylation was set as a fixed modification, with the MS1 and MS2 mass accuracies both set to 10 ppm, and both match-between-runs and RT-dependent cross-run normalisation enabled.

Conventional CRP was analyzed according to standardized routine laboratory methods (cobas® CRP4 by Roche Diagnostics GmbH, Mannheim, Germany). The perioperative CRP measurements featured values below the detection threshold of 3 mg/L. These values were set to a default value of 2.99 mg/L.

2.3. Clinical outcome measures and other study variables

Clinical outcome measures for this analysis were all-cause one-year mortality, length of hospital stay as well as periprocedural myocardial infarction and stroke (recorded until hospital discharge). Myocardial infarction was adjudicated according to the fourth universal definition of myocardial infarction (18) and periprocedural stroke was defined as acute clinically overt neurological deficit with imaging evidence of cerebral ischemia or bleeding.

Pre-, peri-, and postoperative data for each patient were collected from electronic patient charts (Dendrite Clinical Systems Ltd., Henley on-Thames, UK). Information on all-cause mortality was obtained from internal hospital records or from the national records. European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was calculated to assess the presumed risk of 30-day all-cause mortality (19).

2.4. Multi-step hit detection procedure

A graphical representation of our hit protein selection process is provided in **Figure 1**.

Initially, we imposed two data availability criteria: First, a measurement of a particular protein should be available both pre-

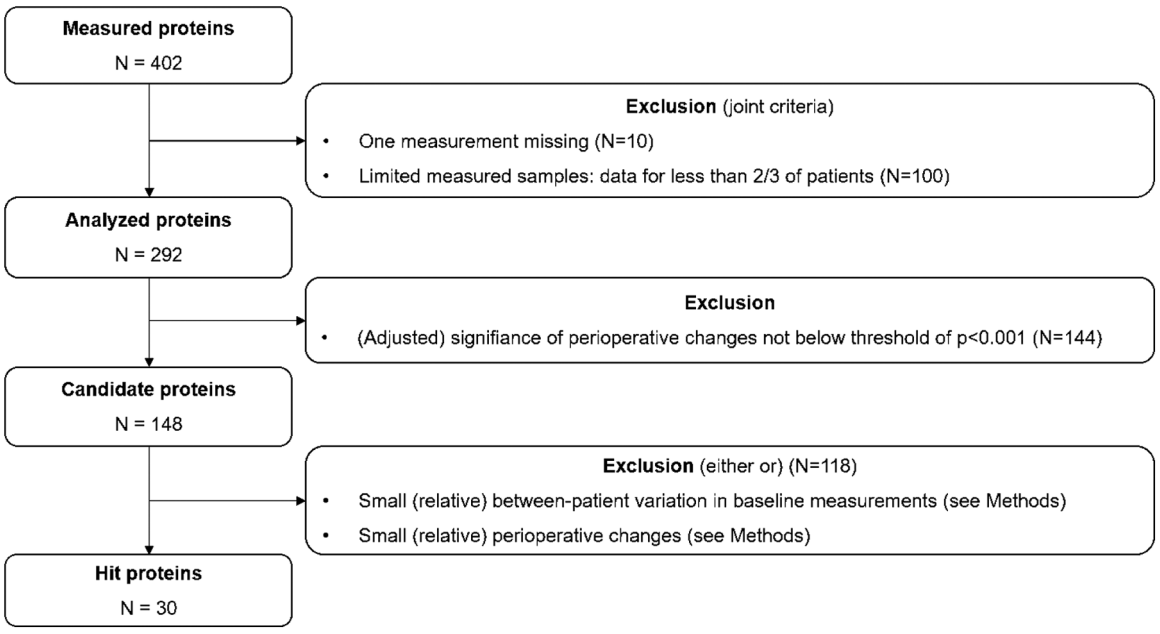

FIGURE 1
Flow chart of the hit protein selection process.

and post-operatively. Second, a measurement of a particular protein should be available in at least two-thirds of the patients. We refer to the remaining set of proteins as the *analysed proteins*. Note that proteins that are not present at all or only present in a minority of patients preoperatively, but emerge during or after the surgery, are therefore—by definition—excluded from this analysis.

In addition, the analysed acute phase proteins were grouped into Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAYS according to the KEGG-PATHWAY database (20), using the following KEGG-PATHWAY-classifications: metabolism, genetic information processing, environmental information processing, cellular processes, organismal systems, multiple categories, unknown/unclassified. This step served as a purely exploratory measure to guide the interpretation of the hit selection procedure.

To be able to compare different proteins, we scaled each protein measurement by first subtracting the median value (pooled across the two time points) and then by dividing the residual by the interquartile range; the scaling is thus similar to the computation of a z-score, but accounts for possible skewness in the measured values by considering the median and interquartile range instead of the mean and standard deviation.

As a next step, we assessed the statistical significance of the perioperative change in the analysed proteins by means of a paired samples Wilcoxon test. Given the large number of candidate proteins, the resulting p-values were adjusted for multiple comparison by means of the Bonferroni correction. Only proteins with adjusted p-values < 0.001 were subsequently considered: we denote this set as the *candidate proteins*.

As final step, a two-dimensional, empirical approach was chosen to determine the final set of hit proteins. The first dimension considers the perioperative change in protein levels among the candidate proteins, which should show either a large decrease or large increase perioperatively. The second dimension requires hit proteins to demonstrate some degree of inter-patient variability: if there is no inter-patient variability, for example all patients feature exactly the same (statistically significant) increase in protein levels, then this change is unlikely to be related to a particular outcome such as length of hospital stay (which does feature inter-patient variability). The joint consideration of these two dimensions defines an area of interest in a two-dimensional space defined by the (scaled) median perioperative change in protein levels ($\boldsymbol{x}$) and the variation (defined by means of the interquartile range) in perioperative protein levels ($\boldsymbol{y}$).

We then defined a distance ($\boldsymbol{d}$) in this space as follows: $\boldsymbol{d}^2 = 0.66^*\boldsymbol{x}^2 + 0.33^*\boldsymbol{y}^2$, thus defining an ellipse in the two-dimensional space. The final set of hit proteins is defined as those 20% of proteins with the largest distances: for these proteins, the distance is greater than the 80%-quantile of all distances [denoted as $\boldsymbol{d}_{\mathbf{q(0.8)}}$]. All computations were performed with R version 4.0.2 (21).

2.5. Outcome analysis

For the final set of hit proteins, we computed both crude and adjusted (age, gender and BMI) odds ratios (ORs) with the four clinical outcomes of interest by means of univariable and multivariable logistic regression. For each clinical outcome individually, the p-values resulting from this analysis were adjusted for multiple comparison by means of the Bonferroni correction. For exploratory purposes, we further calculated univariable association of preoperative protein levels as well as their perioperative changes with a set of baseline covariates (**Supplementary Material**).

3. Results

3.1. Patient / study population characteristics

A total of 192 patients [75.5% male, median age 67.0 (IQR 60.0–73.0)] undergoing cardiac surgery with the use of CPB were included in this analysis. Both baseline characteristics as well as procedural and surgical characteristics have been extensively described previously (**Table 1**) (14, 15). Mean CRP

TABLE 1 Patient and surgical characteristics.

	All patients	N
	N = 192	
Age (years)	67 [60;73]	192
Sex (female)	47 (24.5%)	192
BMI (kg/m^2)	26.1 [23.7;30.4]	192
Diabetes on insulin (Yes)	35 (18.2%)	192
Hypertension (Yes)	130 (68.4%)	190
Dyslipidemia (Yes)	111 (58.1%)	191
Smoker		188
Non-smoker	97 (51.6%)	
Previous / current smoker	91 (48.4%)	
Obesity (Yes)	52 (27.1%)	192
Preoperative renal disease (Yes)	43 (22.4%)	192
Peripheral vascular disease (Yes)	11 (6.2%)	178
Carotid disease (Yes)	6 (3.7%)	162
Myocardial infarction (Yes)	20 (10.5%)	191
COPD (Yes)	23 (12.1%)	190
NYHA (>1)	131 (68.6%)	191
CCS (>0)	71 (37.6%)	189
Ejection Fraction (%)	60 [55;65]	191
EuroSCORE 2	1.73 [0.90;2.93]	184
ECC or MiECC		192
ECC	149 (77.6%)	
MiECC	43 (22.4%)	
Deep hypothermic cardiac arrest (Yes)	19 (10.0%)	191
Aortic valve (Yes)	86 (44.8%)	192
Mitral valve (Yes)	45 (23.4%)	192
Tricuspid valve (Yes)	17 (8.9%)	192
Coronary artery bypass (Yes)	77 (40.1%)	192
Ascending Aortic (Yes)	38 (19.8%)	192
Aortic Arch (Yes)	11 (5.7%)	192
Bypass time (min)	104 [80;132]	192
Aortic cross clamping (min)	68.5 [52.0;91.8]	192
Lowest body temperature (°C)	33.2 [32.1;33.8]	192
Operation duration (min)	234 [195;276]	192

Data expressed as median [IQR] or number (%).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; NYHA, new york heart association; CCS, canadian cardiovascular society.
Both baseline characteristics as well as procedural and surgical characteristics have been extensively described previously (14, 15).

levels measured with conventional routine laboratory methods at baseline were 3.0 mg/dl [3.0; 3.2] and fully reported in Supplementary Table S2 for the perioperative period.

3.2. Multi-step hit detection

In total, we identified 402 proteins in our samples (a list of all detected proteins can be found in the Supplementary: Supplementary Table S1). Out of the 402 identified proteins, 292 / 402 (73%) proteins were detectable at both time points of the serum sampling. Of those, 148 / 402 (37%) showed significant perioperative changes at a threshold below $p < 0.001$. After exclusion of all proteins with only small (relative) in-between patient variation regarding both, baseline measurements and perioperative changes, 30 / 402 proteins (7%) were identified as hit-proteins (Figure 2). An overview of the 30 identified hit-proteins including pre- and postoperative levels, perioperative change and KEGG pathway database category (20) is provided in Table 2. Association of unadjusted preoperative protein levels with baseline characteristics is shown in Supplementary Figures S1, S2, and for perioperative change in Supplementary Figures S3, S4, respectively.

3.3. Association of hit-proteins with clinical outcome measures

After adjusting for age, BMI and gender, several hit-proteins baseline spectral counts ($n = 9/30$, 30%) and perioperative changes ($n = 8/30$, 27%) were significantly associated with clinical outcomes (Tables 3, 4). The three hit-proteins which showed the strongest associations with clinical outcomes were VCAM1, LDHB and IGFBP2, while the SERPINs yielded a large number of associations with outcome measures. After adjustment for multiple comparison, the associations of preoperative levels of IGFBP2 with 1-year all-cause mortality (OR 10.63; 95% CI: 2.93–64.00; p = 0.046), and the associations of preoperative levels of LDHB (OR 5.58; 95% CI: 2.58–8.57; $p = 0.009$) and VCAM1 (OR 2.32; 95% CI: 0.88–3.77; $p = 0.05$) with length of hospital stay remained significant (Table 3), while no association of perioperative change of any protein with clinical outcome measures could be observed (Table 4).

FIGURE 2
Illustration of the selection of hit proteins from the set of candidate proteins (see Figure 1) based on the magnitude of the change from baseline (preoperative) values and the between-patient variation in the perioperative changes. Note that centered (by the median) and scaled (by the interquartile range) protein levels are used. The grey ellipse includes the 80% of proteins with the shortest distances in this two-dimensional space [e.g. distances below the 80% quantile of all distances: $d_{q(0.8)}$; see Methods]. Proteins are declared as hits when their corresponding values are above the threshold values [$d_{q(0.8)}$].

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TABLE 2 Characteristics of the 30 proteins selected for further analysis.

Protein	Preoperative levels	Postoperative levels	Perioperative change	*p* value	Protein name	Protein description	KEGG pathway database classification	Specification of organismal systems
	Median [IQR]	Median [IQR]	Median [IQR]	(adjusted *p*)				
ACTA1	−0.29 [−0.57 to 0.07]	0.47 [−0.03 to 0.89]	0.57 [0.10 to 1.18]	<0.001 (<0.001)	ACTS_HUMAN	Actin, alpha skeletal muscle	4	
ACTB; ACTG1	−0.42 [−0.69 to −0.10]	0.50 [0.12 to 1.04]	0.93 [0.48 to 1.44]	<0.001 (<0.001)	ACTB_HUMAN; ACTG_HUMAN	Actin, cytoplasmic 1	5	Immune system, endocrine system, digestive system, environmental adaptation
AGT	−0.44 [−0.68 to −0.15]	0.45 [0.10 to 0.78]	0.86 [0.57 to 1.18]	<0.001 (<0.001)	ANGT_HUMAN	Angiotensinogen	3; 5	Endocrine, circulatory
ALDOA	−0.45 [−0.67 to −0.13]	0.44 [0.09 to 0.85]	0.85 [0.51 to 1.30]	<0.001 (<0.001)	ALDOA_HUMAN	Fructose-bisphosphate aldolase A	1; 3	
C1S	−0.24 [−0.65 to 0.16]	0.28 [−0.19 to 0.74]	0.58 [−0.03 to 1.09]	<0.001 (<0.001)	C1S_HUMAN	Complement C1s subcomponent	5	Immune
CAT	−0.43 [−0.70 to −0.01]	0.34 [0.00 to 0.92]	0.81 [0.19 to 1.41]	<0.001 (<0.001)	CATA_HUMAN	Catalase	1; 3; 4; 5	Aging
CD14	−0.41 [−0.64 to −0.15]	0.57 [0.18 to 1.01]	0.95 [0.60 to 1.31]	<0.001 (<0.001)	CD14_HUMAN	Monocyte differentiation antigen CD14	3; 4; 5	Immune
CRP	−0.39 [−0.40 to −0.36]	0.61 [0.36 to 0.92]	0.99 [0.71 to 1.28]	<0.001 (<0.001)	CRP_HUMAN	C-reactive protein	no KO	
CST3	−0.23 [−0.70 to 0.19]	0.22 [−0.18 to 0.92]	0.62 [0.10 to 1.18]	<0.001 (<0.001)	CYTC_HUMAN	Cystatin-C	5	Digestive
GAPDH	−0.28 [−0.71 to 0.27]	0.25 [−0.19 to 0.70]	0.60 [−0.09 to 1.06]	<0.001 (<0.001)	G3P_HUMAN	Glyceraldehyde-3-phosphate dehydrogenase	1; 3	
GSTO1	−0.31 [−0.61 to 0.00]	0.54 [0.00 to 1.17]	0.86 [0.35 to 1.29]	<0.001 (<0.001)	GSTO1_HUMAN	Glutathione S-transferase omega-1	1	
IGFBP2	−0.29 [−0.49 to 0.00]	0.50 [0.00 to 1.08]	0.72 [0.38 to 1.37]	<0.001 (<0.001)	IBP2_HUMAN	Insulin-like growth factor-binding protein 2	2	
LBP	−0.35 [−0.43 to −0.27]	0.65 [0.41 to 0.93]	0.96 [0.75 to 1.24]	<0.001 (<0.001)	LBP_HUMAN	Lipopolysaccharide-binding protein	3; 5	Immune
LCP1	−0.40 [−0.75 to 0.00]	0.43 [0.00 to 0.73]	0.72 [0.30 to 1.22]	<0.001 (<0.001)	PLSL_HUMAN	Plastin-2	4	
LDHB	−0.33 [−0.49 to −0.15]	0.66 [0.20 to 1.21]	0.97 [0.60 to 1.43]	<0.001 (<0.001)	LDHB_HUMAN	L-lactate dehydrogenase B chain	1; 3; 5	Endocrine
LRG1	−0.43 [−0.54 to −0.29]	0.52 [0.25 to 0.90]	0.91 [0.66 to 1.23]	<0.001 (<0.001)	A2GL_HUMAN	Leucine-rich alpha-2-glycoprotein	no KO	
MAN1A1	−0.42 [−0.64 to −0.24]	0.56 [0.27 to 0.90]	0.99 [0.68 to 1.31]	<0.001 (<0.001)	MA1A1_HUMAN	Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA	1; 2	
PCSK9	−0.25 [−0.63 to 0.23]	0.28 [−0.16 to 0.83]	0.51 [−0.09 to 1.03]	<0.001 (<0.001)	PCSK9_HUMAN	Proprotein convertase subtilisin/kexin type 9	5	Digestive
PDE4DIP	−0.33 [−0.53 to 0.04]	0.41 [−0.03 to 0.91]	0.64 [0.16 to 1.18]	<0.001 (<0.001)	MYOME_HUMAN	Myomegalin	2	
PFN1	−0.40 [−0.67 to 0.07]	0.31 [−0.09 to 0.79]	0.69 [0.28 to 1.19]	<0.001 (<0.001)	PROF1_HUMAN	Profilin-1	3; 4	
S100A8	−0.39 [−0.58 to −0.14]	0.55 [0.17 to 1.16]	0.92 [0.56 to 1.45]	<0.001 (<0.001)	S10A8_HUMAN	Protein S100-A8	5	Immune
SAA1	−0.27 [−0.27 to −0.25]	0.73 [0.40 to 0.96]	0.95 [0.62 to 1.20]	<0.001 (<0.001)	SAA1_HUMAN	Serum amyloid A-1 protein	4	
SAA4	−0.33 [−0.61 to 0.03]	0.43 [−0.06 to 0.85]	0.74 [0.27 to 1.21]	<0.001 (<0.001)	SAA4_HUMAN	Serum amyloid A-4 protein	4	
SERPINA1	−0.47 [−0.64 to −0.24]	0.52 [0.26 to 0.74]	0.91 [0.65 to 1.18]	<0.001 (<0.001)	A1AT_HUMAN	Alpha-1-antitrypsin	5	Immune
SERPINA10	−0.47 [−0.66 to −0.23]	0.52 [0.22 to 0.77]	0.86 [0.68 to 1.18]	<0.001 (<0.001)	ZPI_HUMAN	Protein Z-dependent protease inhibitor	1	
SERPINA3	−0.51 [−0.60 to −0.37]	0.49 [0.29 to 0.74]	1.00 [0.74 to 1.25]	<0.001 (<0.001)	AACT_HUMAN	Alpha-1-antichymotrypsin	5	Immune (complement and coagulation)
SERPINA5	0.58 [0.22 to 0.92]	−0.35 [−0.59 to −0.11]	−0.92 [−1.20 to −0.60]	<0.001 (<0.001)	IPSP_HUMAN	Plasma serine protease inhibitor	5	Immune (complement and coagulation)
SPP2	0.47 [−0.07 to 0.96]	−0.26 [−0.54 to 0.06]	−0.68 [−1.16 to −0.23]	<0.001 (<0.001)	SPP24_HUMAN	Secreted phosphoprotein 24	no KO	
VCAM1	−0.24 [−0.69 to 0.10]	0.38 [−0.15 to 0.99]	0.65 [0.19 to 1.24]	<0.001 (<0.001)	VCAM1_HUMAN	Vascular cell adhesion protein 1	3; 5	Immune
VCL	−0.37 [−0.64 to −0.02]	0.51 [0.02 to 1.11]	0.94 [0.47 to 1.46]	<0.001 (<0.001)	VINC_HUMAN	Vinculin	4; 5	Immune

Note that centered (by the median) and scaled (by the interquartile range) protein levels are used in the computations (see Methods).

TABLE 3 Adjusted associations of preoperative protein levels with postoperative outcome.

Protein	Stroke		Myocardial infarction		1-year mortality		Length of stay	
	Incidence 12/192 (6.3%)		Incidence 6/192 (3.1%)		Incidence 5/192 (2.6%)		Median 7 [IQR: 6–9] days	
	OR (95%-CI)	*p* (adjusted *p*)	OR (95%-CI)	*p* (adjusted *p*)	OR (95%-CI)	*p* (adjusted *p*)	Beta (95%-CI)	*p* (adjusted *p*)
ACTA1	1.07 (0.24–3.88)	0.92 (>0.99)	0.04 (0.00–1.00)	0.13 (>0.99)	1.56 (0.23–7.67)	0.60 (>0.99)	0.54 (−1.96–3.05)	0.67 (>0.99)
ACTB;ACTG1	0.98 (0.18–4.48)	0.98 (>0.99)	0.10 (0.00–1.24)	0.13 (>0.99)	1.26 (0.13–8.62)	0.82 (>0.99)	1.40 (−0.67–3.46)	0.18 (>0.99)
AGT	1.18 (0.35–3.10)	0.75 (>0.99)	0.05 (0.00–0.67)	0.039 (>0.99)	0.85 (0.08–3.31)	0.86 (>0.99)	2.23 (0.35–4.10)	0.02 (0.61)
ALDOA	1.44 (0.30–5.26)	0.61 (>0.99)	0.21 (0.02–1.50)	0.18 (>0.99)	0.64 (0.04–4.16)	0.70 (>0.99)	1.47 (−0.60–3.53)	0.16 (>0.99)
C1S	0.59 (0.24–1.52)	0.27 (>0.99)	1.84 (0.35–11.78)	0.49 (>0.99)	0.78 (0.24–2.95)	0.70 (>0.99)	0.31 (−0.93–1.56)	0.62 (>0.99)
CAT	1.08 (0.37–2.38)	0.86 (>0.99)	0.03 (0.00–0.70)	0.07 (>0.99)	0.46 (0.03–2.21)	0.49 (>0.99)	0.58 (−0.85–2.00)	0.43 (>0.99)
CD14	1.51 (0.24–9.15)	0.65 (>0.99)	1.19 (0.12–9.17)	0.87 (>0.99)	2.49 (0.20–26.48)	0.46 (>0.99)	−0.90 (−3.43–1.63)	0.48 (>0.99)
CRP	0.35 (0.00–10.49)	0.70 (>0.99)	0.00 (0.00–6.39)	0.29 (>0.99)	2.03 (0.00–40.35)	0.70 (>0.99)	1.27 (−4.84–7.39)	0.68 (>0.99)
CST3	1.56 (0.85–2.73)	0.12 (>0.99)	0.13 (0.01–0.73)	0.049 (>0.99)	2.08 (0.90–4.49)	0.06 (>0.99)	1.02 (−0.09–2.14)	0.07 (>0.99)
GAPDH	0.47 (0.15–1.24)	0.17 (>0.99)	0.47 (0.10–1.57)	0.29 (>0.99)	0.91 (0.22–1.81)	0.87 (>0.99)	−0.45 (−1.31–0.41)	0.30 (>0.99)
GSTO1	0.80 (0.14–3.34)	0.79 (>0.99)	0.07 (0.00–1.63)	0.20 (>0.99)	0.63 (0.03–4.52)	0.72 (>0.99)	0.81 (−1.15–2.78)	0.41 (>0.99)
IGFBP2	1.12 (0.20–3.90)	0.88 (>0.99)	0.24 (0.00–2.73)	0.46 (>0.99)	10.63 (2.93–64.00)	0.002 (0.046)	2.17 (0.25–4.09)	0.027 (0.82)
LBP	2.57 (0.03–67.82)	0.62 (>0.99)	0.50 (0.00–102.71)	0.82 (>0.99)	1.09 (0.00–68.90)	0.97 (>0.99)	1.86 (−3.63–7.35)	0.50 (>0.99)
LCP1	2.08 (0.81–4.80)	0.09 (>0.99)	1.25 (0.20–5.11)	0.78 (>0.99)	0.64 (0.10–2.44)	0.59 (>0.99)	1.48 (0.10–2.86)	0.035 (>0.99)
LDHB	1.60 (0.22–10.29)	0.63 (>0.99)	0.65 (0.02–13.32)	0.80 (>0.99)	0.61 (0.02–10.71)	0.77 (>0.99)	5.58 (2.58–8.57)	0.0003 (0.009)
LRG1	1.09 (0.07–6.77)	0.94 (>0.99)	0.08 (0.00–2.53)	0.34 (>0.99)	4.89 (0.59–28.23)	0.09 (>0.99)	1.29 (−1.77–4.34)	0.41 (>0.99)
MAN1A1	0.28 (0.02–2.41)	0.32 (>0.99)	2.55 (0.09–36.24)	0.55 (>0.99)	0.55 (0.02–5.54)	0.70 (>0.99)	−0.93 (−3.37–1.50)	0.45 (>0.99)
PCSK9	1.25 (0.33–2.78)	0.66 (>0.99)	1.66 (0.54–3.52)	0.24 (>0.99)	0.93 (0.15–2.40)	0.92 (>0.99)	−0.02 (−1.19–1.16)	0.98 (>0.99)
PDE4DIP	0.33 (0.02–1.08)	0.26 (>0.99)	1.29 (0.38–3.15)	0.61 (>0.99)	0.88 (0.19–1.92)	0.81 (>0.99)	0.08 (−1.02–1.19)	0.88 (>0.99)
PFN1	0.49 (0.08–2.16)	0.39 (>0.99)	0.11 (0.00–1.00)	0.15 (>0.99)	1.29 (0.18–7.77)	0.79 (>0.99)	0.50 (−1.53–2.53)	0.63 (>0.99)
S100A8	0.16 (0.01–1.27)	0.17 (>0.99)	0.67 (0.04–2.26)	0.61 (>0.99)	1.25 (0.25–2.87)	0.67 (>0.99)	−0.02 (−1.59–1.56)	0.98 (>0.99)
SAA1	0.07 (0.00–4.93)	0.68 (>0.99)	0.39 (0.00–37.64)	0.81 (>0.99)	1.05 (NA[a] - 10.50)	0.98 (>0.99)	−0.17 (−4.25–3.91)	0.93 (>0.99)
SAA4	0.62 (0.16–1.98)	0.44 (>0.99)	0.45 (0.05–2.38)	0.40 (>0.99)	0.75 (0.11–3.81)	0.75 (>0.99)	0.22 (−1.50–1.94)	0.80 (>0.99)
SERPINA1	0.53 (0.06–3.67)	0.54 (>0.99)	0.01 (0.00–0.78)	0.08 (>0.99)	5.13 (0.51–43.46)	0.14 (>0.99)	3.75 (1.27–6.24)	0.003 (0.1)
SERPINA10	0.67 (0.10–3.79)	0.66 (>0.99)	1.95 (0.09–43.22)	0.66 (>0.99)	1.89 (0.13–22.55)	0.62 (>0.99)	−0.26 (−2.98–2.47)	0.85 (>0.99)
SERPINA3	1.29 (0.06–11.40)	0.85 (>0.99)	0.37 (0.00–5.93)	0.56 (>0.99)	7.76 (0.80–61.44)	0.044 (>0.99)	1.25 (−2.17–4.68)	0.47 (>0.99)
SERPINA5	0.29 (0.09–0.92)	0.038 (>0.99)	1.52 (0.30–9.51)	0.63 (>0.99)	0.24 (0.04–1.17)	0.08 (>0.99)	0.22 (−1.39–1.83)	0.79 (>0.99)
SPP2	0.71 (0.31–1.49)	0.38 (>0.99)	1.18 (0.30–4.40)	0.81 (>0.99)	1.12 (0.34–3.43)	0.85 (>0.99)	−0.84 (−2.08–0.40)	0.18 (>0.99)
VCAM1	1.80 (0.80–4.01)	0.15 (>0.99)	0.50 (0.05–2.94)	0.50 (>0.99)	1.92 (0.54–5.73)	0.26 (>0.99)	2.32 (0.88–3.77)	0.002 (0.05)
VCL	1.60 (0.26–9.58)	0.60 (>0.99)	0.09 (0.00–3.23)	0.26 (>0.99)	1.58 (0.18–12.07)	0.66 (>0.99)	1.98 (−0.59–4.54)	0.13 (>0.99)

[a]Lower bound of profile likelihood confidence interval could not be computed.
Odds ratios (ORs) and 95%-confidence intervals derived from a multivariable linear regression are shown for binary outcomes, whereas regression coefficient and their 95%-confidence intervals computed with a multivariable linear regression are shown for the continuous outcome length of hospital stay. The associations are adjusted for age, gender and BMI. *P*-values are adjusted for multiple comparison for each outcome separately by means of the Bonferroni correction.

