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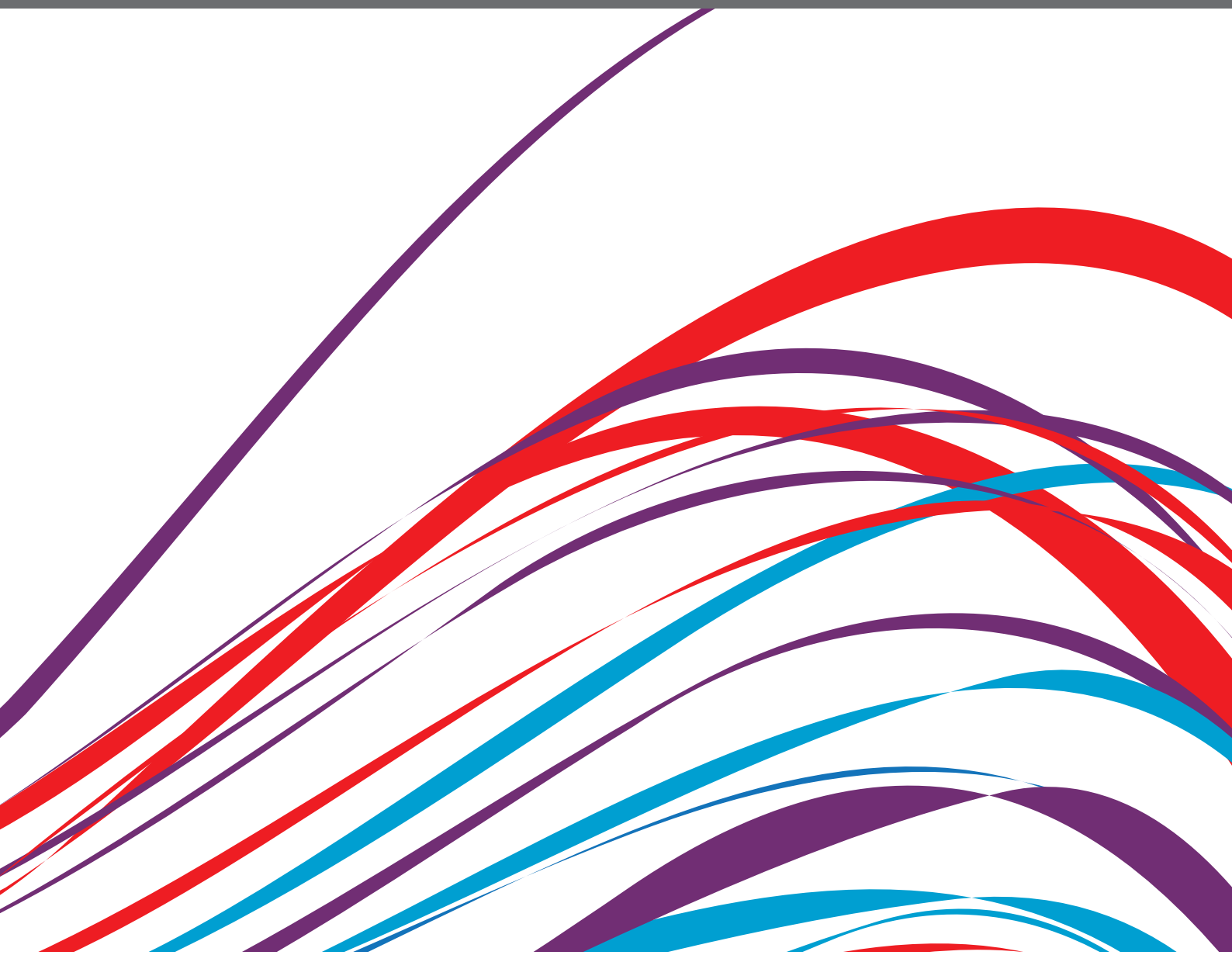

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INSIGHTS IN HEART SURGERY: 2021

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Relationship Between First 24-h Mean Body Temperature and Clinical Outcomes of Post-cardiac Surgery Patients

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Background: This study was aimed to investigate the relationship between first 24-h mean body temperature and clinical outcomes of post cardiac surgery patients admitted to intensive care unit (ICU) in a large public clinical database.

Methods: This is a retrospectively observational research of MIMIC III dataset, a total of 6,122 patients included. Patients were divided into 3 groups according to the distribution of body temperature. Multivariate cox analysis and logistic regression analysis were used to investigate the association between abnormal temperature, and clinical outcomes.

Results: Hypothermia (<36°C) significantly associated with increasing in-hospital mortality (HR 1.665, 95%CI 1.218–2.276; $p = 0.001$), 1-year mortality (HR 1.537, 95% CI 1.205–1.961; $p = 0.001$), 28-day mortality (HR 1.518, 95% CI 1.14–2.021; $p = 0.004$), and 90-day mortality (HR 1.491, 95% CI 1.144–1.943; $p = 0.003$). No statistical differences were observed between short-term or long-term mortality and hyperthermia (>38°C). Hyperthermia was related to the extended length of ICU stay ($p < 0.001$), and hospital stay ($p < 0.001$).

Conclusion: Hypothermia within 24h after ICU admission was associated with the increased mortality of post cardiac surgery patients. Enhanced monitoring of body temperature within 24h after cardiac surgery should be taken into account for improving clinical outcomes.

Keywords: hypothermia, hyperthermia, clinical outcome, post-cardiac surgery, intensive care unit

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INTRODUCTION

The management of body temperature (BT) was very important to the recovery of postoperative patients, especially for critically ill patients who have relatively severe physical conditions. Almost 57.1% patients were exposed to hypothermia (BT < 36.0°C) among the patients admitted to intensive care unit (ICU) after operation (1) which claimed to be associated with mortality (2). Postoperative hyperthermia might be relevant to adverse clinical outcomes (3), and infection (4) in critically ill patients. Previous studies had indicated general anesthesia and surgical influence disturbed normal temperature regulation mechanism (5). Without preventative actions, influence of abnormal body temperature could be exaggerated with serious consequences.

As a special operation type, cardiac surgery had a great impact on circulation and physiology, and also brought enormous challenges to reduce mortality. Hypothermia and hyperthermia might occur after cardiac surgery attributed to long-term anesthesia and surgery exposure, the failure of the temperature maintenance, special hypothermia treatment and inflammatory response, and so on. Hyperthermia after cardiovascular surgery with cardiopulmonary bypass (CPB) could cause cognitive decline (3, 6). Grocott and colleagues revealed that postoperative high fever was associated with cognitive impairment at 6 weeks after coronary artery bypass grafting (6). Besides, there was study reporting that hypothermia effectively promoted endotoxin release through ischemic intestinal mucosa and had bad effects on brain tissue (7). Abnormal body temperature is disadvantageous to the prognosis of patients.

There were few studies explored the relationship between body temperature and adverse outcomes of patients after cardiac surgery, and no unified conclusion was obtained. Body temperature at single point in time raised bias risk inevitably (8), and could not fully reflect the overall effect of early postoperative body temperature. The object of this study was to investigate the association between first 24-h mean body temperature and clinical outcomes of post cardiac surgery patients admitted to ICU in a large public clinical database.

MATERIALS AND METHODS

Data Source

The study is a retrospective study with data collected from Medical Information Mart for Intensive Care-III (MIMIC-III) database (9, 10). This is a large intensive care database open to the public including more than 40,000 patients admitted to ICU from Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) between 2001 and 2012. Beth Israel Deaconess Medical Center and the Beth Israel Deacon Medical Center's institutional review board approved the application of the database (approval code 40043439) and personal informed consent was abandoned.

Study Population

Patients with cardiac surgery were identified using current procedural terminology numbered from 33,010 to 37,799. 18 to 89 years old patients were enrolled into the study. If patients were admitted to hospital or ICU multiple times, only the first record was analyzed. Patients stayed ICU <24h were excluded. Based on the attribution of temperature and existing research (11), Patients were divided into 3 groups: hypothermia group (BT $< 36.0^{\circ}$C), normal group ($36.0^{\circ}\text{C} \leq \text{BT} \leq 38.3^{\circ}$C), hyperthermia group (BT $> 38.3^{\circ}$C).

Data Collection and Definitions

The data was extracted from database by using structure query language (PostgreSQL, version 9.4.6, www.postgresql.org),and the codes in MIMIC Code Repository (https://github.com/MIT-LCP/mimic-website). Variables of this study included demographics, comorbidities, scoring systems, laboratory tests, and vital signs. Calculate the average of vital signs and laboratory tests with multiple results within 24h after ICU admission. Data analysis excluded variables with missing values exceeding 30% to avoid potential bias. Multiple imputation method was used to process variables with missing values <30%.

Outcomes

The primary outcomes were in-hospital and 1-year mortality. The secondary outcomes included survival time, 28-day mortality, 90-day mortality, length of hospital stay and ICU stay, the intervention of continuous renal replacement therapy (CRRT) within 24h admitted to ICU, the incidence of acute kidney injury (AKI) within 7 days after ICU admission. The diagnosis of AKI was confirmed following the Kidney Disease: improving global outcomes (KDIGO) guideline (12).

Statistical Analysis

Most continuous variables in this research were checked to be non-normally distributed and described as medians with interquartile ranges (IQRs), the rest were reported as mean ± standard deviation. Categorical variables were described as

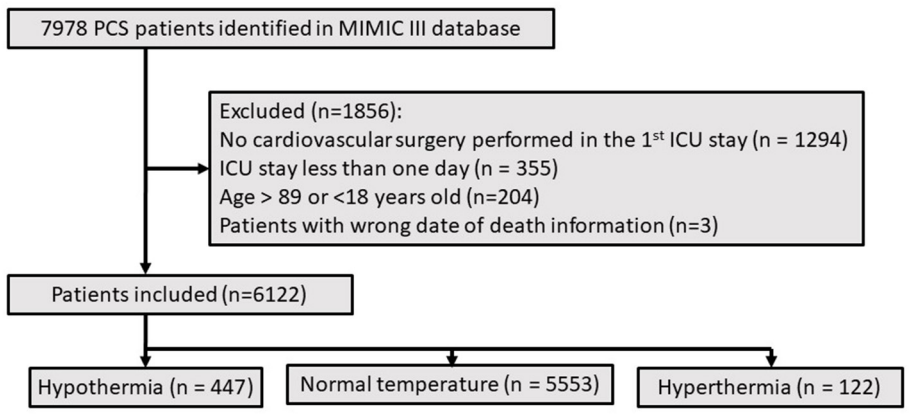

FIGURE 1 | Flowchart of study cohort selection.

TABLE 1 | Clinical and laboratory baseline characteristics of the overall cohort.

Characteristics	Over all (*n* = 6,122)	Low temperature group (*n* = 447)	Normal temperature group (*n* = 5,553)	High temperature group (*n* = 122)	*p*-value
Temperature, median [IQR]	36.81 [36.43, 37.24]	35.8 [35.56, 35.9]	36.86 [36.52, 37.25]	38.58 [38.43, 38.71]	<0.001
Age, median [IQR]	66 [55, 76]	68.0 [59.0, 78.0]	66.0 [55.0, 76.0]	54.0 [40.0, 66.0]	<0.001
BMI, median [IQR]	27.84 [24.39, 31.84]	27.14 [24.21, 31.18]	27.83 [24.37, 31.79]	30.78 [26.7, 35.91]	<0.001
Male gender, n (%)	3,704 (60.503)	259 (57.942)	3,364 (60.580)	81 (66.393)	0.222
Admission type, *n* (%)					
Elective	1,535 (25.074)	100 (22.371)	1,429 (25.734)	6 (4.918)	<0.001
Emergency	4,487 (73.293)	342 (76.510)	4,031 (72.591)	114 (93.443)	
Urgent	100 (1.633)	5 (1.119)	93 (1.675)	2 (1.639)	
Comorbidity, *n* (%)					
Drug abuse, *n* (%)	208 (3.398)	14 (3.132)	186 (3.350)	8 (6.557)	0.146
Alcohol abuse, *n* (%)	474 (7.743)	44 (9.843)	414 (7.455)	16 (13.115)	0.016
Deficiency anemias, *n* (%)	1 340 (21.888)	94 (21.029)	1 209 (21.772)	37 (30.328)	0.070
Rheumatoid arthritis, *n* (%)	182 (2.973)	13 (2.908)	165 (2.971)	4 (3.279)	0.977
Metastatic cancer, *n* (%)	214 (3.496)	12 (2.685)	199 (3.584)	3 (2.459)	0.500
Liver disease, *n* (%)	463 (7.563)	52 (11.633)	408 (7.347)	3 (2.459)	<0.001
Renal failure, *n* (%)	869 (14.195)	81 (18.121)	769 (13.848)	19 (15.574)	0.041
Diabetes uncomplicated, *n* (%)	1,448 (23.652)	97 (21.700)	1,324 (23.843)	27 (22.131)	0.546
Hypertension, *n* (%)	758 (12.382)	66 (14.765)	680 (12.246)	12 (9.836)	0.206
Peripheral vascular, *n* (%)	794 (12.970)	73 (16.331)	709 (12.768)	12 (9.836)	0.057
Pulmonary circulation, *n* (%)	258 (4.214)	28 (6.264)	224 (4.034)	6 (4.918)	0.072
Valvular disease, *n* (%)	254 (4.149)	17 (3.803)	233 (4.196)	4 (3.279)	0.820
Cardiac arrhythmias, *n* (%)	911 (14.881)	87 (19.463)	805 (14.497)	19 (15.574)	0.017
Laboratory tests within 24h after ICU					
F calcium mean, median [IQR]	1.13 [1.08, 1.18]	1.11 [1.06, 1.16]	1.13 [1.08, 1.18]	1.1[1.02, 1.14]	<0.001
T calcium mean, median [IQR]	8.1 [7.65, 8.6]	8.15 [7.7, 8.7]	8.1 [7.65, 8.6]	7.8 [7.2, 8.4]	<0.001
WBC mean, median [IQR]	11.93 [8.9, 15.55]	11.4 [7.84, 14.47]	11.97 [9.0, 15.6]	13.2 [8.43, 17.1]	0.004
BUN mean, median [IQR]	18.33 [13.0, 29.4]	23.5 [15.5, 42.0]	18.0 [13.0, 28.0]	22.5 [14.5, 38.0]	<0.001
PT mean, median [IQR]	14.65 [13.6, 16.2]	15.2 [13.8, 18.05]	14.6 [13.55, 16.1]	14.83 [13.6, 16.6]	<0.001
INR mean, median [IQR]	1.3 [1.2, 1.5]	1.35 [1.2, 1.75]	1.3 [1.2, 1.5]	1.33 [1.2, 1.6]	<0.001
PTT mean, median [IQR]	33.3 [28.65, 41.6]	37.4 [30.7, 49.5]	33.0 [28.55, 41.1]	33.0 [28.05, 40.07]	<0.001
K^+ mean, median [IQR]	4.19[3.87,4.5]	4.22[3.87,4.56]	4.19[3.88,4.5]	4.04[3.7,4.4]	0.004
Platelet mean, median [IQR]	175.33 [130.33, 233.33]	161.67 [111.33, 217.0]	176.0 [132.0, 234.0]	199.5 [134.0, 269.0]	<0.001
Lactate mean, median [IQR]	1.93 [1.4, 2.7]	2.3 [1.52, 3.4]	1.9 [1.4, 2.6]	2.0 [1.25, 3.07]	<0.001
Hemoglobin mean, median [IQR]	10.15 [9.15, 11.4]	10.09 [9.1, 11.2]	10.15 [9.15, 11.4]	10.35 [9.28, 12.3]	0.080
Hematocrit mean, median [IQR]	30.0 [27.3, 33.58]	29.88 [27.0, 33.45]	30.0 [27.3, 33.57]	30.8 [27.82, 36.0]	0.261
Glucose mean, median [IQR]	130.57 [116.0, 150.89]	133.0 [117.0, 159.25]	130.17 [116.0, 150.0]	139.25 [118.67, 165.33]	<0.001
Creatinine mean, median [IQR]	0.95 [0.72, 1.37]	1.05 [0.8, 2.0]	0.93 [0.7, 1.33]	1.08 [0.85, 2.13]	<0.001
Vital sign					
Spo_2 mean, median [IQR]	97.77 [96.52, 98.81]	97.85 [96.39, 98.96]	97.77 [96.56, 98.81]	96.96 [95.33, 98.39]	<0.001
Respirate mean, median [IQR]	18.12 [16.08, 21.17]	17.78 [15.92, 20.85]	18.08 [16.07, 21.03]	23.03 [19.81, 26.62]	<0.001
Mean bp mean, median [IQR]	75.11 [70.17, 81.36]	74.61 [69.46, 80.39]	75.16 [70.24, 81.38]	74.96 [69.63, 83.87]	0.121
Dias bp mean, median [IQR]	58.39 [53.15, 64.3]	58.11 [52.44, 63.88]	58.41 [53.18, 64.29]	58.96 [54.1, 66.07]	0.276
Sys bp mean, median [IQR]	112.86 [105.52, 122.26]	111.13 [102.96, 118.56]	112.97 [105.71, 122.54]	113.15 [104.58, 125.96]	<0.001
Heart rate mean, median [IQR]	85.83 [77.53, 96.52]	80.97 [71.7, 90.64]	86.0 [77.9, 96.5]	105.52 [92.33, 117.19]	<0.001

(Continued)

TABLE 1 | Continued

Characteristics	Over all (n = 6,122)	Low temperature group (n = 447)	Normal temperature group (n = 5,553)	High temperature group (n = 122)	p-value
Score system					
SPAS ii, median [IQR]	38 [30, 48]	44.0 [34.0, 56.0]	37.0 [30.0, 47.0]	43.0 [33.0, 55.0]	<0.001
SOFA, median [IQR]	5 [3, 8]	6.0 [4.0, 9.0]	5.0 [3.0, 7.0]	7.0 [5.0, 10.0]	<0.001
Outcome					
Hospital interval, median [IQR]	9.91 [6.07, 17.69]	10.0 [5.94, 19.09]	9.85 [6.06, 17.27]	17.91 [10.14, 30.06]	<0.001
ICU interval, median [IQR]	3.34 [1.86, 8.14]	3.86 [2.03, 9.15]	3.28 [1.83, 7.86]	9.99 [4.51, 17.22]	<0.001
Survival time, median [IQR]	11.15 [6.26, 27.17]	12.12 [6.03, 31.47]	11.01 [6.25, 26.75]	20.03 [10.34, 33.56]	<0.001
AKI 7-day, n (%)	4,563 (74.534)	360 (80.537)	4,094 (73.726)	109 (89.344)	<0.001
CRRT, n (%)	299 (4.884)	38 (8.501)	252 (4.538)	9 (7.377)	<0.001
Death in hospital, n (%)	925 (15.109)	133 (29.754)	763 (13.740)	29 (23.770)	<0.001
Death 28-day, n (%)	1,114 (18.197)	153 (34.228)	925 (16.658)	36 (29.508)	<0.001
Death 90-day, n (%)	1,301 (21.251)	174 (38.926)	1,089 (19.611)	38 (31.148)	<0.001
Death1-year, n (%)	1,606 (26.233)	201 (44.966)	1,362 (24.527)	43 (35.246)	<0.001

BMI, body mass index; F calcium, free calcium; T calcium, total calcium; WBC, white blood cell count; BUN, Blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; SOFA, sequential organ failure assessment; SPAS, simplified acute physiology score; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ICU, the intensive care unit; SPO2, pulse oxygen saturation; BT, body temperature; Data are represented as median (interquartile range) or n (%), mean (SD, Standard Deviation).

number and rate. Comparisons were performed with Kruskal-Wallis test or Mann-Whitney U or Welch's t test for continuous variables and chi-square or Fisher's exact tests for categorical variables. Propensity score matching (PSM) (13) was performed to adjust the imbalance of baseline between different groups. All selected variables were analyzed by univariate analysis firstly. Multivariate cox analysis or multivariate logistic regression analysis were performed to investigate relationships between abnormal temperature and clinical outcomes through adjusting confounding factors post-matched which had been analyzed in univariate analysis models with $P < 0.05$. Kaplan-Meier survival curves of 1 year mortality in different groups were constructed and compared by the log-rank test.

Data cleaning, statistical analyses and illustrations were conducted by using SPSS software version 24.0 (IBM Corporation, Armonk, NY, USA) and R software (version 4.0.3) consisted of "tableone" (14), "ggplot2" (15), "survival" (16), "survminer" (17), "lubridate" (18), "tidyverse" (19). $P < 0.05$ was considered statistically significant.