3.4. Discussion

Through our innovative multi-step approach, we were able to identify a small subset of proteins within the acute phase proteome, which show relevant associations with clinical outcome measures, and are therefore promising candidates for pre- and perioperative acute phase response monitoring and potentially risk stratification.

As is the case in our patients with CPB, major changes to the serum proteome from the day of induction of anaesthesia to later postoperative stages have been described in cohorts involving individuals undergoing veno-arterial extracorporeal membrane oxygenation (22). In this study, three hit-proteins showed the strongest associations with clinical outcomes, VCAM1, IGFBP2 and LDHB, while the SERPINs yielded a large number of associations with outcome measures.

The SERPINs are known to play an important role in cardiovascular disease (23, 24). They are involved in the finely tuned balance between procoagulant and anticoagulant systems, due to their anticoagulant and antifibrinolytic properties and have even been proposed as a potential therapeutic target (25). Further, SERPINA1 is involved in the immune response by inhibiting ATP-induced interleukin-ß-release (26) and secreted into the bloodstream in response to myocardial infarction (27). Overall, SERPINA1 regulates the expression of chemokines, chemotaxis and cell adhesion and reduces the expression of pro-inflammatory cytokines and up-regulates anti-inflammatory mediators (28). Previous studies have even investigated SERPINA1 augmentation therapy during heart surgery to attenuate postoperative inflammation (26). Both SERPINA3 and SERPINA5 were detected in RNA sequencing of failing right ventricles and proposed as biomarkers for abnormalities in the involved inflammatory processes (29). In another study, SERPINA3 was identified as a potential predictive marker of clinical outcome after myocardial infarction, as the level of this protease inhibitor was found to be directly correlated with other measured inflammatory markers (30). The relevance of the observed association of uncorrected preoperative values with several clinical outcome measures in our study remains to be investigated—speculatively, the SERPINs might serve as a marker of subtle preoperative inflammation and cardiovascular stress.

TABLE 4 Adjusted associations of perioperative change in proteins levels with postoperative outcome.

Protein	Stroke		Myocardial infarction		1-year mortality		Length of stay	
	Incidence 12/192 (6.3%)		Incidence 6/192 (3.1%)		Incidence 5/192 (2.6%)		Median 7 [IQR: 6–9] days	
	OR (95%-CI)	*p* (adjusted *p*)	OR (95%-CI)	*p* (adjusted *p*)	OR (95%-CI)	*p* (adjusted *p*)	Beta (95%-CI)	*p* (adjusted *p*)
ACTA1	1.72 (0.82–3.70)	0.15 (>0.99)	0.98 (0.24–3.29)	0.97 (>0.99)	2.04 (0.81–5.11)	0.12 (>0.99)	0.25 (−1.14–1.64)	0.72 (>0.99)
ACTB;ACTG1	1.64 (0.82–3.39)	0.16 (>0.99)	0.96 (0.23–3.28)	0.95 (>0.99)	3.31 (1.32–8.93)	0.011 (0.32)	0.76 (−0.37–1.90)	0.19 (>0.99)
AGT	0.47 (0.14–1.48)	0.21 (>0.99)	0.79 (0.13–5.10)	0.80 (>0.99)	1.82 (0.29–12.16)	0.52 (>0.99)	−1.63 (−3.44–0.18)	0.08 (>0.99)
ALDOA	1.24 (0.48–2.55)	0.60 (>0.99)	1.07 (0.43–2.15)	0.86 (>0.99)	2.00 (0.84–5.76)	0.12 (>0.99)	0.98 (−0.31–2.27)	0.14 (>0.99)
C1S	0.89 (0.40–1.98)	0.78 (>0.99)	0.94 (0.34–2.59)	0.91 (>0.99)	0.85 (0.30–2.40)	0.77 (>0.99)	0.14 (−0.87–1.16)	0.78 (>0.99)
CAT	1.33 (0.79–2.32)	0.28 (>0.99)	2.01 (0.63–7.04)	0.24 (>0.99)	1.76 (0.71–4.70)	0.22 (>0.99)	−0.40 (−1.32–0.52)	0.39 (>0.99)
CD14	1.61 (0.53–4.56)	0.38 (>0.99)	0.90 (0.17–3.79)	0.89 (>0.99)	1.03 (0.19–4.28)	0.97 (>0.99)	1.02 (−0.50–2.53)	0.19 (>0.99)
CRP	0.99 (0.22–4.70)	0.99 (>0.99)	0.42 (0.02–4.91)	0.50 (>0.99)	1.00 (0.13–7.79)	>0.99 (>0.99)	0.21 (−1.95–2.37)	0.85 (>0.99)
CST3	0.82 (0.38–1.52)	0.58 (>0.99)	0.76 (0.24–2.09)	0.61 (>0.99)	1.48 (0.73–2.55)	0.17 (>0.99)	0.82 (−0.04–1.67)	0.06 (>0.99)
GAPDH	1.62 (0.84–3.14)	0.15 (>0.99)	0.79 (0.40–1.88)	0.54 (>0.99)	1.39 (0.65–3.40)	0.48 (>0.99)	0.52 (−0.19–1.23)	0.15 (>0.99)
GSTO1	2.24 (1.01–5.18)	0.05 (>0.99)	2.46 (0.53–12.31)	0.24 (>0.99)	3.85 (1.27–14.09)	0.021 (0.62)	0.50 (−0.80–1.81)	0.45 (>0.99)
IGFBP2	1.23 (0.66–1.94)	0.42 (>0.99)	0.90 (0.20–1.93)	0.84 (>0.99)	1.83 (1.16–3.06)	0.009 (0.26)	0.96 (0.18–1.74)	0.016 (0.48)
LBP	0.51 (0.06–3.44)	0.51 (>0.99)	0.38 (0.04–2.66)	0.34 (>0.99)	0.29 (0.01–3.79)	0.38 (>0.99)	0.09 (−2.27–2.44)	0.94 (>0.99)
LCP1	0.84 (0.38–1.85)	0.67 (>0.99)	0.82 (0.18–3.62)	0.80 (>0.99)	2.08 (0.68–5.95)	0.18 (>0.99)	−0.66 (−1.77–0.46)	0.25 (>0.99)
LDHB	1.33 (0.55–2.75)	0.48 (>0.99)	2.23 (0.93–6.13)	0.09 (>0.99)	2.51 (1.07–5.80)	0.024 (0.71)	0.63 (−0.53–1.78)	0.29 (>0.99)
LRG1	0.70 (0.12–3.41)	0.67 (>0.99)	0.21 (0.01–2.12)	0.22 (>0.99)	0.21 (0.02–2.02)	0.21 (>0.99)	1.29 (−0.68–3.27)	0.20 (>0.99)
MAN1A1	1.16 (0.36–3.42)	0.79 (>0.99)	0.74 (0.12–3.88)	0.73 (>0.99)	0.49 (0.09–2.45)	0.40 (>0.99)	0.72 (−0.83–2.27)	0.36 (>0.99)
PCSK9	0.75 (0.29–1.99)	0.56 (>0.99)	0.98 (0.41–2.62)	0.97 (>0.99)	0.77 (0.28–2.37)	0.62 (>0.99)	−0.51 (−1.52–0.50)	0.32 (>0.99)
PDE4DIP	1.53 (1.03–2.43)	0.048 (>0.99)	0.44 (0.16–1.03)	0.07 (>0.99)	0.88 (0.49–1.55)	0.67 (>0.99)	0.66 (−0.08–1.40)	0.08 (>0.99)
PFN1	1.25 (0.46–3.56)	0.67 (>0.99)	1.41 (0.31–7.47)	0.67 (>0.99)	1.84 (0.43–9.32)	0.43 (>0.99)	0.48 (−1.12–2.07)	0.56 (>0.99)
S100A8	1.24 (0.87–2.16)	0.30 (>0.99)	0.90 (0.16–1.75)	0.87 (>0.99)	1.88 (1.16–3.65)	0.022 (0.67)	−0.56 (−1.37–0.26)	0.18 (>0.99)
SAA1	0.63 (0.14–2.48)	0.53 (>0.99)	0.91 (0.12–6.34)	0.92 (>0.99)	0.19 (0.02–1.61)	0.16 (>0.99)	−0.57 (−2.45–1.31)	0.55 (>0.99)
SAA4	0.76 (0.35–1.74)	0.49 (>0.99)	0.75 (0.25–2.27)	0.60 (>0.99)	0.45 (0.16–1.34)	0.13 (>0.99)	−0.15 (−1.32–1.02)	0.8 (>0.99)
SERPINA1	0.23 (0.03–1.30)	0.11 (>0.99)	1.48 (0.17–13.56)	0.72 (>0.99)	0.36 (0.03–3.38)	0.39 (>0.99)	−0.74 (−3.04–1.56)	0.53 (>0.99)
SERPINA10	0.25 (0.04–1.35)	0.12 (>0.99)	0.16 (0.01–2.11)	0.19 (>0.99)	0.57 (0.06–5.44)	0.62 (>0.99)	−0.26 (−2.50–1.98)	0.82 (>0.99)
SERPINA3	0.36 (0.05–2.41)	0.30 (>0.99)	0.74 (0.16–3.62)	0.69 (>0.99)	0.47 (0.04–4.57)	0.54 (>0.99)	−0.04 (−2.24–2.15)	0.97 (>0.99)
SERPINA5	1.97 (0.44–9.04)	0.37 (>0.99)	0.81 (0.09–5.95)	0.84 (>0.99)	10.67 (1.31–115.38)	0.034 (>0.99)	−0.19 (−2.12–1.74)	0.85 (>0.99)
SPP2	1.02 (0.44–2.50)	0.97 (>0.99)	1.10 (0.28–5.56)	0.90 (>0.99)	0.89 (0.27–3.42)	0.86 (>0.99)	−0.05 (−1.42–1.31)	0.94 (>0.99)
VCAM1	0.73 (0.33–1.57)	0.43 (>0.99)	2.74 (0.66–13.11)	0.17 (>0.99)	0.52 (0.17–1.49)	0.24 (>0.99)	−0.33 (−1.41–0.75)	0.55 (>0.99)
VCL	2.54 (1.13–6.10)	0.025 (0.76)	0.70 (0.11–3.68)	0.70 (>0.99)	2.06 (0.86–4.70)	0.08 (>0.99)	0.65 (−0.63–1.94)	0.32 (>0.99)

Odds ratios (ORs) and 95%-confidence intervals derived from a multivariable linear regression are shown for binary outcomes, whereas regression coefficient and their 95%-confidence intervals computed with a multivariable linear regression are shown for the continuous outcome length of hospital stay. The associations are adjusted for age, gender and BMI. *P*-values are adjusted for multiple comparison for each outcome separately by means of the Bonferroni correction.

VCAM1, just as SERPINA1, is also involved in inflammatory processes and is activated by tumor necrosis factor alpha and mediates vascular adhesion and trans-endothelial migration of leukocytes (31). This is also the case in myocardial injury, where VCAM1 has been shown to mediate rapid neutrophil mobilization (32). Therefore, the dynamics in VCAM1 levels observed in our study, might be attributed to perioperative myocardial injury and the consecutive inflammatory response. This is important as its serves as a potential target and has been proposed for the treatment of immune disease including autoimmune myocarditis or cancer (33). Furthermore, considering the association of preoperative levels with clinical outcome, VCAM1 has been suggested as a predictive biomarker for heart failure-related mortality and morbidity, endothelial injury in coronary artery disease and arrhythmias such as atrial fibrillation (33). This is also true for the perioperative setting, where an association of high preoperative VCAM1 levels with long-term (median follow-up of 6.7 years) all-cause mortality could be found in patients suffering from cardiovascular disease undergoing on-pump cardiac surgery. This association was independent of inflammatory markers and other cardiovascular risk factors (34). Contrarily, preoperative VCAM1 levels were associated with length of hospital stay but not mortality in our cohort.

IGFPB2 has also been suggested for cardiovascular risk monitoring (35). Its plasma concentration can be used to not only detect heart failure but also distinguish healthy individuals from patients with stable chronic disease. Thus, its diagnostic and prognostic value in heart failure especially when compared to natriuretic peptides is highly promising (36). Further, an early activation of IGFBP2 represents a marker of early smooth muscle cell phenotype modulation in patients suffering from thoracic aortic aneurysms (37). After acute MI, higher IGFPB2-levels were prognostic for higher risks of major adverse cardiac events after discharge (33). Of note, inflammation was shown to be a modulator of the insulin-like growth factor binding protein system in several pathological conditions (38, 39). In light of those findings, it is highly likely, that the association of preoperative IGFBP2 with all-cause mortality is a marker of a higher burden of cardiovascular disease at baseline and that the dynamics during cardiac surgery probably represent further myocardial injury.

The body of evidence confirms that our hit approach led to a conclusive selection of proteins, which are relevant to the dynamics of cardiovascular disease and are heavily altered through the exposition to surgical trauma and CPB. Overall, the identified proteins are likely to play an important role in the acute phase response to cardiac surgery due to their known biological functions in vascular function, coagulation, immune system homeostasis, tissue damage, and hypoxic stress. The inflammatory response to CPB is distinctively different from off-pump surgical trauma, resulting in an upregulation of apoptosis and remodeling markers (40). As shown by Ghorbel et al., cytokines and chemokines after CPB were elevated both at the mRNA level in the myocardium and at the protein level in the blood, suggesting the myocardium as likely source for these proteomic changes (40). The link between myocardial injury, ischemia-reperfusion and inflammation has been extensively investigated (41). While most of the identified proteins are not a direct component of the immune system, their exhibition during myocardial injury together with the interactions with the immune system described above, might reflect the interaction of perioperative myocardial injury with the acute phase response—however, this remains speculative. Most importantly, we cannot deduct whether the dynamics in the perioperative levels of these proteins should be attributed to myocardial injury, the exposition to CPB or a combination of the two. As prophylactically addressing inflammation in cardiac surgery has not shown any advantages (42, 43), a better understanding of the involved pathways during perioperative myocardial injury and the interaction with the acute phase response is crucial to potentially identify new therapeutic targets.

The most established and probably most investigated acute phase protein C-reactive protein (CRP) was also included in our selection of hit proteins. Preoperative CRP levels have been repeatedly shown to be an important determinant of short- and long-term postoperative outcome after on-pump cardiac surgery (44, 45). However, this was not the case in our cohort. Overall, baseline values of the hit-proteins identified in our study seemed to have stronger associations with outcome compared to perioperative change, which might suggest that the preoperative state of the investigated proteins is a stronger determinant of outcome than the perioperative response. Similarly, in contrast to the preoperative levels mentioned above, postoperative CRP levels did not seem be useful for predicting postoperative outcome in several studies (46, 47).

Accordingly, after adjustment for multiple comparison, the associations of preoperative levels of IGFBP2 with 1-year all-cause mortality, and the associations of preoperative levels of LDHB and VCAM1 with length of hospital stay remained significant, while no association of perioperative change of any protein with clinical outcome measures could be observed. As IGFBP2 and VCAM1 have been described above, measuring LDH has traditionally been used as an indicator of myocardial damage or necrosis and has been found to be elevated in patients suffering from valve heart disease, heart failure, and coronary heart disease (48). Levels of preoperative IGFB2 and LDHB were significantly associated with EuroSCORE II (19) at baseline in our cohort, indicating that those patients were probably in a more severe or progressed disease state.

Hence, the identified markers showed potential as prognostic markers before cardiac surgery. Creating combined scores consisting of multiple biomarkers might be a promising new approach for predicting outcome after cardiac surgery and our findings yielded potential candidates for further evaluation. As a most prominent example, the introduction of the cardiac-specific biomarkers natriuretic peptides and cardiac troponins have substantially refined the prognostication of cardiovascular risk in non-cardiac surgery, both independently and complementary to other important indicators of risk (49). Other recent studies have assessed the predictive power of other multimodal scores consisting of hit-proteins and previously identified risk factors such as age, haemoglobin values or serum lactate concentrations to predict neurologic outcomes in emergency patients undergoing cardiac surgery after out-of-hospital cardiac arrest (50). In paediatric patients undergoing on-pump cardiac surgery, a holistic approach to outcome prediction has previously been applied by creating a potential predictor model involving 24 key proteins with significant changes along the perioperative time course (51).

This study has several limitations. The observational design of the study prevents from inferring causal relationship. We did not exclude patients with autoimmune disease or infection. However, a clinically relevant infection is a contraindication for elective heart surgery at our center, which was also represented by the low CRP levels measured at baseline measured by routine laboratory methods, suggesting that the overall preoperative inflammatory status of our patients was low. Further, spectral counting is commonly used for identification and quantitative analysis in proteomics (52). This method has a tendency to mask low-abundance proteins, which are below the detection limit for mass spectrometers (53). Spectral counting allows to indirectly quantify protein levels, but does not represent their biological activity and exact functionality within a complex interrelated system. Further, while our multi-step approach allowed to identify hit-proteins, this methodology might also introduce a selection bias. Most importantly, due to the rigorous predefined selection process, proteins which only emerge during or after surgery or which are only present in a small subset of patients were not included in this analysis. We acknowledge, that those proteins might also play a crucial role in the perioperative acute phase response to cardiac surgery. Further, our analysis protocol led to a very small number of actual hit-proteins. While many of these showed significant associations with clinical outcome measures, an even smaller number of associations remained significant after correcting for multiple testing. However, this correction is essential, as the mass of data generated, might otherwise produce significance by chance. Once again, other important proteins might not have been included in our selection. Overall, despite being clinically motivated, the empirical choices inherent in our multi-step procedures—e.g., the definition of the ellipse when assessing the perioperative changes and the between-patient variation in perioperative protein changes jointly—might be chosen differently.

In conclusion, we were able to identify a subset of promising candidate proteins relevant to outcome after on-pump cardiac

surgery, through applying an innovative multi-step approach. IGFBP2 yielded the most promising results with a strong association with clinical outcome measures and a significant association of preoperative levels with 1-year all-cause mortality. Further proteins with clinically relevant associations were LDHB and VCAM1. We recommend further investigation of these proteins as potential outcome markers after cardiac surgery.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.ebi.ac.uk/pride/archive/projects/PXD046496.

Ethics statement

The local ethics committee approved the study (Cantonal Ethics Commission of Bern, Bern, Switzerland). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. SF: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. BK: Data curation, Investigation, Project administration, Visualization, Writing – review & editing. RF: Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. BK: Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. LR: Investigation, Validation, Visualization, Writing – review & editing. FS: Methodology, Project administration, Resources, Supervision, Writing – review & editing. ML: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

LR reports research grants to the institution by Abbott, Biotronik, Boston Scientific, Heartflow, Infraredx, Swiss National Science Foundation, Sanofi, Regeneron and speaker/consultation Fees by Abbott, Amgen, AstraZeneca, Metronic, Novo Nordisk, Occlutech, Sanofi.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1287724/full#supplementary-material

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EDITED BY
Marco Pocar,
University of Milan, Italy

REVIEWED BY
Matteo Pozzi,
Azienda Socio Sanitaria Territoriale (ASST) di Monza, Italy
Laura DiChiacchio,
The University of Utah, United States

*CORRESPONDENCE
Brock Daughtry
✉ Brock.Daughtry@BHSALA.com

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Case Report: Combined perioperative extracorporeal membrane oxygenation for acute heart failure caused by mitral regurgitation

Brock Daughtry[1]* and John Richardson[2]

[1]Department of Surgery, Brookwood Baptist Health, Birmingham, AL, United States, [2]Department of Cardiothoracic Surgery, Grandview Medical Center, Birmingham, AL, United States

Extracorporeal membrane oxygenation (ECMO) and extracorporeal life support (ECLS) devices are well-established adjunctive treatment measures for patients with heart failure. ECMO can serve as a bridge to transplant in a chronic setting or as a salvage therapy for patients who are unable to be weaned from bypass following cardiac surgery. However, the role of ECMO as a bridge to definitive therapy in a setting of acute heart failure is less established. Similarly, the treatment of patients using combined ECMO and ECLS devices has been, at times, shown to show some benefit; however, these benefits have not been widely studied. In this study, we present the case of a patient who was diagnosed with severe acute onset heart failure secondary to torrential mitral regurgitation following COVID-19 pneumonia. The patient was emergently placed on venoarterial (VA) ECMO with an indwelling centrifugal pump device in the left ventricle. This combination of ECMO and ECLS served as a bridge to open mitral valve replacement 6 days after presentation. Following successful mitral valve replacement, the patient had persistent right ventricular failure, and therefore, a decision was made to incorporate venovenous (VV) ECMO into the VA ECMO circuit. This technique resulted in a VV-VA or VPa-VA configuration, as oxygenated blood was being returned to the pulmonary artery as well as the descending aorta. VA ECMO was discontinued after 4 days of therapy, and the patient was extubated 3 days later. VV ECMO was weaned over the following week, and the patient was decannulated after a total 23 days of ECMO. The patient was then transitioned to inpatient rehabilitation and ultimately discharged home after 18 days. At the 6-month follow-up, the patient was doing well, and objective cardiopulmonary testing revealed normal function. This case is an excellent demonstration of how advanced ECMO and ECLS devices can be used in unique ways through multiple configurations to rescue and optimize patients in the perioperative period.

KEYWORDS

ECMO, Impella, mitral valve, acute heart failure (AHF), mitral regurgitation

Background

Aggressive extracorporeal life support (ECLS) devices have increased in both popularity and availability since their invention in the 1950s. According to the ELSO database, extracorporeal membrane oxygenation (ECMO) devices are now available in over 350 hospitals in the United States (1). The total number of circuits is ever

evolving, as are the indications for use. ECMO and ECLS devices have been used in a setting of chronic heart failure and prolonged pulmonary disease, especially as a bridge to transplant, but the use of these treatment measures in a setting of acute heart failure is less established. The ability to stabilize a patient and achieve medical optimization for cardiac surgery after an acute presentation could potentially be a life-saving advancement for those who would have otherwise been unfit for surgery. Additional areas of interest are the variations of different ECMO configurations, ECMO use before and after cardiac surgery, and combining ECMO devices with additional ECLS devices such as balloon pumps or centrifugal pump devices. Combining venoarterial (VA) ECMO circuits with venovenous (VV) ECMO circuits has been shown to be effective in extreme circumstances (2). In this study, we report the case of a 54-year-old man who presented with acute cardiogenic shock due to severe mitral valve regurgitation. He was placed on VA-ECMO with centrifugal pump support until he underwent mitral valve replacement. Following mitral valve replacement, he developed right heart failure and was subsequently transitioned to VV-VA ECMO with the assistance of a dual lumen internal jugular vein catheter. He was ultimately decannulated in a stepwise fashion and discharged home. At the 6-month follow-up, his physical activity returned to baseline and objective testing showed normal cardiopulmonary function.

Case report

A 54-year-old otherwise healthy man presented to the emergency department with acute cardiogenic shock with respiratory failure (HR 124, SBP 120, RR 38, BNP 15,000) following a 10-day hospitalization 3 months' earlier with COVID-19 pneumonia. The oxygen saturation rates were 68% on room air and 81% on 5 L of nasal cannula. He was also noted to have a lactic acid level elevated to 4. A computed tomography (CT) scan was performed, which showed diffuse pulmonary edema but ruled out pulmonary embolism (Figure 1). Due to respiratory decline, he was urgently intubated. A transthoracic echocardiogram was obtained, which showed severe mitral valve regurgitation with a flattening of the interventricular septum and a left ventricular ejection fraction of 70%. The mitral regurgitation was described as "severe" and the findings were consistent with endocarditis and papillary muscle rupture (Figure 2).

The patient was taken emergently to the operating room for an initiation of VA ECMO and placement of an Impella® device (Abiomed, Inc., Danvers, MA, USA). Right heart catheterization revealed a pulmonary capillary wedge pressure of 50 mmHg and a right atrial pressure of 20 mmHg. The pulmonary artery oxygen saturation rate was noted to be 36% as measured using a Swan-Ganz catheter. Femoral cannulation ensued with flows of 5.4l and an Impella-assisted cardiac output of 4 LPM. A transesophageal echocardiogram was obtained at the time of ECMO cannulation, demonstrating severe mitral regurgitation with the central jet filling the left atrium. The patient was taken to the cardiac intensive care unit for hemodynamic stabilization and preoperative optimization. While in the ICU[AQ: Please define "ICU" at first occurrence.], metabolic acidosis was corrected, overall volume status improved with diuresis, reaching a negative volume balance of 6 L, and hemodynamics stabilized.

On hospital day 6, the patient was again taken to the operating room for mitral valve replacement. This decision was based on his relative clinical stability at the time, while also appreciating the fact that the mechanical valvular failure that led to his acute decompensation would not resolve without surgical intervention.

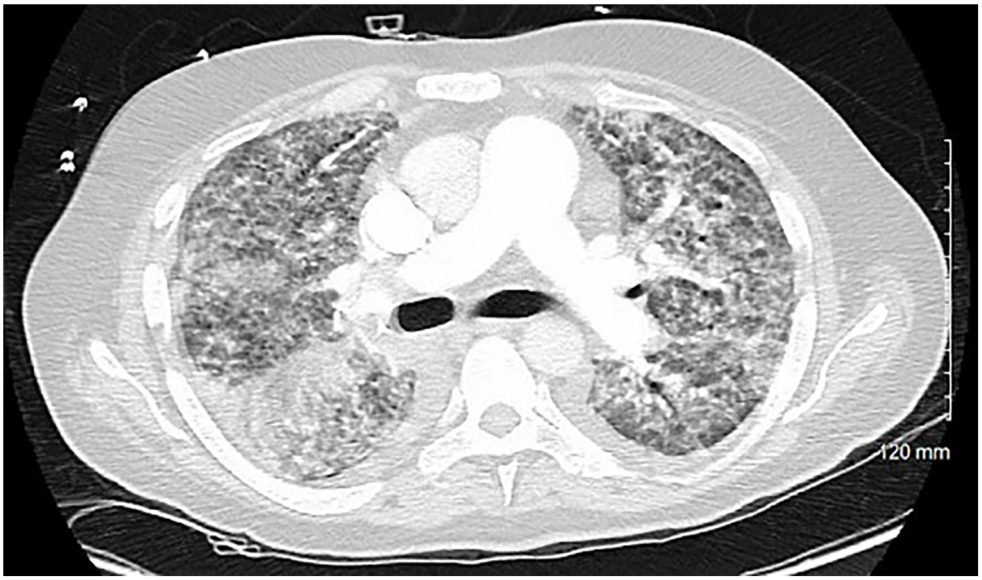

FIGURE 1
A cross-sectional CT scan performed upon arrival to the emergency department that rules out pulmonary embolism and shows bilateral interstitial consolidations consistent with pulmonary edema.

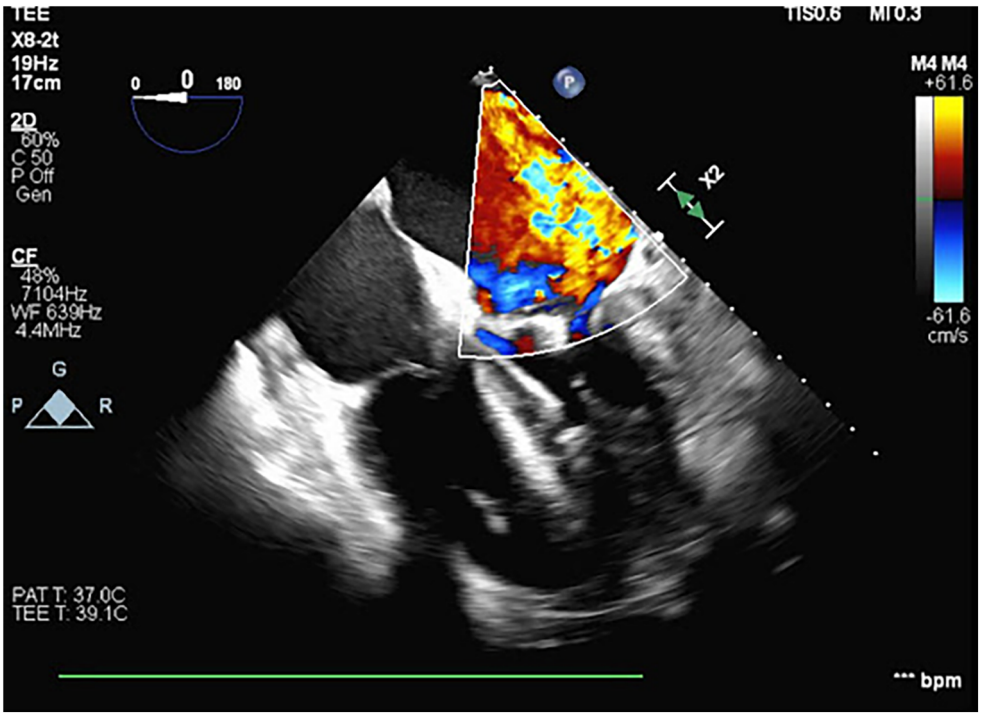

FIGURE 2
A transesophageal echocardiogram performed during VA ECMO cannulation and Impella placement showing severe mitral regurgitation with the central jet and a thickening of the mitral valve leaflets.

On the day of surgery, his lactic acid and CO_2 levels were both within normal limits, his ejection fraction based on transthoracic echo was 60%, and pulmonary artery pressures decreased to 15 mmHg.

The heart was approached via median sternotomy and a peripheral cardiopulmonary bypass was instituted using the existing ECMO cannulas. A cross clamp was placed over the Impella catheter shaft after an echocardiogram confirmed that the drive motor and outflow tract would not be clamped. The Impella device was turned off while on cardiopulmonary bypass. Mitral valve replacement was performed using a 29-mm porcine valve. During the procedure, it was noted that the anterior leaflet of the mitral valve was significantly damaged, the posterior leaflet was necrotic, and there was evidence of infection that could be traced into the left atrium. There was evidence of papillary muscle necrosis but no annular abscess. The final pathology of the specimen showed nodular calcifications measuring 0.6 cm in diameter as well as Gram-positive cocci in chains on the Gram stain. Following replacement of the valve, the patient was placed back on VA ECMO with Impella support. Postoperatively, the patient returned to the ICU on VA ECMO support with RPMs of 6,000 and flows of 4 LPM. The Impella flowed at 0.8 LPM.

Unfortunately, the patient had significant coagulopathy and ongoing mediastinal bleeding requiring transfusion and ultimately needed a return to the operating room for hematoma evacuation and hemorrhage control. Due to this, the patient was unable to be anticoagulated. This led to eventual thrombosis of the Impella device. Flows from the device were negligible, and therefore, it was removed. During removal, the patient was observed with no changes in hemodynamics, and therefore, the device was not replaced.

On the third postoperative day, a repeat echocardiogram showed an ejection fraction of 20% with a severely reduced right ventricular systolic function. Despite this, and the recent removal of the Impella device, the need for vasopressors saw a decrease. Considering the patient's need for nitric oxide, the evidence of pulmonary edema and fibrosis noted on the initial CT scan, and the concern for prolonged pulmonary support after myocardial recovery, a decision was made to incorporate a VV ECMO circuit into the existing VA ECMO circuit (Figure 3).

A wire was passed down the Swan-Ganz catheter in the right internal jugular vein and guided into the pulmonary artery. Using the Seldinger technique and a series of dilations, a 31Fr Protek Duo® (LivaNova PLC, London, UK) single-site, dual-lumen cannula was inserted under fluoroscopic guidance. This provided venous drainage from the right atrium and oxygenated arterial return into the pulmonary artery, bypassing and unloading the right ventricle. The venous drainage was connected in a Y fashion to the venous line of the VA ECMO circuit, allowing for venous drainage from the right atrium and the right femoral vein. Arterial return was now directed to the pulmonary artery via the VV circuit at the aorta via the VA circuit. Flows through both circuits were set to 3 L with stable hemodynamics. After the patient returned to the ICU, the VA

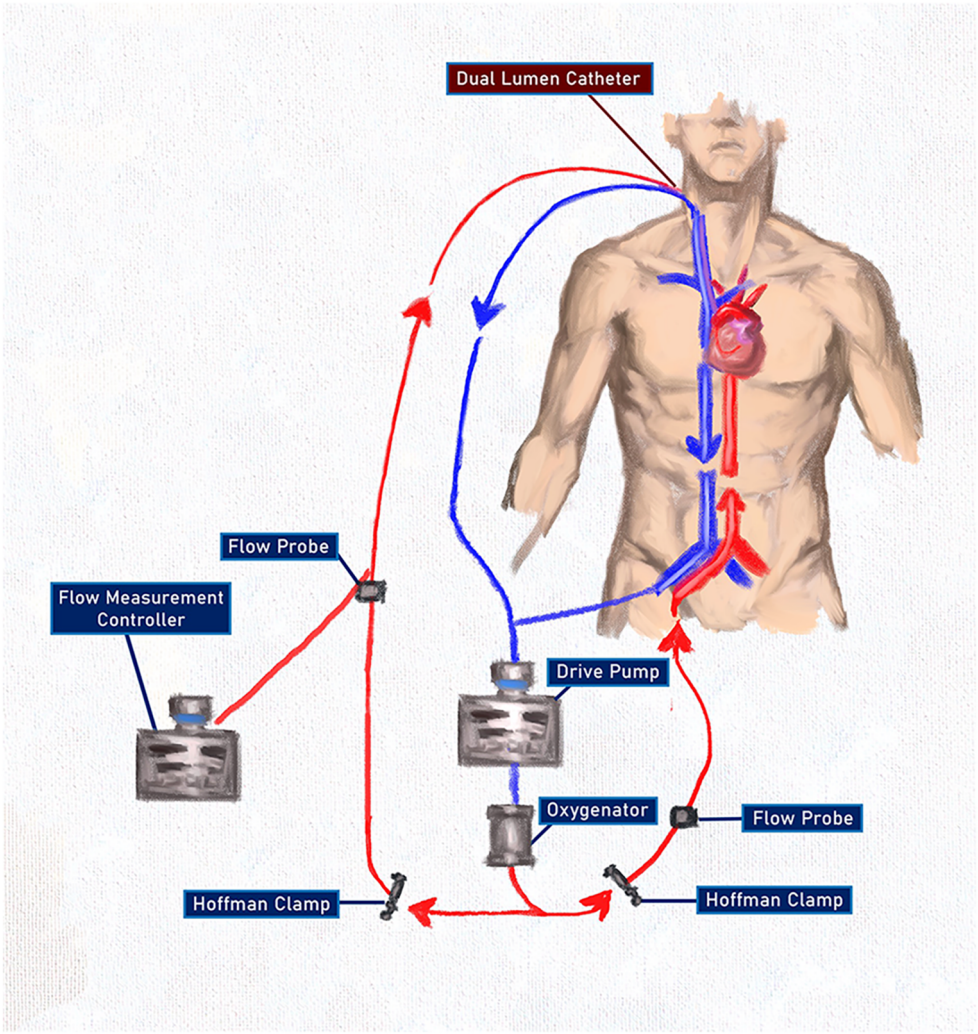

FIGURE 3
An ECMO configuration after combining VV and VA ECMO using a single pump and oxygenator with oxygenated blood delivered to both the pulmonary and the systemic circulations. The use of the Hoffman clamps allowed for titration of flow through both systems without the complications associated with two competing pumps. The flow measurement controller on the arterial side of the VV circuit was used only as a flow-measuring device and RPMs were not titrated.

ECMO circuit was titrated to 6,500 RPM, creating a flow of 4.8 LPM. Using a Hoffman clamp for outflow restriction, the VV ECMO circuit was titrated to flows of 2.9 LPM with a sweep rate of 2.5.

Over the following days, flows for the VA circuit were weaned by titrating both the pump speed and the Hoffman clamp occlusion. Flows through the VA limb of the ECMO circuit were decreased to less than 2 LPM of flow for several days, and the patient was able to be weaned from epinephrine. Ventilator requirements were now significantly reduced to very low tidal volumes and pressures. Four days after the placement of the Protek Duo cannula, the patient was decannulated from VA ECMO. An echocardiogram at that time demonstrated a left ventricular ejection fraction of 45% with minimal milrinone support.

Three days after VA decannulation, the patient was extubated and began working with physical therapy and ambulating while on VV ECMO. Flows through the Protek system at that time ranged between 2 and 3.5 LPM of flow. Eventually, 14 days after the Protek Duo cannula was placed, the patient was decannulated. After another week of optimization and continued critical care, the patient was discharged to inpatient rehab. The total hospitalization time was 31 days with a total ECMO time of 23 days. The patient spent 18 days in rehab and was then discharged home. The patient was doing well and reported only slight dyspnea with exercise. Follow-up testing showed adequate pulmonary recovery both radiographically and on pulmonary function tests (Figure 4).

Discussion

This case first highlights the preoperative use of ECLS devices to optimize and bridge to eventual cardiac surgery in a setting of

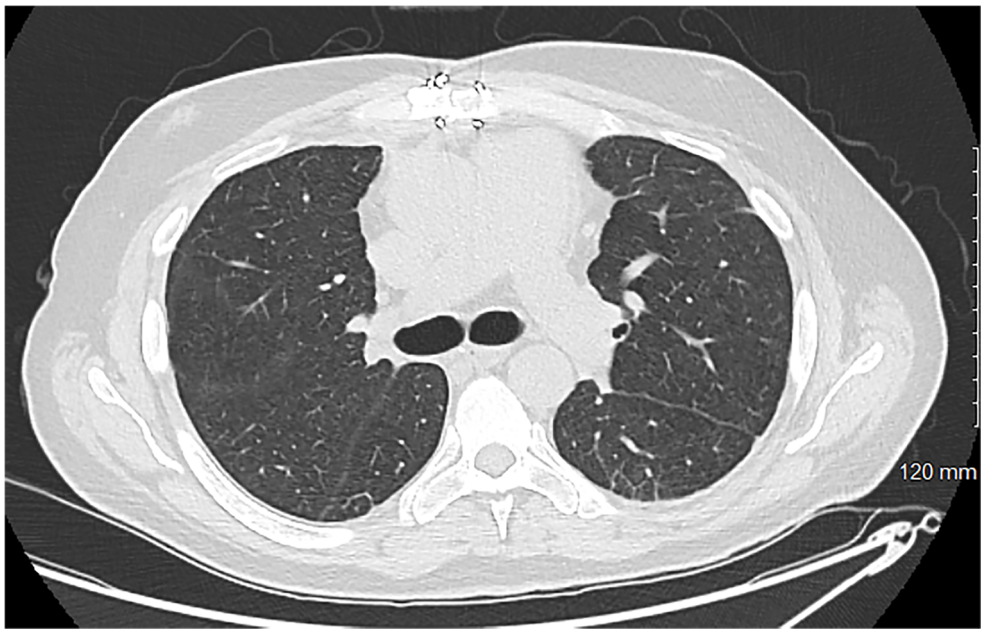

FIGURE 4
A cross-sectional CT scan obtained for a 3-month follow-up showing minimal basilar scarring with complete resolution of the previously noted edema. More inferior images show a well-placed mitral prosthesis and a well-approximated sternum.

acute cardiogenic shock. The strategy of bridging is common and well established for patients with chronic heart failure needing a transplant, but its use in the acute setting is less well established and is mostly shown in case reports and small case series. Ekanem et al. describe a three-case series of VA-ECMO and Impella support for cardiogenic shock following postinfarct papillary muscle rupture (3). They successfully bridged two of three patients to eventual surgery, both of whom survived their hospitalization period. ECMO alone has also been proved to serve as a successful bridge to definitive operation (4–6). In all of these cases, the patients underwent successful surgery and were discharged from the hospital. Coyan et al. provide an excellent review of VA-ECMO and Impella in their 2022 review of 25 studies compiling 83 patients for whom ECLS strategies were employed following a postinfarction ventricular septal rupture (7). In our patient in this study, the expedient initiation of ECLS devices proved to be both a life-saving measure and a successful bridge to eventual cardiac surgery. During that time, he was on maximal medical support including VA ECMO, Impella therapy, mechanical ventilation with moderate ventilator requirements and inhaled nitric oxide, as well as multiple vasopressors and inotropes for hemodynamic support. The time between initiation of the initial configuration of VA ECMO and Impella was used to optimize the patient for mitral valve replacement to a point of medical stability. It was felt that there was a narrow window for intervention during this improved state before the effects of the significant mitral regurgitation could not be overcome despite maximal support.

Another aspect of ECLS underscored by this case is the hybrid use of ECMO configurations for additional cardiopulmonary support. Brasseur et al. best described the ECMO configuration used in this case as VPa-VA ECMO (8), highlighting that not only was venous blood drained from the right atrium and the inferior vena cava as in VVA, but that oxygenated blood was being returned to the pulmonary circulation via the Protek Duo cannula and to the systemic circulation via the VA system. Camboni described similar blood flow using a surgical approach requiring sternotomy (9); however, the construction described here achieved the same blood flow through a percutaneous approach. Reconfiguring and combining ECLS systems has proved to be successful in several scenarios previously. Matsuyoshi et al. described transitioning from VA to VAV to VV ECMO following cardiac arrest due to massive pulmonary embolism with eventual decannulation and discharge (2). Haldenwang and colleagues presented eight patients treated with combined cardiac and pulmonary failure who underwent initial VA ECMO and were then transitioned to VVA and ultimately to VV ECMO prior to being weaned (10). They were able to successfully wean 75% of patients and achieve a 30-day survival rate of 50%. The notable difference in the case presented here when compared with the previously mentioned studies is that oxygenated blood was returned to both the systemic system and the pulmonary systems, while allowing myocardial rest and recovery for both the right and the left heart. This configuration provided both right ventricular support and assistance with oxygenation, while also being able to wean, and eventually remove, the left ventricular support. Given our unique situation of pulmonary insult from both recent COVID-19 pneumonia and significant pulmonary edema from the defective mitral valve, the continued pulmonary support offered by the VV ECMO circuit proved vital and allowed for lung protective ventilation and earlier extubation, initiation of ambulation, and likely earlier discharge.

This case highlights several complex perioperative factors that influence patient outcomes when dealing with cardiogenic shock, as well as salvage measures that can be employed. Cardiogenic shock due to acute valvular emergencies is both a medical and a surgical emergency, with an operative mortality rate reaching as high as 22% (11). Sperry et al. describe the cardiothoracic surgeon's role specifically, stating, "surgeons play a critical role in the management of cardiogenic shock due to their contributions to both the short-term and long-term decision making." They reference the cardiac surgeon's expertise in deranged cardiac physiology, familiarity with a wide range of devices, and ability to offer definitive therapies as reasons why surgeons should be involved immediately when cardiogenic shock is diagnosed (12). In the case previously described, early involvement of the cardiac surgical team led to a prompt initiation of ECLS and subsequent management and reconfigurations both pre- and postoperatively.

Conclusion

The ability to rescue acutely ill patients at the time of presentation allows valuable time for patient optimization and transition to surgery. Likewise, postoperative use of ECLS devices in different configurations can allow time for cardiac and pulmonary recovery and potentially lead to better outcomes for all patients. In our patient, VA ECMO combined with an Impella device was used to optimize the patient for cardiac surgery. Postoperatively, right ventricular recovery was impeded by the significant pulmonary edema, and therefore, a Protek Duo cannula was placed and joined with the VA ECMO circuit to facilitate right ventricular off-loading, while providing oxygenated blood to both the pulmonary and the systemic circulations. As the left heart continued to improve, VA ECMO was removed, and the patient was extubated, allowed to ambulate, and eventually decannulated entirely. This case proves the utility of early ECMO initiation and the potential benefit of different configurations of ECLS devices to improve patient outcomes.

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 humans were approved by the MetroWest Medical Center Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BD: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing. JR: Conceptualization, Resources, Supervision, Writing – review & editing.

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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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EDITED BY
Cristina Barbero,
A.O.U. City of Health and Science of Turin, Italy

REVIEWED BY
Philemon Gukop,
St George's University Hospitals NHS Foundation Trust, United Kingdom
Farzad Masoud Kabir,
Tehran University of Medical Sciences, Iran

*CORRESPONDENCE
Jungchan Park
jc83.park@samsung.com

†These authors have contributed equally to this work

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Preoperative C-reactive protein/albumin ratio and mortality of off-pump coronary artery bypass graft

Ah Ran Oh[1,2†], Ji-Hye Kwon[1†], Jungchan Park[1*], Jeong-Jin Min[1], Jong-Hwan Lee[1], Seung Yeon Yoo[1], Dong Jae Lee[1], Wooksung Kim[3], Hyun Sung Cho[1], Chung Su Kim[1] and Sangmin Maria Lee[1]

[1]Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [2]Department of Anesthesiology and Pain Medicine, Kangwon National University Hospital, Chuncheon, Republic of Korea, [3]Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background: We sought to investigate the prognostic value of preoperative C-reactive protein (CRP)-to-albumin ratio (CAR) for the prediction of mortality in patients undergoing off-pump coronary artery bypass grafting (OPCAB).
Methods: From January 2010 to August 2016, adult patients undergoing OPCAB were analyzed retrospectively. In a total of 2,082 patients, preoperative inflammatory markers including CAR, CRP, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio were recorded. Receiver operating characteristic (ROC) curves were used to determine the optimal threshold and compare the predictive values of the markers. The patients were divided into two groups according to the cut-off value of CAR, and then the outcomes were compared. The primary end point was 1-year mortality.
Results: During the 1-year follow-up period, 25 patients (1.2%) died after OPCAB. The area under the curve of CAR for 1-year mortality was 0.767, which was significantly higher than other inflammatory markers. According to the calculated cut-off value of 1.326, the patients were divided into two groups: 1,580 (75.9%) patients were placed in the low CAR group vs. 502 (24.1%) patients in the high CAR group. After adjustment with inverse probability weighting, high CAR was significantly associated with increased risk of 1-year mortality after OPCAB (Hazard ratio, 5.01; 95% Confidence interval, 2.01–12.50; $p < 0.001$).
Conclusions: In this study, we demonstrated that preoperative CAR was associated with 1-year mortality following OPCAB. Compared to previous inflammatory markers, CAR may offer superior predictive power for mortality in patients undergoing OPCAB. For validation of our findings, further prospective studies are needed.

KEYWORDS

albumin, biomarker, coronary artery bypass, C-reactive protein, mortality

Introduction

Coronary artery bypass grafting (CABG) is the most effective treatment for multivessel coronary artery disease (CAD), and the most frequently performed open cardiac surgery worldwide (1, 2). Despite improvements in perioperative care and operative techniques, CABG remains a complex and high-risk procedure with significant morbidity and mortality (3). Inflammation plays a key role in the pathogenesis and progression of CAD (4, 5). When performing surgical revascularization, potent inflammatory mediators are released, adversely affecting patient status (6, 7). In this context, several studies have evaluated the association between inflammatory markers and adverse outcomes after CABG in terms of prognostic value (8–11).

Recently, C-reactive protein (CRP)/albumin ratio (CAR) has been used as a novel indicator of inflammation and a prognostic marker for patients with severe critical illness (12, 13). High levels of CRP indicate an active inflammation process, which is associated with increased risk of cardiac events in patients with CAD (14). Albumin is inversely related to inflammation and low albumin level also has been recognized as a risk factor for cardiovascular disease (15). Therefore, the use of both CRP and albumin together may reflect inflammatory status better than either marker alone in CAD. Previous studies have confirmed that CAR is superior to CRP or albumin alone for assessing the severity and prognosis of patients with CAD (16, 17). However, the relationship between CAR and mortality has not been evaluated in patients undergoing CABG. Therefore, we sought to determine whether preoperative CAR is a predictor of postoperative mortality after off-pump CABG (OPCAB). The results of this study may help to identify patients at high risk for mortality after OPCAB, allowing for earlier interventions and improved outcomes.

Methods

This retrospective observational cohort study was approved by the Institutional Review Board at Samsung Medical Center (reference number 2022-05-087). It adhered to the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Due to the low risk to participants and the retrospective nature of the study, the requirement for written consent from individual patients was waived.

Study population and data collection

For this study, we reviewed the records of consecutive adult patients who underwent OPCAB at our hospital between January 2010 and August 2016. In the case of re-operation, only the first operation was included in analysis, and patients without preoperative CRP or albumin were excluded. We included only the initial operation was to maintain uniformity in our dataset and reduce the complexity associated with repeated surgeries. Multiple surgeries in the same individual may introduce additional variables, such as variations in postoperative care, recovery trajectories, and underlying health conditions, which could complicate the analysis.It was a single center cohort of multiple surgeons with different OPCAB technique. We created this cohort by accessing an electronic archive system containing information on over four million patients, including more than 1.2 billion laboratory results and 300 million prescriptions. The data were obtained in de-identified form from our electronic system, the "Clinical Data Warehouse DARWIN-C" of Samsung Medical Center. All relevant information such as demographic, laboratory, and outcome data were organized by independent investigators who were not involved in this study. The laboratory tests were conducted within a period of 6 months prior to the surgery. This timeframe aligns with the institution's protocol, which deems blood lab test results within six months as an acceptable and practical reflection of patients' baseline health status.To calculate the CAR value, the CRP (mg/L) level was divided by the serum albumin (g/dl) level. The ratio of neutrophils to lymphocytes (NLR) was calculated by taking the number of neutrophils and dividing it by the number of lymphocytes. Similarly, the ratio of platelets to lymphocytes (PLR) was determined by dividing the number of platelets by the number of lymphocytes. Our electronic system regularly receives updates to the mortality data from the National Population Registry of Korea.

Study endpoint

The primary endpoint of this study was all-cause mortality during 1-year follow-up. Secondary endpoints were the major cardiovascular and cerebrovascular events (MACCE) during 1-year follow-up and all-cause mortality during three and 5-year follow-ups. MACCE was defined as a composite of following outcomes: all-cause death, graft failure, coronary revascularization, myocardial infarction, and stroke.

Statistical analysis

Continuous variables were presented as means with standard deviation or medians with interquartile range (IQR), and categorical variables were expressed as numbers with percentages. To compare the differences between the two groups, continuous variables were evaluated using *t*-test or the Mann–Whitney test, while categorical variables were assessed with the χ^2 test or Fisher's exact test. To determine the best threshold for CAR, CRP, NLR, and PLR in predicting 1-year mortality, we used receiver operating characteristic (ROC) curve analysis and calculated Youden's index. To assess the predictive power of the markers, the values of the area under the curve (AUC) with 95% confidence interval (CI) were compared using DeLong's test (18). The patients were divided into low and high groups based on the calculated cut-off value of CAR. To minimize the impact of

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selection bias and confounding factors, we conducted inverse probability weighting (IPW) to adjust for differences in the baseline characteristics of the patients using all relevant variables shown in Table 1 (19). To calculate the weight for each patient, we estimated a probability that predicts the likelihood of being included in the high CAR group, and the weight for each patient was calculated as the inverse of the probability. A standardized mean difference of less than 10% was considered as an adequate balance between the two groups. To compare the mortality and MACCE, we used Cox regression analysis and weighted Cox proportional hazard analysis with IPW, and the results were presented as a hazard ratio (HR) and 95% CI. Kaplan–Meier curves were constructed for 1-year MACCE and compared with the log-rank test. Statistical analysis for this study was conducted using R 4.2.0 (Vienna, Austria; http://www.R-project.org/) and a *P*-value of less than 0.05 was considered statistically significant.

TABLE 1 Baseline characteristics according to 1-year mortality.