RESULT

Baseline Characteristics

There were 6,122 patients concluded in our study (**Figure 1**), 447 patients (7.3%) belonged to hypothermia, 122 patients (2.0%) belonged to hyperthermia, 5,553 patients (90.7%) belonged to normal group. Clinical and laboratory test baseline characteristics of the populations were reported in **Table 1**. The association between body temperature and in-hospital mortality was described in **Figure 2A** (95% CI −0.043, −0.016, $p < 0.001$). The relationship between body temperature and 1-year mortality was shown in **Figure 2B** (95% CI −0.065, −0.032, $p < 0.001$). There were statistical differences between body temperature distribution of first 24- h after ICU admission and long-term mortality, that was described in **Figure 3** (log-rank $p < 0.001$).

Hypothermia

The comparison between hypothermia and normal group was performed before (**Supplemental Table 1**) and after (**Supplemental Table 2**, **Table 2**) PSM. There were no significant differences in hospital interval, ICU interval and survival time (**Table 2**) across univariate analysis. After adjusting potential confounding factors, the results of multivariate cox analysis and multivariate logistic regression analysis were that in-hospital mortality (HR 1.665, 95% CI 1.218–2.276; $p = 0.001$) and 1-year mortality (HR 1.537, 95% CI 1.205–1.961; $p = 0.001$) significantly increased in hypothermia group. There were higher 28-day mortality (HR 1.518, 95% CI 1.14–2.021; $p = 0.004$) and 90-day mortality (HR 1.491, 95% CI 1.144–1.943; $p = 0.003$) compared to normal group. The incidence of AKI within 7-day and intervention of CRRT within the first day after ICU admission were both showed no significant differences between 2 groups (**Table 3**).

Hyperthermia

The comparison between hyperthermia and normal group was conducted before (**Supplemental Table 3**) and after (**Supplemental Table 4**, **Table 4**) PSM. The length of hospital stay and ICU stay were longer in hyperthermia group than normal group, respectively ($p < 0.001$,**Table 4**) across univariate analysis. After adjustment for potential confounding factors, there were no statistical differences in in-hospital mortality, 28-day mortality, 90-day mortality, 1-year mortality, the incidence of AKI within 7-day or the intervention of CRRT within the first day after ICU admission between hyperthermia group and normal group across multivariate analysis (**Table 5**).

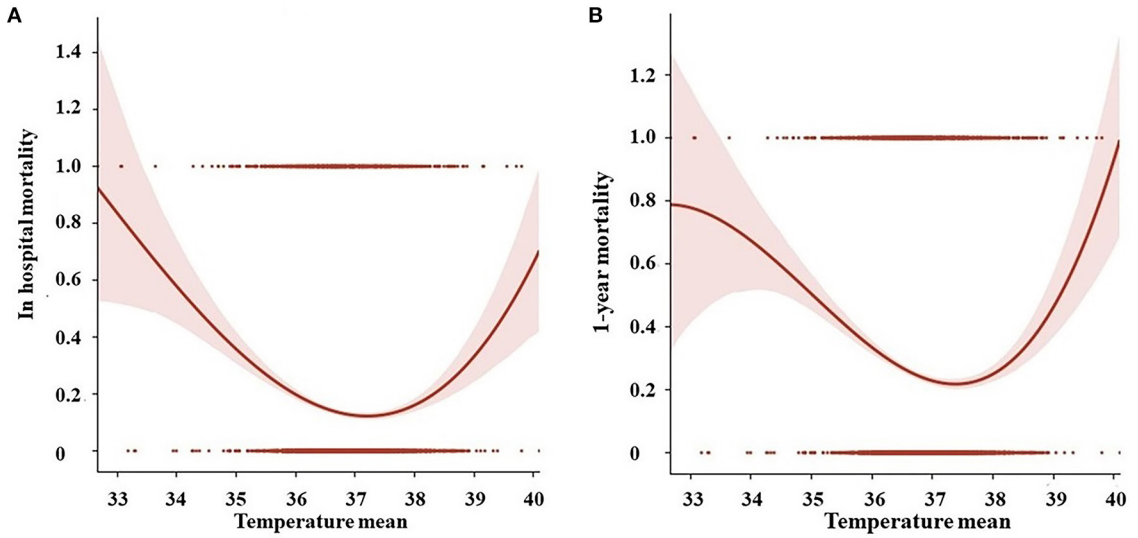

FIGURE 2 | The relationship between **(A)** body temperature and in-hospital mortality; **(B)** body temperature and 1-year mortality by Polynomial regression.

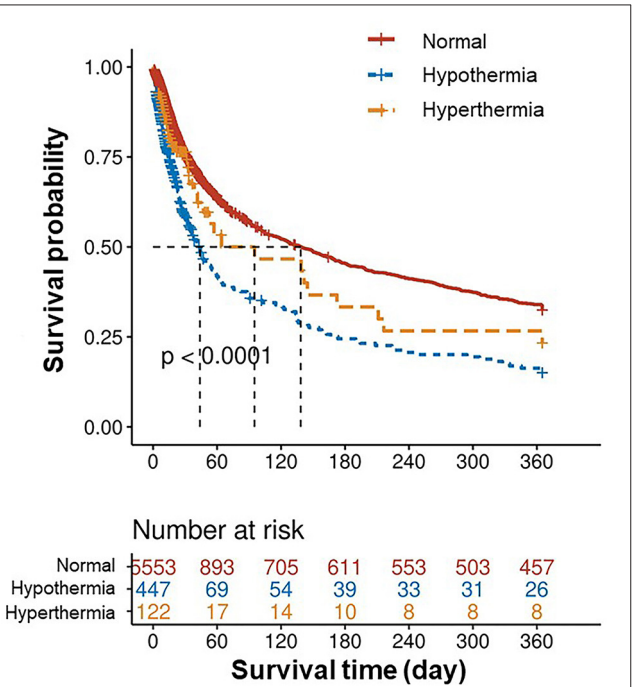

FIGURE 3 | Kaplan-Meier curves of 1-year mortality by temperature category.

DISCUSSION

This study demonstrated hypothermia within first 24-h after ICU admission was significantly associated with the increased short-term mortality and long-term mortality of post-cardiac surgery patients. Otherwise, no statistical associations were observed between hyperthermia and mortality. Hyperthermia was related to the prolonged length of hospital stay and ICU stay. Incidence of acute renal injury and intervention of continuous renal replacement therapy were not associated with hypothermia or hyperthermia.

Previous study considered body temperature could be used to assess prognostic risk independently. Hypothermia increased one-year mortality and seemed more harmful than hyperthermia (20). This is in line with our results. The reason may be relative to the great physiological changes produced by hypothermia (such as left shift of oxygenation curve, decline of coagulation function and arrhythmia and so on), which may lead to aggravate tissue hypoxia, aggravation of multiple organ functions (21), and failure of fluid resuscitation (22). For patients who were diagnosed sepsis within 24h, hypothermia (< 36.0°C) could increase 28-day mortality and 1-year mortality (23). Besides, hypothermia was also associated with the mortality of none-elderly sepsis patients (11). Moreover, patients whose bladder core temperature were <36°C after ICU admission associated with worse outcomes after coronary artery bypass grafting (CABG) under CPB (5). The results of these researches are consistent with ours. Contrary to our study, Jiwook Kim's study suggested hypothermia or hyperthermia were not interrelated with long-term mortality of severe surgery patients except cardiovascular surgery patients (24). This can be explained by the inconsistence at the key time of temperature. Owing to enlarge sample size in our study, association between the distribution of body temperature and long-term mortality was significant. Relative research confirmed that changes in body temperature could easily induce acute and further cardiovascular outcomes (25). Thus, temperature monitoring of critically ill patients is extremely necessary. Emphasizing the importance of temperature monitoring within first 24-h after ICU admission is a new sight to improve the clinical outcomes of post-cardiac surgery patients.

TABLE 2 | Post-PSM matched between hypothermia and normal group.

	Over all ($n = 894$)	Normal ($n = 447$)	Hypothermia ($n = 447$)	*p*-value
Laboratory tests within 24h after ICU				
F calcium mean, median [IQR]	1.12 [1.07, 1.18]	1.13 [1.09, 1.19]	1.11 [1.06, 1.16]	<0.001
T calcium mean, median [IQR]	8.1 [7.67, 8.7]	8.1 [7.65, 8.6]	8.15 [7.7, 8.7]	0.281
WBC mean, median [IQR]	11.47 [8.37, 15.05]	11.57 [8.8, 15.4]	11.4 [7.84, 14.47]	0.068
BUN mean, median [IQR]	20.0 [14.5, 35.25]	18.5 [14.0, 30.67]	23.5 [15.5, 42.0]	<0.001
PT mean, median [IQR]	14.97 [13.8, 17.1]	14.7 [13.8, 16.4]	15.2 [13.8, 18.05]	0.003
INR mean, median [IQR]	1.35 [1.2, 1.6]	1.3 [1.2, 1.5]	1.35 [1.2, 1.75]	0.006
PTT mean, median [IQR]	35.3 [29.75, 44.9]	33.8 [29.1, 41.9]	37.4 [30.7, 49.5]	<0.001
K^+ mean, median [IQR]	4.2 [3.87, 4.53]	4.2 [3.89, 4.51]	4.22 [3.87, 4.56]	0.649
Platelet mean, median [IQR]	166.0 [121.0, 223.0]	169.0 [130.0, 226.33]	161.67 [111.33, 217.0]	0.018
Lactate mean, median [IQR]	2.1 [1.45, 3.09]	2.0 [1.4, 2.8]	2.3 [1.52, 3.4]	<0.001
Hemoglobin mean median [IQR]	10.04 [9.07, 11.28]	10.0 [9.07, 11.37]	10.09 [9.1, 11.2]	0.789
Hematocrit mean median [IQR]	29.8 [27.2, 33.46]	29.52 [27.32, 33.43]	29.88 [27.0, 33.45]	0.886
Glucose mean median [IQR]	132.6 [116.29, 153.0]	131.7 [115.62, 150.0]	133.0 [117.0, 159.25]	0.166
Creatinine mean median [IQR]	1.0 [0.75, 1.6]	0.95 [0.73, 1.4]	1.05 [0.8, 2.0]	<0.001
Score system				
SPAS ii, median [IQR]	41 [32, 53]	38.0 [31.0, 49.0]	44.0 [34.0, 56.0]	<0.001
SOFA, median [IQR]	6 [4, 8]	5.0 [3.0, 8.0]	6.0 [4.0, 9.0]	<0.001
Vital sign				
Spo_2 mean, median [IQR]	97.79 [96.46, 98.95]	97.78 [96.56, 98.9]	97.85 [96.39, 98.96]	0.859
Temperature mean, median [IQR]	35.99 [35.8, 36.86]	36.86 [36.52, 37.2]	35.8 [35.56, 35.9]	<0.001
Respirate mean, median [IQR]	17.88 [15.97, 20.93]	18.05 [16.07, 20.95]	17.78 [15.92, 20.85]	0.359
Mean bp mean, median [IQR]	74.71 [69.71, 80.35]	74.84 [70.1, 80.23]	74.61 [69.46, 80.39]	0.592
Dias bp mean, median [IQR]	57.91 [52.33, 63.58]	57.55 [52.19, 63.19]	58.11 [52.44, 63.88]	0.530
Sys bp mean, median [IQR]	112.11 [104.14, 120.28]	113.08 [105.27, 122.84]	111.13 [102.96, 118.56]	<0.001
Heart rate mean, mean (SD)	83.53 [74.5, 93.04]	86.21 [78.3, 95.29]	80.97 [71.7, 90.64]	<0.001
Outcomes				
Hospital interval, median [IQR]	9.97 [6.03, 17.97]	9.9 [6.33, 17.04]	10.0 [5.94, 19.09]	0.873
ICU interval, median [IQR]	3.77 [2.0, 8.7]	3.47 [1.98, 8.11]	3.86 [2.03, 9.15]	0.621
Survival time, median [IQR]	11.8 [6.31, 30.0]	11.7 [6.97, 29.29]	12.12 [6.03, 31.47]	0.341
Death in hospital, *n* (%)	205 (22.931)	72 (16.107)	133 (29.754)	<0.001
CRRT, *n* (%)	59 (6.600)	21 (4.698)	38 (8.501)	0.022
AKI 7-day, *n* (%)	689 (77.069)	329 (73.602)	360 (80.537)	0.014
Death 28-day, *n* (%)	241 (26.957)	88 (19.687)	153 (34.228)	< 0.001
Death 90-day, *n* (%)	280 (31.320)	106 (23.714)	174 (38.926)	< 0.001
Death 1-year, *n* (%)	329 (36.801)	128 (28.635)	201 (44.966)	<0.001

F calcium, free calcium; T calcium, total calcium; WBC, white blood cell count; BUN, Blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; SOFA, sequential organ failure assessment; SPAS, simplified acute physiology score; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ICU, the intensive care unit; SPO2, pulse oxygen saturation; BT, body temperature; Data are represented as median (interquartile range) or n (%), mean (SD, Standard Deviation).

The effects of hyperthermia and hypothermia on human body were complicated (26, 27). Hyperthermia was likely a powerful factor in strengthening immunity to remove subsequent pathogen by itself (28). Infection (29) and systemic inflammatory response syndrome (SIRS) caused by CPB (30) both lead to hyperthermia after cardiac surgery (31). Recent study claimed that hyperthermia in first 24h can be used to diagnose inflammatory response and possible outcomes after CPB, in this study in-hospital mortality was not significantly different comparing SIRS with no SIRS patients, while length of ICU stay was longer in SIRS patients (30). Besides, earlier studies suggested hyperthermia was beneficial for some outcomes (23, 32) and did not improve 1-year mortality of post-cardiac surgery patients (24). In line with our research, relationship between hyperthermia and mortality was not statistically significant, but hyperthermia was related to the prolonged length of ICU and hospital stay.

The strength of our study is focusing on the impact of overall body temperature changes within 24h after cardiac surgery on clinical outcomes rather than emphasizing the

TABLE 3 | Multivariable cox regression and logistic regression analysis for hypothermia.

	<36.0°C (Pre-matched)			<36.0°C (Post-matched)		
	HR/OR	**95%CI**	***P*-value**	**HR/OR**	**95%CI**	***p*-value**
Death in-hospital	1.475	1.204–1.806	<001	1.665	1.218 – 2.276	0.001
Death 1-year	1.409	1.199–1.655	<001	1.537	1.205–1.961	0.001
Death 28-day	1.387	1.15–1.674	0.001	1.518	1.14–2.021	0.004
Death 90-day	1.389	1.166–1.656	<001	1.491	1.144–1.943	0.003
AKI 7-day	0.871	0.521–1.417	0.588	1.094	0.762–1.573	0.627
CRRT	1.004	0.764–1.329	0.976	1.021	0.457–2.31	0.959

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; HR, hazard ratio; OR, odds ratio.

TABLE 4 | Post-PSM matched between hyperthermia and normal group.

	Over all (*n* = 244)	**Normal (*n* = 122)**	**Hyperthermia(*n* = 122)**	***p*-value**
Laboratory tests within 24h after ICU				
F calcium mean, median [IQR]	1.11 [1.06, 1.15]	1.12[1.08, 1.16]	1.1 [1.02, 1.14]	0.002
T calcium mean, median [IQR]	8.03 [7.4, 8.5]	8.2 [7.7, 8.55]	7.8 [7.2, 8.4]	0.003
WBC mean, median [IQR]	12.43 [8.77, 16.73]	11.85 [8.8, 16.05]	13.2 [8.43, 17.1]	0.617
BUN mean, median [IQR]	18.67 [13.0, 33.0]	17.0 [12.0, 24.67]	22.5 [14.5, 38.0]	0.005
PT mean, median [IQR]	14.57 [13.6, 16.4]	14.3 [13.4, 15.9]	14.83 [13.6, 16.6]	0.122
INR mean, median [IQR]	1.3 [1.2, 1.55]	1.3 [1.2, 1.5]	1.33 [1.2, 1.6]	0.113
PTT mean, median [IQR]	32.1 [27.9, 38.36]	30.7 [27.7, 37.65]	33.0 [28.05, 40.07]	0.104
K^+ mean, median [IQR]	4.11 [3.75, 4.4]	4.14 [3.81, 4.41]	4.04 [3.7, 4.4]	0.146
Platelet mean, median [IQR]	202.5 [140.5, 267.0]	206.8 [147.0, 263.0]	199.5 [134.0, 269.0]	0.565
Lactate mean, median [IQR]	1.9[1.37, 2.68]	1.85 [1.4, 2.4]	2.0 [1.25, 3.07]	0.626
Hemoglobin mean, median [IQR]	10.5 [9.37, 12.3]	10.6 [9.5, 12.5]	10.35 [9.28, 12.3]	0.544
Hematocrit mean, median [IQR]	31.0 [27.62, 35.3]	31.1 [27.53, 35.03]	30.8 [27.82, 36.0]	0.657
Glucose mean, median [IQR]	136.2 [117.88, 157.75]	131.0 [117.25, 149.2]	139.25 [118.67, 165.33]	0.044
Creatinine mean, median [IQR]	1.0 [0.8, 1.65]	0.95 [0.7, 1.2]	1.08 [0.85, 2.13]	0.005
Score system				
SPAS ii, median [IQR]	37 [29, 49]	34.0 [25.0, 42.0]	43.0 [33.0, 55.0]	<0.001
SOFA, median [IQR]	6 [4, 9]	5.0 [2.0, 7.0]	7.0 [5.0, 10.0]	<0.001
Vital sign				
SpO_2 mean, median [IQR]	97.59 [96.04, 98.9]	97.92 [96.7, 99.18]	96.96 [95.33, 98.39]	<0.001
Temperature mean, median [IQR]	38.31 [37.0, 38.58]	36.99 [36.64, 37.44]	38.58 [38.43, 38.71]	<0.001
Resp rate mean, median [IQR]	20.42 [17.3, 24.38]	17.82 [15.97, 21.29]	23.03 [19.81, 26.62]	<0.001
Mean bp mean, median [IQR]	76.14 [70.0, 84.69]	77.1 [70.58, 87.36]	74.96 [69.63, 83.87]	0.092
Dias bp mean, median [IQR]	59.91 [54.68, 67.32]	61.45 [55.07, 68.72]	58.96 [54.1, 66.07]	0.155
Sys bp mean, median [IQR]	114.83 [105.94, 125.07]	114.94 [108.25, 125.07]	113.15 [104.58, 125.96]	0.279
Heart rate mean, mean (SD)	97.326 (17.954)	90.644 (15.142)	104.008 (18.059)	<0.001
Outcomes				
Hospital interval, median [IQR]	14.18 [7.76, 24.93]	10.84 [6.25, 20.44]	17.91 [10.14, 30.06]	<0.001
ICU interval, median [IQR]	6.29 [2.58, 13.2]	3.74 [2.04, 9.01]	9.99 [4.51, 17.22]	<0.001
Survival time, median [IQR]	15.7 [7.9, 30.67]	12.25 [6.31, 24.2]	20.03 [10.34, 33.56]	0.001
CRRT, *n* (%)	14 (5.738)	5 (4.098)	9 (7.377)	0.271
AKI 7-day, *n* (%)	193 (79.098)	84 (68.852)	109 (89.344)	<0.001
Death in hospital, *n* (%)	46 (18.852)	17 (13.934)	29 (23.770)	0.050
Death 28-day, *n* (%)	55 (22.541)	19 (15.574)	36 (29.508)	0.009
Death 90-day, *n* (%)	62 (25.410)	24 (19.672)	38 (31.148)	0.040
Death 1-year, *n* (%)	67 (27.459)	24 (19.672)	43 (35.246)	0.006

F calcium,free calcium; T calcium, total calcium; WBC, white blood cell count; BUN, Blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; SOFA, sequential organ failure assessment; SPAS, simplified acute physiology score; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ICU, the intensive care unit; SPO2, pulse oxygen saturation; BT, body temperature; Data are represented as median (interquartile range) or n (%), mean (SD, Standard Deviation).

TABLE 5 | Multivariable cox regression and logistic regression analysis for hyperthermia.