	Survivor ($N = 2,057$)	Non-survivor ($N = 25$)	*p*-value
C-reactive protein/albumin ratio	0.33 (0.12–1.21)	1.74 (0.82–5.15)	<0.001
Neutrophil/lymphocyte ratio	1.95 (1.46–2.73)	2.41 (1.86–2.84)	0.13
Platelet/lymphocyte ratio	7.07 (5.46–9.25)	7.88 (5.75–12.39)	0.13
C-reactive protein, mg/L	1.4 (0.5–4.9)	6.9 (3.1–17.5)	<0.001
Albumin, g/dl	4.2 (4.0–4.4)	3.9 (3.5–4.1)	<0.001
Neutrophil	58.8 (52.3–65.6)	61.4 (55.0–65.5)	0.61
Lymphocyte	30.0 (23.7–36.0)	26.5 (21.9–30.6)	0.05
Platelet, K/mcL	209 (175–247)	203 (175–241)	0.85
Age, years	63.2 (±10.0)	71.6 (±7.5)	<0.001
Male	1,601 (77.8)	20 (80.0)	0.99
Smoking	545 (26.5)	5 (20.0)	0.61
Body mass index	24.6 (±3.0)	24.3 (±3.6)	0.63
Hypertension	1,633 (79.4)	20 (80.0)	>0.99
Diabetes	937 (45.6)	9 (36.0)	0.45
Old myocardial infarction	183 (8.9)	3 (12.0)	0.85
Acute myocardial infarction	221 (10.7)	4 (16.0)	0.61
Ejection fraction	57.0 (±12.3)	50.0 (±15.9)	0.01
Previous coronary intervention			
Percutaneous intervention	360 (17.5)	1 (4.0)	0.13
Bypass grafting	7 (0.3)	0	>0.99
Previous disease			
Peripheral arterial occlusive disease	105 (5.1)	3 (12.0)	0.28
Chronic obstructive pulmonary disease	27 (1.3)	2 (8.0)	0.05
Stroke	257 (12.5)	6 (24.0)	0.16
Chronic kidney disease	112 (5.4)	5 (20.0)	0.01
Dialysis	58 (2.8)	4 (16.0)	0.001
Heart failure	29 (1.4)	0	>0.99
Valvular disease	10 (0.5)	0	>0.99
Aortic disease	15 (0.7)	0	>0.99
Drug use			
Statin	1,065 (51.8)	10 (40.0)	0.33
Antiplatelet	1,937 (94.2)	24 (96.0)	>0.99
Renin-angiotensin-aldosterone system inhibitor	649 (31.6)	11 (44.0)	0.27
Beta blocker	688 (33.4)	7 (28.0)	0.72
Calcium channel blocker	641 (31.2)	11 (44.0)	0.25
Operative variables			
Urgency operation	49 (2.4)	1 (4.0)	>0.99
Operative duration, min	269.1 (±68.7)	283.2 (±66.4)	0.31
Red blood cell transfusion, pack	2.2 (±1.5)	3.6 (±1.2)	<0.001

Values are *n* (%) or mean (±SD)/median (interquartile range).

Results

From January 2010 to August 2016, a total of 2,082 adult patients who underwent OPCAB in our institution were enrolled in final analysis. During the 1-year follow-up period, 25 patients (1.2%) died after OPCAB. The baseline characteristics of the patients according to 1-year mortality are summarized in Table 1. The median values of CAR and CRP were significantly higher in the non-survivor group, but albumin was significantly lower.

We generated the ROC curves of CAR, CRP, NLR, and PLR for the prediction of 1-year mortality, and the AUCs with 95% CI were 0.767 (0.684–0.850), 0.759 (0.675–0.842), 0.588 (0.475–0.701), and 0.589 (0.461–0.716), respectively (Figure 1A). On comparison of the AUC values, CAR showed significantly better predictive power than other inflammatory markers ($Z = 2.86$, $p = 0.004$ for CAR vs. CRP). Based on maximum Youden's index, the optimal threshold of CAR, CRP, NLR, and PLR for predicting 1-year mortality were 1.326, 5.150, 2.273, and 9.793, respectively.

According to the calculated cut-off value of CAR, the patients were divided into two groups: 1,580 (75.9%) patients in the low CAR group vs. 502 (24.1%) patients in the high CAR group. The baseline characteristics of patients according to CAR level are presented in Table 2. The median [IQR] value of preoperative CAR was 0.02 [0.09–0.49] in the low CAR group and 3.32 [1.85–7.23] in the high CAR group ($p < 0.001$). Other inflammatory markers were also significantly higher in the high CAR group, whereas albumin and lymphocyte were significantly lower. The high CAR group was older and had a higher frequency of acute myocardial infarction, peripheral arterial occlusive disease, stroke, and chronic kidney disease, while having decreased ejection fraction and a lower history of statin use. After IPW adjustment, the covariates were well balanced between the two groups. The results of Cox regression analyses are presented in Table 3. The unadjusted analysis demonstrated that the high CAR was significantly associated with increased mortality risk regardless of follow-up period (0.5% vs. 3.4%; HR, 6.97; 95% CI, 3.01–16.15; $p < 0.001$ for 1-year mortality, 1.5% vs. 5.0%; HR, 3.57; 95% CI, 2.04–6.25; $p < 0.001$ for 3-year mortality, 2.6% vs. 6.4%; HR, 2.80; 95% CI, 1.76–4.44; $p < 0.001$ for 5-year mortality), but 1-year MACCE was not significantly associated with high CAR (5.4% vs. 6.2%; HR, 1.23; 95% CI, 0.81–1.85; $p = 0.33$). This trend persisted after adjustment with IPW (HR, 5.01; 95% CI, 2.01–12.50; $p < 0.001$ for 1-year mortality, HR, 2.44; 95% CI, 1.31–4.54; $p = 0.01$ for 3-year mortality, HR, 1.91; 95% CI, 1.15–3.21; $p = 0.01$ for 5-year mortality, HR, 1.11; 95% CI, 0.69–1.78; $p = 0.66$ for 1-year MACCE). The ROC curves of CAR for 1-year mortality and MACCE are presented in Figure 1B. The AUC values for predicting 1-year mortality and MACCE were 0.767

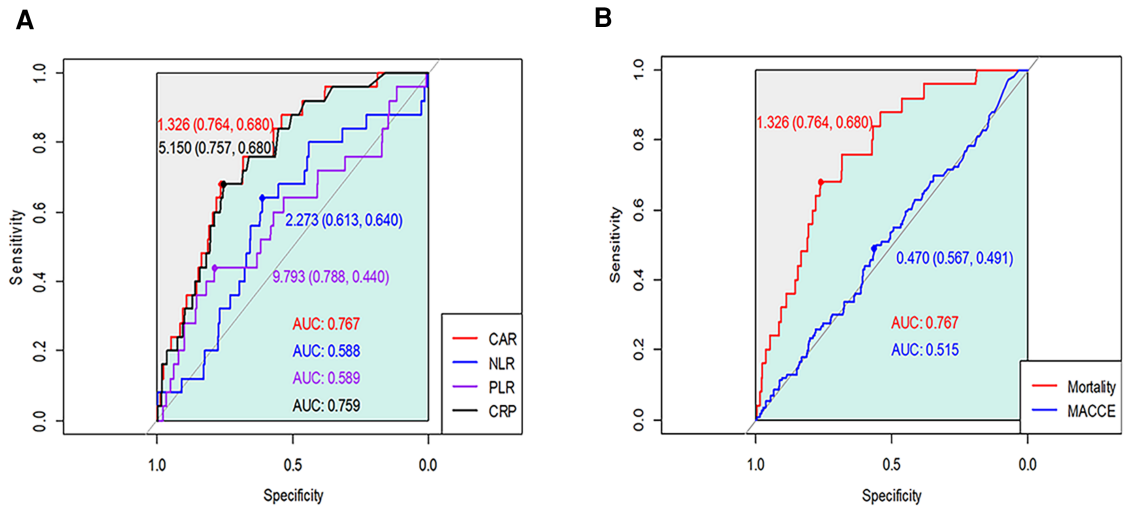

FIGURE 1
Receiver operating characteristic curves of CAR, CRP, NLR, and PLR for (A) 1-year mortality and (B) major cardiovascular and cerebrovascular events after OPCAB.

and 0.515, respectively. The Kaplan-Meier curves for 1-year mortality stratified by CAR group are presented in Figure 2.

Discussion

In this retrospective study, we investigated the relationship between preoperative CAR and 1-year mortality in patients undergoing OPCAB. We found that the incidence of 1-year mortality was higher in the high CAR group, and an elevated CAR during preoperative period was significantly associated with increased mortality risk after OPCAB. Additionally, CAR demonstrated superior predictive accuracy compared to conventional inflammatory markers, indicating that it could be a feasible prognostic marker in cardiac surgery.

In recent years, the role of inflammation in the development of CAD has been extensively studied and attracted a great deal of attention. Inflammatory processes are not only responsible for the initiation and progression of atherosclerosis, but also contribute significantly to the precipitation of acute thrombotic complications (20). Accumulating data indicate that elevated inflammatory markers, such as CRP, NLR, and PLR, have prognostic value for cardiovascular outcomes in patients with CAD (21–23). Thus, inflammation can serve as a potential prognostic factor in CAD, providing valuable clinical information with considerable practical usefulness. However, the usefulness of inflammatory status alone for predicting prognosis may be limited, as it does not account for nutritional status associated with poor clinical outcomes.

CAR is a newly developed marker that provides insight into both the inflammation and nutritional status of patients. Inflammation and malnutrition are closely related, both leading to adverse outcomes including cardiovascular events (24). Inflammation can cause malnutrition, which in turn can negatively impact the management of inflammation (25). It has been reported that an elevated CAR was independently associated with stent restenosis, acute kidney injury, and higher burden of coronary thrombus in acute coronary syndrome (16, 26, 27). Also, CAR presented a higher accuracy for the prediction of outcomes than either of the individual markers (28, 29). To evaluate the association between mortality and CAR in patients undergoing CABG, we hypothesized that the predictive value of CAR would be more evident in OPCAB, a procedure that involves less inflammation compared to on-pump CABG without the use of cardiopulmonary bypass (30, 31). In this study, we found that elevated level of preoperative CAR was also associated with a higher risk of death and had better prognostic value than traditional inflammatory markers in OPCAB patients.

Although previous studies have demonstrated that inflammatory markers are linked to an increased risk of MACCE (32), our study did not find a significant association between the CAR and MACCE. A potential explanation for the lack of significance is that the incidence of MACCE within our study cohort may have been too low to detect a statistically significant association. Specifically, the overall incidence of MACCE in this study was approximately 5.6% (116 of 1,580) within the first year of follow-up, suggesting that our study may not have had sufficient statistical power to detect a significant association. The relationship between CAR and MACCE could be nuanced and may extend over the long term. Therefore, a longer follow-up duration may be necessary to capture the full spectrum of the effect of CAR on MACCE. The relatively short follow-up duration in our study might not fully capture the potential impact of CAR on the occurrence of MACCE, especially if the association is gradual or cumulative over time. Furthermore, it is

TABLE 2 Baseline characteristics according to the estimated cut-off point of C-reactive protein/albumin ratio >1.326.

	Low group (*N* = 1,580)	High group (*N* = 502)	*p*-value	ASD before IPW	ASD after IPW
C-reactive protein/albumin ratio	0.20 (0.09–0.49)	3.32 (1.85–7.23)	<0.001		
Neutrophil/lymphocyte ratio	1.86 (1.39–2.55)	2.42 (1.77–3.33)	<0.001		
Platelet/lymphocyte ratio	6.67 (5.28–8.63)	8.63 (6.27–11.46)	<0.001		
C-reactive protein, mg/l	0.8 (0.4–2.0)	13.9 (7.8–28.1)	<0.001		
Albumin, g/dl	4.3 (4.1–4.5)	4.0 (3.7–4.3)	<0.001		
Neutrophil	58.1 (51.1–64.4)	62.1 (55.5–68.3)	<0.001		
Lymphocyte	31.1 (25.2–36.7)	25.4 (20.4–31.8)	<0.001		
Platelet, K/mcL	207 (176–244)	215 (174–257)	0.01		
Age, years	62.8 (±10.0)	64.7 (±10.0)	<0.001	18.4	2.3
Male	1,242 (78.6)	379 (75.5)	0.16	7.4	6.3
Smoking	405 (25.6)	145 (28.9)	0.17	7.3	3
Body mass index	24.7 (±3.1)	24.5 (±2.9)	0.32	5.2	1.8
Hypertension	1,255 (79.4)	398 (79.3)	0.99	0.4	2.4
Diabetes	706 (44.7)	240 (47.8)	0.24	6.3	1.7
Old myocardial infarction	134 (8.5)	52 (10.4)	0.23	6.4	3.9
Acute myocardial infarction	115 (7.3)	110 (21.9)	<0.001	42.4	9.4
Ejection fraction	58.0 (±11.9)	53.4 (±13.4)	<0.001	36.2	7.1
Previous coronary intervention					
Percutaneous intervention	288 (18.2)	73 (14.5)	0.07	10	1.8
Bypass grafting	6 (0.4)	1 (0.2)	0.87	3.4	1
Previous disease					
Peripheral arterial occlusive disease	68 (4.3)	40 (8.0)	0.002	15.3	2.1
Chronic obstructive pulmonary disease	17 (1.1)	12 (2.4)	0.05	10.1	3.2
Stroke	185 (11.7)	78 (15.5)	0.03	11.2	1.4
Chronic kidney disease	65 (4.1)	52 (10.4)	<0.001	24.3	4.2
Dialysis	29 (1.8)	33 (6.6)	<0.001	23.8	2.7
Heart failure	21 (1.3)	8 (1.6)	0.82	2.2	2.3
Valvular disease	9 (0.6)	1 (0.2)	0.5	6	1.3
Aortic disease	8 (0.5)	7 (1.4)	0.08	9.2	2.6
Drug use					
Statin	849 (53.7)	226 (45.0)	0.001	17.5	2
Antiplatelet	1,485 (94.0)	476 (94.8)	0.56	3.6	3.4
Renin-angiotensin-aldosterone system inhibitor	497 (31.5)	163 (32.5)	0.71	2.2	4.8
Beta blocker	546 (34.6)	149 (29.7)	0.05	10.5	1.5
Calcium channel blocker	492 (31.1)	160 (31.9)	0.8	1.6	2.7
Operative variables					
Urgency operation	35 (2.2)	15 (3.0)	0.41	4.9	2.5
Operative duration, min	270.2 (±69.8)	266.6 (±65.1)	0.31	5.3	1.9
Red blood cell transfusion, pack	2.1 (±1.5)	2.4 (±1.6)	0.001	16.5	5.3

Values are *n* (%) or mean (±SD)/median (interquartile range).

TABLE 3 Risk of adverse events according to the estimated cut-off point of C-reactive protein/albumin ratio >1.326.

	Low group (*N* = 1,580)	High group (*N* = 502)	Unaddjusted HR (95% CI)	*p*-value	IPW adjusted HR	*p*-value
1-year mortality	8 (0.5)	17 (3.4)	6.97 (3.01–16.15)	<0.001	5.01 (2.01–12.5)	<0.001
1-year MACCE	85 (5.4)	31 (6.2)	1.23 (0.81–1.85)	0.33	1.11 (0.69–1.78)	0.66
1-year mortality	8 (0.5)	17 (3.4)				
Graft failure	28 (1.8)	3 (0.6)				
Percutaneous coronary intervention	20 (1.3)	4 (0.8)				
Myocardial infarction	9 (0.6)	5 (1.0)				
Stroke	33 (2.1)	6 (1.2)				
3-year mortality	24 (1.5)	25 (5.0)	3.57 (2.04–6.25)	<0.001	2.44 (1.31–4.54)	0.01
5-year mortality	41 (2.6)	32 (6.4)	2.80 (1.76–4.44)	<0.001	1.91 (1.15–3.21)	0.01

CI, confidence interval; HR, hazard ratio; IPW, inverse probability of weighting; MACCE, major adverse cardio and cerebrovascular events.

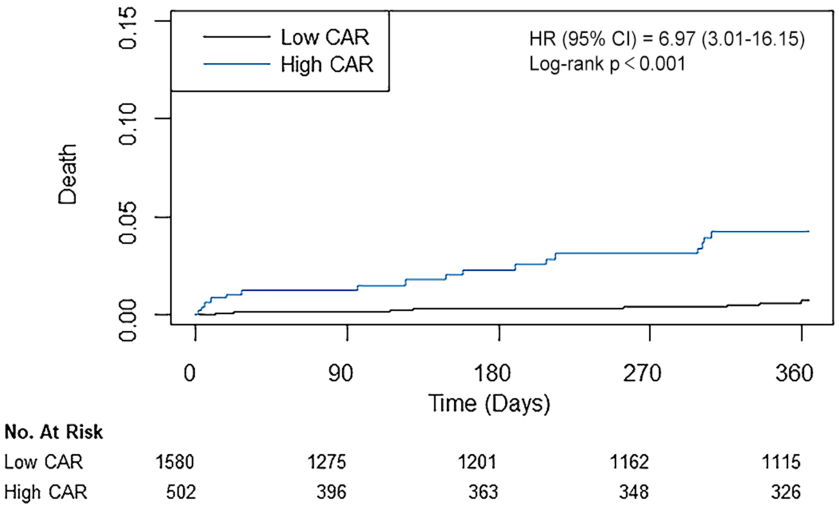

FIGURE 2
Kaplan–meier curves for 1-year mortality.

crucial to acknowledge that the relationship between inflammatory markers and MACCE is complex and not yet fully understood. Our study explored CAR as a potential predictor, but other factors such as surgical complexity and post-operative complications may have exerted a more substantial influence on MACCE risk in surgical patients (33). These factors could act as confounders, potentially overshadowing the association between CAR and MACCE. Given the complexity of these relationships, further investigation is warranted to better understand the precise role of CAR in predicting the risk of MACCE after Off-Pump Coronary Artery Bypass (OPCAB). Future studies could explore extended follow-up periods, incorporate a more comprehensive set of confounding variables, and consider additional inflammatory markers to elucidate the intricate interplay between inflammation, CAR, and MACCE in the context of cardiac surgery. While our study did not reveal a significant association between CAR and MACCE within the observed timeframe, it serves as a valuable contribution to the ongoing discourse surrounding inflammatory markers and cardiovascular outcomes in the context of OPCAB. Continued research efforts are essential for refining risk prediction models and informing clinical decision-making in cardiac surgery patients.

There are several limitations that should be considered when interpreting the results of this study. First, this was a retrospective study conducted at a single center, so our results may lack causality. And it may not be applicable to other patients treated with different perioperative management or surgical techniques. While we controlled for known confounding factors, there may still be unidentified confounding factors that could affect the observed associations. By including only the initial operation, there may be a potential impact on biases, such as selection bias or survival-ship bias. Additionally, the low incidence of 1-year mortality (1.2%) may cause bias or lead to underpowered analyses. Second, this study only considered CAR values during the preoperative period, so it would be valuable to conduct further research that assess changes in CAR during the perioperative period for better understanding of prognosis. Furthermore, there is a potential limitation associated with using blood laboratory tests within six months before surgery, particularly in capturing dynamic changes in acute phase reactants. Third, our study included only the patients undergoing OPCAB without cardiopulmonary bypass. On-pump CABG is related to a stronger inflammatory reaction than OPCAB. Therefore, the CAR may have different effects on mortality in patients undergoing on-pump CABG or other cardiac surgeries using cardiopulmonary bypass. Lastly, whether CAR is a modifiable risk factor in OPCAB is indeterminate in this study. Future studies are required to determine whether preoperative use of anti-inflammatory drugs or albumin correction can improve postoperative outcomes. Nevertheless, our study is noteworthy in that it was the first study to reveal the relationship between preoperative CAR and mortality in patients undergoing OPCAB. CAR may be a useful tool for risk stratification of OPCAB patients with broad clinical applications due to its ease of access.

Conclusion

In this study, we demonstrated that preoperative CAR was associated with 1-year mortality following OPCAB. CAR may be used as a valuable biomarker to predict mortality in patients undergoing OPCAB with superior predictive power than previous inflammatory markers. Further prospective studies are necessary to validate our findings.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Institutional Review Board at Samsung Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the data was curated in de-identified form.

Author contributions

AO: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. J-HK: Conceptualization, Writing – original draft, Writing – review & editing. JP: Conceptualization, Data curation, Investigation, Writing – original draft. J-JM: Conceptualization, Data curation, Writing – review & editing. J-HL: Data curation, Methodology, Writing – review & editing. SY: Data curation, Writing – review & editing. DL: Writing – review & editing. WK: Data curation, Writing – review & editing. HC: Data curation, Writing – review & editing. CK: Data curation, Investigation, Writing – review & editing. SL: Data curation, Writing – review & editing.

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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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EDITED BY
Cristina Barbero,
A.O.U. City of Health and Science of Turin, Italy

REVIEWED BY
Antonino S. Rubino,
University of Campania Luigi Vanvitelli, Italy
Thomas Theologou,
University of Patras, Greece

*CORRESPONDENCE
Andreas Schaefer
✉ and.schaefer@uke.de

†These authors have contributed equally to this work

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Association of HbA1c and utilization of internal mammary arteries with wound infections in CABG

Tim Knochenhauer†, Andreas Schaefer*†, Jens Brickwedel, Beate Reiter, Shiho Naito, Svante Zipfel, Yvonne Schneeberger, Hermann Reichenspurner and Bjoern Sill

Department of Cardiovascular Surgery, University Heart and Vascular Center Hamburg, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Background: Deep sternal wound infection (DSWI) remains a serious complication after coronary artery bypass grafting (CABG). We herein aimed to stratify diabetic patients who underwent CABG using bilateral internal mammary artery (BIMA) for levels of glycated hemoglobin A1C (HbA1c) and compare postoperative outcomes.

Methods: Between January 2010 and August 2020, 4,186 consecutive patients underwent isolated CABG at our center. In 3,229 patients, preoperative HbA1c levels were available. Primary endpoints were wound healing disorder (WHD), DSWI, and 30-day mortality. Patients were stratified according to preoperative HbA1c levels. Patients were further divided into subgroups according to utilization of BIMA.

Results: After adjustment, no differences in mortality and stroke rates were seen between group 1 (HbA1c < 6.5%) vs. group 2 (HbA1c ≥ 6.5%). WHD was more frequent in group 2 [2.8 vs. 5.6%; adjusted $p = 0.002$; adjusted odds ratio (OR), 1.853 (1.243–2.711)] but not DSWI [1.0 vs. 1.5%; adjusted $p = 0.543$; adjusted OR, 1.247 (0.612–2.5409)]. BIMA use showed a higher rate of WHD [no BIMA: 3.0%; BIMA: 7.7%; adjusted $p = 0.002$; adjusted OR, 4.766 (1.747–13.002)] but not DSWI [no BIMA: 1.1%; BIMA: 1.8%; adjusted $p = 0.615$; adjusted OR, 1.591 (0.260–9.749)] in patients with HbA1c ≥ 6.5%.

Conclusions: Intraoperative utilization of BIMA is not connected with an increase of DSWI but higher rates of WHD in patients with poor diabetic status and HbA1c ≥ 6.5%. Therefore, application of BIMA should be taken into consideration even in patients with poor diabetic status, while identification of special subsets of patients who are at particular high risk for DSWI is of paramount importance to prevent this serious complication.

KEYWORDS

HbA1c, coronary artery bypass grafting, coronary artery disease, wound healing disorder, deep sternal wound infection

Abbreviations

BIMA, bilateral internal mammary artery; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DM, diabetes mellitus; DSWI, deep sternal wound infection; HbA1c, glycated hemoglobin A1C; LIMA, left internal mammary artery; RIMA, right internal mammary artery; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; WHD, wound healing disorder.

Introduction

According to recent guidelines, for myocardial revascularization, coronary artery bypass grafting (CABG) is in particular recommended for treatment of complex coronary artery disease (CAD) in patients with intermediate to high SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score and with type 2 diabetes (1, 2). Although results of randomized controlled trials and retrospective studies are partly contradictory, there is a wide consensus for utilization of the left (LIMA) and right internal mammary artery (RIMA), usually referred to as bilateral mammary artery (BIMA), in CABG since long-term patency rates were shown to be superior compared to saphenous vein grafts or the radial artery (3, 4). Especially patients with diabetes mellitus (DM) and reduced left ventricular function benefit from the utilization of BIMA during CABG in terms of long-term survival and freedom from re-revascularization (5, 6). However, a major concern regarding BIMA application in diabetic patients remains an increased risk of wound healing disorders (WHD) or deep sternal wound infections (DSWI) after CABG. Although WHD and DSWI after CABG are highly likely a multifactorial process including the impact on the patient's nutritional status, technique of IMA harvesting (skeletonized vs. pedicled), and/or the presence of metabolic syndrome and obesity (7–9), there are several reports suggesting a detrimental effect of BIMA usage in diabetic patients regarding WHD and DSWI (10, 11), while still resulting in decreased hospital mortality, cerebrovascular events, and re-revascularization rates (12). However, especially DSWI remains a serious complication after CABG with reported in-hospital mortality rates between 7% and 35% and a major socioeconomic impact (13), and therefore the identification of special subsets of patients who are at a particular high risk for DSWI is of utmost interest. So far, there is no report stratifying diabetic patients who underwent CABG using BIMA for levels of glycated hemoglobin A1C (HbA1c), as expression of adequate preoperative management of blood sugar levels. We herein aimed to perform this stratification at a high-volume tertiary heart center and correlate these subsets of diabetic patients with postoperative outcomes with a special emphasis on WHD and DSWI.

Patients and methods

Ethical statement

Data acquisition was performed anonymized and retrospectively. Therefore, in accordance with German law, no ethical approval is needed and informed patient consent was waived.

Patients

Between January 2010 and August 2020, 4,186 consecutive patients underwent isolated CABG at our center. In 3,229 patients, preoperative HbA1c levels were available and retrospective inclusion of those patients into a dedicated database was performed. A patient inclusion flow chart is shown in Figure 1. Harvesting of IMA grafts was performed in a skeletonized fashion. Application of topical vancomycin paste prior to sternum closure was in use since 2017 in all patients. The general closure technique included utilization of sternal wires, inserted in a single or figure of eight fashion and closure of subcutaneous layers using running or single Vicryl sutures. Skin closure was performed with intracutaneous absorbable sutures or a skin stapler. Vacuum therapy was conducted using the KCI system (Kinetic Concepts Inc., San Antonio, TX, USA).

Primary endpoints for this study were WHD, DSWI, and 30-day mortality. Secondary endpoints comprised of major adverse cardiac and cereborvascular events (MACCE; stroke, myocardial infarction) and postoperative renal failure and sepsis. Patients were stratified according to preoperative HbA1c levels with the standard cut-off value of 6.5% and definition of poor diabetic status in patients with HbA1c > 6.5% (14). DSWI was defined as postoperative infection involving the sternum and mediastinal space. WHD was defined as wound infection involving the subcutaneous layer without involvement of the sternum or mediastinal space or as inappropriate healing of the subcutaneous layer due to malperfusion of tissue without signs of infection.

Patients with poor diabetic status were further divided into subgroups according to the utilization of BIMA during CABG. The absence of BIMA use was defined as the application of single IMA, solely veins, single IMA + radial artery or the combination of single IMA + vein.

Statistical analyses

Continuous variables are shown as mean ± standard deviation and are compared using the Mann–Whitney *U*-test. Binary variables are shown as counts (frequencies) and are compared

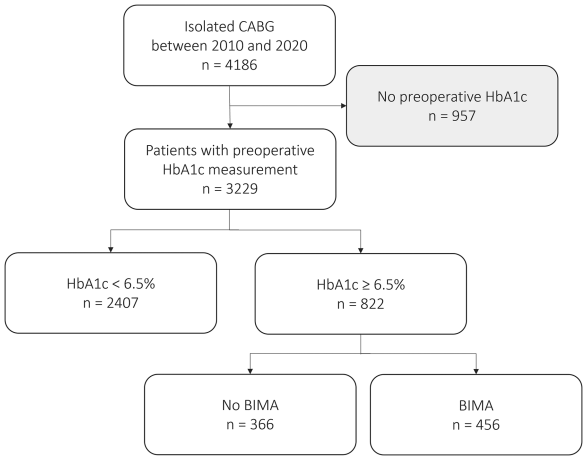

FIGURE 1
Patient inclusion flow chart.

using the χ^2 test. Logistic regression was performed to identify the odds ratio (OR) for outcome parameters. Procedural and outcome parameters were adjusted for body mass index (BMI), left ventricular ejection fraction (LVEF) <35%, prior stroke, extent of CAD, European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), prior CABG, HbA1c, and extracardiac arteriopathy.

A p-value of <0.05 was considered statistically significant. All analyses were performed with SPSS statistical software version 26 (IBM Inc., Armonk, NY, USA).

Results

Baseline demographics

Patients with HbA1c ≥ 6.5% (group 1) showed a significant comorbidity burden less frequently compared to patients with HbA1C > 6.5% (group 2). In particular, patients with a poor diabetic status presented preoperatively with a higher body mass index (27.63 ± 5.37 vs. 29.52 ± 4.79 kg/m^2; $p < 0.001$), more frequent severely reduced left ventricular function (left ventricular ejection fraction <35%: 4.7% vs. 7.5%; $p = 0.002$), more prior strokes (7.7% vs. 12.3%; $p < 0.001$), a greater extent of CAD (number of diseased vessels: 2.46 ± 1.0 vs. 2.58 ± 0.93; $p < 0.001$), prior CABG (0.5% vs. 1.2%; $p = 0.046$), and a higher rate of extracardiac arteriopathy (17.3% vs. 22.6%; $p = 0.001$). Overall, this resulted in a higher EuroSCORE II in patients with a poor diabetic status (1.38% ± 1.16% vs. 1.69% ± 1.86%; $p < 0.001$). Further baseline characteristics showed no significant differences between both groups.

Detailed patient demographics are summarized in Table 1.

TABLE 1 Baseline data.

	HbA1c < 6.5% (n = 2,407)	HbA1c ≥ 6.5% (n = 822)	p-value
Age, years	67.6 (±9.7)	67.7 (±9.5)	0.827
Male gender, n (%)	1,982 (82.3)	670 (81.5)	0.590
STEMI, n (%)	156 (6.5)	41 (5.0)	0.124
BMI, kg/m^2	27.6 (±5.4)	29.5 (±4.8)	<0.001
COPD[a], n (%)	164 (6.8)	62 (7.5)	0.479
LVEF < 35%, n (%)	112 (4.7)	62 (7.5)	0.002
Prior stroke, n (%)	185 (7.7)	101 (12.3)	<0.001
Creatinine clearance	86.5 (±30.9)	88.0 (±35.2)	0.254
Dialysis, n (%)	24 (1.0)	13 (1.6)	0.174
Number of diseased vessels	2.5 (±1.0)	2.6 (±0.9)	0.003
EuroSCORE II, %	1.4 (±1.2)	1.7 (±1.9)	<0.001
Prior CABG, n (%)	13 (0.5)	10 (1.2)	0.046
Prior PCI, n (%)	461 (19.2)	174 (21.2)	0.327
Extracardiac arteriopathy[b], n (%)	417 (17.3)	186 (22.6)	0.001
NYHA ≥ III, n (%)	972 (40.4)	620 (75.4)	0.114

STEMI, ST-elevation myocardial infarction; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; NYHA, New York Heart Association.
[a]Extracardiac arteriopathy.
[b]COPD according to EuroSCORE definitions.

Periprocedural data

In patients with a poor diabetic status, a less frequent use of BIMA grafting was seen (60.3% vs. 55.5%; $p = 0.016$). Furthermore, in the early postoperative stage, these patients were more frequently prone to prolonged ventilation >24 h (3.0% vs. 5.5%; $p = 0.001$) and a prolonged need for inotropes >24 h (2.6% vs. 4.0%; $p = 0.041$). Majority of patients in both groups were referred for CABG as elective procedures. No statistically significant differences between groups were seen regarding the applied intraoperative techniques (off-pump coronary artery bypass, skeletonized harvesting of internal mammary arteries), number of performed bypasses, and documented procedure times including time of extracorporeal circulation and aortic cross-clamp time.

Detailed periprocedural data are summarized in Table 2.

Thirty-day outcome parameters

In unadjusted analysis, patients with a poor diabetic status presented with a higher rate of WHD (2.8% vs. 5.6%; $p < 0.001$) but not DSWI (1.0% vs. 1.5%; $p = 0.3$). These patients also presented a higher mortality rate (0.9% vs. 2.1%, $p = 0.006$), more frequent stroke (1.5% vs. 2.8%, $p = 0.037$), more frequent renal failure (5.6% vs. 8.5%, $p = 0.025$), and a prolonged postoperative intensive care unit (ICU) stay (2.52 ± 2.59 vs. 3.08 ± 5.60 days; $p < 0.001$).

However, after adjusting for differing baseline characteristics, no differences regarding 30-day mortality and stroke rates were seen. The analysis showed a higher rate of WHD in patients with an HbA1c higher than 6.5% [2.8% vs. 5.6%; adjusted $p = 0.002$; adjusted OR, 1.853 (1.243–2.711)] without significant differences with regard to DSWI [1.0% vs. 1.5%; adjusted $p = 0.543$; adjusted OR, 1.247 (0.612–2.5409)]. Patients with a poor diabetic status still presented a higher rate of 30-day renal failure [5.6% vs. 8.5%; adjusted $p = 0.042$; adjusted OR, 1.373 (1.012–1.864)] and a longer ICU stay [2.52 ± 2.59 vs. 3.08 ± 5.60 days; adjusted

TABLE 2 Periprocedural data.

	HbA1c < 6.5% (n = 2,407)	HbA1c ≥ 6.5% (n = 822)	p-value
Elective procedure, n (%)	2,078 (86.3)	710 (86.4)	0.975
OPCAB, n (%)	1,373 (57.0)	458 (55.7)	0.508
Skeletonized IMA harvesting, n (%)	2,055 (85.4)	719 (87.5)	0.222
Procedure time, min	260.4 (±76.3)	265.4 (±77.4)	0.104
ECC, min	68.8 (±62.6)	70.4 (±65.3)	0.534
ACC, min	45.0 (±43.8)	44.6 (±44.7)	0.832
Number of bypasses, n	2.46 (±0.79)	2.49 (±0.80)	0.474
BIMA grafting, n (%)	1,451 (60.3)	456 (55.5)	0.016
Prolonged inotropes ≥24 h, n (%)	63 (2.6)	33 (4.0)	0.041
Prolonged ventilation ≥24 h, n (%)	73 (3.0)	45 (5.5)	0.001
Extracorporeal circulation support, n (%)	48 (1.9)	21 (2.6)	0.588

ECC, extracorporeal circulation time; ACC, aortic cross-clamp time; IMA, internal mammary artery; BIMA, bilateral internal mammary artery; OPCAB, off-pump coronary artery bypass.

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TABLE 3 30-day outcome parameter.

	HbA1c < 6.5% (n = 2,407)	HbA1c ≥ 6.5% (n = 822)	Unadjusted p-value	Adjusted OR (95% CI)	Adjusted p-value
WHD, n (%)	68 (2.8)	46 (5.6)	<0.001	1.835 (1.243–2.711)	0.002
DSWI, n (%)	24 (1.0)	13 (1.5)	0.301	1.247 (0.612–2.540)	0.543
ICU stay, days	2.52 (±2.59)	3.08 (±5.60)	<0.001	0.405 (0.115–0.695)	0.006
Hospital stay, days	8.44 (±15.98)	9.95 (±28.9)	0.063	1.404 (−0.224–3.033)	0.091
Myocardial infarction, n (%)	48 (2.0)	15 (1.8)	0.804	0.818 (0.436–1.537)	0.533
Mortality, n (%)	21 (0.9)	17 (2.1)	0.006	1.753 (0.878–3.500)	0.111
Stroke, n (%)	35 (1.5)	23 (2.8)	0.037	1.684 (0.975–2.908)	0.062
Renal failure, n (%)	134 (5.6)	70 (8.5)	0.025	1.373 (1.012–1.864)	0.042
Sepsis, n (%)	14 (0.6)	11 (1.3)	0.086	1.526 (0.648–3.594)	0.334

WHD, wound healing disorder; DSWI, deep sternal wound infection; ICU, intensive care unit.

p = 0.006; adjusted OR, 0.405 (0.115–0.695)]. No differences regarding 30-day myocardial infarction or sepsis were seen between groups in unadjusted and adjusted analysis. When stratifying WHD/DSWI according to the different levels of HbA1c, a significant increase of WHD/DSWI was seen in patients with HbA1c > 9% even when compared to patients with HbA1c > 6% (HbA1c 5–5.9% vs. >9%: WHD/DSWI 2.5% vs. 15%; p < 0.001; HbA1c 6–6.9% vs. >9%: WHD/DSWI 2.5% vs. 4.5%; p = 0.01).

Detailed 30-day outcome parameters are summarized in Table 3. The distribution of WHD and DSWI according to HbA1c levels is shown in Figure 2.

Spectrum of pathogens and antimicrobial therapy in patients with WHD and DSWI (HbA1c < 6.5% vs. HbA1c ≥ 6.5%)

There were no significant differences between groups regarding the distribution of causal pathogens for WHD and DSWI with a large proportion of patients in both groups with no evidence of any bacterial wound infection. Most frequent pathogens were gram + species in both groups followed by gram − species. The proportion of antimicrobial treatment was not different between groups, whereas a higher but not statistically significant proportion of patients with HbA1c < 6.5% presented with resistant bacteria in microbiological culturing of intraoperative tissue specimen. The rate of antibiotic treatment and type of bacteria in patients with HbA1c < 6.5% vs. HbA1c ≥ 6.5% are shown in Figure 3.

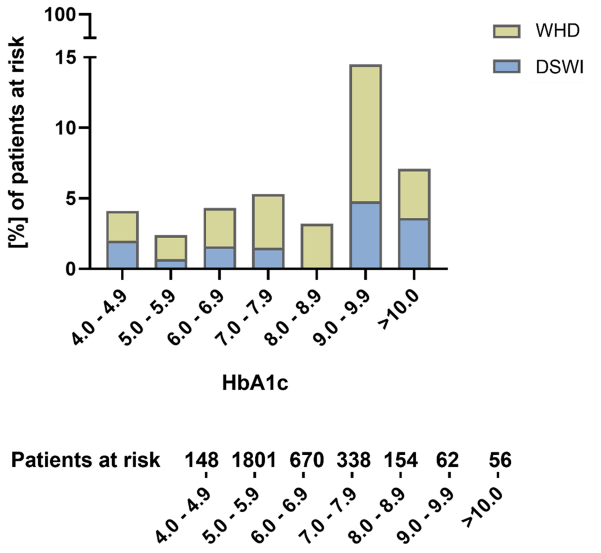

FIGURE 2
Distribution of wound healing disorders and deep sternal wound infections according to preoperative HbA1c levels.

Subgroup analysis: WHD and DSWI in patients with BIMA use and HbA1c ≥ 6.5%

In a subgroup analysis of patients with a poor diabetic status and comparison of BIMA vs. no BIMA use, BIMA use showed a higher rate of WHD [no BIMA: 3.0%; BIMA: 7.7%; adjusted p = 0.002; adjusted OR, 4.766 (1.747–13.002)] but no difference in the rate of DSWI [no BIMA: 1.1%; BIMA: 1.8%; adjusted p = 0.615; adjusted OR, 1.591 (0.260–9.749)]. There was no significant difference in 30-day MACCE between no BIMA and BIMA use in patients with an HbA1c ≥ 6.5%. The rate of antibiotic treatment and type of bacteria in patients with BIMA use vs. no BIMA use are shown in Figure 4. Since higher age was described as a potential risk factor for postoperative WHD and DSWI, an additional logistic regression analysis was performed to determine the significance of age as a risk factor for WHD and DSWI. Here, age presented no significance (see Supplementary Table S1).

Detailed baseline characteristic subgroups and rates of WHD and DSWI in patients with BIMA use are summarized in Tables 4, 5.

Comment

Main findings of the herein conducted study are (I) in adjusted analysis, CABG in patients with a poor diabetic status is not associated with an increase in mortality, stroke, or DSWI while presenting a higher rate of WHD and renal failure compared to patients with HbA1c < 6.5%; (II) in our cohort, BIMA was

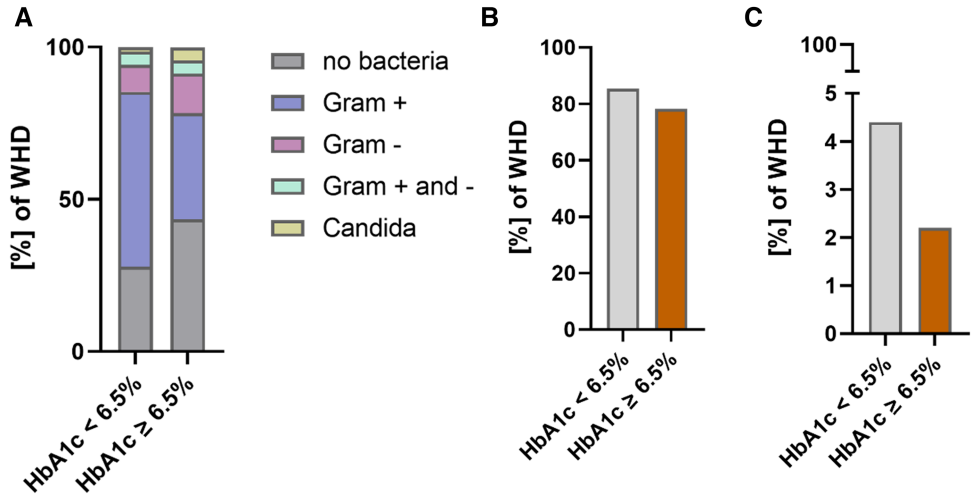

FIGURE 3
Bacteria and antimicrobial treatment in patients with WHD (HbA1c < 6.5% vs. HbA1c ≥ 6.5%). (A) Bacterial species in patients with WHD. (B) Proportion of antimicrobial treatment in patients with WHD. (C) Percentage of resistant bacteria in patients with WHD.

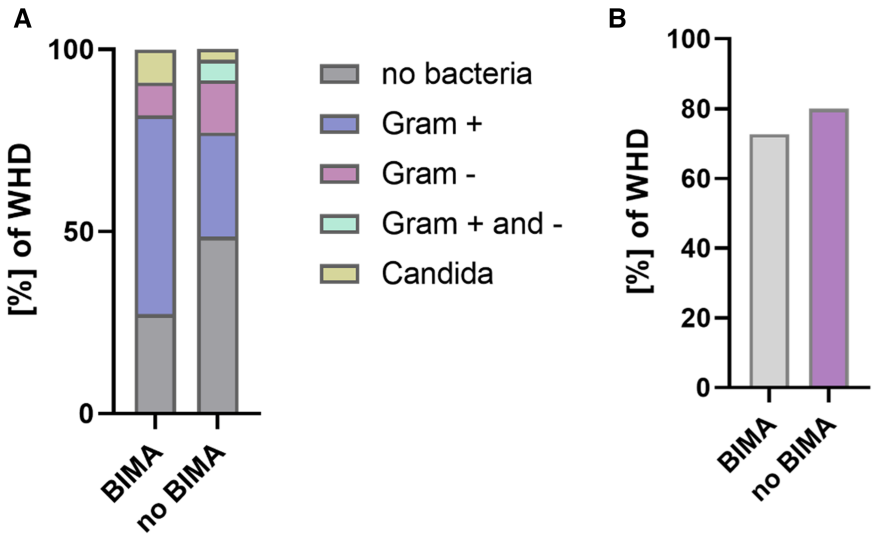

FIGURE 4
Bacteria and antimicrobial treatment in WHD/DSWI (BIMA vs. no BIMA in patients with HbA1c ≥ 6.5%). (A) Bacterial species in patients with WHD. (B) Proportion of antimicrobial treatment in patients with WHD.

significantly less applied in patients with poor diabetic status; (III) most WHD and DSWI were seen in patients with HbA1c > 9%; and (IV) BIMA utilization in patients with HbA1c ≥ 6.5% presents excellent short-term results, largely without an increase in primary or secondary endpoints and in particular no increase of DSWI while yielding a higher rate of WHD.

While several analyses suggest a detrimental effect of elevated HbA1c levels in patients undergoing CABG with regard to postoperative mortality, stroke, and myocardial infarction (15, 16), our results presented no increase in the mentioned clinical endpoints. However, with higher rates of renal failure in patients with HbA1c ≥ 6.5%, the results presented herein are in accordance with the work of Oezkur et al. (17) who reported that in 307 patients undergoing CABG chronic hyperglycemia was independently associated with postoperative acute kidney injury. Reasons for these partly contradictory results remain speculative but the herein documented high rates of elective procedures and utilization of off pump coronary artery bypass (OPCAB) technique in more than 50% of patients in both groups may have contributed to the low rates of stroke and

TABLE 4 Baseline data subgroup analysis: BIMA use in patients with HbA1c ≥ 6.5%.

	no BIMA ($n = 366$)	BIMA ($n = 456$)	p-value
Age, years	71.8 (±9.0)	64.3 (±8.6)	<0.001
Male gender, n (%)	272 (74.3)	398 (87.3)	<0.001
STEMI, n (%)	20 (5.5)	21 (4.6)	0.579
BMI, kg/m^2	29.5 (±5.2)	29.6 (±4.4)	0.791
COPD[a], n (%)	37 (10.1)	25 (5.5)	0.013
LVEF < 35%, n (%)	32 (8.7)	30 (6.6)	0.243
Prior stroke, n (%)	49 (13.4)	52 (11.4)	0.389
Creatinine clearance	76.6 (±30.7)	97.2 (±36.0)	<0.001
Dialysis, n (%)	7 (1.9)	6 (1.3)	0.495
Number of diseased vessels, n	2.5 (±1.0)	2.6 (±0.9)	0.173
EuroSCORE II, %	2.3 (±2.5)	1.2 (±0.9)	<0.001
Prior CABG, n (%)	8 (2.2)	2 (0.4)	0.023
Prior PCI, n (%)	86 (23.5)	88 (19.3)	0.143
Extracardiac arteriopathy[b], n (%)	88 (24.0)	98 (21.5)	0.385
NYHA ≥ III, n (%)	175 (47.8)	171 (37.5)	0.001

STEMI, ST-elevation myocardial infarction; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; NYHA, New York Heart Association.
[a]Extracardiac arteriopathy.
[b]COPD according to EuroSCORE definitions.

postoperative myocardial infarction seen herein, since OPCAB is considered to potentially reduce stroke rates in CABG (18) and elective procedures are connected with lower rates of mortality and myocardial infarction compared to emergency CABG as seen in larger registries (19). While WHD were more frequent in patients with a poor diabetic status, DSWI presented no significant increase in the patient cohort investigated herein. This effect persisted in adjusted analysis and in comparison of BIMA utilization in patients with HbA1c ≥6.5% and ≥6.5%. Contrary to our results, the E-CABG registry reported a clear adverse effect of poor diabetic status on postoperative rates of DSWI in CABG (20), while it has to be emphasized that in the mentioned work, the chosen HbA1c cut-off was different (4.6%; 70 mmol/mol) to the herein used cut-off value, which may partly explain the differences in the results. Furthermore, a meta-analysis from Dai et al. presented a detrimental effect of BIMA utilization in diabetic patients with regard to postoperative DSWI (21), an effect that was also not seen in the patients investigated herein and which may be caused by lack of adjustment for preoperative risk factors and diffuse definition and separation of WHD and DSWI in the included 32 studies. Although retrospectively conducted, our work conclusively showed that patients with poor diabetic status and patients with poor diabetic status provided with BIMA during CABG are not prone to increased rates of DSWI. Measures that may have contributed to the described low rates of DSWI may be the routine use of topical vancomycin paste (22) and high rates of skeletonized IMA harvesting (23), techniques that are considered to reduce the risk of DSWI. When considering advantages of BIMA in patients with diabetes, which are mainly improved long-term survival and reduced re-revascularization rates (5), our results suggest that BIMA utilization in all diabetic patients and especially also in patients with poor diabetic status and preoperative HbA1c ≥ 6.5% is reasonable, since DSWI were not increased. Although, a higher rate of superficial WHD was seen, the mentioned benefits of BIMA should outweigh the drawbacks of WHD, which are usually simple to treat.

However, our results suggest that special attention should be paid to patients with HbA1c > 9%, since a clear trend toward a significant increase of WHD and DSWI was seen and benefits of BIMA should be weighed against possible complications connected with DSWI. Therefore, further analysis for the identification of patient subsets that are at particular high risk for DSWI after CABG and in particular after CABG using BIMA are required to further reduce risk of DSWI, which remains a serious and harmful complication after cardiac surgery.

Limitations

Limitations are inherent in the retrospective, single-center study design with limited patient numbers: patients were not randomized to a specific treatment; therefore, patient preselection with hidden confounders may apply. Moreover, data on preoperative medication (e.g., immunosuppressant drugs) that may influence wound healing were not available.

Conclusions

CABG presents excellent short-term outcomes in terms of mortality, stroke, and myocardial infarction independent from preoperative HbA1c levels with no increase of DSWI, but higher rates of WHD and renal failure in patients with poor diabetic status and HbA1c ≥ 6.5%. Intraoperative utilization of BIMA is not connected with an increase of DSWI but higher rates of

TABLE 5 Thirty-day outcomes subgroup analysis: BIMA use in patients with HbA1c ≥ 6.5%.

	no BIMA ($n = 366$)	BIMA ($n = 456$)	p-value	Adjusted OR (95% CI)	Adjusted p-value
WHD, n (%)	11 (3.0)	35 (7.7)	0.004	4.766 (1.747–13.00)	0.002
DSWI, n (%)	4 (1.1)	8 (1.8)	0.374	1.591 (0.260–9.749)	0.615
Myocardial infarction, n (%)	10 (2.7)	5 (1.1)	0.082	0.980 (0.206–4.649)	0.979
Mortality, n (%)	11 (3.0)	6 (1.3)	0.091	1.689 (0.383–6.123)	0.489
Stroke, n (%)	11 (3.0)	12 (2.6)	0.747	1.257 (0.407–3.877)	0.691
Renal failure, n (%)	41 (11.2)	31 (6.8)	0.026	1.035 (0.518–2.066)	0.923
Sepsis, n (%)	7 (1.9)	4 (0.9)	0.199	1.302 (0.239–7.106)	0.761

WHD, wound healing disorder; DSWI, deep sternal wound infection.

WHD in patients with poor diabetic status and HbA1c $\geq$ 6.5%. Therefore, the application of BIMA should be taken into consideration in CABG even in patients with poor diabetic status, while the identification of special subsets of patients who are at particular high risk for DSWI is of paramount importance to prevent this serious complication.

Data availability statement

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

Ethics statement

Ethical approval was not required for the studies involving humans because data acquisition was performed anonymized and retrospectively. Therefore, in accordance with German law, ethical approval is not needed and informed patient consent was waived. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because data acquisition was performed anonymized and retrospectively. Therefore, in accordance with German law, ethical approval is not needed and informed patient consent was waived.

Author contributions

TK: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. AS: Writing – original draft, Project administration, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. JB: Writing – review & editing, Validation, Methodology, Investigation. BR: Writing – review & editing, Validation, Investigation. SN: Writing – review & editing, Supervision, Methodology. SZ: Writing – review & editing, Supervision, Methodology. YS: Writing – review & editing, Supervision, Methodology, Investigation. HR: Writing – review & editing, Validation, Supervision, Methodology, Investigation. BS: Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation.

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Conflict of interest

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Supplementary material

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EDITED BY
Marco Pocar,
University of Milan, Italy

REVIEWED BY
Luca Paolo Weltert,
European Hospital, Italy
Suvitesh Luthra,
University Hospital Southampton NHS Foundation Trust, United Kingdom

*CORRESPONDENCE
Denis Berdajs
✉ denis.berdajs@bluewin.ch

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Early silent coronary bypass graft occlusion following coronary bypass surgery, implication of routine coronary computed tomography angiography

Islam Salikhanov[1], Luca Koechlin[1], Brigitta Gahl[1], Oliver Reuthebuch[1], Michael Zellweger[2], Philip Haaf[2], Jens Bremerich[3], Maurice Pradella[3], Christian Müller[2] and Denis Berdajs[1]*

[1]Department of Cardiac Surgery, University Hospital Basel, Basel, Switzerland, [2]Department of Cardiology, University Hospital Basel, Basel, Switzerland, [3]Department of Radiology, University Hospital Basel, Basel, Switzerland

Objective: To evaluate incidence and predictors of early silent bypass occlusion following coronary bypass surgery using cardiac computed tomography angiography.
Methods: A total of 439 consecutive patients with mean age of 66 ± 10 years comprising 17% ($n = 75$) females underwent isolated coronary bypass surgery followed by CT scan before discharge. Graft patency was evaluated in 1,319 anastomoses where 44% ($n = 580$) arterial and 56% ($n = 739$) vein graft anastomosis were performed. Cardiovascular risk factors, demographics, and intraoperative variables were analyzed. We conducted univariable and multivariable logistic regression analyses to analyze variables potentially associated with graft occlusion following CABG. Variables included gender, surgery duration, graft flow, pulsatility index, vein vs. artery graft, and recent MI.
Results: Overall incidence of graft occlusion was 2.4% (31/1,319), and it was diagnosed in 6.6% (29/439) of patients. The difference in occlusion between arterial (2.1%) and vein (2.6%) grafts was not significant, $p = 0.68$. The duration of intervention $p = 0.034$, cross clamp time $p = 0.024$ as well the number of distal anastomosis $p = 0.034$ were significantly higher in occlusion group. The univariate and multivariate logistic regression indicated duration of surgery being predictive for bypass graft occlusion with OR = 1.18; 95% CI: 1.01–1.38; $p = 0.035$.

Abbreviations
AUC, area under the curve; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian cardiovascular society; CK, creatine kinase; CK-MB, muscle brain creatine kinase; CPB, cardiopulmonary bypass; CT, computed tomography; CX, circumflex artery; DF, diastolic filling; DM, diagonal branch of the left anterior descending artery; ECG, electrocardiogram; EuroSCOREII, European system for cardiac operative risk evaluation; GF, graft flow; GFR, glomerular filtration rate; hs-cTn, high-sensitivity cardiac troponin; ICU, intensive care unit; LIMA, left internal mammary artery; MACCE, major adverse cardiovascular or cerebrovascular event; MI, myocardial infarction; MIDCABG, minimal invasive direct coronary artery bypass grafting; MiECC, minimal extracorporeal circulation; MRI, magnetic resonance imaging; NYHA, New York heart association; OM, left marginal artery; OPCBAG, off-pump coronary bypass revascularization; OR, odds ratio; PCI, percutaneous coronary intervention; PET/CT, positron emission tomography/computed tomography; PI, pulsatility index; RAD, radial artery; RCA, right coronary artery; RCX, right circumflex artery; RIMA, right internal mammary artery; RIVA, ramus interventricularis anterior; RIVPO, ramus interventricularis posterior; RPLD, ramus posterolateralis dexter; SD, standard deviation; SVG, saphenous vein graft; TIA, transient ischemic attack.