	>38.3°C (Pre-matched)			>38.3°C (Post-matched)		
	HR/OR	**95%CI**	***P*-value**	**HR/OR**	**95%CI**	***P*-value**
Death in-hospital	1.001	0.686–1.46	0.995	1.061	0.492–2.29	0.88
Death 1-year	1.069	0.785–1.456	0.672	1.049	0.567–1.94	0.878
Death 28-day	1.068	0.761–1.499	0.704	1.126	0.561–2.259	0.739
Death 90-day	1.033	0.743–1.436	0.846	0.917	0.484–1.74	0.791
AKI 7-day	1.573	0.869–3.061	0.155	2.329	0.938–6.058	0.073
CRRT	0.684	0.251–1.644	0.427	3.909	0.656–34.76	0.164

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; HR, hazard ratio; OR, odds ratio.

adverse results associated with a single time point. This study may be of beneficial in alleviating the adverse outcomes of hypothermia in post-cardiac surgery patients. Our study also has some limitations. Firstly, number of hyperthermia samples is relatively small, enlarging sample size and multicenter database are necessary for verification in future. Secondly, method and site of body temperature measurement were not clarified in MIMIC-III database which could cause bias to results, more researches deserve to carry out to clarify details. Thirdly, this is a retrospective single center study, results should be explained with caution in other populations and regions.

CONCLUSION

This retrospective observational study confirmed hypothermia within 24-h after ICU admission was associated with the elevated mortality of post-cardiac surgery patients while hyperthermia was not. The importance of temperature monitoring is worthy of attention to improve clinical outcomes after cardiac surgery in clinical treatment.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FX, CL, and SB gathered and processed the data. CL and CZ prepared the results. FX and SB contributed in writing the manuscript. JG put forward the idea and revised the manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Application of Homograft Valved Conduit in Cardiac Surgery

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Valved conduits often correct the blood flow of congenital heart disease by connecting the right ventricle to the pulmonary artery (RV-PA). The homograft valved conduit was invented in the 1960s, but its wide application is limited due to the lack of effective sterilization and preservation methods. Modern cryopreservation prolongs the preservation time of homograft valved conduit, which makes it become the most important treatment at present, and is widely used in Ross and other operations. However, homograft valved conduit has limited biocompatibility and durability and lacks any additional growth capacity. Therefore, decellularized valved conduit has been proposed as an effective improved method, which can reduce immune response and calcification, and has potential growth ability. In addition, as a possible substitute, commercial xenograft valved conduit has certain advantages in clinical application, and tissue engineering artificial valved conduit needs to be further studied.

Keywords: homograft valved conduit, cardiac surgery, xenograft valved conduit, decellularized valved conduit, tissue engineered substitutes

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INTRODUCTION

In tetralogy of Fallot combined with pulmonary atresia or other types of severe cardiac malformations, the use of valved conduits to reconstruct the ventricular outflow tract is required to restore normal hemodynamics. From the 1960s, when valved conduits were first used, improvements in preservation methods have greatly expanded the use of homograft valved conduits in clinical practice. This technology has been rapidly developed at present. The basic research, clinical trials, and follow-up reports on valved conduits have been published continuously, opening up new avenues for the treatment of complex precordial and vascular disease. This article reviews the advances in homograft valved conduit and its clinical applications and provides an outlook on this field.

METHODS

An electronic search in PubMed was performed from inception until 31 April 2021. The search strategy consisted of free and controlled terms for homograft valved conduit. The search was limited to publications in English. Reference lists of previous reviews of the subject as well as the included articles were hand-searched to identify additional eligible studies. Following retrieval of the search results, the title and abstract of the remaining records were screened. Relevant articles and articles of which eligibility could not be assessed properly were selected for full-text assessment. Then select relevant articles to be included in this review.

THE HISTORY OF HOMOGRAFT VALVED CONDUIT

In 1966, Ross et al. used homograft valved conduit to connect right ventricular outflow tract and pulmonary artery for the first time. They used valved homograft aorta and pulmonary artery to treat pulmonary atresia, and then gradually expanded to tetralogy of Fallot, double outlet of right ventricle, transposition of great arteries, single ventricle, permanent truncus arteriosus, and many other complex congenital heart diseases. In the 1960s, five cases of pulmonary atresia variant transposition of aorta with occlusion of left ventricular outflow tract were reported, all of which were repaired with valved homograft aorta at the site of pulmonary artery (1, 2). At the Mayo Clinic, there is relatively large early experience in radiation cryopreservation of homograft valved conduit. However, the graft was found to have calcification and rapid degeneration 1–3 years after operation, resulting in severe stenosis (3). Subsequently, several international centers disinfected the homograft valved conduit with antibiotics and preserved them in a tissue medium at 4°C (4, 5). In the experience of a limited number of centers, these conduits performed well in the location of the pulmonary artery. However, the shelf life of this kind of conduits is very short, so it is difficult to become a widely used homograft technology.

The development of homograft valved conduit preservation methods can be broadly divided into four phases: the first stage (mid-1960s) was the *in situ* operation method, in which fresh homograft valved conduit was obtained under sterile conditions and perform surgical treatment within a few hours. In the second stage (mid-1960s to mid-1970s), chemical reagents or radiation sterilization were used, followed by cryopreservation at −79°C (6). Because sterilization also leads to loss of biological activity of the homograft valve, the valve is prone to degeneration, calcification after surgery, and poor long-term results. In the third stage (mid-1970s to mid-1980s), isolated homograft valved conduit were sterilized in antibiotic solution for 24 h and then stored at a low temperature of 4°C in a nutrient solution containing low concentrations of antibiotics, which maintained their biological activity and short and long-term clinical outcomes, but the maximum storage time was only 6 weeks, which was still unsatisfactory (7). The fourth stage (after the mid-1980s) used antibiotic sterilization, controlled rate cooling, and liquid nitrogen deep cryopreservation (8). This is currently the most widely used and studied method internationally. The main process is to sterilize isolated homograft valved conduit with antibiotic solution at 37°C for 24 h, then put into RPMI1640 medium containing dimethyl sulfoxide (DMSO) and cool down to −80°C at a rate of −1°C/min, and then transfer to liquid nitrogen for deep cryopreservation for long-term storage. **Figure 1** illustrates the development of valved conduits, including milestones of homograft valved conduits and some xenograft valved conduit.

PRESERVATION METHODS FOR HOMOGRAFT VALVED CONDUIT

The biological activity of homograft valved conduit and the integrity of its tissue structure are the keys to preserve its function. The biological activity of homograft valved conduit refers to the number of living cells it contains and its functional state, while the integrity of tissue structure refers to the composition and structural integrity of the extracellular matrix. Fibroblasts can synthesize extracellular matrix and play an important role in maintaining the stability of valved conduit (9). The increased possibility of thrombosis caused by the loss of endothelial cells will also accelerate the failure of homograft (10). Current research advances in homograft valved conduit preservation methods focus on donor conditions, warm ischemia time, sterilization methods, freezing methods, and rewarming methods (11).

The health status of the donor itself determines the biological activity and the structural integrity of the tissue of the homograft valved conduit. In clinical applications, Sadowski et al. found that valves removed from elderly donors were prone to complications such as degeneration and incomplete closure (12). Verghese et al. noted that homograft valved conduit from individuals after organ or tissue transplantation readily induces an immune response in the recipient and should not be used as a donor (13). Gall et al. quantitatively evaluated the initial activity of homograft valved conduit in normal and cardiac arrest donors by thin-layer radiographic autoradiography, and the initial activity of homograft valved conduit in normal donors was significantly higher (92 ± 2)% than that in cardiac arrest donors (66 ± 3)%, suggesting that the biological activity of homograft valved conduit is significantly reduced after cardiac arrest due to the lack of oxygen and nutrient supply (14). Therefore, to maximize preservation of homograft valved conduit activity prior to operation, it should be removed as soon as possible after donor cardiac arrest, or if the corpse is cryopreserved it can still be collected within 24 h. Donors currently used in clinical practice are generally selected from brain dead or autopsied patients under 45 years of age (6) who have no major vascular disease, valve disease, infectious disease or autoimmune disease in their lifetime. Homograft valved conduit are removed under strict aseptic conditions, placed in saline or Hank's solution containing antibiotics, packed in double-layer sterile bags, and shipped as soon as possible at 4°C for trimming and subsequent processing.

Warm ischemia time is a period of time between when homograft valved conduit loses blood supply after cardiac arrest and when it is taken out and stored at 0–4°C. Mohan et al. found that when warm ischemia time >24 h, homograft valved conduit endothelial cells basically die and fall off, and the synthesis of prostacyclin stops. The collagen fibers in the artery wall are destroyed, and the structural integrity is also destroyed (14). Suh et al. studied the activity of porcine aortic valve fibroblasts under different conditions. Fibroblast activity was (92.25 ± 2.7)% at 2 h of heat ischemia and (57.0 ± 10)% at 24 h of heat ischemia ($P < 0.05$), suggesting a significant decrease in fibroblast activity with increasing warm ischemia time. Suh et al. studied

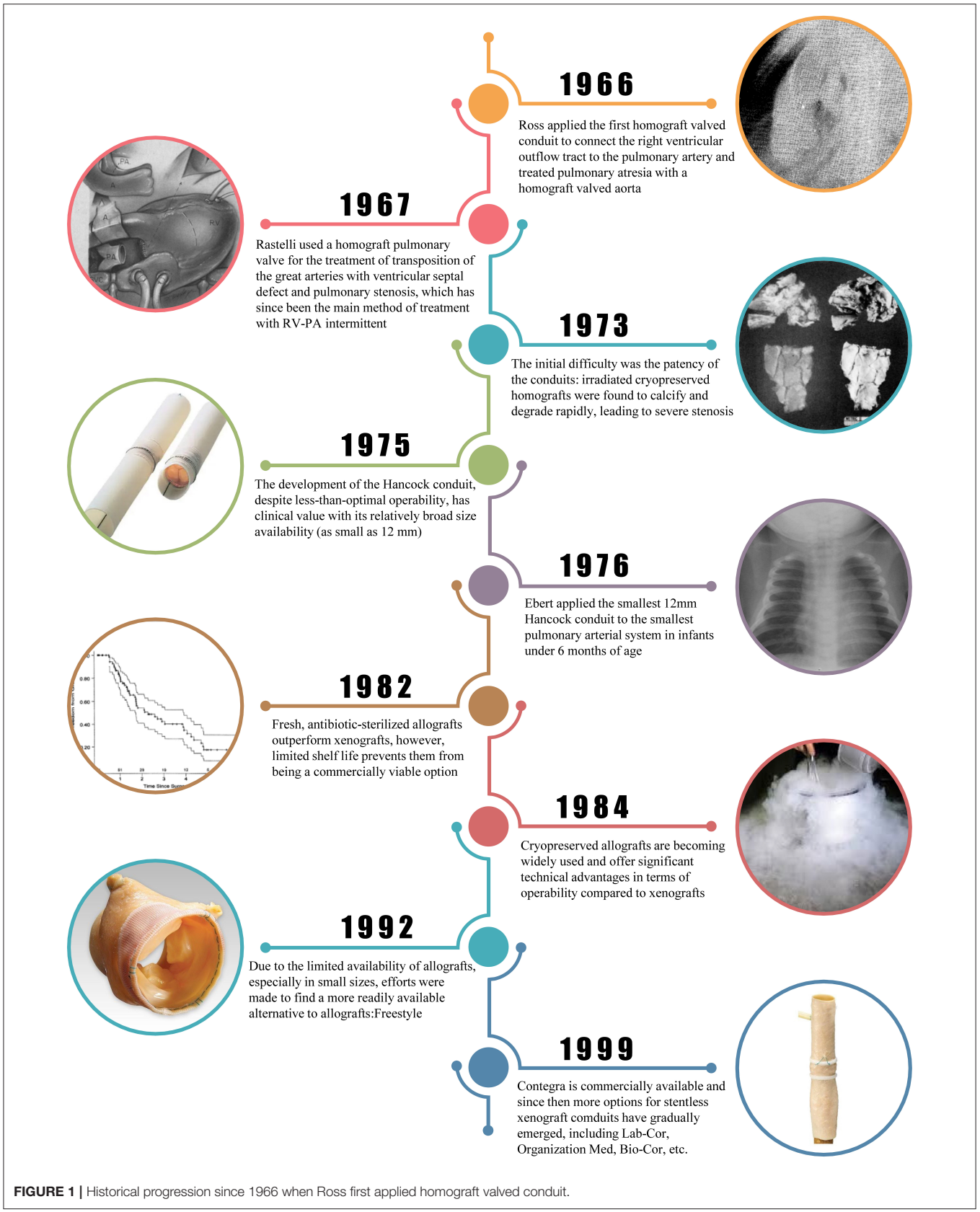

FIGURE 1 | Historical progression since 1966 when Ross first applied homograft valved conduit.

the activity of porcine aortic valve fibroblasts under different conditions. Fibroblast activity was (92.25 ± 2.7)% at 2 h of warm ischemia and (57.0 ± 10)% at 24 h of warm ischemia ($P < 0.05$), suggesting a significant decrease in fibroblast activity with increasing warm ischemia time (15). Burkert et al. applied scanning electron microscopy to observe the effects of different warm ischemia time on human aortic valves. When the valve was left at room temperature for 12 h, the continuity between valve endothelial cells was disrupted, some endothelial cells were shed into the lumen, and endothelial cell loss occurred. When warm ischemia time reached 48 h, the vascular endothelial cells were completely shed, while the vessel wall structure was destroyed. By comparing the degree of damage to the homograft valved conduit by different warm ischemia time, it is recommended that warm ischemia time should be controlled within 24 h as much as possible (16). Stemper et al. found that vascular tissue mechanics were significantly reduced after more than 24 h compared to fresh vessels, even after storage at 4°C (17). The above studies provide an objective experimental basis for clinical control of homograft valved conduit with a warm ischemia time of <24 h.

The classic antibiotic solution formulation is penicillin 50 U/ml, streptomycin 50 μg/ml, and amphotericin B 10 μg/ml. However, Strickett et al. found that amphotericin B and streptomycin are highly cytotoxic and can significantly reduce the activity of valvular fibroblasts (17). Yu Haibin et al. used cefoxitin 240 mg/L, polymyxin B 100 mg/L, lincomycin 120 mg/L, and vancomycin 50 mg/L for sterilization treatment, which ensured sterilization and avoided the effect of streptomycin and amphotericin B on cell activity. Jashari et al. found that the removal of cefoxitin and the use of lower concentrations of lincomycin, polymyxin B, and vancomycin had no significant effect on cell survival and the sterilization effect was reliable (18). Since antibiotics are sterilized primarily during the bacterial multiplication phase, antibiotic sterilization activity is greatest at 37°C. However, the normal metabolic rate of valve tissue at 37°C inevitably leads to inactivation of valve tissue cells due to hypoxia and nutrient deficiency. The 4°C incubation sterilization protocol was first proposed by Kinklin et al. found that valve sterilization at 4°C for 20 h resulted in a slower metabolic rate and increased tolerance to lack of oxygen and nutrients, but a positive sterilization effect (19).

Currently, the main clinical methods used are incubation sterilization with antibiotic solution, controlled rate cooling, and liquid nitrogen freezing, as proposed by O'Brien. The main mechanism is that the deep cryogenic environment can interfere with cell metabolism and inhibit the biochemical activities of the organism. Brockbank et al. compared the protein synthesis function of homograft valved conduit fibroblasts preserved by different methods. After 2 years of preservation by liquid nitrogen freezing, the fibroblasts still had protein synthesis function, and the protein synthesis function of freeze-dried fibroblasts gradually decreased with time. The protein synthesis function of fibroblasts preserved at 4°C for 2 weeks was only 15% of that of the liquid nitrogen preservation group (20). Liquid nitrogen freezing is effective in preserving tissues and organs, but cryoinjury still exists. Dimethyl sulfoxide is currently the most commonly used homograft valved conduit liquid nitrogen cryoprotectant. It can rapidly penetrate cell membranes, lower the freezing point, slow down the cryopreservation process, increase the intracellular ion concentration, and reduce intracellular ice crystal formation, thereby reducing cellular damage. However, high concentrations of DMSO are inherently cytotoxic and can cause osmotic damage. The optimal concentration of DMSO in cryopreservation solution is currently considered to be 15% (21). Wosteman et al. found that replacing sodium salts with vitamin B complexes in cryopreservation solutions prevented DMSO from exerting its toxic effects (22). Mazur et al. found that during rapid freezing, water molecules in the intracellular fluid do not have time to penetrate outside the cell and form ice crystals inside the cell, which disrupt the ultrastructure of the cell and lead to cell death. During slow freezing, cells are exposed to hyperosmotic extracellular fluid and toxic antifreeze for too long, which may also lead to cell death (23). Therefore, the cooling rate is very important to maintain the biological activity of cells. The use of a program-controlled hypothermia instrument to control homograft valved conduit cooling at a relatively stable and reasonable rate can minimize cryo-damage. −1°C/min was found by Vander et al. to be the best cooling rate to maximize fibroblast activity (24). In recent years, the concept of phase change point has received increasing attention in the process of programmed cooling. The phase change point is the temperature point at which the sample transforms from liquid to solid during the freezing process, and a large amount of melt heat is released during the morphological transformation, causing the local sample to condense, and then increase in temperature and melt, and then condense again. During this process, the cells are susceptible to repeated damage by ice crystals, which affects the preservation effect of homograft valved conduit. To overcome the phase transition heat, increasing the cooling rate near the phase transition point to prevent the temperature increase during the phase transition and decreasing the cooling rate after complete phase transition to continue cooling at −1°C/min can reduce the damage to the homograft valved conduit from the phase transition. The phase transition point of human homograft aortic valved conduits is −4 to −6°C. During this period, increasing the cooling rate to −4°C/min instead of −1°C/min can effectively reduce cell damage.

Liquid nitrogen cryopreserved homograft valved conduit needs to be thawed and resuscitated before it can be used in the clinic. Rapid rewarming in a 42°C water bath is now commonly accepted in clinical practice. Rapid rewarming is particularly important for frozen cells. For cells containing ice crystals, rapid rewarming can limit the phenomenon of migratory recrystallization within the cells and reduce the damage caused by repeated crystallization, thus improving cell survival for cytoprotection. Since DMSO is toxic to cells at room temperature, when homograft valved conduit is rewarmed and melted, it should be quickly removed and replaced by "graded series rinsing" to reduce its damage to cells. This preservation method not only retains the biological activity of the valved conduit, but also retains a certain degree of antigenicity. Most patients implanted with valved conduit have humoral immunity against human leukocyte antigen (HLA) (25). It has been found that donor-derived dendritic cells and

endothelial cells expressing HLA-II molecules in valved conduits can directly present antigens and activate receptor immunity (26, 27). Other studies have shown that there are mild to moderate mononuclear inflammatory cell infiltration composed of T cells and macrophages in valvular tissue (28). **Figure 2** summarizes the processing flow of homograft valved conduit preservation method (29).

CLINICAL APPLICATION OF HOMOGRAFT VALVED CONDUIT

One of the tasks frequently faced by congenital heart surgeons is the reconstruction of the right ventricular outflow tract, i.e., the creation of a channel between the right ventricle and the pulmonary artery. Depending on the etiology of the pathological changes of the pulmonary outflow tract, it can be classified as tetralogy of Fallot combined with pulmonary atresia, congenital arterial trunk right ventricular outflow tract or pulmonary artery agenesis, transposition of the great arteries with ventricular septal defect and pulmonary stenosis, corrected transposition of the great arteries with pulmonary stenosis, complex right ventricular double outlet, and Ross procedure of medical origin (30).