Conclusions: Early graft occlusion was associated with surgical factors. The number of distant anastamoses, along duration of surgical intervention were, significantly influenced the risk of EGO. Prolonged procedural time reflecting complex coronary pathology and time-consuming revascularization procedure was as well associated to the elevated risk of occlusion.

KEYWORDS

early coronary bypass occlusion, coronary bypass surgery, coronary computed tomography, CABG, coronary angiography

1 Introduction

Coronary artery bypass grafting (CABG) surgery, as a therapy modality, is the standard of care in treatment of severe coronary artery disease (1, 2). It is the most frequently performed cardiosurgical intervention (1, 2). Although CABG, as a procedure, is considered a routine intervention, the potential risk is considerable, especially in patients with advanced cardiovascular risk profile (1, 2).

Perioperative myocardial infarction (MI) is a serious complication following CABG surgery (3, 4). Due to the lack of classical clinical symptoms, the diagnosis of post-operative MI is a clinical challenge and is based on a modification in electrocardiogram (ECG) refractory malignant arrhythmias, an elevation of cardiac biomarkers, and new echocardiography wall motion abnormalities (4, 5). From 25% to 35% of patients with above-mentioned clinical signs suggestive of post-CABG MI have no evidence of coronary bypass graft occlusion (4). Perioperative MI due to the early bypass graft occlusion ranges between 5% and 17% and may have a major impact on early and short-term outcome (6–10). Real prevalence of early bypass occlusion remains unclear due to the absence of symptomatic manifestations of MI in some patients and the consequent lack of adequate diagnosis. Because of a limited number of reports on bypass occlusion in the early postoperative period, early diagnosis of CABG occlusion remains a major unaddressed clinical need (6, 7).

Cardiac CT, which has 96% sensitivity and specificity for diagnosing graft failure, is becoming a feasible, minimally invasive alternative to traditional invasive angiography in the diagnosis of coronary vessel pathology (6–8). This diagnostic tool complements our routine postoperative quality control measures by allowing early identification of graft occlusions before patient discharge. Therefore, this retrospective analysis aimed to determine the incidence and predictors of coronary bypass graft occlusion detected by coronary CT in the early postoperative period. The secondary aim of our study was to investigate the incidence of key postoperative complications, including myocardial infarction, mortality, stroke, and MACCE.

2 Material and methods

2.1 Ethics statement

The local ethical committee at the University of Basel, Basel, Switzerland (Ethikkomission Nordwest und Zentralschweiz, BASEC-Nr. 2023-01850) approved the protocol of this retrospective study. A written informed consent was waived due to the retrospective nature of the study.

2.2 Study population

From March 2020 to September 2023, 690 patients underwent coronary bypass surgery (CABG). General exclusion criteria were concomitant surgical procedure, renal failure, refusal of postoperative CT scan, and signs of myocardial infarction (electrocardiographic changes, elevated cardiac enzymes, clinical symptoms of angina pectoris) leading to a postoperative angiographic examination. Renal failure was defined as serum creatinine level >170 mmol/L and estimated glomerular filtration rate (GFR) <30 ml/min/1.73 m^2, demonstrating at least moderate impairment of renal function (11). We excluded 213 patients due to concomitant procedures and 38 patients due to renal impairment (Figure 1). The remaining 439 patients were classified into two groups. In the first group, we classified those with all anastomoses open, and in the second group, we included those with at least one occluded anastomosis.

2.3 Surgical technique

Minimal extracorporeal circulation (MiECC) assisted CABG, or off-pump coronary bypass revascularization (OPCBAG), is the standard procedure for isolated coronary revascularization in our institution. The surgical technique of CABG on MiECC was described earlier (12, 13). In all patients with multi-vessel diseases, CABG was performed through a midline sternotomy. In of-pump, CABG stabilization of the target coronary arteries was accomplished with a tissue stabilizer (Octopus, Medtronic Corporation, Minneapolis, MN). In all cases, an intracoronary shunt (Medtronic Corporation, Minneapolis, MN) for all distal anastomosis was used. At the end of the procedure, just prior to the pericardial closure, mean graft flow (GF), the pulsatility index (PI), and the diastolic filling (DF) were measured. Criteria for acceptable blood flow were as follows: (a) stable shape of blood flow waveform and (b) PI < 5; GF > 15 ml/min. Graft revision was considered in case of insufficient graft flow, low PI conjoined to the new local wall motion in echocardiogram, and/or pathological ST finding in electrocardiogram. Postoperative care included the administration of heparin (14,400 units/h) 6 h

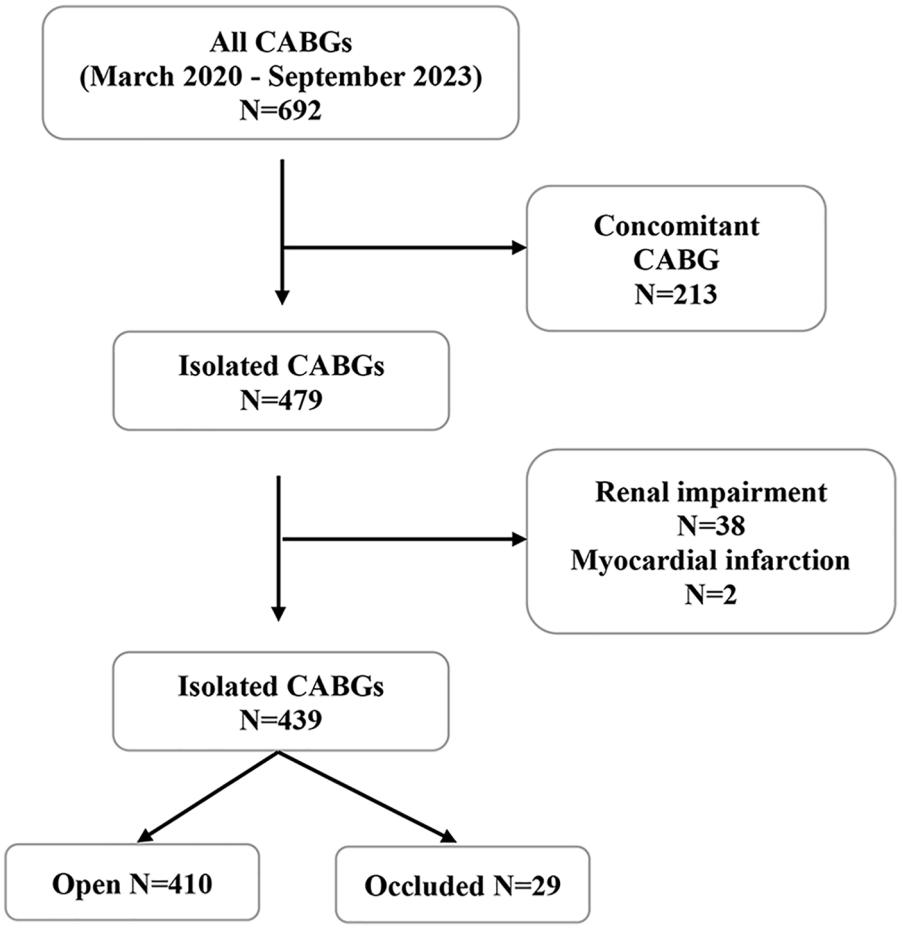

FIGURE 1
Patient selection flowchart depicting the inclusion criteria for the study on isolated CABG from March 2020 to September 2023. From the initial 690 CABGs, 213 concomitant procedures were excluded. Following exclusion of 38 patients with renal impairment, 439 patients were evaluated, resulting in 410 with patent grafts and 29 with occluded grafts. CABG, coronary artery bypass grafting.

post-surgery and aspirin (100 mg) 6 h post-intervention. Clopidogrel (75 mg) or Ticagrelor (90 mg twice a day) was given 6 h post-surgery to all patients with acute coronary syndrome, and all patients were prescribed a lifetime regimen of aspirin (14).

2.4 Cardiac computed tomography angiography

Cardiac CT scans, comprising 256 slices, were conducted before patient discharge. Early bypass occlusion was defined as occlusion during the hospital stay. All CT scans were reviewed by both, cardiologists, and radiologists with specific expertise in cardiac CT. We assessed the total number of distal anastomoses, evaluating the number that were patent vs. those that were occluded. Graft occlusion was defined by the lack of contrast medium presence in either (a) the bypass graft or the distal runoff of the anastomosed target vessel, and (b) within the target vessel itself.

2.5 Clinical parameters

In-hospital mortality was described as death before discharge. A neurologic event was defined according to the Valve Academic Research Consortium, and a perioperative stroke was expressed as any neurological deficit with or without evidence of cerebral injury in a CT scan and/or in magnetic resonance imaging (MRI) (15). Perioperative myocardial infarction was defined according to the current guidelines (5).

2.6 Outcomes

The primary outcome was the incidence of coronary bypass occlusion. Secondary outcomes were incidence of myocardial infarction, mortality, stroke, and incidence of combined major adverse cardiovascular or cerebrovascular events (MACCE). MACCE was specified as a combined event of major in-hospital events such as mortality, stroke, and myocardial infarction.

2.7 Statistical analysis

In this study, we aimed to identify variables associated with early graft occlusion following CABG by conducting a comprehensive analysis that included both univariable and multivariable logistic regression models. Variables considered in our analysis were selected based on their potential relevance to graft occlusion, e.g., patient gender, emergency status, duration of surgery, graft flow, pulsatility index (PI), and the time since most recent myocardial infarction (MI). Due to the close association between emergency procedures and recent MI, we opted not to include emergency as a separate variable but instead included a differentiation between vein and artery grafts, acknowledging that graft flow characteristics significantly depend on the graft material. Several intra-operative variables differing between patients with and without occlusion were highly correlated (duration of surgery, CABP-time, x-clamp time, number of anastomoses). So to avoid collinearity, we had to select one of these and chose duration of surgery. The analysis was conducted at the graft level, with patients modelled as a random factor in the model to account for within-patient correlation of multiple grafts. The duration of surgery was operationalized in increments of 10 min.

Statistical evaluations was conducted utilizing Stata 16 statistical software (StataCorp LLC. College Station, TX) and SPSS (IBM Corp. Released 2022. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp). For descriptive statistics, the cohort was grouped by outcome into "open" and "occluded" groups. Continuous variables were described as mean ± SD or as median with interquartile range, as appropriate, and compared using Student's *t*-Test or Wilcoxon–Mann–Whitney test accordingly. Nominal and categorical variables were presented as absolute figures and percentages (%). The Mann–Whitney *U*-test facilitated the analysis of numerical data, while binary data were assessed using Pearson's χ^2 test or Fischer's exact test. The analytical framework encompassed preoperative baseline data and perioperative data within the univariate analysis. A statistical significance threshold was set at $p < 0.05$, consistent with conventional standards.

3 Results

3.1 Patient characteristics

In the final analysis, 439 patients were included. Baseline patient demographics are presented in Table 1. The mean age was 66 ± 10 years, and 17% ($n = 75$) were females. Mean EuroSCORE II was 1.46 [IQR: 0.87–2.72], and 8.9% ($n = 49$) of patients were classified as the New York Heart Association (NYHA) class ≥III/IV heart failure, whereas 47.6% ($n = 209$) of patients were classified as Canadian Cardiovascular Society (CCS) angina class III/IV. Left main disease was present in 15% ($n = 64$) of cases.

Out of 1,319 performed anastomoses, 31 were occluded, and 1,288 were patent. In the occluded cohort, 72% ($n = 21$) of patients were males, and 48% ($n = 14$) received treatment for diabetes mellitus. Cardiovascular risk factors, such as hypertension, impaired renal function, and chronic lung disease, did not differ significantly from patients with no coronary bypass occlusion (Table 1). Patients who underwent CABG with newly diagnosed MI within 7 days before the surgery (35%, $n = 154$) were more likely to have early graft occlusion compared to those with MI more than 7 days before CABG ($p = 0.045$). Elective CABG was performed in 65% ($n = 286$) of cases. The on-pump CABG with MiECC was performed in 81% ($n = 355$) and of-pump in 19% ($n = 84$) cases. Surgical details are presented in Table 2.

TABLE 1 Baseline clinical characteristics.

	Total ($N = 439$)	Open ($N = 410$)	Occluded ($N = 29$)	*p*
Age (years)	66 ± 10	67 ± 10	65 ± 10	0.41
Gender				0.13
Female	75 (17%)	67 (16%)	8 (28%)	
Male	364 (83%)	343 (84%)	21 (72%)	
BMI	27 ± 4.3	27 ± 4.3	27 ± 3.9	0.96
EuroSCORE II	1.46 [0.87–2.72]	1.48 [0.87–2.72]	1.36 [0.95–2.33]	0.85
Angina CCS III or IV	209 (47.6%)	195 (15%)	14 (21%)	0.84
NYHA III or IV	49 (8.9%)	47 (9.0%)	2 (6.9%)	0.98
Diabetes mellitus	179 (41%)	165 (40%)	14 (48%)	0.44
Current smoker	126 (29%)	118 (29%)	8 (28%)	0.58
Hypertension	337 (77%)	316 (77%)	21 (72%)	0.65
Hypercholesterolemia	306 (70%)	282 (69%)	24 (83%)	0.14
COPD	36 (8.2%)	35 (8.5%)	1 (3.4%)	0.50
Previous cardiac surgery	2 (0.46%)	1 (0.24%)	1 (3.4%)	0.13
Extracardiac arteriopathy	95 (22%)	87 (21%)	8 (28%)	0.48
Previous cerebrovascular event	36 (8.2%)	34 (8.3%)	2 (6.9%)	1.00
Left ventricular ejection fraction value (%)	53 ± 11	54 ± 11	51 ± 12	0.15

Values are *n* (%) for categorical variables or mean ± SD for continuous variables. Angina (CCS III or IV) and heart failure (NYHA III or IV) prevalence are shown as counts with the corresponding percentages of the total. Comorbidities are reported as counts with percentages.
BMI, body mass index; CCS, Canadian cardiovascular society; NYHA, the New York heart association; EuroScoreII, European system for cardiac operative risk evaluation; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

TABLE 2 Surgical characteristics.

	Total ($N = 439$)	Open ($N = 410$)	Occluded ($N = 29$)	p
Duration of surgery (min)	238 ± 56	236 ± 55	259 ± 54	0.034
CPB-time (min)	107 ± 28	106 ± 28	119 ± 28	0.024
Duration of x-clamp (min)	70 ± 21	69 ± 21	80 ± 18	0.014
Operation urgency				0.52
Elective	284 (65%)	265 (65%)	19 (66%)	
Urgent	155 (35%)	145 (35%)	10 (34%)	
Cardio-pulmonary bypass	355 (81%)	331 (81%)	24 (83%)	1.00
Perfusion				1.00
Off-pump	84 (19%)	79 (19%)	5 (17%)	
MiECC	355 (81%)	331 (81%)	24 (83%)	
Number of distal anastomoses	3.4 ± 1.1	3.4 ± 1.1	3.8 ± 1.1	0.034

Data presented as mean ± SD for continuous variables and n (%) for categorical ones. p-values assess differences between groups.
CPB, cardiopulmonary bypass; MiECC, minimal invasive extracorporeal circulation.

3.2 In hospital outcome

The postoperative results are presented in Table 3. We observed a favorable short-term outcome with no mortality within 30 days post-surgery. The incidence of postoperative complications was relatively low, with stroke occurring in 0.91% of the cases ($n = 4$), and perioperative myocardial infarction being even less frequent, at 0.46% ($n = 2$). The incidence of MACCE during hospital stay was 1.3% ($n = 6$), and 15% ($n = 68$) of patients had atrial fibrillation diagnosed till discharge. The mean duration of ICU stay was 1.8 ± 1.9 days, and the mean hospital stay was 8.8 ± 3.6 days.

3.3 Coronary bypass patency/occlusion and bypass characteristics

CT scan was performed at 6 ± 2 days following CABG. A total of 1,319 distal anastomoses, 43% ($n = 580$) arterial and 56% ($n = 739$) venous, were performed, with a mean of 3.4 ± 1.1 distal anastomoses per patient (Table 2). The overall incidence of bypass graft occlusion was 2.4% ($n = 31$), there was no difference between arterial (2.1%) vs. venous (2.6%) conduits occlusions ($p = 0.68$). A higher number of distal anastomoses was associated with an elevated risk for bypass occlusion ($p = 0.034$) (Table 2). Graft distribution and patency for 439 patients are presented in Supplementary Table S2. Patients with occluded grafts had a longer hospital stay of 10.6 ± 5.1 vs. 8.6 ± 3.5 days ($p < 0.001$). Adverse events, such as atrial fibrillation ($p = 0.79$) and perioperative MI ($p = 0.13$), showed no significant difference between groups (Table 3). Mean duration of intervention was 238 ± 56 min and was significantly longer in patients with bypass occlusion ($p = 0.034$). A similar pattern emerged for cardiopulmonary bypass (CPB) time ($p = 0.024$) and for cross-clamp time ($p = 0.014$).

Mean flow and PI were 50 ± 26 ml/min and 1.6 ± 0.8 in arterial and 65 ± 34 ml/min and 1.5 ± 0.6 in vein grafts, respectively ($p < 0.01$) (Supplementary Table S2). The difference in flow between the open and the occluded vein grafts was significant 67 ± 35 ml/min vs. 51 ± 25 ml/min, ($p = 0.02$), respectively. The mean PI in the occluded graft group was 1.75 ± 0.92, vs. 1.71 ± 0.65 in the open group; $p = 0.48$.

Univariable and multivariable model analysis revealed that only the duration of surgery was a statistically significant predictor of graft occlusion in both, with an odds ratio (OR) of 1.16 (95% CI: 1.00–1.33, $p = 0.043$) in the univariable model and 1.18 (95% CI: 1.01–1.38, $p = 0.035$) in the multivariable model (Table 4). Other variables, including graft flow, PI, graft type (vein vs. artery), and recent MI, were not significant predictors of occlusion in our study. Notably, female gender showed a higher odds ratio (OR = 4.76; 95% CI: 0.72–31.6) in the multivariable model, though this did not reach statistical significance ($p = 0.106$).

The predictive margins for early graft occlusion post-CABG with 95% confidence intervals may be seen in Figures 2–3 present. The influence of MI 7 days prior to CABG on the likelihood of graft occlusion is presented in Figure 2.

TABLE 3 Postoperative outcomes.

	Total ($N = 439$)	Open ($n = 410$)	Occluded ($n = 29$)	p
ICU stay (days)	1 [1–2]	1 [1–2]	1 [1–2]	0.6
Definitive pacemaker	3 (0.68%)	3 (0.73%)	0 (0.00%)	1.00
Atrial fibrillation	68 (15%)	63 (15%)	5 (17%)	0.79
Pericardial effusion/tamponade	7 (1.6%)	7 (1.7%)	0 (0.00%)	1.00
Max. CK	595 [410–934]	598 [410–913]	563 [406–1,015]	0.61
Max. CK-MB	37 ± 56	35 ± 55	73 ± 78	0.15
Max. Hs-cTn T	290 [193–595]	289 [192–595]	403 [228–902]	0.14
Pulmonary complication	22 (5.0%)	19 (4.6%)	3 (10%)	0.17
Cerebrovascular event				0.27
TIA	5 (1.1%)	5 (1.2%)	0 (0.00%)	
Stroke	4 (0.91%)	3 (0.73%)	1 (3.4%)	
Length of hospital stay (days)	8.8 ± 3.6	8.6 ± 3.5	10.6 ± 5.1	<0.001

Maximal levels of CK, CK-MB, are reported in units per liter (U/L), and nanograms per liter (ng/L) for Hs-cTn T. Values are mean ± SD for continuous and n (%) for categorical variables, with p-values for group comparisons.
ICU, intensive care unit; MI, myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase-MB; Hs-cTn T, high-sensitivity troponin T; TIA, transient ischemic attack; SD, standard deviation.

TABLE 4 Predictive variables for graft occlusion.

	Odds ratio (95% CI)	*p*
Univariable		
Graft flow	0.99 (0.97–1.02)	0.574
Pulsatility index	1.04 (0.57–1.93)	0.889
Vein graft	1.10 (0.37–3.29)	0.865
MI within 7 days	1.36 (0.30–6.25)	0.693
Duration of surgery	1.16 (1.00–1.33)	0.043
Female sex	4.89 (0.63–38.0)	0.129
Multivariable		0.350
Graft flow	0.99 (0.97–1.02)	0.631
Pulsatility index	1.00 (0.51–1.97)	0.990
Vein graft	1.10 (0.34–3.53)	0.874
MI within 7 days	1.39 (0.28–6.96)	0.691
Duration of surgery	1.18 (1.01–1.38)	0.035
Female sex	4.76 (0.72–31.6)	0.106

The table Illustrates the findings of a univariable and multivariable logistic regression, evaluating potential predictors for graft occlusion. The table lists the Odds Ratios (OR) with their 95% Confidence Intervals (CI), alongside the corresponding *p*-values. The multivariable analysis accounts for potential confounders by including all predictors in the model simultaneously. "MI", myocardial infarction.

The patients with a recent MI exhibit a higher predictive margin of graft occlusion compared to those without, and this margin increases with the length of the surgical procedure.

The relationship between graft flow rates and the likelihood of occlusion for different graft types presented in Figure 3. The predictive margins for venous grafts show a slight decrease as flow rates increase, while arterial grafts display a consistent risk across flow rates. The overlapping confidence intervals for both arterial and venous grafts suggest that graft type alone is not a definitive predictor of occlusion risk.

4 Discussion

Our study conducted with 439 patients yielded significant findings on graft patency after CABG. The accuracy of post-CABG graft patency is key in the prognosis and long-term outcomes of cardiac surgery patients. We delineated the factors contributing to early graft occlusion by analyzing postoperative CT findings from patients who were operated between March 2020 and September 2023. One of the most important findings was a very low incidence of graft occlusion that occurred in 2.4%, considerably less than reported in recent literature. Recent studies, restricted to a few reports focusing on the mechanism of early coronary bypass occlusion, have reported higher occlusion rates, ranging between 5% and 17% (6, 7). Zientara et al. found an incidence of early graft occlusion of 17% among a cohort of 192 patients, and Han et al. indicated a 5% incidence of early occlusion among a cohort of 346 patients following CABG (6, 7).

We suppose that the low incidence of graft occlusion observed in our study may be attributable to the use of intraluminal shunts serving as a preventive measure against graft failure. Intraluminal shunts serve as temporary conduit ensuring continuous blood flow and are used especially in off-pump and MiECC-assisted CABG procedures in our department. The presence of the shunt

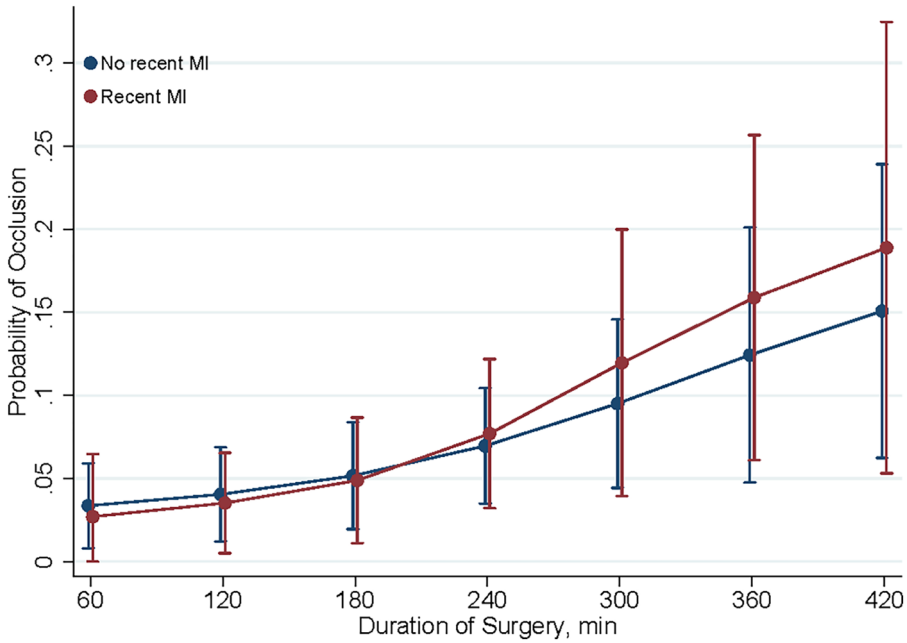

FIGURE 2
Predictive margins of MI within 7 days for graft occlusion. This figure shows the predictive margins of graft occlusion over different durations of surgery, comparing patients with (red line) and without (blue line) myocardial infarction (MI) within 7 days post-CABG. Vertical bars indicate 95% confidence intervals.

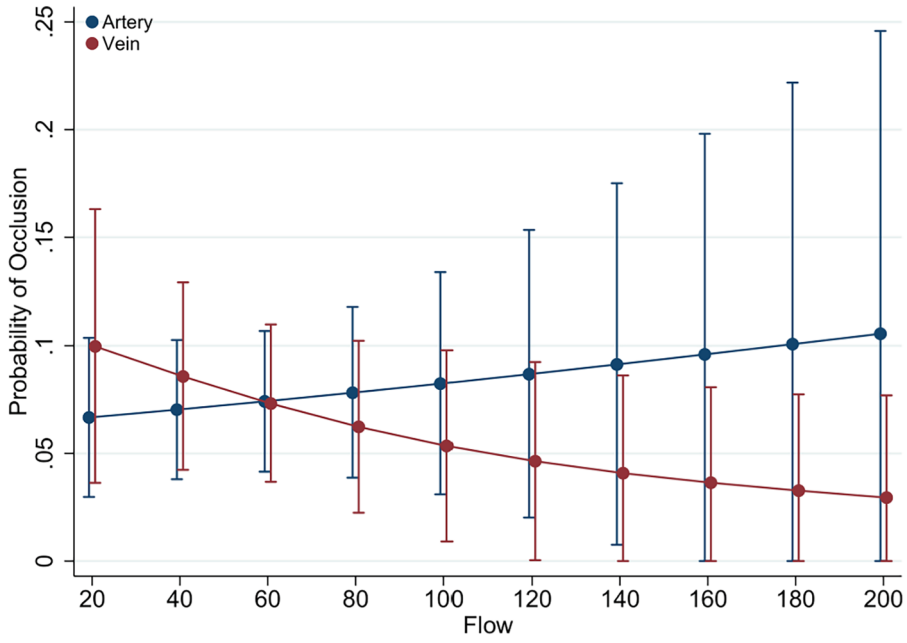

FIGURE 3
Predictive margins of graft type (vein vs. artery) for graft occlusion. Illustrated here are the predictive margins of graft occlusion across a range of graft flow rates, contrasting venous (red line) with arterial (blue line) grafts. The 95% confidence intervals are represented by the vertical error bars.

in native vessel helps balance the alignment of suture line on the upper edges of the target vessel. We suppose that meticulous surgical technique plays a decisive role in anastomosis integrity and patency, at least in short term. On the other hand, the shunt prevents the accumulation of debris at the anastomosis site, which could otherwise elicit thrombus formation and subsequent graft occlusion (16–18).

In our practice the transit time flow measurement was applied routinely for intraoperative assessment of coronary bypass grafts. The low flow and PI were significantly different in group with graft failure, result consistent with finding in the study by Zientara et al., which reported that the low flow predicted the bypass occlusion (6). However, in multivariate analysis the flow and PI were not predictive for bypass occlusion. This may be in part be probably explained due to the low case load in investigation group. Considering the recent controversy in surgical community on this subject we believe that the role of PI and flow in silent early bypass patency deserves further investigations. Namely the recent guidelines suggest a cut-off value of 5 for an optimal graft, while some surgeons have considered a PI under 3 as an indicator of a good graft, which is in accordance with our results (18, 19).

Given the limited number of patients with graft occlusions ($n = 29$) compared to those without occlusions ($n = 410$), the statistical power is probably insufficient to detect any significant differences in demographic characteristics between the groups. This could explain why, in contrast to existing literature the female gender in our study did not came up as predictor for coronary graft occlusion (6, 7). Although the almost 30% of cohort with bypass occlusion were females in univariate as well in multivariate analysis gender *per se* didn't come up as significant element being associated to the silent coronary bypass occlusion rate. However, the relative high proportion of females in occlusion cohort is remarkable. We suppose that the explanation may be in smaller and more fragile target vessels where consequently the revascularization from technical point of view may be more challenging.

However, the incidence of occlusion in patients undergoing urgent CABG during the index hospital stay was considerably higher. In 35% of cases, CABG was performed as an urgent procedure within the time frame of less than seven days following an acute coronary event. In these, PCI was not performed due to the amenable anatomical conditions, suggesting that complexity of coronary anatomy contributes greatly to surgical failure of anastomoses.

That the underlaying coronary pathology plays an important role in bypass patency is supported by the fact that the duration of surgical intervention was also associated with graft failure, implying that advanced coronary pathology is one of the decisive elements for graft failure. The mean time of intervention was 238 min in our "open" cohort and about 30 min longer in our occlusion group, suggesting a complex coronary situation resulting in more time-consuming revascularization.

Through a retrospective analysis of CT scans out study meticulously examined the incidence of graft occlusion in post-CABG patients. We observed a notably low incidence of early graft occlusion following CABG. Key findings highlighted that a longer duration of surgery was a significant predictor of graft

occlusion. Insights of our study are instrumental in influencing clinical decision-making processes, offering a robust foundation for developing targeted interventions. The study underscores the necessity for further clinical research to explore the effects of utilizing intraluminal coronary shunts, aiming to optimize patient outcomes in cardiac surgery.

4.1 Limitations

This study was confined to a single-center experience, and as such, the findings may not be generalizable to other settings or populations. The study reflected the practices and patient demographics in one institution and, therefore, may not have captured the full range of surgical techniques, technologies, or post-operative care protocols employed elsewhere.

The impact of early bypass occlusion on clinical outcome, was not completely implemented in our analysis. Regarding the in-hospital outcome there was no difference among two groups. Indeed, the impact of bypass occlusion on follow up outcome here with focus on myocardial ischemia event, revascularization and mortality may be a subject of further investigations. The study's strength lies in its clinical outcomes, underscored by a low incidence of occlusions (31 out of 1,319 anastomoses). However, this very clinical success presents a methodological challenge, as the disparity in group sizes—31 occluded grafts in 29 patients vs. 1,288 open grafts in 410 patients—poses a limitation to the analysis. The smaller sample size of occluded grafts may have decreased the robustness of statistical results; thus, they should be interpreted with caution. Therefore, the marked difference in group sizes may have distorted statistical assessments and complicated the comparison between the groups. While the total size of our sample adds robustness to our study, its single-center nature and the specific patient demographics necessitate further research across multiple centers to broaden the applicability of our findings.

Data availability statement

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

Ethics statement

The studies involving humans were approved by local ethical committee at the University of Basel, Basel, Switzerland (Ethikkomission Nordwest und Zentralschweiz, BASEC-Nr. 2023-01850) . The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin due to the retrospective nature of the study.

Author contributions

IS: Data curation, Investigation, Visualization, Writing – original draft, Writing – review & editing. LK: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. BG: Methodology, Supervision, Writing – original draft, Writing – review & editing. OR: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. MZ: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. PH: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. JB: Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. MP: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. CM: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. DB: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing, Data curation, Funding acquisition, Investigation, Project administration, Validation.

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Supplementary material

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EDITED BY
Cristina Barbero,
A.O.U. City of Health and Science of Turin, Italy

REVIEWED BY
Ömer Faruk Çiçek,
Selcuk University, Türkiye
Paolo Monardo,
Papardo Hospital, Italy

*CORRESPONDENCE
Jia-feng Wang
✉ jfwang@smmu.edu.cn
Jin-jun Bian
✉ jinjunbian@smmu.edu.cn

†These authors have contributed equally to this work

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The incidence, risk factors, and prognosis of acute kidney injury in patients after cardiac surgery

Xian-dong Wang†, Rui Bao†, Yang Lan†, Zhen-zhen Zhao, Xin-yue Yang, Yun-yun Wang, Zhi-yong Quan, Jia-feng Wang* and Jin-jun Bian*

Faculty of Anesthesiology, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Acute kidney injury (AKI) represents a significant complication following cardiac surgery, associated with increased morbidity and mortality rates. Despite its clinical importance, there is a lack of universally applicable and reliable methods for the early identification and diagnosis of AKI. This study aimed to examine the incidence of AKI after cardiac surgery, identify associated risk factors, and evaluate the prognosis of patients with AKI.
Method: This retrospective study included adult patients who underwent cardiac surgery at Changhai Hospital between January 7, 2021, and December 31, 2021. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Perioperative data were retrospectively obtained from electronic health records. Logistic regression analyses were used to identify independent risk factors for AKI. The 30-day survival was assessed using the Kaplan–Meier method, and differences between survival curves for different AKI severity levels were compared using the log-rank test.
Results: Postoperative AKI occurred in 257 patients (29.6%), categorized as stage 1 (179 patients, 20.6%), stage 2 (39 patients, 4.5%), and stage 3 (39 patients, 4.5%). The key independent risk factors for AKI included increased mean platelet volume (MPV) and the volume of intraoperative cryoprecipitate transfusions. The 30-day mortality rate was 3.2%. Kaplan–Meier analysis showed a lower survival rate in the AKI group (89.1%) compared to the non-AKI group (100%, $P < 0.001$).
Conclusion: AKI was notably prevalent following cardiac surgery in this study, significantly impacting survival rates. Notably, MPV and administration of cryoprecipitate may have new considerable predictive significance. Proactive identification and management of high-risk individuals are essential for reducing postoperative complications and mortality.

KEYWORDS

acute kidney injury, cardiac surgery, risk factors, mean platelet volume, perioperative care

1 Introduction

Acute kidney injury (AKI) is a significant complication following cardiac surgery, with reported incidence rates ranging from 5% to 42%, depending on various factors such as baseline characteristics, surgical types, and definitions employed (1). Moreover, postoperative dialysis may be required by up to 5.1% of the overall population (2). The precise underlying mechanism of cardiac surgery-associated AKI (CS-AKI) remains incompletely understood and involves an intricate interplay of factors including renal ischemia-reperfusion injury, inflammation, oxidative stress, and nephrotoxins (3). CS-AKI is associated with unfavorable outcomes such as prolonged ICU stay, increased hospitalization

duration, a heightened risk of developing chronic kidney disease (CKD), and elevated mortality rates (4). Given the short- and long-term impact of AKI, early identification of high-risk individuals is crucial for preventing complications and reducing mortality.

Early identification and diagnosis of AKI still remain challenging. Timely recognition and diagnosis of AKI are crucial, as delayed detection has been identified as an independent risk factor for in-hospital mortality (5). Currently, the kidney disease improving global outcomes (KDIGO) criteria represent the prevailing epidemiological and clinical standard for diagnosing acute kidney injury, including CS-AKI (3). Serum creatinine, a significant clinical indicator of renal function and essential component of the KDIGO criteria, however, is recognized as an unreliable marker for early AKI detection, particularly during the initial stages when glomerular filtration rate alterations may not manifest immediately. This lag period required to achieve a steady state can hinder the accuracy of serum creatinine as an indicator of AKI onset. Another challenge arises from the potential dilution effect of intravenous fluid administration during the intraoperative period, which can further delay the diagnosis of AKI (6). All these factors diminish the predictive value of creatinine.

Recent studies have investigated several novel AKI biomarkers in patients undergoing cardiac surgery, providing new methods for the early diagnosis of AKI (7–11). Tissue inhibitor metalloproteinase-2·insulin-like growth factor-binding protein 7 (TIMP-2·IGFBP7) are markers of renal tubular stress, potentially detectable before the onset of tubular damage. It has been reported that the postoperative use of TIMP-2·IGFBP7 enhanced the prediction accuracy of CSA-AKI and could assist in identifying patients at risk of short-term adverse outcomes (8). Another study reported that urinary C-C motif chemokine ligand 14 (CCL14), a newly discovered biomarker for persistent acute kidney injury (AKI), may help improve the clinical management of AKI patients (9). However, the validity and broader applicability of these biomarkers require further clarification. At the same time, the costs associated with these tests also limit their widespread implementation in clinical practice.

Therefore, identifying new clinical markers as risk factors for AKI remains of paramount importance. Yet, recent clinical studies have mainly emphasized preoperative risk factors, incorporating only a limited number of intraoperative variables (2, 12–14). The multitude of potential covariates encountered during surgery might influence the incidence of AKI, thereby diminishing the efficacy of preoperative predictive indicators in diverse clinical scenarios.

The objective of this study was to determine the incidence of CS-AKI as defined by the KDIGO criteria in a tertiary hospital, and to analyze the perioperative risk factors associated with AKI. Furthermore, we aimed to establish the mortality rates to gain insight into the prognosis of AKI patients after cardiac surgery.

2 Materials and methods

This retrospective, observational, single-center, case-control study was conducted at a tertiary hospital in Shanghai, China, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study protocol was approved by the institutional review board at hospital. As this study involved minimal risk and had a retrospective design, the requirement for informed consent was waived. All procedures performed in this study were in accordance with the ethical standards outlined in the Declaration of Helsinki.

2.1 Study population

The study cohort included all adult patients (aged 18 years or older) who underwent cardiac surgery at a tertiary hospital, Shanghai, China, between January 7th, 2021 and December 31st, 2021. The exclusion criteria were as follows: (a) patients with preoperative renal dysfunction, defined as a serum creatinine level above 176 μmol/L or the need for renal replacement therapy (13); (b)patients with history of a kidney transplantation; (c) patients with unavailable, incomplete, or invalid demographic, baseline, and perioperative data; (d) patients whose renal artery was involved in aortic disease or surgery; and (e) patients who died during the operation, or whose legally authorized representative requested discharge against medical advice on the first postoperative day due to critical condition, were excluded from the analysis.

2.2 Data collection and definition of outcome

All data were retrospectively obtained from the electronic health records and extracted by expert medical researchers who were unaware of the study hypothesis. The collected data encompassed demographic information, American Society of Anesthesiologists (ASA) physical status, perioperative laboratory test results, comorbidities, intraoperative details, and other perioperative data.

The primary outcome of this study was the occurrence of postoperative AKI at any stage, which was defined and staged according to the KDIGO classification. Secondary outcomes included the severity of AKI, the need for continuous renal replacement therapy (CRRT), 30-day mortality and in-hospital mortality. Following the KDIGO clinical practice guideline (15) and considering the patient's specific clinical situation, CRRT was initiated after a comprehensive assessment of the patient's risks and benefits. Serum creatinine concentration values were recorded both before and after surgery. Preoperative serum creatinine concentration was determined based on the measurement obtained from the closest metabolic panel blood draw prior to the surgery. Due to the lack of available data on postoperative urine volumes and the usage of diuretics, urine output was not considered in the analysis. AKI stage 1 was defined as a rise in serum creatinine levels ≥26.4 μmol/L within 48 h or an increase to 1.5–1.9 times of the baseline value within 7 days. AKI stage 2 was defined as an increase in serum creatinine levels to 2.0–2.9 times of the baseline value, while AKI stage 3 was defined as an increase in serum creatinine levels to

≥3 times of the baseline value, an absolute increase in serum creatinine levels of ≥354 μmol/L, or the initiation of renal replacement therapy (RRT). The estimated creatinine-based glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.

2.3 Anesthesia and perfusion management

Induction of anesthesia commonly involved a combination of propofol or etomidate, benzodiazepines, muscle relaxants, and opioids. During the surgical procedure, sevoflurane inhalation, opioids, and cis-atracurium were administered to maintain anesthesia. The standard roller pump cardiopulmonary bypass (CPB) circuit was deployed. Throughout CPB, perfusion flow rates were consistently maintained between 2.2 and 2.8 L/min/m^2, mean arterial pressure was kept within 50–80 mmHg, and mixed venous oxygen saturation was ensured to be 75% or higher. Additionally, the activated clotting time (ACT) was effectively managed to surpass 480 s by using heparin. In most surgical procedures, the target for nasopharyngeal temperature was set between 34.5–35 °C and for bladder temperature between 34.5–35.5 °C. Notably, in aortic operations employing deep hypothermic circulatory arrest (DHCA), the nasopharyngeal temperature goal was adjusted to a range of 22 °C–25 °C, depending on the complexity and urgency of the surgery. Moreover, myocardial protection is achieved through the administration of cold blood cardioplegia.

2.4 Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median [interquartile range (IQR)], following the Shapiro-Wilk test to assess normal distribution. Categorical variables were presented as frequencies and proportions. To compare continuous variables, the Student *t*-test and Wilcoxon Rank Sum test were employed. For categorical variables, the Wilcoxon Rank Sum test, chi-square test, or Fisher's exact test were utilized. Differences between AKI-stage 1, 2, and 3 groups were assessed using either one-way ANOVA or Kruskal–Wallis test.

Nonlinear associations between continuous factors and postoperative AKI were evaluated using restricted cubic spline (RCS) models with four knots to flexibly model and visualize the relationships. For those factors showing nonlinearity, they were transformed into categorical variables based on the RCS models and commonly used clinical cut-off values. Three clinical factors with nonlinear associations were identified and are presented in Supplementary Figure S1. To assess multicollinearity among the variables, correlation coefficients and variance inflation factor were calculated. Logistic regression analyses were performed to identify independent risk factors for AKI. Initially, univariate analysis was conducted to select variables that were statistically significant for subsequent stepwise multivariate logistic regression analyses. $P < 0.01$ was considered as statistically significant. The fit of the model was assessed by the Hosmer–Lemeshow good-of-fit test. The c-index, which equals the area under the receiver operating characteristics curve (AUC), was used to evaluate the discrimination of the model.

The unadjusted prognostic significance of AKI classification on event-free survival was assessed using the Kaplan-Meier method. Differences between survival curves were compared using the log-rank test. In a sensitivity analysis, cases undergoing off-pump cardiac surgery and heart transplantation were excluded, and the results remained consistent (see Supplementary Table). Statistical analyses were conducted using SPSS software version 21.0 (SPSS, Chicago, IL, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Characteristics of study cohorts

The study included a total of 868 participants. The patient selection process for the study cohorts is illustrated in Figure 1. The mean age of the participants was 58.0 (50.0, 67.0) years, with 63.5% being male. Among the participants, 72.7% were classified as ASA ≥ 3. Table 1 provides a summary of the baseline characteristics, comorbidities, intraoperative factors, postoperative outcomes, and laboratory data of the participants. The baseline serum creatinine level was 73.00 (61.00, 85.00) μmol/L. Furthermore, the duration of surgery was recorded as 235.0 (200.0, 285.0) min. A total of 49 (5.6%) patients underwent off-pump cardiac surgery. Supplementary Table S1 provides the additional baseline data of the study population.

3.2 Incidence and severity of AKI after cardiac surgery

A total of 257 patients (29.6%) in the study cohort developed stage 1 or worse AKI according to the KDIGO classification following the surgical procedure. The distribution of AKI stages among these patients was as follows: stage 1–179 patients (20.6%), stage 2–39 patients (4.5%), and stage 3–39 patients (4.5%). The rate of CRRT after surgery was 2.9% (25 patients). The AKI population was significantly younger than the non-AKI population, with a median age of 57.0 years compared to 62.0 years ($P < 0.001$). Patients with AKI were more likely to be classified as ASA III or greater (88.7% vs. 66.0%, $P < 0.001$) and were more frequently complicated with atrial fibrillation (22.3% vs. 10.1%, $P < 0.001$). Baseline laboratory and preoperative test results differed significantly between patients with and without AKI, as shown in Table 1. The preoperative serum creatinine levels were 78.0 (65.0–96.0) μmol/L in AKI patients, whereas they were only 71.0 (60.0–82.0) μmol/L in non-AKI patients. Baseline brain natriuretic peptide (BNP), international normalized ratio (INR), and hemoglobin (Hb) levels, analyzed as categorical variables based on RCS models (Supplementary Figure S1) and commonly used clinical cut-off values, also showed significant differences between the groups.

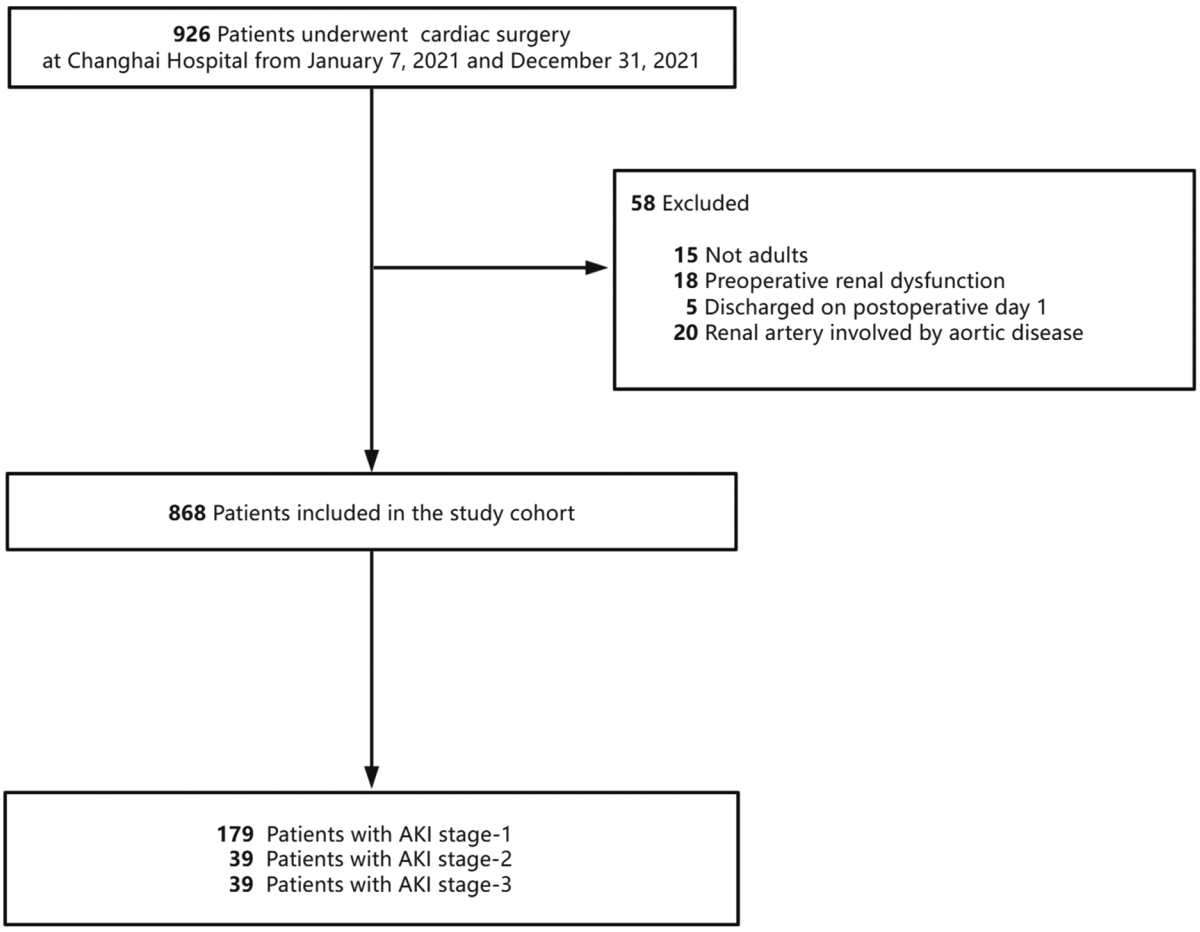

FIGURE 1
Study cohort used to explore the risk factors for acute kidney injury (AKI) after cardiac surgery.

In the analysis of intraoperative factors, AKI patients received higher doses of blood products and underwent longer surgical procedures. Compared to non-AKI patients, AKI patients had significantly higher maximum intraoperative lactate levels (median of 3.5 vs. 2.5 mmol/L, $P < 0.001$), lower minimum intraoperative Hb levels (median of 7.0 vs. 7.4 g/dl, $P < 0.001$), and lower minimum intraoperative Hct levels (median of 22.0% vs. 23.0%, $P < 0.001$).

3.3 Outcome of AKI after cardiac surgery

Regarding postoperative outcomes, the AKI group displayed a significantly higher incidence of postoperative complications, including cardiac arrest (n% of 3.5 vs. 0.3, $P < 0.001$), reintubation (n% of 6.6 vs. 1.1, $P < 0.001$), tracheostomy (n% of 5.4 vs. 0, $P < 0.001$), 30-day mortality (n% of 10.9 vs. 0, $P < 0.001$) and in-hospital mortality (n% of 12.8 vs. 0.2, $P < 0.001$), relative to the non-AKI group. Figure 2 illustrates the comparative incidence of postoperative AKI and 30-day mortality. Notably, patients with the most severe AKI had the lowest event-free survival rates compared to those with AKI stage 1 or 2. Additional patient characteristics are presented in Table 2, Supplementary Tables S2, S3.

3.4 Risk factors for AKI in patients after cardiac surgery

Variables showing a significant statistical difference ($P < 0.01$) in the univariate analyses were included in a stepwise forward logistic regression model, as shown in Supplementary Table S4. In the overall study cohort, multivariate logistic regression analysis identified several independent predictors for AKI following cardiac surgery. Significant predictors included maximum intraoperative lactate level [odds ratio (OR): 1.423, 95% CI: 1.258–1.609; $P < 0.001$], age (OR: 1.248, 95% CI: 1.136–1.372; $P < 0.001$), atrial fibrillation (OR: 2.183, 95% CI: 1.266–3.762; $P = 0.05$), intraoperative cryoprecipitate transfusion volume (OR: 1.111, 95% CI: 1.055–1.170; $P < 0.001$), ASA classification ≥3 (OR: 2.929, 95% CI: 1.680–5.105; $P < 0.001$), MPV (OR: 1.148, 95% CI: 1.350–1.610; $P = 0.015$), and higher BNP levels (BNP 100–400 vs. BNP < 100, OR: 1.674, 95% CI: 1.011–2.771; BNP >400 vs. BNP < 100, OR: 2.220, 95% CI: 1.251–3.938). Figure 3 showed the results of the multivariate analysis for AKI predictors. The logistic model exhibited robust discrimination, with an AUC of 0.800 (95% CI 0.765–0.834) (Figure 4). The

TABLE 1 Demographic data of the total population, patients with or without AKI.