The Ross procedure, using the autograft pulmonary valve to replace the diseased aortic valve and a non-autograft valved conduit to replace the pulmonary valve, has become the procedure of choice for young people with irreparable aortic root disease. There are two main techniques for Ross procedure: the subcoronary and root replacement techniques. The subcoronary technique can be technically challenging because the aortic and pulmonary roots often have different dimensions and commissural distribution. Therefore, many surgeons use the full root replacement technique for Ross procedures (31, 32). The Ross procedure is reserved for patients with non-repairable, non-spareable aortic valves. Otherwise, isolated aortic valve repair or valve-sparing root replacement should be chosen. Ideal candidates for the Ross procedure are young or middle-aged (<50 years old). Patients presenting with mechanical or bioprosthetic aortic valve dysfunction and patients with active endocarditis also appear to be appropriate candidates for

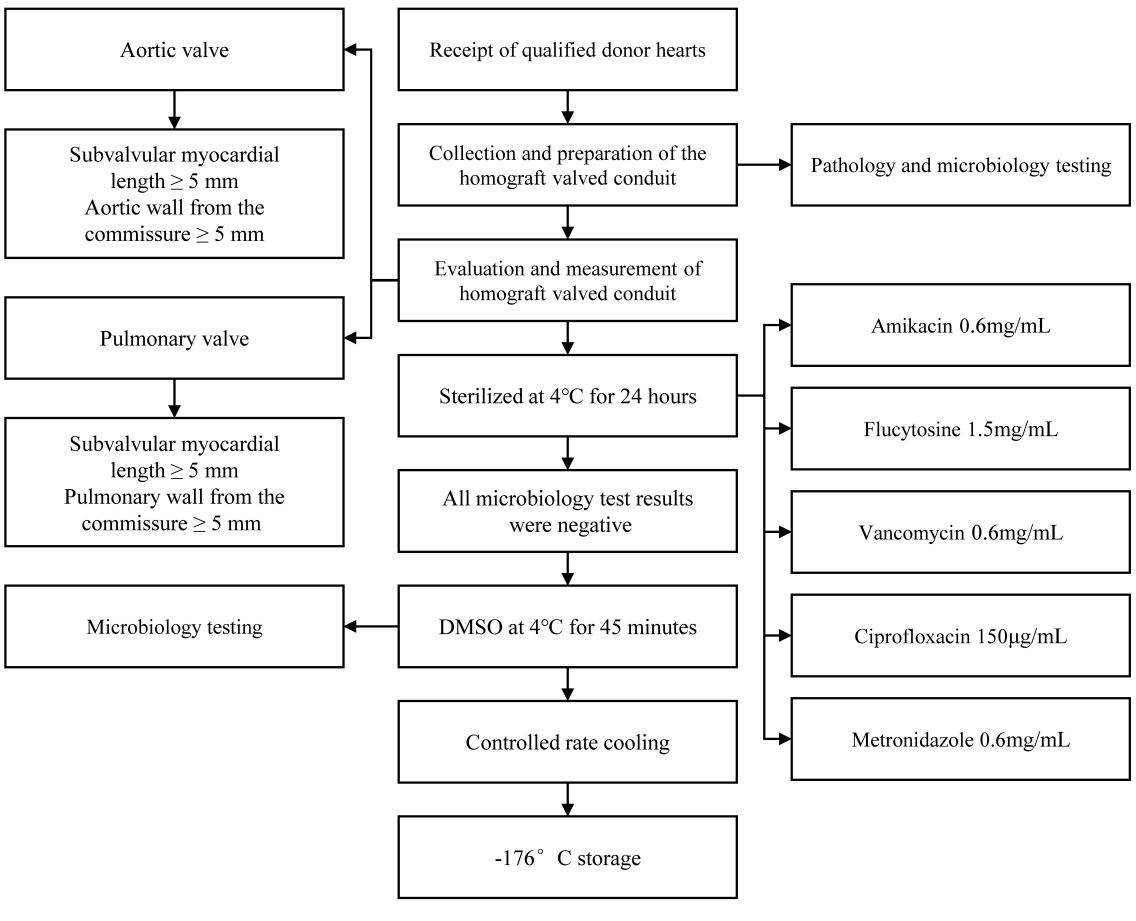

FIGURE 2 | Specific handling of homograft valved conduit from donor acquisition to deep cryogenic storage. It is important to note that (1) extra care must be taken throughout the processing and repeated microbiological tests must be performed to ensure complete sterile processing and storage, as any contamination could be catastrophic to the recipient; (2) the sterilization recipe in the figure is the protocol of Berlin, Germany, and different sterilization protocols may exist in other institutions, and there is no uniform protocol yet, sterilization to meet microbiological testing standards is a feasible solution.

surgery. Athletes are also suitable because of the absence of anticoagulation and extreme physiological and hemodynamic consequences (33). Chronic complications after the Ross surgery including aortic valve insufficiency, right ventricular outflow tract obstruction, autograft aortic valve dilatation, and homograft pulmonary valve stenosis. Potential long-term failure of both valves (aortic and pulmonary) has been considered the Achilles' heel of the Ross procedure (34). Reece et al. (35) reported a three-fold increase in mortality with the Ross procedure compared with conventional AVR. However, the Ross procedure is more complex than standard AVR. Some of the steps required in the Ross procedure—but not in conventional AVR—include dissection of the aortic root, mobilization of the coronary arteries, harvesting of the pulmonary autograft, proximal autograft anastomosis, coronary artery reimplantation, and pulmonary homograft implantation. Each of these steps increases the risk of the procedure (36). Importantly, the increase in mortality was mainly observed in low-volume centers. Therefore, for the complex surgery, these suboptimal outcomes are not surprising (37). In contrast, several experienced high-volume centers have demonstrated that the mortality rate for performing Ross surgery is similar to that of conventional AVR (31). This emphasizes the importance of the surgeon expertise and adequate surgical volume to achieve excellent outcomes in Ross surgery.

There are some findings in echocardiograms at follow-up after right ventricular outflow tract reconstruction. Pulmonary autograft dilatation is common in adults after Ross surgery, which may be the reason for reoperation. This dilatation develops over time and is usually accompanied by a dilatation of the native aorta. In a study of 71 patients with a median follow-up of 8.9 years (38), the proportion of patients with enlarged autografts and proximal ascending aorta was 13 and 16%, increasing to 33 and 44%, respectively. A retrospective multicenter international cohort study monitored the peak transvalvular gradients and regurgitation grade. Female sex, tricuspid natural aortic valve, and higher preoperative gradients were significantly associated with higher autograft gradients. Female sex was significantly associated with lower gradients of homografts, but also increased the likelihood of significant regurgitation. In contrast, the use of homografts rather than bioprosthesis and older donor age was associated with a lower likelihood of significant regurgitation (39). Another study showed that age and homograft diameter at the time of operation was also associated with valve function (40).

Homograft pulmonary artery is the best option for reconstructing RVOT, has good durability, and is not necessary for adults to undergo valve replacement again. Alexander et al. (41) evaluated 741 adult patients who underwent the Ross procedure. Right ventricular outflow tract reconstruction included 175 (23.6%) homograft pulmonary arteries, 561 (75.7%) porcine or bovine grafts, and 5 (0.7%) polytetrafluoroethylene duct reconstructions. The mean follow-up time was 5.8 $\pm$ 2.2 years. The 10-year survival rate was 90.7%, comparable to the age- and sex-matched general population. The 5- and 10-year graft reoperation rates were 94.1 and 88.3%, respectively. The probability of not reoperation at 10 years for allografts, pericardial xenografts treated with bicycloxide or glutaraldehyde, and porcine aortic root grafts was 100, 94.4, 82.7, and 80.6%, respectively. Jamie et al. (40) reported the implantation of 701 homograft pulmonary valved conduits in 604 patients. At 25 years of follow-up, the survival rate was 84 $\pm$ 4% and the valve replacement rate was 56 $\pm$ 6%. The probability of not requiring valve replacement after 15 years was 28 $\pm$ 14% in patients younger than 1 year, 59 $\pm$ 8% in patients 1–18 years, and 82 $\pm$ 5% in patients older than 18 years. Patients reported lower levels of physical strength and general health compared with the sex- and age-matched Dutch population, but significantly less physical pain. Pieter et al. (42) reported a total of 133 homograft valved conduits implanted in 126 patients with tetralogy of Fallot, including 126 pulmonary valved conduits and 7 aortic valved conduits. At long-term follow-up, the homograft conduits functioned satisfactorily in the pulmonary artery location. Clinical study data from Parth et al. (43) showed good mid-term durability of the homograft pulmonary valved conduits when used for right ventricular outflow tract reconstruction for the Ross procedure. At present, the main clinical application is pulmonary valved conduit, while aortic valved conduit is less. The reason may be that atherosclerosis and calcification are easy to involve the aorta, so the source of this kind of valved conduit is relatively limited. Anatomical, histological and biomechanical tests *in vitro* show that both conduits can meet the needs of clinical application (44, 45), but there is a lack of randomized controlled trials to compare the two conduits. The results of retrospective clinical studies are controversial. Some studies do not show significant differences (46, 47), while other studies have shown that the survival rate of pulmonary valved conduit is higher than that of aortic valved conduit (48, 49).

Homograft pulmonary arteries perform well in adult cardiac surgery, but have no significant clinical advantage in pediatric cardiac surgery due to limited sources and size. John et al. (50) reported 40 cases of Rastelli's procedure. There were 32 cases of right ventricular outflow tract obstruction and eight cases of atresia. Follow-up was obtained in all but one case with a mean of (8.6 $\pm$ 5.6) years. The right ventricular outflow tract was reconstructed using homograft conduits (25 cases), bovine jugular vein (BJV) (eight cases), valveless polyester conduits (five cases), and porcine valved conduits (two cases). The conduit-free replacement rates at 5, 10, 15, and 20 years were 86, 74, 63, and 59%, respectively. Multifactorial analysis showed that younger intraoperative age was a risk factor for conduit replacement ($p < 0.001$). Early performance of small BJVs may be more favorable than homografts. Andrew et al. (51) compared the results of initial placement of smaller diameter BJVs (12–14 mm) and homograft pulmonary valved conduits (10–15 mm) in children younger than 2.84 years (mean age 8.4 $\pm$ 8.5 months). Eighty-four children received BJV ($n = 51$) or homograft pulmonary artery ($n = 32$) conduit placement. Early and late mortality rates were similar (BJV 80%; pulmonary artery 88%; $P = 0.55$). None of the deaths were graft-related. The degree of functional recovery was significantly better in the BJV group at 5 and 10 years after surgery (85 and 90% in the bovine jugular group; 71 and 24% in the pulmonary artery group, respectively; $P < 0.05$). In the pulmonary valved conduit cohort, the probability of conduit failure at 5 and 10 years was higher (85 and 67% in the BJV group; 75 and 45% in the pulmonary artery group,

respectively; $P = 0.06$). The probability of avoiding reoperation was significantly better in patients with implanted BJV conduits than in the pulmonary artery group (85 and 47%, respectively; $P < 0.001$). Although the early performance of BJVs may be superior to that of homografts, the incidence of infective endocarditis after right ventricle-pulmonary artery conduit implantation suggests that conduits of bovine origin are more susceptible to endocarditis (52, 53), which may be associated with suboptimal hemodynamics (54) and thrombus apposition at the basis of conduit valve sinus (55). Meanwhile, Mercer et al. (56) demonstrated that polytetrafluoroethylene conduits with mitral valves are ideal for right ventricular outflow tract reconstruction in children under 2 years of age. Their availability, low cost, and lack of potential sensitization make them an attractive alternative to homograft conduits. Based on the above problems, we can consider using bicuspidalized to reduce the size of valved conduit in infants (57, 58). A retrospective study analyzed 93 conduits which are <20 mm implanted for more than 23 years, including 40 standard pulmonary conduits, 12 standard aortic conduits, 17 bicuspidalized conduits and 24 xenografts (59). The average follow-up time was 7.6 ± 5.9 years. The percentage of patients without structural valve degeneration for 10 years was 47 ± 6%, including 68 ± 8% of pulmonary conduits, 42 ± 16% of bicuspidalized conduits, 31 ± 15% of aortic conduits, and 20 ± 9% of xenografts (log rank $P < 0.001$). Therefore, the appropriate size of pulmonary valved conduit is still the most durable choice for right ventricular outflow tract in children. However, when there is no available size, the mid-term follow-up results show that bicuspidalization can provide an effective alternative compared to xenograft. Other studies have also shown that bicuspidalized valved conduit seems to be a feasible option to solve the problem of limited supply of small size allografts, with acceptable survival rate and reoperation rate (60–62).

Homograft valved femoral veins with both smaller size and less risk of infection have shown good potential in pediatric cardiac surgery. The Yasui procedure is indicated for ventricular septal defects with interrupted aortic arch and associated subaortic stenosis. Manan et al. (63) described a modified Yasui procedure in which aortic reconstruction is simplified using a valveless homograft femoral vein connecting the pulmonary artery to the descending aorta. The homograft femoral vein is laterally anastomosed to the ascending aorta to complete the new aortic reconstruction. The anomalous opening from the left ventricle to the pulmonary artery is repaired with a patch, followed by restoration of continuity of the right ventricular outflow tract using a valved homograft femoral vein. This eponymous repair technique for aortic arch disruption and severe left ventricular outflow tract obstruction using a homograft valved femoral vein was first described in a case report by Yasui. According to Kumar et al. (64), the homograft femoral vein is safe as a conduit from the right ventricle to the pulmonary artery (RV-PA) in the Norwood procedure, and echocardiography shows good pulmonary artery growth and preserved ventricular function. Ofer et al. (65) reported that homograft valved femoral veins have similar short- and medium-term performance to homograft aorta or pulmonary artery in reconstructing the right ventricular outflow tract and are an attractive alternative to the smaller conduits used in neonates and infants. Histopathological evaluation showed that the valve maintained most of its function, and venous wall remodeling included only mild inflammation and calcification (66). A summary of clinical trials of homograft valved conduits over the past decade is shown in **Table 1**.

Homograft valved conduit has good biological properties and clinical results, but its durability is not very satisfactory (67). Age ≤9 years old is one of the main factors affecting durability (68, 69). Small size congduits (<19 mm) are also associated with decreased graft survival (70, 71). The type of conduits is considered to be one of the most important factors in long-term durability, for example, the survival rate of pulmonary conduit is higher than that of aortic conduit (70, 72). Baltivala et al. found that the graft survival rate of patients with a history of transplantation was worse than that of other patients (73). The relationship between bioactivity and durability of homograft valved conduit is still controversial. Fibroblasts living in the graft can reshape and reconstruct collagen structure and extracellular matrix, thus enhancing durability (74). However, these unevenly distributed fibroblasts may have phenotypic change and abnormal biological behavior due to immune response or environmental changes. Valve distortion or loss of elasticity caused by punctate or extensive hypertrophy, resulting in easy to rupture (75). The existence of endothelial cells reduces the possibility of thrombosis, but at the same time increases the antigenicity of the graft. The immune response is related to the early degeneration and dysfunction of the graft (76). Other factors related to the preservation process, including donor conditions, WIT, etc. will also affect the durability of valved conduits.

XENOGRAFT VALVED CONDUITS AND OTHER POSSIBLE ALTERNATIVES

Xenograft valved conduit can prolong the time of freedom from operation and has a good long-term survival rate (77). The Medtronic Freestyle (Minneapolis, MN) is a glutaraldehyde fixed stentless porcine aortic valved conduit. Because of its standard availability from 19 to 29 mm in diameter and potential for longer valve function compared to homograft, several authors have published a series of studies on the Freestyle implantation, primarily for phase II RVOT reconstruction (78, 79). Early results performed satisfactorily with minimal pressure gradients and little or no valvular regurgitation. In the published reports, the follow-up time was <3 years. Long-term data for this conduit have not been published. Although the Freestyle performs well *in situ*, in most adult patients, the Freestyle is usually not long enough to reach the pulmonary artery from the free wall of the right ventricle, which can be addressed by anastomosing the Freestyle graft to the pulmonary artery and then connecting the Freestyle proximally to the right ventricle with an expanded large-bore polytetrafluoroethylene or braided polyester conduit. Ezelsoy et al. (80) reported 77 patients with ascending aortic aneurysm combined with aortic valve insufficiency who underwent total root replacement using Freestyle. The median follow-up was 11.2 years. The probability of freedom from aortic

TABLE 1 | Clinical trial data of homograft valved conduits in the last decade.

Period	Number of patients	Number of patients receiving homograft valved conduit	Mean age (years)	Mean follow-up time (years)	Surgical procedure	Avoiding of valve replacement rates	Conference
1998–2014	741	175	47.4	5.8	Ross	10 years: 100%	(41)
1986–2017	604	604	19.5	11.4	RVOT reconstruction	25 years: 76%	(40)
1987–2009	126	126	27.8	8.1	TOF	10years: 83%	(42)
1998–2016	30	15	3.3	6.8	Ross	5 years: 87%	(43)
1988–2008	40	25	4	8.6	Rastelli	10 years: 74%	(50)
1998–2009	84	32	0.7	5.9	RVOT reconstruction	10 years: 55%	(51)
2004–2014	54	26	0.35	2.7	RVOT reconstruction	End of follow-up: 48%	(56)

valve reoperation at 5 and 10 years was 97.4 ± 1.2 and 93.4 ± 4.9%, respectively. Freestyle demonstrated favorable clinical outcomes in terms of survival and structural degeneration of the valve. Freestyle is a viable option for patients who are undergoing bioprosthetic aortic valve replacement and expect long-term durability. Mehdiani et al. found that the mid-term clinical and hemodynamic results of BioIntegral composite biological and stentless Freestyle conduits in patients undergoing full aortic root replacement are similar, but the simplified implantation technique of BioIntegral shortens the time of cardiopulmonary bypass and operation (81). The RVOT Elan conduit consists of a stentless valve (Vascutek Elan porcine stentless heart valve) sewn into a vascular graft (Vascutek Biblex Valsalva), showed good hemodynamic performance during an one-year short-term follow-up (82). Another type of diepoxy-treated porcine aortic conduit showed a higher risk of calcification during follow-up (83).

Despite satisfactory early outcome data for porcine-derived valved conduits, manufacturers are now focusing on another xenograft conduit for pediatric RVOT reconstruction, the valved BJV. Originally developed by VenPro (Irvine, CA) and currently owned and marketed by Medtronic, ConIntegra is a glutaraldehyde-fixed BJV conduit for RVOT reconstruction conduit option. Although several centers have reported that this conduit is more clinically beneficial than homograft (84, 85). However, these data are rather preliminary due to the published mean follow-up period of 12 months or less. At the same time, TakashiKido et al. have shown that early conduit dysfunction can still be caused by more than mild pulmonary hypertension and lower body weight during surgery of <3.0 kg (86). In addition, one center reported significant early fibrous epidermis formation at the distal anastomosis, as well as significant dilation and regurgitation of the conduit in the case of pulmonary hypertension or distal obstruction of the aforementioned distal anastomosis (87). Some studies have shown that BJV conduits have good medium-term durability, but have not been compared with the homograft or other types of conduits (88, 89). Therefore, this conduit will require further observation at longer follow-up times to clarify the differences in performance compared to equivalent sized cryopreserved homograft (43). Alessandro et al. (90) suggests that the 12 mm ConIntegra is an effective alternative to small homogaft valved conduit in the neonatal patient population.

In addition to xenograft valved conduits, synthetic material conduits or conduits containing part of synthetic materials are also gradually being developed for clinical use. The mid-term results of a multicenter clinical trial of simplified tricuspid polytetrafluoroethylene valved conduit show that it has an acceptable functional outcome and service life, freedom from conduit dysfunction was 58.5% at 5 years (91). KONECT RESILIA aortic valved conduit (Edwards Lifesciences, Irvine, Calif) is a noval type of bovine pericardial valved conduit, preassembled with the PERIMOUNT Magna Ease valve and RESILIA tissue with stent. This kind of conduit improves the anti-calcification performance and has dry storage capacity. *In vitro* experiments show that the simulation of sinuses of valsalva structure improves the hemodynamic performance (92).

Porcine small intestinal submucosa extracellular matrix (CorMatrix; CorMatrix Cardiovascular, Rosewell, GA) is a relatively novel tissue substitute. Preclinical experiments applied to pig models show that this biodegradable conduit cannot be reconstructed in a structured and anatomical in the arterial environment. Fibrosis, scarring, and calcification begin at 4 months, and chronic inflammation persists (93). There are also no satisfactory results in the sheep models (94). PTFE valved conduits show excellent hemodynamic performance in preclinical *in vitro* and *in vivo* experiments (95–97). The results of mid-term clinical trials showed less need for further intervention and severe valvular dysfunction (98, 99), especially in valvular regurgitation (100). And the failure incidence of this conduit is lower than that of autologous pericardial valved conduit operation (101). A clinical study involving 502 patients also showed satisfactory long-term results, freedom from conduit explantation was 89.0% at 10 years (102). Histopathological analysis showed that protein infiltration into the valve was thought to be the cause of future calcification and subsequent stenosis failure. Modification of polytetrafluoroethylene to prevent protein infiltration may help to improve the durability of the pipeline (103).

ADVANTAGES AND DISADVANTAGES OF HOMOGRAFT AND XENOGRAFT VALVED CONDUIT

Although homograft valved conduit was used as early as the 1960s, its widespread use was limited by the lack of effective sterilization and preservation methods (1). Early methods of dealing with homograft valved conduit led to early calcification and progressive stenosis. Current storage methods, deep cryopreservation, delay the onset of these problems, but they still occur in the medium to long term (104). Despite this, compared with other types of valved conduits, homograft valved conduits still have the advantages of biological activity and tissue structural integrity, ease of use, good hemodynamics, intact valve function, long valve life, and no need for anticoagulation. The patency of the conduit after operation is excellent and basically conforms to the anatomical structure of the ventricular outflow tract, corrects cardiac malformations anatomically and hemodynamically, facilitates the recovery of cardiac function, and is less prone to heart failure. The homograft valved conduit has good resistance to infection, and complications caused by implantation such as bacterial endocarditis and hemolysis are rare, but its access is limited.