	Total ($n = 868$)	Non-AKI ($n = 611$)	AKI ($n = 257$)	*p value*
Age (year), Median (IQR)	58.0 (50.0, 67.0)	57.0 (48.0, 66.0)	62.0 (53.0, 69.0)	< 0.001
Gender, *n* (%)				0.366
Male	551 (63.5)	382 (62.5)	169 (65.8)	
BMI (kg/m^2), Median (IQR)	23.5 (21.5, 26.0)	23.5 (21.6, 25.8)	23.4 (21.4, 26.4)	0.784
ASA physical status, *n* (%)				< 0.001
ASA 1,2	237 (27.3)	208 (33.9)	29 (11.4)	
ASA ≥3	631 (72.7)	403 (66)	228 (88.7)	
Diabetes mellitus, *n* (%)	80 (9.2)	55 (9)	25 (9.8)	0.736
Hypertension *n* (%)	166 (19.1)	114 (18.6)	52 (20.4)	0.59
Chronic liver disease, *n* (%)	12 (1.4)	10 (1.6)	2 (0.8)	0.525
Atrial fibrillation, *n* (%)	119 (13.7)	62 (10.1)	57 (22.2)	<0.001
Preoperative ECMO/IABP/or both support, *n* (%)	9 (1.0)	3 (0.5)	6 (2.3)	0.023
EF (%), Median (IQR)	58.0 (49.8, 66.0)	59.0 (51.5, 66.0)	56.0 (44.0, 64.0)	<0.001
Cr (μmol/L), Median (IQR)	73.0 (61.0, 85.0)	71.0 (60.0, 82.0)	78.0 (65.0, 96.0)	<0.001
Estimated glomerular filtration rate [ml/(min*1.73 m^2)], Median (IQR)	95.0 (78.2, 109.8)	97.6 (81.4, 111.4)	88.2 (70.0, 100.9)	<0.001
Albumin (g/L), Median (IQR)	41.0 (38.0, 44.0)	41.0 (39.0, 44.0)	40.0 (37.0, 43.0)	<0.001
Hemoglobin (g/L), Mean ± SD	133.9 ± 19.9	136.0 ± 18.3	128.9 ± 22.5	<0.001
MPV (fL), Mean ± SD	11.2 ± 1.3	11.1 ± 1.2	11.4 ± 1.4	0.002
Platelet count (10^9/L), Median (IQR)	188.0 (148.0, 229.0)	194.0 (155.0, 233.0)	169.0 (132.0, 223.0)	<0.001
BNP (pg/ml), Median (IQR)	113.7 (48.8, 282.8)	86.8 (38.7, 227.0)	174.0 (88.9, 445.7)	<0.001
INR, Median (IQR)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.1 (1.0, 1.2)	<0.001
Surgery-related characteristics				
Emergency operation, *n* (%)	78 (9.0)	29 (4.8)	49 (19.1)	<0.001
Off pump operation, *n* (%)	49 (5.6)	42 (6.9)	7 (2.7)	0.016
Surgical types, *n* (%)				<0.001
CABG only	183 (21.1)	150 (24.5)	33 (12.8)	
Single-valve replacement only	138 (15.9)	115 (18.8)	23 (8.9)	
Multiple-valve replacement surgery only	117 (13.5)	75 (12.3)	42 (16.3)	
Combined CABG-valve procedure	31 (3.6)	18 (2.9)	13 (5.1)	
Aortic procedure	122 (14.1)	65 (10.6)	57 (22.2)	
Heart transplantation	24 (2.8)	10 (1.6)	14 (5.4)	
Others	253 (29.1)	178 (29.1)	75 (29.2)	
Aortic dissection surgery, *n* (%)	49 (5.6)	14 (2.3)	35 (13.6)	<0.001
Intraoperative factors				
Intraoperative crystalloid infusion (ml), Median (IQR)	1,100.0 (1,100.0, 1,400.0)	1,100.0 (1,100.0, 1,300.0)	1,200.0 (1,100.0, 1,600.0)	<0.001
Intraoperative transfusion volume, Median (IQR)				
Total (unit)	0.0 (0.0, 6.0)	0.0 (0.0, 0.0)	3.0 (0.0, 20.0)	<0.001
Erythrocytes(ml)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 400.0)	<0.001
Plasma(ml)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 400.0)	<0.001
Platelet (unit)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 10.0)	<0.001
Cryoprecipitate (unit)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 10.0)	<0.001
Intraoperative blood loss(ml), Median (IQR)	300.0 (200.0, 500.0)	300.0 (200.0, 400.0)	300.0 (200.0, 500.0)	0.001
Intraoperative urine output(ml), Median (IQR)	1,000.0 (700.0, 1,500.0)	1,000.0 (700.0, 1,400.0)	1,000.0 (700.0, 1,600.0)	0.107
Duration of surgery(min), Median (IQR)	235.0 (200.0, 285.0)	225.0 (190.0, 265.0)	265.0 (225.0, 330.0)	<0.001
DHCA, *n* (%)	10 (1.2)	5 (0.8)	5 (2)	0.174
Minimum intraoperative Hb level (g/L), Median (IQR)	7.2 (6.1, 8.6)	7.4 (6.2, 8.8)	7.0 (5.9, 8.2)	0.005
Minimum intraoperative Hct level (%), Median (IQR)	23.0 (20.0, 26.0)	23.0 (20.0, 27.0)	22.0 (19.0, 25.0)	<0.001
Minimum intraoperative PaO_2(mmHg), Median (IQR)	259.0 (166.0, 309.5)	260.0 (171.0, 312.0)	252.5 (147.0, 307.0)	0.131
Maximum intraoperative lactate level (mmol/L), Median (IQR)	2.7 (2.0, 3.9)	2.5 (1.9, 3.4)	3.5 (2.5, 5.6)	<0.001

BMI, body mass index; ASA, American Society of Anesthesiologists; ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pump; EF, ejection fraction; Cr, creatinine; MPV, mean platelet volume; INR, international normalized ratio; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft surgery; DHCA, deep hypothermic circulatory arrest; Hb, hemoglobin; Hct, hematocrit; PaO_2, partial pressure of oxygen in arterial blood; AKI, acute kidney injury.

Hosmer–Lemeshow goodness-of-fit test indicated good calibration of the logistic model ($P = 0.961$). In a sensitivity analysis, exclusion of patients undergoing heart transplants and off-pump surgeries from the study population yielded similar results (see Supplementary Tables S5–S10).

4 Discussion

This retrospective study presented an analysis of the incidence and associated risk factors of AKI following cardiac surgery. Through the utilization of a multivariate logistic regression

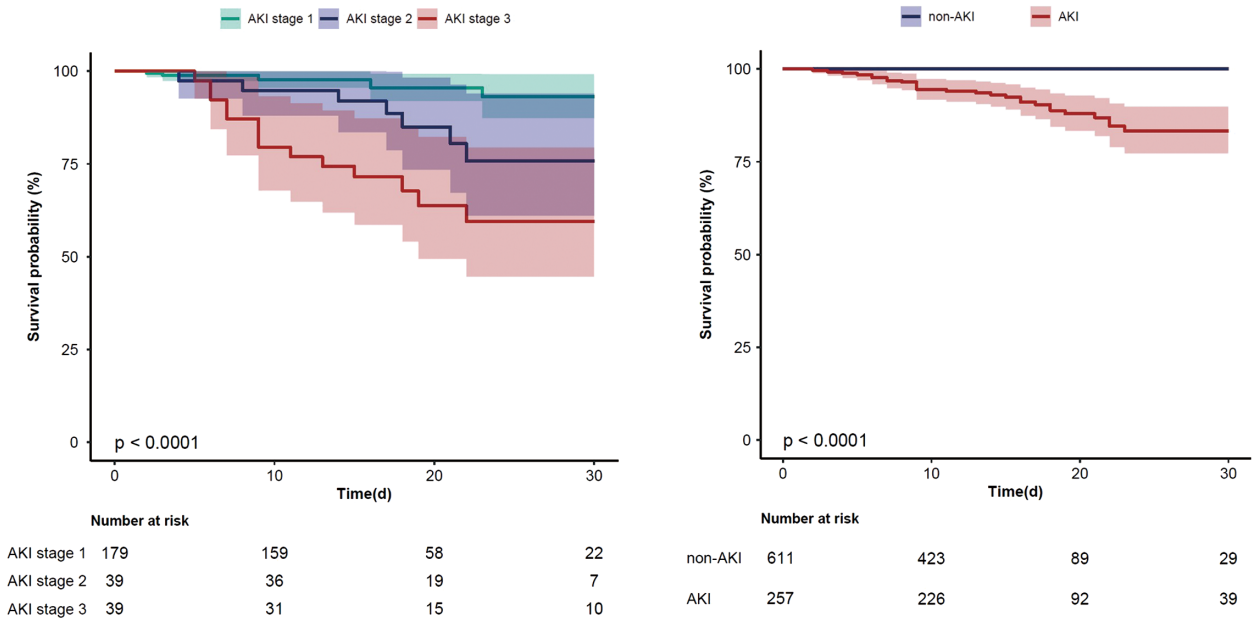

FIGURE 2
The Kaplan–Meier curve for 30-day mortality in all AKI stages patients and AKI/non-AKI patients (95% confidence interval).

TABLE 2 Postoperative outcomes of the total population, patients with or without AKI.

	Total ($n = 868$)	Non-AKI ($n = 611$)	AKI ($n = 257$)	p value
Postoperative outcomes				
Duration of mechanical ventilation in ICU (h), Median (IQR)	8.5 (4.5, 20.0)	6.0 (4.3, 16.8)	19.0 (9.0, 24.1)	<0.001
>24 h	118 (13.6)	45 (7.4)	73 (28.4)	<0.001
>48 h	49 (5.6)	10 (1.6)	39 (15.2)	<0.001
Reintubation, *n* (%)	24 (2.8)	7 (1.1)	17 (6.6)	<0.001
Tracheostomy, *n* (%)	14 (1.6)	0 (0)	14 (5.4)	<0.001
Maximum postoperative PCT level (ng/ml), Median (IQR)	1.2 (0.5, 4.2)	0.9 (0.4, 1.9)	4.1 (1.1, 10.9)	<0.001
Initiation of CRRT, *n* (%)	25 (2.9)	0 (0)	25 (9.7)	<0.001
Cardiac arrest, *n* (%)	11 (1.3)	2 (0.3)	9 (3.5)	<0.001
Redo surgery, *n* (%)	47 (5.4)	23 (3.8)	24 (9.4)	<0.001
Postoperative ECMO/IABP/or both support, *n* (%)	53 (6.1)	12 (2)	41 (16)	<0.001
LOS-ICU(d), Median (IQR)	3.0 (2.0, 5.0)	2.0 (1.0, 3.0)	5.0 (3.0, 9.0)	<0.001
LOS (d), Median (IQR)	19.0 (15.0, 25.2)	17.0 (14.0, 23.0)	23.0 (18.5, 31.5)	<0.001
Postoperative LOS(d), Median (IQR)	13.0 (9.0, 18.0)	12.0 (9.0, 16.0)	16.0 (12.0, 23.0)	<0.001
In-hospital mortality, *n* (%)	34 (3.9)	1 (0.2)	33 (12.8)	<0.001
30-day mortality, *n* (%)	28 (3.2)	0 (0)	28 (10.9)	<0.001

ICU, intensive care unit; PCT, procalcitonin; CRRT, continuous renal replacement therapy; LOS, length of stay; LOS-ICU, length of stay in ICU; AKI, acute kidney injury.

analysis, our findings revealed the significant independent association of seven variables with CSA-AKI. These identified factors exhibited robust discrimination performance in predicting the occurrence of CSA-AKI, and MPV and administration of cryoprecipitate may have new considerable predictive significance. After sensitivity analyses, we derived similar conclusions. These risk factors are easily monitored and available, and of significant clinical value for guiding perioperative renal protection strategies. Moreover, our study further established a statistically significant relationship between the presence and severity of AKI and subsequent 30-day mortality following cardiac surgery. This study was conducted at a large tertiary hospital that specializes in complex and various types of cardiac surgeries, enhancing the credibility and generalizability of the study results.

Among the patients included in this study, it was observed that 257 individuals (29.6%) developed AKI, which was consistent with the incidence rates reported in other studies (1, 2, 16). This study demonstrated that the in-hospital mortality rate and 30-day mortality rate of patients with AKI were significantly higher than those of non-AKI individuals. Patients with AKI exhibited poorer clinical outcomes. Importantly, early identification and timely

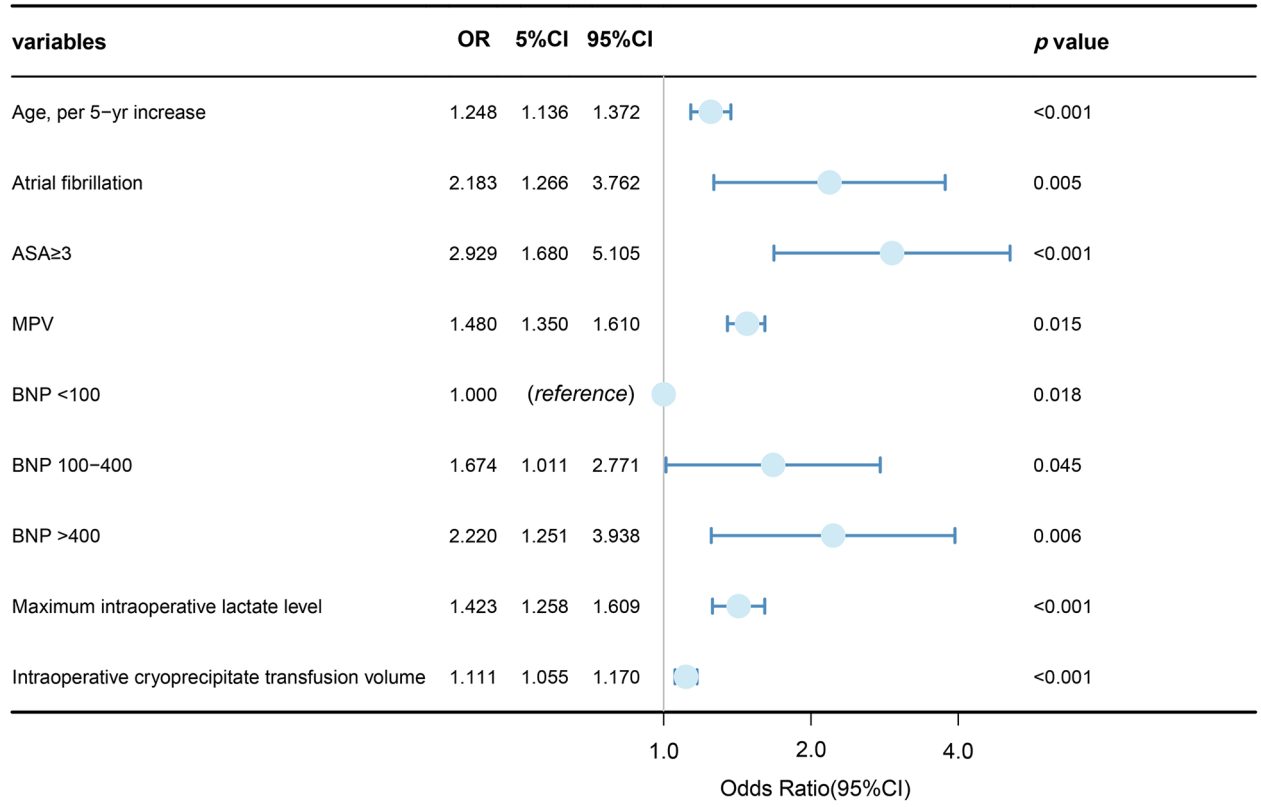

FIGURE 3
Logistic multivariable regression analysis showing the risk variables of AKI after cardiac surgery.

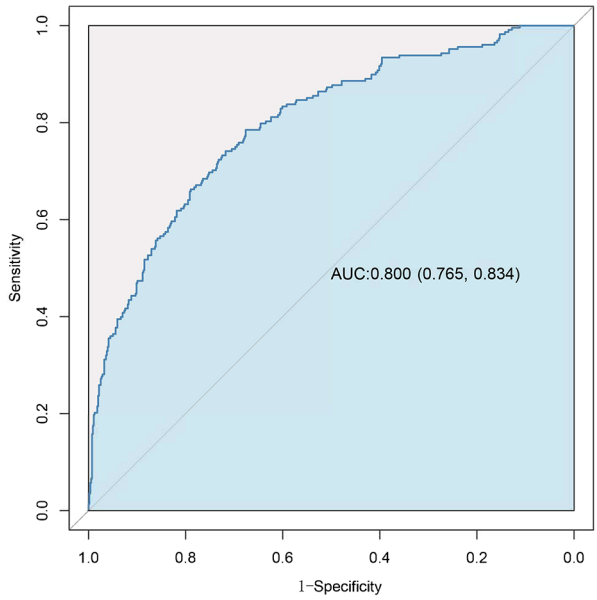

FIGURE 4
Receiver-operating characteristic (ROC) curve for evaluating the discrimination performance of the logistic model in the study cohort.

intervention in AKI, as well as allocating relatively more clinical care to AKI patients, may help improve their clinical outcomes.

Several major underlying injury pathways are involved in the development of CSA-AKI, including hypoperfusion, ischemia-reperfusion injury, neurohumoral activation, inflammation, oxidative stress, nephrotoxins, and mechanical factors (3). Recent studies have focused on investigating clinical risk factors associated with AKI following cardiac surgery. However, these studies have predominantly concentrated on preoperative risk factors and have limited inclusion of intraoperative variables (2, 12–14). In our study, we aimed to provide a more comprehensive evaluation by incorporating detailed intraoperative variables. Our findings revealed that out of the numerous variables examined, only seven remained statistically significant in the final multivariate logistic model. Notably, two of these significant predictors were intraoperative variables: maximum intraoperative lactate level and intraoperative cryoprecipitate transfusion volume. Some of these results are consistent with previous research, which has also identified older age and higher ASA scores as factors associated with AKI after cardiac surgery (2, 13, 14). Age has consistently emerged as a crucial risk factor for CSA-AKI, underscoring the importance of prioritizing post-operative cardiac kidney injury in elderly patients (17). Additionally, it is worth noting that patients aged over 70 years undergoing cardiac surgery have been found to

exhibit three times higher odds of long-term mortality compared to their younger counterparts (1). These findings indicate that patients of advanced age and those with higher ASA scores are more prone to comorbidities and complications, warranting greater clinical attention.

The logistic regression analysis conducted in our study has identified that a higher intraoperative lactate level is a significant risk factor for CS-AKI. Elevated lactate levels are commonly regarded as an indicator of inadequate tissue perfusion. In a study by Juan et al. (17), involving the analysis of 2,940 patients, it was found that higher arterial lactate levels 24 h after admission were independently associated with postoperative AKI in cardiac surgery patients. Similarly, Hauer et al. (18) reported that a serum lactate level exceeding 1.1 mmol/L within the first 24 h following surgery proved to be the strongest predictor for the development of renal failure after cardiac surgery. Furthermore, various factors such as procedures involving CPB, hemodilution, hypothermia, low-flow CPB, and excessive neurohormonal activation have also been linked to the occurrence of lactic acidosis during CPB (19, 20). Hence, perioperative lactate levels should be given due attention as they represent a significant risk factor for the development of AKI. This easily available and measurable indicator has important clinical implications, emphasizing that ensuring adequate organ perfusion and oxygenation, along with maintaining homeostasis, is fundamental to protecting renal function. Preoperative optimization of hemoglobin levels, appropriate intraoperative CPB perfusion and ventilation strategies, monitoring of blood gas analysis, and maintaining homeostasis may be effective measures to reduce the risk of renal injury.

Platelets play a critical role in acute hemostasis and inflammation and are associated with various inflammatory diseases (21–23). They adhere to the endothelial wall, modify vascular permeability, recruit and interact with leukocytes, and activate the complement system, all of which significantly contribute to the hemodynamic and inflammatory processes of AKI (23). Jansen et al. (24) reported that platelet activation, platelet-neutrophil interaction, and neutrophil extracellular trap (NET) formation lead to renal inflammation and further kidney injury. MPV is a simple and cost-effective measure conducted by hematological analyzers. It is increasingly recognized as an important parameter of platelet function and activity. Platelets with elevated MPV are assumed to be younger and more reactive (25), containing more α-granules, including thrombospondin, P-selectin, and platelet factor 4, as well as several factors involved in coagulation. These prothrombotic substances can aggravate inflammation when released (23, 26). While several previous studies have reported that increased MPV is a significant prognostic risk factor in AKI and critically ill patients (27), few studies have investigated the association between MPV and the occurrence of AKI after cardiac surgery. The results of our study suggest that a higher baseline MPV (OR: 1.148, 95% CI: 1.350–1.610; $P = 0.015$) was associated with an increased risk of AKI. Abinaya et al. (28) retrospectively analyzed 4,204 patients who underwent cardiac surgery and found an independent association between the magnitude of postoperative MPV changes and the development and severity of postoperative AKI. Their results suggested that increased baseline MPV values indicated an elevated risk for postoperative AKI, but this association did not remain statistically significant after adjusting for relevant clinical variables. To facilitate clinical application and avoid the effect of intraoperative platelet transfusion on postoperative MPV, we only considered and included baseline MPV as a potential risk factor without recording the perioperative change of MPV. Additionally, based on the results of our literature search, this is the first time MPV has been identified as a strong predictor of postoperative AKI in a broad range of cardiac surgery. Compared to the study by Abinaya et al. (28), where nearly one-third of patients had non-coronary cardiac procedures, our analysis expanded the cohort to include cardiac procedures such as heart transplantation, aortic surgery with CPB, and other complex combined procedures. MPV may serve as a significant biomarker with important clinical implications, yet its value is often overlooked and underestimated. However, the complex association between preoperative MPV, the role of platelets, and postoperative AKI needs to be further explored in future research. For instance, whether commonly used antiplatelet drugs in cardiac surgery patients affect MPV and the incidence of AKI could be a potential area for intervention.

Furthermore, our findings revealed a significant association between increased intraoperative cryoprecipitate transfusion volume and the risk of developing AKI (OR: 1.110, 95% CI: 1.050–1.173; $P < 0.001$). Transfusion is commonly administered during cardiac surgery and its detrimental effects are multifaceted, including a systemic inflammatory response that contributes to postoperative AKI development (29, 30). Cryoprecipitate, containing Factor VIII, Factor XIII, von Willebrand Factor, fibrinogen, and fibronectin, is primarily used to treat acquired hypofibrinogenemia in cardiac surgery. In Europe, there has been a gradual shift towards using fibrinogen concentrate due to its convenience in clinical application and concerns regarding viral transmission risks, although high-quality evidence in this area is still lacking (31). However, reports examining the association between intraoperative cryoprecipitate transfusion in adult cardiac surgery and postoperative AKI are scarce. Hinton et al. (32) analyzed data from the Medical Information Mart for Intensive Care (MIMIC) III and IV databases and found that cryoprecipitate administration after cardiac surgery was infrequent, and postoperative cryoprecipitate transfusion was not significantly associated with AKI (OR: 1.03, 99% CI 0.65–1.62, $P = 0.876$). Conversely, Jake et al. (33) conducted a study involving 119,132 eligible patients and concluded that postoperative cryoprecipitate transfusion was associated with a reduction in acute kidney injury (OR: 0.85, 99% CI, 0.73–0.98; $P = 0.0037$). A substantial amount of cryoprecipitate transfusion in cardiac surgery reflects excessive surgical bleeding, resulting in renal hypoperfusion and ischemia, which may be linked to AKI. With this consideration, INR, intraoperative bleeding volume, and the volume of transfused blood products were included in the multivariable logistic regression, and the results still showed a significant association between cryoprecipitate and AKI. To gain a deeper

understanding of the underlying mechanism linking intraoperative cryoprecipitate transfusion and renal injury, further high-quality research is warranted. Optimizing perioperative transfusion management could have significant implications for postoperative renal outcomes.

Moreover, our study demonstrated a significant elevation in baseline BNP levels among patients with AKI compared to those without AKI. By examining the nonlinear relationship between baseline BNP levels and AKI occurrence following cardiac surgery, we discovered that the commonly used cutoff value for heart failure diagnosis (34) exhibited excellent predictive capabilities for AKI development. Heart failure often leads to venous congestion, which is associated with adverse renal events after surgery (35). In multivariable logistic regression, after adjusting for preoperative ejection fraction and cardiac chamber size, BNP remained significantly associated with AKI. Consistent with previous research, preoperative BNP levels emerged as a risk factor for AKI post-cardiac surgery (36). Our study encompassed a diverse population of patients undergoing cardiac surgery, including various surgical subtypes, thus validating the clinical applicability of BNP as a predictive tool. Optimizing perioperative organ function status and monitoring and adjusting BNP levels may provide crucial guidance in reducing the risk of AKI.

Furthermore, the findings of our study indicate that preoperative atrial fibrillation is a predictive factor for CS-AKI (OR: 2.183, 95% CI: 1.266–3.762; $P = 0.005$). Previous studies have also suggested a correlation between preoperative atrial fibrillation and adverse kidney events subsequent to cardiac surgery (35). AF represents the most prevalent heart rhythm disorder, and recent studies have consistently demonstrated a close association between AF and AKI (37, 38). Chan et al. (39) observed a significant five-fold increase in the incidence of AKI necessitating dialysis among 3,497,677 individuals hospitalized for AF between 2003 and 2012 in the United States. Li et al. (40) reported a significant association between preoperative atrial fibrillation and AKI diagnosed within 48 h to 7 days following on-pump cardiac surgery. The relationship between AF and AKI subsequent to cardiac surgery is complex, highlighting the need for improved clinical management of cardiac surgery patients with atrial fibrillation during the perioperative period.

5 Limitation

This study had several limitations that should be acknowledged. Firstly, it was a retrospective, single-center, observational case-control study, potentially limiting the generalizability of our findings to other settings. Future multi-center studies are necessary to validate our results across different healthcare environment, even in non-cardiac surgeries. Secondly, the retrospective nature of our study imposed potential bias. Reliance on medical records may introduce information bias. Unrecognized or undetermined confounders may also mediate the occurrence of kidney injury. Thirdly, in this study, the diagnosis and classification of AKI were solely based on creatinine levels and did not incorporate urine output criteria or the detection of early novel kidney injury biomarkers. Lastly, this study lacks the identification and research of long-term renal outcomes, such as CKD, as well as targeted prospective clinical intervention studies for the identified risk factors, necessitating further investigation in future research.

6 Conclusion

In summary, this study found that postoperative AKI was prevalent among patients undergoing cardiac surgery and was associated with higher in-hospital mortality, particularly in stages AKI-II and AKI-III. Several independent risk factors for postoperative AKI were identified in patients undergoing various types of cardiac surgeries. Notably, MPV and administration of cryoprecipitate may have new considerable predictive significance. The study also highlights the need for optimizing perioperative management to prevent or mitigate the impact of AKI, such as maintaining normal levels of lactate and other homeostatic factors, and optimizing the perioperative transfusion management. Meanwhile, our findings may guide the allocation of more healthcare resources before AKI patients develop more severe complications, leading to better clinical outcome.

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 humans were approved by the institutional review board at Changhai Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this study was a retrospective study without any intervention on participants, involving minimal risk.

Author contributions

X-dW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. RB: Conceptualization, Data curation, Formal Analysis, Investigation, Software, Validation, Writing – review & editing. YL: Conceptualization, Data curation, Investigation, Software, Validation, Writing – original draft. Z-zZ: Data curation, Validation, Visualization, Writing – original draft. X-yY: Investigation, Validation, Writing – original draft. Y-yW: Investigation, Visualization, Writing – original draft. Z-yQ: Investigation, Writing – original draft. J-fW:

Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. J-jB: Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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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/fcvm.2024.1396889/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Non-linear associations of BNP, INR, and Hb with AKI.

SUPPLEMENTARY FIGURE 2
Sensitivity analysis: Receiver-operating characteristic (ROC) curve for evaluating the discrimination performance of the logistic model in the study cohort.

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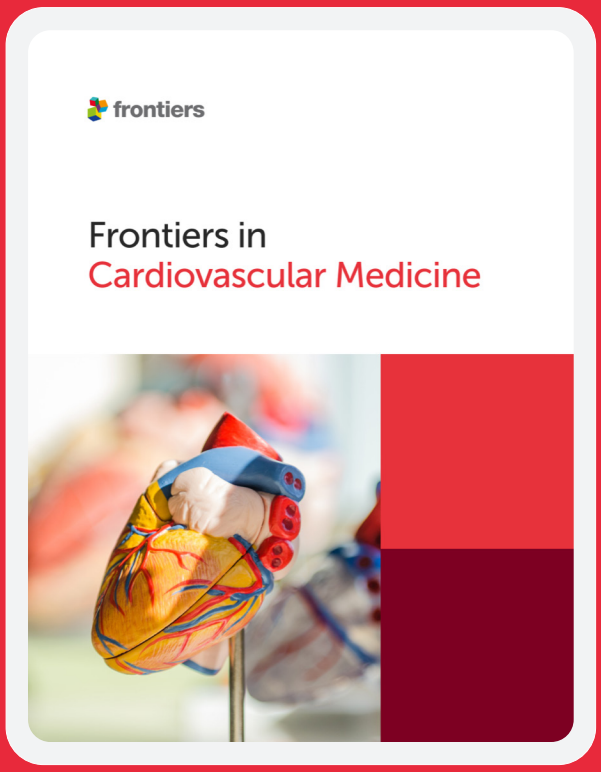

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