The BJV graft was introduced in 1999 as an option, which contains a trilobular venous valve (105). Preservation with glutaraldehyde solution under vacuum conditions preserves the flexibility of the valve (106). Because a variety of sizes are readily available, these tubes are more commonly used in clinical practice. The good valvular performance of BJV may be associated with an enlarged leaflet alignment area and reduced sensitivity to deformation of surrounding structures, including the right ventricle, aorta, and chest wall. BJV is associated with distal anastomotic stenosis and a higher incidence of endocarditis compared with homograft (107–112). The Hancock, a stented polyester conduit with porcine valve (113), can also be used in adult cardiac surgery. However, in pediatric applications, calcification as well as poor intraoperative properties due to the polyester conduit, make the Hancock not a common choice.

Current homograft and xenograft conduits lack any capacity for additional growth. As children grow, the fixed size of the conduit means that there is a progressive size mismatch between the patient and the conduit, which necessitates future reoperation. Typically, a new conduit is required approximately 4–5 years after the initial conduit placement in an infant or young child (110). Critically, studies reporting the time of reoperation often combine patients with very different anatomic features, thereby confounding the analysis of outcomes. For example, placement of an RV-PA conduit in pulmonary atresia involves a non-*in situ* and tortuous pathway that allows blood to flow anteriorly from the right ventricle, across the surface of the heart, and then backward to the pulmonary artery. In contrast, placement of the RV-PA conduit in Ross procedure is essentially *in situ* placement of the implant. This may have less turbulence and energy loss than in patients with pulmonary artery atresia, factors that may affect the durability of the conduit.

In addition to body growth, a variety of other problems can lead to conduit failure. These include distal anastomotic stenosis, sternal compression, aneurysm formation at the proximal anastomotic enlargement site, valve stenosis (114), and donor-specific and non-specific immune responses. A study has shown that both homograft and xenograft can trigger an immune response in the recipient, leading to calcification, endothelial thickening or vascular membrane formation, stenosis, and deterioration of valve function (115).

POSSIBLE FUTURE DIRECTIONS FOR IMPROVEMENT

Cryopreserved homograft valved conduit has low clotting activity, good hemodynamic properties, and high resistance to infection, but cannot grow and develop in the recipient. Because cryopreserved homograft valved conduits carry donor cells that express relevant antigens, these cells can cause adverse host immune responses and lead to calcification, which in turn may require reoperation in young patients who receive a homograft valved conduit. Therefore, removal of the cellular component of the homograft valved conduit prior to implantation may reduce the immune response and calcification (116). In addition, removal of donor cells may encourage the proliferation of the cells with the ability to repair and remodel in receptor, thereby overcoming the limitations of degeneration of the homograft valved conduit over time and creating a valve with growth potential in younger patients, thus eliminating the need for reoperation. Decellularized valved conduits demonstrate almost complete removal of cells and cellular components by histological and immunocytochemical analysis without corresponding changes in biomechanics *in vitro* (117). Previous studies have shown that the decellularization process does not affect the *in vivo* performance of homograft valved conduit, and good clinical performance in the short to medium term has been reported for decellularized pulmonary valves, with similar (118–122) or better (123–125) outcomes than conventional deep cryopreserved homograft in adults and children at a mean follow-up of 4 years. However, longer-term data are needed to determine whether they can reduce or eliminate the need for reoperation (126).

SynerGraft (CryoLife Inc., Kennesaw, GA) decellularized pulmonary allograft (SGDPA) is an alternative to standard cryopreserved allograft (SCA) Ross aortic valve replacement. John et al. (127) reported 29 patients underwent SGDPA and 34 underwent SCA during Ross aortic valve replacement. Early clinical and hemodynamic outcomes were favorable but not significantly different from SCA. There were no early or late deaths or major pathologic events during a mean follow-up of 4.9 $\pm$ 2.7 years. None of the patients required reoperation. No deterioration in conduit or valve function was seen in the SGDPA group. Several patients with SCA developed mild regurgitation, and one patient developed moderate regurgitation. Thus, the SynerGraft technique

may provide a more durable option for patients requiring right ventricular outflow tract reconstruction. Mark et al. (124) also suggests that the medium-term performance of decellularized cryopreserved homograft may be superior to that of standard cryopreserved homograft. Decellularized aortic homograft can withstand the stresses of the body circulation, provide a good effective orifice area, and may be an alternative graft for aortic valve replacement in younger patients. Enlarged aortic root replacement using decellularized aortic homograft is a further option for aortic valve disease associated with dilatation of the ascending aorta, as it avoids the use of any prosthetic material. Igor et al. (128) reported the replacement of the dilated ascending aorta with decellularized aortic homograft in 18 patients with enlarged aortic root replacement. None of the grafts had any degree of dilatation observed during the relatively short follow-up period (mean 2.0 ± 1.8 years, maximum 7.6 years). Intraoperative and postoperative histological analysis of the grafts showed no calcification and revealed extensive recellularization and no inflammation.

Reconstruction of the right ventricular outflow tract in children with decellularized homograft has a low incidence of structural deterioration of the valve and conduit failure. Francisco et al. (129) reported 59 patients who underwent decellularized allograft RVOT reconstruction. The most common procedure was the Ross procedure (34%) and the mean follow-up was 5.4 years. Structural valve deterioration occurred in 13 patients, including five with stenosis and eight with valvular insufficiency. The incidence of no structural valve deterioration from any cause 8 years after surgery was 64.9%. During the follow-up period, CT scans showed no or minimal calcification of the conduit. Grauss et al. (130) believes that decellularization techniques cause much less damage to the valve than recipient's immune response. *In vitro* removal of live cells from cryopreserved homograft may reduce the probability of graft failure. Implantation of autologous or major histocompatibility complex-matched donor endothelial cells would be necessary to reduce damage due to lack of blood-tissue barrier. Willem et al. (131) found that encapsulation of decellularized homograft with FN/SDF-1α prevented cryopreserved heart valve-mediated immune responses, conduit calcification and vascular scar formation, and stimulated reendothelialization.

Decellularization as a promising improvement method not only improves the performance of homografts, but decellularized xenografts also perform well in clinical practice. Decellularized porcine pulmonary artery valved conduits have excellent potential as a substitute for right ventricular outflow tract reconstruction. Ji Luo et al. (132) developed a method for decellularization of porcine pulmonary arterial with minimal effects on biomechanical, hydrodynamic, and leaflet dynamics properties, and immunohistochemical labeling and antibody uptake assays confirmed the lack of α-gal epitopes in decellularized porcine pulmonary artery valve and conduit. *In vitro* biocompatibility studies demonstrated no cytotoxicity in decellularized pulmonary artery valve and conduit. Decellularized bovine pericardial valves also exhibited potent anti-calcification effects in a sheep circulating model (133). However, study by Higuita et al. has shown that the commonly used SDS acellular method may change or eliminate ECM protein, and will lead to the destruction of valve function, while the use of antigen removal tissue treatment can retain the subtle ECM structure and composition of natural tissue, thus preserving the function of natural valve (134). Therefore, the best acellular method needs to be further explored in the field of tissue engineering. **Table 2** compares in detail the advantages and disadvantages of different types of valved conduit.

PROSPECT

Tissue engineering is an emerging technology with the potential to create implants that can provide structural and mechanical support and are biologically functional. Ideally, grafts with good biocompatibility, the ability to grow in proportion to host tissue growth, and minimal clinical complications will be produced, thus eliminating the need for further surgery. Considering the specific and highly variable cardiac anatomy of patients with congenital heart disease, significant research challenges remain in the design and fabrication of well-durable valved conduits.

Artificial conduit biomaterials need to mimic the mechanical properties of natural arteries and their biomechanical behavior such as hemodynamics while possessing good biocompatibility to avoid clinical complications. In addition, the human arterial structure consists of cytoskeletal proteins such as collagen and elastin deposited in a directional manner, which ensures that natural vessels exhibit complex anisotropic mechanical behavior (135). For example, arterial walls exhibit non-linear elastic properties under stress and hysteresis behavior in response to changes in circulating pressure (136). The key point is that none of the currently available tissue engineering valved conduits has the same material properties as natural tissues, especially anisotropic properties. Computational fluid dynamics can be used to optimize the geometric design of valved conduits and tissue engineering materials. Therefore, fluid mechanics and structural calculation models will continue to play an important role in optimizing the design and manufacturing of patient-specific conduit.

With the development of manufacturing technology, the use of tissue engineering technology to construct artificial valved conduits is under continuous exploration. Traditional 3D porous biodegradable scaffolds planted with cells usually lack the ability of cell differentiation and function, and cannot fully reconstruct the characteristics of natural tissues (137). The advent of technologies such as electrospinning and 3D bioprinting has led to the creation of more complex designs that mimic valved conduit (138). Poly(lactic acid-caprolactone) [P(LA-CL)]-reinforced electrospinning polyglycolic acid (PGA) mesh has been used as a promising composite scaffold and were able to survive in patients, but some developed conduit stenosis, which may be related to the acidic environment caused by the degradation product lactic acid (139). Electrospinning nanofiber grafts are made from composite materials such as polyethylene

TABLE 2 | Advantages and disadvantages of the three types of valved conduits in current clinical application.

Type of valved conduit	Advantages	Disadvantages
Homograft valved conduit	Good hemodynamic and valvular performance, better medium- to long-term clinical outcomes than xenograft valved conduits, relatively low reoperate rates	Restricted source especially in small sizes, presence of some antigenicity that may lead to rejection and early calcification of the conduit especially in pediatric patients, no potential for *in vivo* growth
Xenograft valved conduit	The 12–22 mm size with unlimited sources provides a wide range of applications in pediatric patients	Risk of thrombosis, higher risk of postoperative infection than homograft valved conduit, no potential for *in vivo* growth
SynerGraft decellularized pulmonary allograft	Minimizing rejection and calcification and improving long-term durability, *in vivo* growth potential, current clinical results show that the function and longevity of the conduit is no less than homograft valved conduit and with more significant advantages in pediatric patients	The available evidence is not sufficient to demonstrate the advantages of the long-term effects of decellularized valved conduit and further long-term follow-up is needed

glycol dimethacrylate, PLA, PCL, and polyvinyl alcohol to mimic the structural and mechanical properties of natural valves, but electrospinning scaffolds are less efficient to fabricate and have limited ability to create complex 3D structures (140). The Xeltis graft is a pulmonary artery valved conduit made from a range of synthetic materials, including a wall made of polycaprolactone and a valve made of polycarbonate, with modifiable mechanical properties and biodegradability, and has demonstrated good and durable hemodynamic performance in preclinical studies with no stenosis or obstruction or severe regurgitation 2 years after implantation (141). Compared with the histology of Hancock conduit, significant calcification was rarely observed in Xeltis, while Hancock formed more neointimal thickness with the calcification of aortic root (142). 3D bioprinted trilobular valved conduits based on hyaluronic acid methacrylate and gelatin methacrylate have been successfully implanted in mouse models and have shown high cell survival and remodeling potential (143). But 3D printing geometrically complex structures with similar biological behavior to natural tissues remains a great challenge, and ideal scaffold materials and conduit fabrication methods remain an area for continued effort and innovation. Current research advances in tissue engineering scaffolds are mostly limited to preclinical trials (144).

The clinical use of homograft valved conduits is widespread with good long-term outcomes. Although there are still some limitations, with the development of cardiac surgery and other disciplines, research is continuously exploring the best ways to improve the efficacy of homograft valved conduit operation by improving preservation methods, using low-dose immunosuppressive agents, and matching ABO and HLA antigens to mitigate post-transplant immune reactions to extend the life of homograft valved conduits. The development of genetic engineering technology is expected to induce immune tolerance and mitigate immune response through molecular biology techniques. It is also expected that the construction of recipient cellularized tissue-engineered conduit by implanting recipient-derived endothelial cells on decellularized valved conduits or degradable synthetic materials will be an ideal biologic valved conduits substitution for heart disease treatment.

AUTHOR CONTRIBUTIONS

YH wrote the text, performed the literature search, and review under guidance from YC. JS reviewed the text. YC and JS revising the manuscript. All authors contributed to the article and approved the submitted version.

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Application of a Novel Common-Iliac-Artery Skirt Technology (CST) in Treating Challenge Aorto-Iliac or Isolated Iliac Artery Aneurysms

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Purpose: To report a novel common-iliac-artery skirt technology (CST) in treating challenge iliac artery aneurysms.

Methods: When required healthy landing zone of common iliac artery (CIA) is not available, CST is a strategy to exclude the internal iliac artery (IIA) and prevent IIA reflux without need of embolization. Patients who received endovascular aneurysm repair (EVAR) in our center from 2014 to 2020 were retrospectively screened, and patients treated with CST or with IIA embolization (IIAE) were enrolled.

Results: After retrospective screen of 524 EVAR patients, 39 CST patients, 26 IIAE patients, and 7 CST + IIAE patients were enrolled in this study. CST group suggested to have more aged, hyperlipemia, and smoking patients than IIAE group. Two groups had comparable maximal diameter of abdominal aorta (AA), CIA, EIA, but larger diameter of IIA (CST 19.82 ± 2.281 vs. IIAE 27.82 ± 3.401, $p = 0.048$), and CIA bifurcation (CST 25.01 ± 1.316 vs. IIAE 29.76 ± 2.775, $p = 0.087$) was found in IIAE group. Anatomy of 79.5% of CST patients and 92.3% of IIAE patients ($p = 0.293$) was not suitable for potential use of iliac branch device. CST group had significant shorter surgery time (CST 97.42 ± 3.891 vs. IIAE 141.0 ± 8.010, $p < 0.001$), shorter hospital stay (CST 15.35 ± 0.873 vs. IIAE 19.32 ± 1.067, $p = 0.009$), lower in-hospital [CST 0% (0/39) vs. IIAE 11.5% (3/26), $p = 0.059$] and 1-year follow-up stent related MAEs [CST 6.7% (2/30) vs. IIAE 28.6% (6/21), $p = 0.052$], but comparable mortality and stent related MAEs for all-cohort follow-up analysis comparing to IIAE group. In our study, a lower in-hospital buttock claudication (BC) rate for CST (CST 20.5% vs. IIAE 46.2%, $p = 0.053$) and a comparable erectile dysfunction (ED) rate (CST 10.3% vs. IIAE 23.1%, $p = 0.352$) were found between CST and IIAE groups. After 1 year, both groups had about one third relief of BC symptoms [CST 33.3% (4/12) vs. IIAE 30.7% (4/13), $p = 1.000$]. Subgroup analysis of 14 patents concomitant with IIA aneurysm in CST group and the 7 CST + IIAE patients

were carried out, and no difference was found in mortality, stent MAEs, sac dilation, or reintervention rate. Last, illustration of seven typical CST cases was presented.

Conclusion: In selected cases, the CST is a safe, feasible-and-effective choose in treating challenge iliac artery aneurysms and preventing IIA endoleak.

Keywords: aorto-iliac artery aneurysm, iliac artery aneurysm, internal iliac artery, novel technology, endovascular, aortic surgery

INTRODUCTION

Endovascular aneurysm repair (EVAR) has become the preferred way to treat abdominal aortic aneurysms (AAA) with suitable anatomy and life expectancy (1, 2). Iliac artery aneurysms (IAAs) are commonly coexisting with AAAs as aorto-iliac aneurysms in about 10–30% of AAA (3, 4), which poses significant clinical and technical challenges during EVAR (5, 6). Specifically, if the distal common iliac artery (CIA) does not present an adequate healthy landing zone, exclusion of internal iliac artery (IIA) or hypogastric artery is often required. Though benefits of preserving IIAs are now well-acknowledged and different strategies, devices, such as iliac branch device (IBD), are developed (7). Nevertheless, such techniques would significantly increase the surgery time and complexity and could be limited by anatomical constraints, technique experience, and availability of grafts. Remarkably, only 40.9% patients were suitable for use of iliac branch devices in an on-label fashion according to the manufacturer's instructions (8), and IBDs are not available in China until March 2021. And also, aneurysmal patients often complicated with cardiovascular diseases that require a feasible-and-effective procedure, particular for ruptured AAA patients (9, 10).

On the other hand, exclusion of the IIA is widely used and has been proven safe (11–15), and minimal adverse events of possible ischemic complications can be achieved as long as the contralateral IIA is fluent (14, 15). Coil or plug embolization of IIA, direct extension of graft to EIA, or combination of both is the main method for IIA exclusion. Extension of graft to EIA has risk of type II endoleak (16), while coil embolization is challenging and time-consuming with unfeasible anatomy. Here, we described a novel common-iliac-artery skirt technique (CST) in treating challenge aorto-iliac or isolated iliac artery aneurysms, which preserve the advantages of extension of graft to EIA and diminish risk of type II endoleak.

MATERIALS AND METHODS

Enrollment and Data Collection

We retrospectively screened patients diagnosed with abdominal or iliac artery aneurysm and treated by endovascular procedures from 2014 to 2020 in our center. Among them, patients treated with CST or IIA embolization (IIAE) were enrolled in this study. Demographic data, risk factors and comorbidity, diagnosis, pre-procedure, procedure and in-hospital data, and follow-up results were analyzed. All patients received informed consent before the surgery, and this study was approved by the Institutional Review Board and the Medical Ethics Committee of our hospital.

A pre-surgical computed tomography angiogram (CTA) was used in all patients to assess extent of aneurysmal disease, tortuosity of the iliac vessels, and patency of the internal and external iliac arteries. Diameter of abdominal aortic and ipsilateral iliac arteries of IIAE or CST were measured from outer-wall to outer-wall of the long-axis. Length of CIA was retrospective collected by DSA with help of centimeter sizing pigtail catheter (Cook Medical Inc). Diameter and length were measured by two authors, and the average value of two authors' was used. Evaluation of erectile dysfunction was only carried out on male patients who are under 70s and had normal erectile function before surgery. Surgery time was calculated from anesthesia induction to the last frame of angiography. Two DSA rooms were routinely used by our group and due to the deficiency of one old-fashion DSA system; unfortunately, not all patients had radiation time and dosage data, so they were not analyzed in this study.

Indications for CST or IIAE

CIAA without adequate healthy landing zone was the indication for CST or IIAE. Surgical method selection was based on general condition, comorbilities and vascular anatomy of each patient, and also patient's own will. In the IIAE group, embolization was performed preferentially *via* a contralateral approach before EVAR. IIAE was achieved using embolization coils (Cook Medical Inc) at the proximal site of the bifurcation of primary branches.

Primary and Secondary End Points

Technical successful rate was defined as primary end points, and technique success including complete exclusion of aneurysms and no endoleak from IIA during surgery.

Secondary end points include surgery time, hospital stay, mortality, stent related major adverse events (MAEs), and reintervetion, while stent related MAEs include endoleak, limb occlusion, stent migration, contralateral IIA occlusion, and pelvic ischemia.

Follow-Up and Statistics

Survival and reintervention events were followed by telephone calls directly with patients regularly. CTA imaging was carried out with available follow-up patients. Data are presented as median (range) or mean ± standard deviation. Data between two groups were analyzed using the Student *t* test, Chi-square, or Fisher's exact test analysis. A two-tailed *P* value of <0.05 indicated statistical significance.

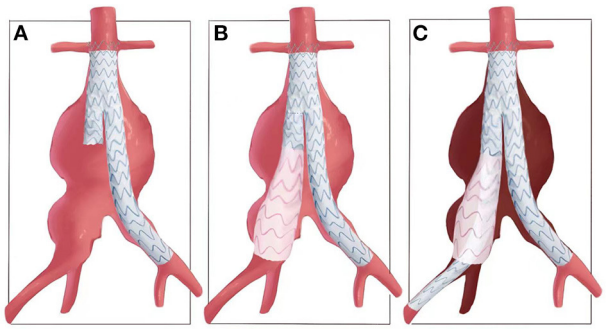

FIGURE 1 | Illustration of common-iliac-artery skirt technology. **(A)** An aorto-iliac artery aneurysm and release of the bifurcated main body graft. **(B)** Then, a flared iliac limb is deployed at aneurysmal CIA and with its distal end locating at and sealing the iliac bifurcation, which is named as skirt-limb. **(C)** Another iliac limb with the same proximal diameter of skirt limb is deployed overlap with skirt-limb and elongated to EIA, with IIA excluded and possible reflux of IIA was restricted between the two iliac limbs.

RESULTS

Procedure of a Classical Common-Iliac-Artery Skirt Technique (CST)

As illustrated in **Figure 1**, after deployment of the aortic bifurcated grafts, with the shorter leg placed in aneurysmal CIA side, a flared iliac extension limb (skirt-limb) was deployed at aneurysmal CIA and with its distal end locating at and sealing the iliac bifurcation. The proximal end of skirt-limb with an identical diameter of the bifurcated shorter leg was placed within the leg, the diameter of distal end of skirt-limb should not smaller than the iliac bifurcation, and a 10% oversize of diameter was recommended but not obligatory.

And then, another iliac limb graft with the same proximal diameter of skirt limb was deployed overlap with skirt-limb and elongated to EIA, with IIA excluded and possible reflux of IIA restricted between two iliac limbs (**Figure 1**). Relationship of the two iliac stent grafts was similar with lady's skirt and leg, respectively.

For challenge iliac aneurysm, aortic extension configuration or cuff, or double CST skill can also be used in CST, which will be shown hereinafter.

Demographics and Pre-Procedural Data

Retrospective screen found 524 patients received EVAR in our center from 2014 to 2020, and 39 CST patients, 26 IIAE patients, and 7 CST + IIAE patients were enrolled in this study. Given the small sample size of CST + IIAE group, regular statistical analysis only carried out between CST and IIAE group and most data of CST + IIAE group was not presented in the text, which but can be provided upon reasonable inquiry.

Demographic data, risk factors and comorbidity analysis suggested that CST group trend to have more aged, hyperlipidemia, and smoking patients than IIAE group, though not all data were statistically significant (**Table 1**). Male patients were overwhelming in both group, 97.4% for CST and 96.2% for IIAE group. Average age was 70.23 ± 0.969 for CST vs. 67.54 ± 1.383 for IIAE group ($p = 0.105$). Hypertension percentage was 66.7% for CST vs. 65.4% for IIAE ($p = 1.000$). CST group had a trend to have more patients with hyperlipidemia (CST 46.2% vs. IIAE 23.1%, $p = 0.07$), but two groups had no difference on coronary artery disease percentage (CST 20.5% vs. IIAE 23.1%, $p = 1.000$). CST group had a significant higher proportion of smoking patients (CST 94.8% vs. IIAE 61.5%, $p = 0.002$) and non-significant higher proportion of COPD patients (CST 23.1% vs. IIAE 11.5%, $p = 0.334$). Both groups had low prevalence of chronic kidney disease, while CST group had more patients with history of cerebral infarction (CST 15.4% vs. IIAE 3.85%, $p = 0.228$), though not significant.

TABLE 1 | Demographics and preprocedural data.

	CST	IIAE	*p*
Male	97.4% (38/39)	96.2% (25/26)	1.000
Age	70.23 ± 0.969	67.54 ± 1.383	0.105
Hypertension	66.7% (26/39)	65.4% (17/26)	1.000
Hyperlipidemia	46.2% (18/39)	23.1% (6/26)	0.071
Smoking	94.8% (33/36)	61.5% (16/26)	0.002
CAD	20.5% (8/39)	23.1% (6/26)	1.000
COPD	23.1% (9/39)	11.5% (3/26)	0.334
CKD	2.56% (1/39)	0% (0/26)	1.000
History of CI	15.4% (6/39)	3.85% (1/26)	0.228
Diagnosis			0.253
AAA + CIAA	30.8% (12/39)	26.9% (7/26)	/
AAA + CIAA + IIAA	35.8% (14/39)	19.2% (5/26)	/
CIAA	15.4% (6/39)	15.4% (4/26)	/
CIAA + IIAA	18% (7/39)	38.5% (10/26)	/
Diameter of (mm)			
AAA	40.25 ± 2.218	34.40 ± 3.203	0.129
CIA	41.22 ± 7.600	35.59 ± 2.893	0.585
CIA length	39.45 ± 3.676	33.79 ± 3.492	0.271
CIA_b	25.01 ± 1.316	29.76 ± 2.775	0.087
IIA	19.82 ± 2.281	27.82 ± 3.401	0.048
EIA	9.951 ± 0.174	10.34 ± 0.290	0.231
Exclusion of IBD	79.5% (31/39)	92.3% (24/26)	0.293

CAD, coronary artery disease; CKD, chronic kidney disease; CI, cerebral infarction; IBD, iliac branch device.

Comparison of diagnosis and vascular anatomy confirmed that all enrolled patients were diagnosed with AAA concomitant with IAA or isolated IAA. Patients were divided into four categories based on diagnosis: AAA + CIAA, AAA + CIAA + IIAA, CIAA, CIAA + IIAA. No significant difference was found on proportion of diagnosis between CST and IIAE group ($p = 0.253$).

Two groups had comparable maximal diameter of AA (CST 40.25 ± 2.218 vs. IIAE 34.40 ± 3.203, $p = 0.129$), CIA (CST 41.22 ± 7.600 vs. IIAE 35.59 ± 2.893, $p = 0.585$), EIA (CST 9.95 ± 0.174 vs. IIAE 10.34 ± 0.290, $p = 0.231$) (**Table 1**), but larger diameter of IIA (CST 19.82 ± 2.281 vs. IIAE 27.82 ± 3.401, $p = 0.048$), and CIA bifurcation (CST 25.01 ± 1.316 vs. IIAE 29.76 ± 2.775, $p = 0.087$) was found in IIAE group. Based on

TABLE 2 | Procedure and in-hospital data.

	CST	IIAE	*p*
Primary end points			
Technique successful rates	100%	100%	1.000
Secondary end points			
In hospital results			
Surgery time (min)	97.42 ± 3.891	141.0 ± 8.010	<0.001
Hospital stay (day)	15.35 ± 0.873	19.32 ± 1.067	0.009
ICU stay rate	5.13% (2/39)	7.69% (2/26)	1.000
Distal diameter of Skirt stent (mm)	23.90 ± 0.344	/	/
20	12.8% (5/39)	/	/
24	74.4% (29/39)	/	/
28	12.8% (5/39)	/	/
28–28 cuff	7.69% (3/39)	/	/
Save of contralateral IIA	92.3% (36/39)	76.9% (20/26)	0.140
All-cause mortality	0% (0/39)	0% (0/26)	1.000
Stent related MAEs	0% (0/39)	11.5% (3/26)	0.059
Endoleak	0% (0/39)	0% (0/26)	1.000
Limb occlusion	0% (0/39)	3.8% (1/26)	0.400
Migration	0% (0/39)	0% (0/26)	1.000
Contralateral IIA occlusion	0% (0/39)	3.8% (1/26)	0.400
Ineffective IIAE	0% (0/39)	3.8% (1/26)	0.400
Reintervetion	0% (0/39)	3.8% (1/26)	0.400
Buttock claudication	20.5% (8/39)	46.2% (12/26)	0.053
Erectile dysfunction	10.3% (3/29)	23.1% (3/13)	0.352
Colonic ischemia	0% (0/39)	0% (0/26)	1.000
Pelvic necrosis	0% (0/39)	0% (0/26)	1.000

TABLE 3 | Follow-up results.

	CST	IIAE	*p*
1-year results			
Follow-up rates	82.1% (32/39)	92.3% (24/26)	0.296
All-cause mortality	6.3% (2/32)	12.5% (3/24)	0.639
Stent related MAEs	6.7% (2/30)	28.6% (6/21)	0.052
Endoleak	0% (0/30)	0% (0/21)	1.000
Limb occlusion	3.3% (1/30)	14.3% (3/21)	0.293
Migration	0% (0/30)	0% (0/21)	1.000
Contral IIA occlusion	3.3% (1/30)	14.3% (3/21)	0.293
Endotension or Aneurysm sac dilation	0% (0/30)	0% (0/21)	1.000
Reintervetion	3.3% (1/30)	4.8% (1/21)	1.000
Relived buttock claudication	37.5% (3/8)	33.3% (4/12)	1.000
Relived erectile dysfunction	0% (0/3)	33.3% (1/3)	/
Colonic ischaemia	0% (0/30)	0% (0/21)	1.000
Pelvic necrosis	0% (0/30)	0% (0/21)	1.000
All-corhot results			
Follow-up (month)	13–82 m	12–79 m	0.203
Median follow-up	35	26	0.203
All-cause mortality	9.38% (3/32)	12.5% (3/24)	0.679
Stent related MAEs	18.8% (6/32)	25% (6/24)	0.744
Endoleak	3.13% (1/32)	0% (0/24)	1.000
Limb occlusion	6.25% (2/32)	12.5% (3/24)	0.642
Migration	3.13% (1/32)	0% (0/24)	1.000
Other IIA thrombosis	6.25% (2/32)	12.5% (3/24)	0.642
Endotension or aneurysm sac dilation	3.13% (1/32)	0% (0/24)	1.000
Reintervetion	6.9% (2/32)	4.2% (1/24)	1.000

the inclusion/exclusion criteria of the Gore Excluder Iliac Branch Endoprosthesis Trial and the Cook Zenith Iliac Branch Device Clinical Study (17, 18), enrolled patients in our study had a high exclusion rate for potential IBD use (CST 79.5% vs. IIAE 92.3%, $p = 0.293$).

Procedure and In-Hospital Data

All surgeries were elective and performed under general anesthesia and by the same surgery team. Access was routinely achieved by cut-down femoral artery exposure. For primary end points, both groups had 100% technique successful rates and complete exclusion of aneurysms, though one case of IIAE group only achieved partial IIA embolization, but no endoleak from IIA was found after angiography (**Table 2**). For secondary end points, CST group had significant shorter surgery time (CST 97.42 ± 3.891 vs. IIAE 141.0 ± 8.010, $p < 0.001$) and shorter hospital stay (CST 15.35 ± 0.8734 vs. IIAE 19.32 ± 1.067, $p = 0.009$) compared to IIAE group. Both groups had low rate of Intensive Care Unit stay [CST 5.13% (2/39) vs. IIAE 7.69% (2/26), $p = 1.000$]. By analyzing skirt-limb's distal diameter, we found that 74.4% had a diameter of 24 mm, and 12.8% had a diameter of 28, including three 28–28 mm cuff. Preserve of contralateral IIA was guaranteed as long as suitable anatomy existed, and both groups had high rate of saving contralateral IIA (CST 92.3% vs. IIAE 76.9%, $p = 0.140$).

Analysis of in-hospital results found none mortality for both groups. CST had lower stent related major adverse events compared to IIAE group [CST 0% (0/39) vs. IIAE 11.5% (3/26), $p = 0.059$]. IIAE group had one limb occlusion, one unintended contralateral IIA occlusion, and one ineffective embolization of IIA. No endoleak or stent migration was found in both group. One reintervetion was applied in IIAE group due to limb occlusion. Both groups had pelvic ischemia complications, while CST had lower rate of buttock claudication (BC) (CST 20.5% vs. IIAE 46.2%, $p = 0.053$). Comparable erectile dysfunction (ED) (CST 10.3% vs. IIAE 23.1%, $p = 0.352$) was found, but no severe BC or ED require reintervention existed. No colonic ischemia and pelvic necrosis happened (**Table 2**).

Follow-Up Results

CST group had 82.1% (32/39) and IIAE group had 92.3% (24/26) ($p = 0.296$) 1-year follow-up (**Table 3**). One-year all cause-mortality rate was 6.3% (2/32) for CST vs. 12.5% (3/24) for IIAE, $p = 0.639$. Stent MAEs increased in both groups after 1 year and IIAE group suggested having higher MAE events [CST 6.7% (2/30) vs. IIAE 28.6% (6/21), $p = 0.052$], which is consistent with in-hospital MAEs. In IIAE group, three limb occlusion and three contralateral IIA occlusion happened. In CST group, one limb occlusion and one contralateral IIA occlusion happened. No endoleak, stent migration, endotension or aneurysm sac

TABLE 4 | Results of different IIAA treatment strategies in CST group.

	CST	CST + IIAE	*p*
Diagnosis			0.642
AAA + CIAA + IIAA	50% (7/14)	28.6% (2/7)	/
CIAA + IIAA	50% (7/14)	71.4% (5/7)	/
Diameter of (mm)			
CIA	34.98 ± 4.175	46.14 ± 6.244	0.146
CIA_b	29.01 ± 4.179	42.40 ± 6.047	0.082
IIA	35.31 ± 3.823	48.47 ± 3.230	0.038
IIA > 35 mm	42.9% (6/14)	100% (7/7)	0.018
Surgery time (min)	100.3 ± 5.781	120.6 ± 6.962	0.047
Save of IIA of other side	85.7% (12/14)	42.9% (3/7)	0.120
Loss of follow-up	21.4% (3/14)	14.3% (1/7)	1.000
Follow-up (month)	18–70 m	15–30 m	0.296
Median FU	25.5	22.5	0.296
All-cause mortality	9.1% (1/11)	16.7% (1/6)	1.000
Stent related MAEs	9.1% (1/11)	33.3% (2/6)	0.546
Endoleak	0% (0/11)	16.7% (1/6)	1.000
Limb occlusion	0% (0/11)	16.7% (1/6)	0.353
Migration	9.1% (1/11)	0% (0/6)	1.000
Endotension or Aneurysm sac dilation	0% (0/11)	16.7% (1/6)	0.353
Reintervetion	9.1% (1/11)	16.7% (1/6)	1.000

dilation happened for both groups. Both groups only had one reintervetion [CST 3.3% (1/30) vs. IIAE 4.8% (1/21), $p = 1.000$] for symptomatic MAEs. After 1 year, both groups had about one third relief of BC symptoms [CST 33.3% (4/12) vs. IIAE 30.7% (4/13), $p = 1.000$], and IIAE had 33.3% (1/3) relief of erectile dysfunction.

Analysis of all-cohort follow-up data was also carried out. The median follow-up month for CST was 35 (range 13–82), and 26 (range 12–79) for IIAE group ($p = 0.203$). No difference in mortality (CST 9.38% vs. IIAE 12.5%, $p = 0.679$), stent MAEs (CST 18.8% vs. IIAE 25%, $p = 0.744$), and reintervetion rate (CST 6.9% vs. IIAE 4.2%, $p = 1.000$) was found between two groups. CST group had one type II endoleak and sac enlargement of 5 mm from inferior mesenteric artery at 2-year follow-up, and regular follow-up was in process according to patient's willing (**Table 3**).

Results of Different IIAA Treatment Strategies in CST Group

For patients diagnosed with IIAA, concerns may remain on risk of future IIAA enlargement by only covering the orifice of IIA. So subgroup analysis of 14 patents concomitant with IIA dilation in CST group without IIAE and the 7 CST+IIAE patients were performed (**Table 4**). The proportion of diagnosis was comparable. CST+IIAE group had larger diameter of CIA bifurcation (CST 29.01 ± 4.179 vs. CST+IIAE 42.40 ± 6.047, $p = 0.082$) and IIA (CST 35.31 ± 3.823 vs. CST+IIAE 48.47 ± 3.230, $p = 0.038$) and higher percentage of IIA > 35 mm [CST 42.9% (6/14) vs. CST+IIAE 100% (7/7), $p = 0.018$], and longer surgery time (CST 100.3 ± 5.781 vs. CST+IIAE 120.6 ± 6.962, $p = 0.047$). But all-cohort analysis with a median follow-up of 25.5 months for CST and 22.5 months for CST+IIAE ($p = 0.296$) showed no difference in mortality, stent MAEs, sac dilation, or reintervetion between two groups. Notably, both groups had one sac enlargement event. The one in CST group was described previously, and the sac enlargement in IIAAE group was thought to result from endotension, and open surgery was performed after 5-year follow-up (**Table 4**).

Illustration of Typical and Challenge Cases With CST

To illustrate the application and advantage of CST, we presented several typical and challenge CST cases. Cases 1–3 showed three cases of AAA concomitant with a huge or short CIAA (**Figure 2**), and cases 1 and 3 were concomitant with IIAA at the same time. A Medtronic 16–28 mm flared skirt-limb placed in CIA and a 16–13 mm iliac limb extended to EIA was used to seal the CIAA and exclusion of one side IIA. From the DSA, we could notice that the reflux of IIA was contained between the skirt graft and the extended iliac limb (white arrow in **Figures 2C,H,M**). One year follow-up results all showed no endoleak or aneurysm sac dilation, and thrombosis formed in space between skirt-limb and extended iliac limb (white arrow in **Figures 2E,J,O**).

Cases 4 and 5 showed application of CST for isolated CIAAs (**Figure 3**). Case 4 showed a satisfactory result of sealing a 50.3 mm CIAA sequentially by a 16–24 mm graft, a 28–28 mm iliac limb, and two 16–16 mm iliac limbs, with the first 16–24 skirt limb located at the orifice of CIA and second 28–28 skirt limb located at the distal bifurcation of CIA. The double skirt-technology fully prevented any potential endoleaks to the aortic sac. Case 5 showed a long and huge CIA with 61 mm maximal diameter, which was also excluded by double CST skill, composed by a graft series of a 16–24, a 16–16, another 16–24 and 16–16 mm graft.

Cases 6 and 7 showed different strategies in treating IIAA in CST group (**Figure 4**). Both cases showed bilateral CIAA concomitant with IIAAs. For case 6, a series of 28–28, 16–13, 16–13 mm grafts were formed a CST for the right side, and a 16–24 followed with a 16–13 mm graft were used for the left side. Post-surgery and 1-year follow-up results showed complete seal of aneurysm, exclusion of IIA blood flow, no endoleak, and no aneurysm sac enlargement. For case 7, both CIAAs were treated by a 28–28 graft combined with a 16–13 mm iliac limb after coil embolization of the IIA. One-year follow-up showed satisfactory seal of aneurysm and complete embolization of IIA, though light type II endoleak from inferior mesenteric artery existed.

DISCUSSION

Strategies of treating IIA changed during the development of AAA treatment. At the early stage of AAA open surgery, preservation of at least one IIA was thought to be necessary and bypass of IIA to graft was used both in our center and others (19). Then, with the development of endovasular surgery as first line therapy and more and more data of safety on IIA exclusion, save of IIA was secondary to providing adequate landing zone and complete sealing of aneurysms (11, 13, 15). However, with development of new devices and technologies, preservation of

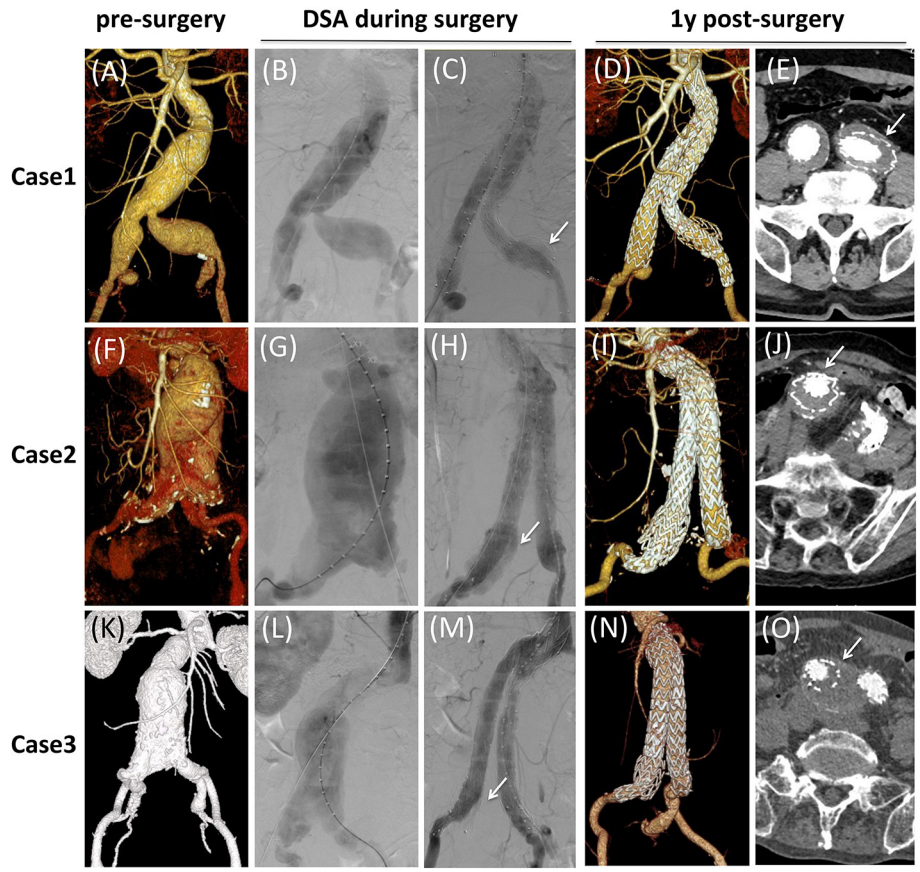

FIGURE 2 | Typical cases of CST for aorto-iliac aneurysms. **(A,F,K)** Pre-surgical CTA 3D reconstruction. **(B,G,L)** DSA of aneurysms. **(C,H,M)** DSA after CST procedure. The white arrow indicates reflux of IIA was contained between the skirt graft and the extended iliac limb. **(D,I,N)** One-year follow-up CTA 3D reconstruction. **(E,J,O)** Transverse section of 1-year follow-up CTA. The white arrow indicates thrombosis formed in space between skirt graft and extended iliac limb.

IIA and effort to decrease BC and ED become more and more important. With development of IBDs and improved Quality Control of AAA surgery, a preservation era of IIA is thought coming (20).

But, such new techniques still could be limited by anatomical constraints, technique experience, and availability of grafts. For example, IBDs were not available in China until March 2021. After full evaluation of patient condition, activity level, length, tortuosity and thrombus burden of iliac arteries, and cost, exclusion of IIA was still an indispensable technology in selected cases. And here we reported a novel common iliac artery skirt technology for feasible-and-effective IIA exclusion.

Based on retrospective analysis of data from 39 CST and 26 IIAE patients, our experience showed both groups had comparable primary end points and CST had better secondary end points, including significant short surgery time and hospital stay, lower in-hospital and 1-year stent MAEs, comparable mortality, and stent MAEs for all-cohort follow-up. Results of CST showed clear advantages over IIAE in excluding IIA and at the same time preventing the occurrence of type II endoleaks. Actually, the use of a flared grafts in excluding IIA with or without embolization also published in case reports, either with an upside-down or reversed bell-bottom technique (21–24). But, either a manually unsheathed-and-mounted procedure or a contralateral femoral access and crossover process is needed, respectively, which are not necessary for our CST.

Advantages of CST come from its simplicity and which results in short-time surgery and anesthesia, and less endovascular procedures. Ischemia of pelvic is the main concern and complication for exclusion of hypogastric artery. Literature reports of BC rate were 36.5% for bilateral IIA interruption and 27.2% for unilateral IIA interruption (25), and the erectile dysfunction rate was 12.7%. In our study, the in-hospital BC rate was 20.5% for CST vs. 46.2% for IIAE, $p = 0.053$ and the ED rate was 10.3% for CST vs. 23.1% for IIAE, $p = 0.352$. The direct coverage of orifice of IIA was suggested to have lower rate of BC than embolization of IIA in our study, and evidence was also reported in published data (11, 26–28). Nevertheless, the high preserve rate of contralateral IIA in CST should also not be ignored, thought not statistically significant. After 1 year, about one third BC was relived in both groups (CST 37.5% vs. IIAE 33.3%, $p = 1.000$), and which all happened on patients who had a preserved contralateral IAA. Thus, the save of at least one IIA should be guaranteed

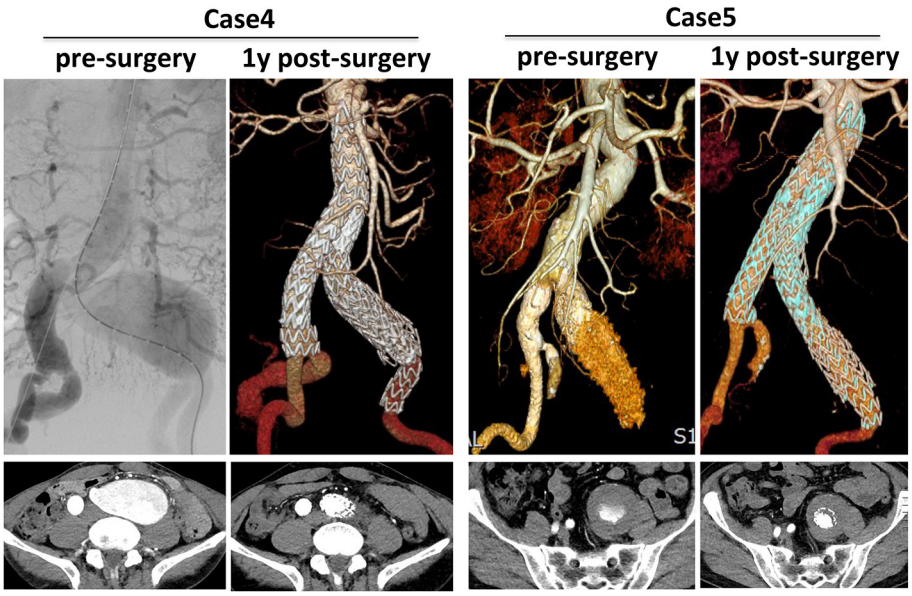

FIGURE 3 | Typical cases of CST for isolated iliac aneurysms. 3D CTA pre-surgery and 1-year post-surgery was compared and corresponding transverse section was also presented.

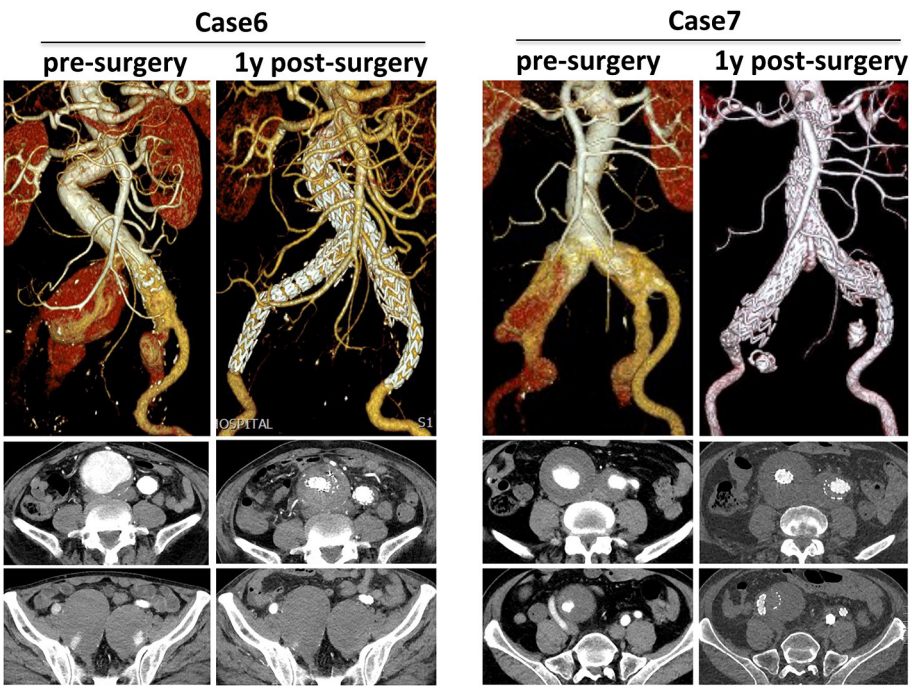

FIGURE 4 | Different strategies in treating IIAA in CST group. 3D CTA pre-surgery and 1-year post-surgery was compared and corresponding transverse section was also presented.

as long as possible, as per guidelines (1, 29). And as both CST and IIAE have high and comparable technique successful rate and exclusion of IIA in this study by our group, no difference of mortality and stent MAEs in long term follow-up was found.

Whereas, the critical size for isolated IIAAs treatment is considered to be 3–4 cm (30–32), whether its benefit to treat smaller IIAAs in patients undergoing EVAR for aorta-common iliac aneurysm to avoid the need for secondary interventions is still not clear. And also, for CST group, concerns may

remain on risk of future IIAA enlargement by only covering the orifice of IAA. In our study, by subgroup analysis of 14 patents concomitant with IIA dilation in CST group without IIAE and the 7 CST+IIAE patients, no difference was found in mortality, stent MAEs, sac dilation, or reintervetion between two groups. However, considering the challenging of secondary interventions for IIAAs after CST, we recommend that CST plus IIA embolization or other IIAAs procedures should be applied for IIAAs > 35 mm (33).

Overall, the common-iliac-artery skirt technology is simple, since it does not require neither particular endovascular expertise of the operator nor peculiar devices, which has decisive advantage in ruptured patients as a fast and life-saving treatment option. Besides, as the application of CST only restricted by the diameter of CIA bifurcation and the 10% oversize was not strictly needed for the skirt limb, CST was available for majority cases by using available flared iliac limbs and cuffs (maximal 36 mm). Comparing to IIAE, our experience showed CST had advantages in reducing surgery time, hospital stay, stent related MAEs, and BC rates. Satisfying safety and sealing of CIAAs without type II endoleak was also obtained.

Unilateral application of CST plus a patency or preserved contralateral IIA could be a satisfactory solution for most challenge iliac artery aneurysms. Nevertheless, larger sample size and long-term follow-up is warranted to assess the durability of the technology and absence of re-interventions.

As a retrospectively study, limitations of this study may include potential selection bias of patients for surgical method. However, comparable results of majority risk factors were found between groups.

CONCLUSION

In selected cases, the CST can be used for the complete exclusion of challenge iliac artery aneurysms and preventing type II endoleak from the IIA, especially for those who has advanced age, or contralateral health IIA, or cannot tolerate long-time surgery and is limited in activities, or when preservation of IIA does more harm than good or is not practical.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the 2nd Xiangya Hospital, Central South University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CS, LW, QL, ML, HH, and XL contributed to conception and design of the study. LW, YS, JQ, TW, CY, MW, and JL collected data and organized the database. HW and LS performed the statistical analysis. LW wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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Exploring the Correlation and Protective Role of Diabetes Mellitus in Aortic Aneurysm Disease

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Introduction: Diabetes mellitus is recognised as a significant risk factor for cardiovascular and peripheral vascular disease, as the abnormal metabolic state increases the risk for atherosclerosis, occlusive arterial disease and vascular dysfunction. There have been reports of potential association across the literature that illustrates a link between diabetes mellitus and aortic aneurysm, with the former having a protective role on the development of the latter.

Methods: A thorough literature search was performed through electronic databases, to provide a comprehensive review of the study's reporting on the association of diabetes mellitus and aortic aneurysm, discussing the mechanisms that have been reported; furthemore, we reviewed the reports of the impact of oral hypoglycameic agents on aortic aneurysms.

Results: Various proposed mechanisms are involved in this protective process including endothelial dysfunction, chronic hyperglycemia and insulin resistance. The evidence suggests a negative association between these disease process, with prevelance of diabetes mellitus resulting in lower rates of aortic aneurysm, *via* its protective mechanistic action. The increase in advanced glycation end products, increased arterial stiffness and vascular remodelling seen in diabetes, was found to have a profound impact on aneurysm development, its slow progression and lower rupture rate in these individuals. This review has also highlighted the role of oral hypoglycaemic agents having a protective effect against AA disease.

Conclusion: A decrease in development, progression and mortality from aortic aneurysms as well as reduced rates of dissection, have been observed in those with diabetes. This review has provided a comprehensive insight on the effect of diabetes and its physiological processes, and elements of its con-committant treatment, having a protective role against these aortic diseases.

Keywords: diabetes mellitus, aorta, aneurysm, dissection, hyperglycemia, insulin resistance, protection

INTRODUCTION

Diabetes mellitus (DM) is one of today's fastest rising healthcare challenges that we are facing, with almost half a billion adults between the ages of 20 and 79 estimated to currently have the disease. This is equivalent to just under 10% of the global population in this given age range. Predictions concerning the rising diabetic population expect a rapid growth to near 600 and 700 million by 2030 and 2045, respectively. In 2019, deaths associated with DM and the consequent complications of the disease were approximated at 4.2 million (1).

Aortic aneurysms (AA), caused by underlying weakness of the aortic wall which subsequently develops into permanent dilation of the aortic lumen, are most commonly asymptomatic until the catastrophic event of rupture and are associated with a mortality rate of 80%. Whilst AA can occur at any level of the thoracic or abdominal aorta, the most common locations are the infrarenal and proximal thoracic regions. AA show a male preponderance with advancing age, smoking, positive family history, hypertension, hyperlipidaemia and atherosclerosis attributed as the other risk factors (2, 3). Abdominal aortic aneurysms (AAA) are responsible for 1–3% of male deaths between the ages of 65 and 85 in developed regions (2, 4, 5).

Whilst there are many similarities in the mechanism of thoracic aortic aneurysms (TAA) and AAA, distinctive features also contrast the two. The complex pathological process leading to AAA formation involves alteration or depletion of vascular smooth muscle cells (VSMC) linked to inflammatory cell infiltration, re-modelling of the extra-cellular matrix (ECM), intraluminal thrombus development and oxidative stress. Changes in the ECM and the tone of VSMC have significant associations with TAA development, which typically occurs at a younger age, is associated with genetic disorders and frequently leads to aortic dissection (AD).

DM represents a major cardiovascular risk factor but numerous epidemiological reports have shown a negative association between DM and both AAA and TAA, thereby conferring a protective effect on them (6, 7). This review aims to summarise the current available knowledge on the underlying mechanisms of this inverse relationship between these disease processes.

PATHOLOGY OF ANEURYSM FORMATION

Aneurysm, derived from the Greek term *Aneurysma*, meaning widening, is characterised by permanent irreversible dilatation of a vessel. Conventional diagnosis of AAA requires an aortic diameter of greater than 30 mm, affecting all three layers of the arterial wall (4).

The mechanism of AA formation is complex, with inflammatory cell infiltrate (namely monocytes and macrophages) in the tunica media layer of the aortic wall playing an important role. The macrophage increase results in ECM remodelling which requires a balance between proteases like matrix metalloproteinases (MMPs) and its inhibitors (8). The characteristic dilatation of the aortic wall seen in AA, could partially be due to an imbalanced relation between wall stress and strength. Furthermore, studies have suggested an unmediated association between significant aortic wall stress and AA rupture risk. Aortic wall remodelling is both an expected and vital response to increased wall stress (9–13).

The walls of AAA show widespread inflammation, VSMC depletion and ECM degradation. These changes in the ECM are associated with extensive proteolysis causing the destruction of collagen and elastin. MMPs are a type of proteolytic enzyme whose activity is thought to be augmented in AAA, as evidenced by analysis of human aneurysmal tissue (14, 15). The increase in MMPs and a decrease in tissue inhibitors of MMPs lead to the break down of collagen and elastin in the ECM as well as VSMC depletion, resulting in degradation of the ECM. This leads to thinning and destruction of the normal aortic wall architecture, predisposing the individual to dilational changes and aneurysm development (8, 16–18). Apoptosis of VSMC characterised by inflammatory cell infiltrate, reactive oxygen species (ROS), and endoplasmic reticulum stress with the degeneration of aortic media, are the hallmark of AAA pathology (19).

Data related to the mechanism of TAA represent it as more than just a degenerative process, but rather a multifaceted culmination of both intracellular and extracellular alterations. It is characterised by abnormalities in ECM that compromise the structural integrity of the aorta (19).

DIABETES MELLITUS IMPACTING AORTIC ANEURYSMS

The Epidemiological Picture

DM, a chronic metabolic disorder characterised by hyperglycemia, insulin resistance and/or deficiency (relative or absolute), is associated with various microvascular and macrovascular complications contributing to major morbidity and mortality (20). DM is a significant risk factor for cardiovascular disease and reports have shown an inverse relationship between the disease and both AA prevalence and incidence (21, 22).

An ultrasound screening done in a regional veterans health care system as part of the Aneurysm Detection and Management study showed a lower prevalence of AA in the diabetic group. A significant number of other epidemiological studies have also confirmed the negative association of DM and AA, suggesting it to be protective in the formation and expansion of AA (23). A paradoxical inverse relationship was observed between the severity of DM and AA and also a reduced prevalence was seen in an Asian population study (24). Experimental studies in animal models also show attenuation of AA development in the presence of hyperglycemia.

The Viborg Vascular randomised screening trials of Central Denmark showed an inverse relationship between AA growth rate and HbA1c concentration (25). Certain retrospective studies have also observed a realistic association between DM and AA indicating a diabetic subset less likely to have an aneurysmal rupture and death (26). Another epidemiological study investigated the comparison of age at rupture and showed

diabetics under the age of 65 had no aneurysmal rupture. Conversely, 15% non-diabetics developed rupture under the age of 65 years (26, 27). Other studies showed the growth rate of smaller AA and associated expansion much slower than in non-diabetics, again suggesting a negative association (28).

Furthermore, the effect DM has on the outcome of AA repair revealed no significant difference in the morbidity and mortality (29, 30), whereas a few other studies showed lower mortality rates in the diabetic population (31). Complications associated with open AAA repair can include myocardial infarction, pancreatitis and infections such as pneumonia; higher rates of these complications were observed in the diabetic population post-operatively (30).

Impact on TAA

TAA in the vast majority is asymptomatic and diagnosed *via* echocardiography or CT performed for other indications, until a catastrophic event like AD-related complications occur, such as cardiac tamponade, acute aortic regurgitation or stroke (32). A negative correlation between DM and TAA formation and growth rate was also found. Additionally, a case study analysis showed the prevalence of DM in TAA was significantly lower (8). Prakash et al. (33) found an inverse association between DM and hospitalisations due to TAA. Also, those with DM complications had the lowest rate of TAA. Hyperglycemia, which is associated with reduced adventitial neovascularisation and decreased inflammatory cell infiltration in the medial layer of the aorta, probably inhibits progression of TAA by reducing VSMC death and ECM degradation (33). A Spanish study involving Spanish national data revealed a higher indicidence of TAA in the non-diabetic population compared to the diabetic population. Additionally, the mortality associated was significantly lower in the diabetic than the non-diabetic population (34).

Impact on AAA

AAA have increased in the past two decades adding substantial burden to the healthcare of developed countries. They are often asymptomatic, being detected incidentally *via* routine imaging or as a medical emergency in case of rupture (3, 4). Multiple studies were done to determine the impact of DM on the incidence, growth rate, prevalence, morbidity and mortality of AAA.

De Rango et al. (35) and other prospective studies showed significant decrease in the incidence of new AAA in a diabetic population. Takagi et al. (36) assessed the growth rate in both diabetic and non-diabetic groups and established that DM is associated with a reduced rate of AAA growth. Reduced aneurysmal growth rate and expansion was also confirmed by Vega et al. (27). The life threatening complication of aneurysmal rupture and the associated mortality was also found to be lower in diabetics than non-diabetics (26, 28). The association was also more significant in diabetic males than females (36, 37).

Golledge et al. demonstrated the role of DM and glycation on AAA expansion: DM was associated with slower progression of AAA. The glycated ECM was found to markedly inhibit monocyte MMP production thus explaining the protective role of DM on AAA. There were lower levels of IL-6, MMP-2 and MMP-9 being secreted in the glycated ECM (7). On the contrary, a higher myocardial infarction and wound infection rate in the first 30 days was observed in diabetics with AAA by Treiman et al. Also the long term survival was found to be lower in diabetic patients adding to the increased cardio-vascular burden in a series of studies (35, 38, 39).

A study in the Asian population revealed significant reduction in association of advanced and severe Type 2 DM (T2DM) with AAA without rupture and also a decreased prevalence of AAA in the diabetic population (24). Dua et al. demonstrated an increase in the PAI-1 level with decreased plasmin and thus a low MMP-2 and MMP-9 levels in the DM-AAA induced mice population. This reinforces the protective role of hyperglycemia might have on aneurysm formation and aortic diameter (40). A study by Miyama et al. (41) investigated the role hyperglycemia has on aneurysm progression and found reduced levels of macrophage infiltration, neovessel density and MMP-9 levels, thus conferring protection against aneurysm formation.

Data surveillance from CAESAR, a multicentre randomised trial that compares the efficacy of surveillance vs. endovascular aortic repair in small AAA, by De Rango et al. compared diabetics and non-diabetics. Though the aneurysmal growth rate in the first year was similar in both the groups, later increase was higher in the non-diabetic group. Patients with DM in the surveillance group required lower rates of endovascular aortic repair after 30 months but no significant difference in adverse events between diabetics and non-diabetics was observed (35).

Impact on AD

Acute Aortic dissection is relatively uncommon and first described over 200 years ago (42). AD involves a tear of the aortic intima, resulting in the formation of a false lumen, with inflow of blood in to the medial layer. The consequential false lumen may propagate distally or even retrogradely making it an aortic emergency (43). The pathology involves acute separation of layers within the aortic wall following an initial intimal tear. Luminal blood enters the intima-media layer creating a life threatening condition requiring immediate assessment and management with 20% patients dying before they reach the hospital and 30% during the hospital admission. Patients with enlarged AA, carry with them a risk of 10% per-year of sudden death as a result of the occurrence of AD. Hypertension, substance abuse, connective tissue disorders, family history of thoracic aortic diseases, vascular inflammation, congenital disorders are all risk factors for the occurrence of AD (43).

Data from inpatient sampling to determine the association between AD and DM established that DM was significantly and negatively associated with TAA and AD; this was found to be independent of multiple clinical characterisitcs and variables, including: type of hospital, the region, age of the patient and income. Hospitalisation due to TAA and AD occurred at a lower rate in diabetics (33). The achieved results in the literature that illustrated this inverse association was seen in both men and women, appearing to be strongest amongst those with diabetic complications. Therefore, the aforementioned suggests that the inverse relation of DM with TAA and AD may further be influenced by the severity and duration of hyperglycemia, as well as the level of susceptibilty a patient has to vascular injury. A

nationwide observational study comparing T2DM patient group with a control group, reported a lower short term mortality post-hospitalisation, reaching upto greater results at 2-years with better survival rates for the diabetes group (33). Alteration of aortic tissue through systemic cross linkages contribute to the protective effect of diabetes toward stabilisation of the aorta, preventing dilatation, growth and rupture (44).

A non-western population case control study performed to assess the correlation between AD risk and DM also concluded that DM was significantly associated with a decreased risk of AD. However, it is important to note that the authors reported no significant difference in in-hospital mortality when comparing the DM and non-diabetic patients (45).

OVERCOMING A CHALLENGE: THE USE OF ANIMAL MODELS

It is challenging to define AA mechanisms in humans, which commonly results in the use of animal models to gain a deeper understanding of the pathophysiology. Although it is difficult to obtain the exact pathophysiology using animals, several probable mechanisms have been studied addressing the deficiencies in animal models (46). Dissecting and non-dissecting AAA models are used, with the non-dissecting AAA created through calcium chloride or porcine pancreatic elastase (PPE) perfusion.

There is evidence of reduced expression of Cell Division AutoAntigen (CDA-1) in the aortic biopsies of human AAA. The CDA-1 which enhances transforming growth factor (TGF)-β signalling is found to be upregulated in diabetes and is also found to play a key role in the protective effect conferred by DM on AA (47). In a study by Jiaze Li et al., DM was induced in male wild-type CDA-1 knockout (KO), Apolipoprotein E (ApoE) KO and CDA-1/ApoE double KO mice. This model was characterised by Angiotensin II (Ag-II) induced aneurysms, and the results demonstrated that CDA-1 lacking mice with diabetes developed aneurysms. On the other hand, with CDA-1 present, the severity of these aneurysms was reduced in diabetic mice and was characterised by reduced fatal aortic rupture and attenuated supra-aortic expansion (47).

The study by Miyama et al. involved hyperglycemic and euglycemic murine (mice) models. Through intra-aortic PPE infusion or by Ag-II subcutaneous infusion, the formation of AA was induced in the mice. To assess the effect of decreasing serum glucose levels, insulin therapy was also instituted in a separate cohort. The study showed hyperglycemia was linked with reduced mural neovascularisation, macrophage infiltration, and medial elastolysis. Also insulin mediated glucose reductions did partially negate the protection rendered by hyperglycemia on AA (41).

Calcium phosphate can contribute to aneurysm formation by causing apoptosis of VSMCs with subsequent macrophage infiltration. The study done by Tanaka et al. was on Type 1 and Type 2 Diabetic mice (murine models) and in them calcium phosphate induced aneurysm formation was found to be significantly suppressed in the presence of hyperglycemia. The mechanism was found to be through suppression of macrophage activation and aneurysmal degeneration through the activation of Nr1h2 (liver X receptor α and β) (48).

DIABETES, A PROTECTIVE FACTOR? POTENTIAL MECHANISMS LEADING THE WAY

Wall Stress

In comparison to other arteries, the aortic wall suffers from much greater stress. A typical ageing process is aortic dilation, which occurs in about a quarter of otherwise fit and healthy patients. Although the aortic wall is thicker alongside increasing age, wall stress autoregulation seems to be faulty in males, implying that the aorta is an artery susceptible to damage. Compared to non-diabetics, the AAA expansion rate is at 30%, which is not a substantial difference. An altered remodelling response observed in diabetic patients with AA compared to healthy subjects leads the protective response of AA in DM (49–51).

One of the critical factors in causing and enlarging AAA is aortic wall stress. However, diabetics are known to have a larger matrix volume leading to thicker aortic walls, which reduce aortic wall stress (7, 49, 52). Recent studies show the hyperglycemia associated with DM plays a significant role in stabilising the collagen network through crosslinking of collagen in the aortic wall media (7, 49).

Matrix Metalloproteinases

MMPs are secreted *via* endothelial cells and macrophages, which exhibit increased activity, through proteolytic action in human aneurysmal tissue and are activated by wall stress. Specifically, through the enzymatic process of disintegrating various proteins such as elastin and collagen within the vessel wall, both MMP-2 (released *via* smooth muscle) and MMP-9 (released *via* macrophages) are involved in destructing the matrix. It has been observed that both MMP-2 and MMP-9 are increased in patients with AAA, whereas mice lacking these enzymes do not develop any dilatation of the aorta (53–57). This may be the potential mechanism through which diabetic patients have a preserved aortic matrix- due to decreased MMP activity. A lower concentration of MMP-1, MMP-2, and MMP-9 has been observed by a study that investigated the differences in MMP activity and presence in both diabetics and non-diabetics (58). Hence, it can be concluded that the potential mechanism for reduced aneurysmal events in diabetics may be through reduced MMP activity primarily, through the effects of high glucose levels (21, 49, 50).

ECM Remodelling, Glycation, and Advanced Glycation End Products

The vascular ECM contributes to the cellular structure and tissue organisation, which comprises a vast system of components that include: elastin, basement membrane, collagen and proteoglycans (6). The interaction of the ECM and the various cells of the arterial wall play an important role when it comes to vessel remodelling. An example of this cellular remodelling can be seen in diabetic patients, with the advanced glycation of ECM

proteins such as collagen, as a result of hyperglycemia. A crucial step involved in the formation and progression of AA is the secretion of MMPs, which result in proteolysis. The crosslinking of collagen and elastin resultant of the advanced glycation of the ECM within the aortic wall of the abdomen, results in the inhibition of MMP secretion and subsequently the aforementioned mechanism (6, 7).

Polysacchiride glycosaminoglycans are a component of the ECM by covalent bonding with the existing proteins forming proteoglycans. There is an abundance of biglycans in the normal aorta, however, it is decreased in the setting of AAA. Biglycans can regulate TGF-beta signalling pathway and *vice-versa*. This implies the presence of regulation *via* a mutual positive feedback mechanism, allowing the ECM's preservation, thereby providing protection against the progression of AA. The direct impact of DM on biglycans is uncertain; there may be the augmented pathway of the TGF-β signalling caused by upregulation of CDA-1 (59, 60). Furthermore, the physiological process of other glycosaminoglycans in the aorta, involving deposition, production and degradation, can be affected by the presence of DM (61).

DM and chronic hyperglycemia lead to advanced glycation end products (AGE), which influence the activation of monocyte-macrophages. This is achieved *via* unique receptors for AGE (RAGE), the engagement of which results in AGEs bringing about non-enzymatic crosslinking between ECM basement membrane components (6, 7). These mechanistic processes add to the pathophysiology of atherosclerosis, and result in numeorus signalling pathways being stimulated. It thus contributes to arterial stiffness, protecting against mechanical structural loss and resists proteolysis. The distinct properties of ECM in diabetic patients confer a protective effect on AAA (6, 7, 14, 62, 63).

The Role of Inflammation

Inflammatory processes have a vital role in AAA and have a significant influence on many of the factors of remodelling of the wall of the aorta (16). The role inflammation plays in the negative association of DM and AAA is complex (16). The exact mechanism through which DM influences inflammation in AAA might include the stimulation of T-cell insulin receptors, the monocyte-macrophage system or through C-peptide production (41). Patients with T2DM often have increased C-peptide levels.

A study by Cifarelli et al. demonstrated that physiological levels of C-peptide can decrease hyperglycemia induced VSMC proliferation (41, 64). Haidet et al. investigated the effect of C-peptide presence on monocyte cell lines surrounded by a glucose solution. The study demonstrated a decreased expression of multiple pro-inflammatory cytokines through the NF-KB mediated pathway in the presence of C-peptide (65, 66). Studies in mice have shown low levels of IL-6 restricts both TAA and AAA progression. Glycation additionally has the potential to alter monocyte-macrophage function toward an anti-inflammatory phenotype which decreases IL-6 production (7). Additionally, Mendelian randomisation approaches support the involvement of IL-6 receptor pathway in human AAA. Glycation of IL-6 could be another factor contributing to the protective effect of DM on AA (67).

Aortic Mural Neoangiogenesis

An important element in pathophysiological processes for aneurysms, and potential rupture, is the role played by aortic mural neoangiogenesis. In the event of AAA, there is often the linked formation of a mural thrombus; the thrombus undergoes continuous remodelling as a result of the maintained blood flow throught the abdominal aorta. The thrombus can significantly lower the wall stress, there is the impeding influence of the greater wall thickness. This structural change can subsequently result in the inner aspect of the media to be exposed to hypoxic conditions locally, which consequently leads to inflammatory response and augmented medial neovascularisation (68).

In hyperglycaemic mice, it has been found that the reduced AA diameter is concomittant with lower levels of medial elastolysis, macrophage infiltration, in addition to lower level of this neoangiogenesis. In murine models, hyperglycemia inhibiting neovessel formation by down regulation of activation of vascular endothelial growth factor expression and angiogenic response was observed. Beyond neovascularisation and macrophage infiltration, additional mechanisms include hyperglycaemic influence on the fibrinolytic system, RAGE and progenitor cell function (41).

Intra-luminal Thrombus

Intra luminal thrombus (ILT) implicated in the pathogenesis of AA, has high concentration of MMP-9 within the thrombus and signs of collagenolytic activity. During the process of thrombus renewal, MMPs that can be found inside the thrombus are released through various processes including fibrinolysis (69–71). Dunn et al. (72) showed the clots in diabetes are denser and lower level of susceptibility to fibrinolysis.

T2DM is often associated with hyperinsulinemia which could also have a protective influence by preventing ILT renewal. Hyperinsulinemia increases PAI-1 levels and inhibits plasmin being converted from plasminogen, which decreases fibrinolysis. This in turn decreases expression of MMP, as plasmin is needed to convert proMMP to its active form (73–75). These fibrinolytic changes and renewal potential reduce clot degradation of ILT in AAA. Stability of the aortic wall can be improved through this along with reducing the rate at which the aneurysm expands (71, 72).

Vascular Smooth Muscle Cell Homeostasis

Another vital component of the pathophysiological processes involved in the development of an aneurysm are the VSMC. Most VSMC are of contractile phenotype contributing to the vascular tone. These cells play a key role in vascular remodelling due to their ability to differentiate their phenotype, to a synthetic form. Synthetic phenotype switching triggered by oxidative stress, inflammation and injury is characterised by decreased contractile protein expression and increased MMPs. The synthetic phenotype also leads to calcification, in turn leading to risk of aneurysmal progression and rupture. AA is characterised by disrupted vessel wall structure with characteristic histology of VSMC apoptosis. TAA and AAA share a common feature of VSMC depletion and ECM proteolysis (76).

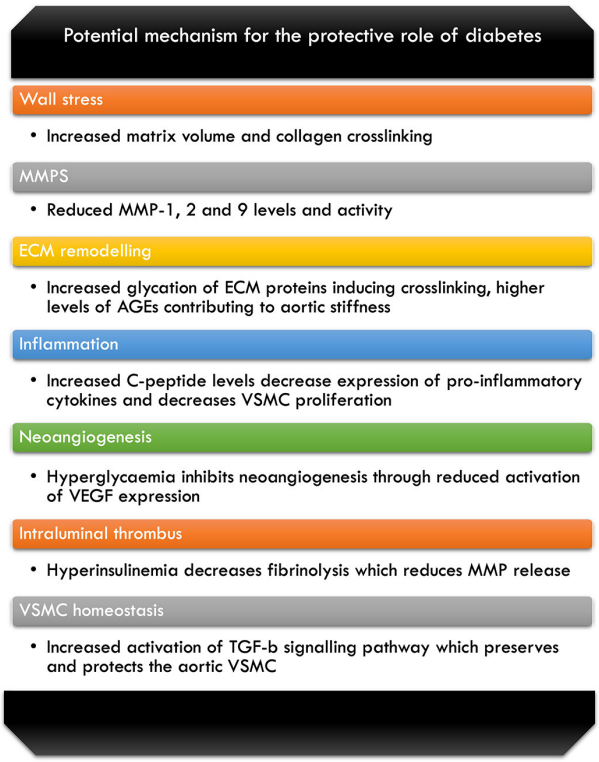

FIGURE 1 | Breakdown of some of the potential mechanism for the protective role of diabetes against AA disease (6, 7, 14, 41, 49, 52, 58, 63–66, 69–72).

TGF-β is required for inducing and maintaining the homeostatic and differentiating processes of the VSMC, for the mechanisms discussed. The environment created as a result of DM causes greater stimulation of the TGF-β signalling pathways, which has local and systemic effect on the VSMC of the aorta, hence plays an important protective role (6). Furthermore, as the hyperglycaemic state in the DM patients influences the VSMC, it contributes to the protection against development of aneurysm and AD through its homeostatic actions in the wall of the aorta (6) (**Figure 1**).

HYPOGLYCAEMIC AGENTS: THE TRUE HEROES?

A number of factors, in DM patients, must be controlled to maintain a tight glycaemic control that is dependent on various medical regimes—these aim to reduce the severe risks associated with DM. Apart from a patient centric approach with life style modification, involving dietary changes and regular exercise regimens, the effective management of diabetes also involves choosing appropriate pharmacological treatment for the blood glucose control. The anti-diabetic medications used include Biguanides, SGLT2-inhibitors, dipeptidyl peptidase (DPP4) inhibitors, thiazolidinediones, glucagon-like-peptide (GLP)-1 receptor agonists, sulfonylureas and insulin therapy (77).

Various studies of different experimental designs have concluded that drugs used to manage DM have a protective role against AA.

Biguanides—Metformin

Metformin is one of the oldest first line oral hypoglycaemic agent used in DM management. The mechanism of action of Metformin involves a reduction in the hepatic glucose production and also improvement in the tissue sensitivity to insulin. It has pleiotropic anti-inflammatory and vasculoprotective effects through various mechanisms including limiting aortic inflammation, reduction in the ECM remodelling and decreasing the oxidative stress (57, 78).

Studies by Golledge et al. and a nationwide analysis of of Veterans Affairs with DM also showed that Metformin did limit the growth of AAA (79, 80). Mice experiments by Fujimura et al. showed that the administration of Metformin during both aneurysm induction and progression periods reduces the initiation and progression of AAA in non-diabetic mice. The Metformin mediated resistance to AA was associated with reduced inflammation, elastin degradation and VSMC depletion in the histopathologic examination (81).

An improvement in the aortic elasticity was observed in a study by the addition of Metformin to oral contraceptive pills (82). Vasamsetti et al. (83) demonstrated in an Ag-II treated mice that the presence of Metformin reduced the proinflammatory cytokine levels indicating the protective role it has against aneurysm formation.

In-vitro studies have shown Metformin additionally reduces MMP-2 and VSMC proliferation in human aortic cells. Additionally, lower incidence of AAA associated events were found in diabetics on Metformin compared to those not on Metformin (14).

PPAR Gamma Agonists—Thiazolidinediones

Thiazolidenediones include Pioglitazone and Rosiglitazone and these drugs act as PPAR-γ agonists and exhibit their anti-inflammatory effects by lowering tumour necrosis factor (TNF)-α levels.

Motoki et al. studied the effect of PPAR-γ agonists on the aortic wall in patients with AA and found that it may prevent or delay the progression of the aneurysm in patients *via* decreasing the expression of MMP-9 and TNF-α in the wall of the AA (84).

Piranov et al. investigated in ApoE deficient mice, the mechanism of Rosiglitazone in the earlier phases of AAs induced by Ag-II, looking at potential sites at which the drug would act. Rosiglitazone worked by inhibiting c-Jun N-terminal kinase phosphorylation and reduces the regulation of toll-like receptor 4 (TLR4) being expressed at the location at which the lesion is being formed during the initiation stage of experimental AA development. The authors further discussed an additional mechanism *via* which the initiation stages of aneurysm formation is blocked. They explain the relation of the drug with lowered levels of MIP-1α and MCP-1 chemokines, which are pro-inflammatory, as well as declining the level of CD4 antigen (85).

The action of PPAR ligands were studied by Golledje et al. investigating their impact on AA in mouse models. This study reported a significant association of Pioglitazone with lower expansion of the suprarenal aorta. This linkage may potentially be due to down regulation of osteopontin, a chemotactic factor which has an association with AAA in humans (86).

Rosiglitazone could also exert its protective effect on AAA development by reducing serum levels of MMP-9 in individuals with T2DM and thus playing a role in ECM preservation (87). Jones et al. showed that Rosiglitazone led to less inflammation due to the lower amounts of mediators IL-6 and TNF-α. Furthermore, the use of the drug makes the ECM thicker, as a result of its associated amplified production of collagen, thus reducing chances of rupture and death (88).

Dipeptidyl Peptidase Inhibitors

DPP4 inhibitors like Sitagliptin, Vildagliptin, Teneligliptin and Alogliptin act by inhibiting the proteolytic enzyme DPP4 thus prolonging the action of GLP and delaying gastric emptying, improving glycemic control by increasing meal stimulated insulin secretion and inhibiting glucagon release.

Boa et al. studied the protective effect of DPP-4 inhibitor, Alogliptin. The study investigated on rat AAA models and found that the drug attenuated the formation and expansion of aneurysms in a dose-dependent manner *via* an antioxidative action. Rats on alogliptin showed lower rates of reactive oxygen species (ROS) activity, thus inhibiting aortic wall destruction. A reduction in the MMP-2 and MMP-9 levels were also observed. A significant reduction in aortic dilatation in the DPP-4 inhibitor-treated rats compared to the control group was observed in macroscopic findings (89).

Lu et al. studied the protective effect of Sitagliptin in induced AAA mice models. The incidence of AAA in Sitagliptin treated mice was much lower, around 4–8%. Sitagliptin-treated models showed attenuation of elastin and collagen disruptions with decreased MMP-9 and MMP-2 activity, substantial reduction in macrophage infiltration and reduced apoptosis in the wall of the aorta, thus indicative of a potential protective role of sitagliptin in AA formation (90).

Sulfonylureas

Sulfonylureas are one of the commonly used potent oral hypoglycaemic agents. A case control analysis done by Hsu et al. with the use of Taiwan's national health insurance research database concluded that diabetic patients on oral hypoglycaemic agents, including sulfonylurea, biguanides and thiazolidinediones were associated with decreased risk of AA development. The exact mechanism by which sulfonylureas exert their protective effect is not known, as no direct clinical or experimental studies are available in this specific area.

The probable mechanism may be through the SUR-2 receptor mainly expressed on the VSMC wall (91). Indirect evidence for the aforementioned was suggested in a study by Hiraki et al. (92) reporting on a patient with AA from a family with Cantu Syndrome, a genetic disorder characterised by ABCC9 mutation affecting both the SUR-2A and SUR-2B.

GLP-1 Receptor Agonists—Lixisenatide

Yu et al. demonstrated the protective effect of subcutaneous Lixisenatide on development of an aneurysm. The use of Lixisenatide resulted in reduction in ROS and macrophage infiltration; additionally, there is inhibition of the expression of the genes for MMP9, TNF and MMP2 in the walls of the aorta of the experimental rats. These processes instigates the protective action that Lixisenatide has *via* anti-inflammatory and anti-oxidant actions, as well as preserving ECM (93).

In Ag-II infused ApoE KO mice, Liraglutide administration was found to reduce the formation of AAA, as discussed by Lu et al. (90). This was achieved by increasing the circulating active form of GLP-1, reducing the infiltration of macrophages, and decreased expression of MMP-2 and MMP-9, thereby preserving the elastin content (90).

SGLT2 Inhibitors—Showing Promise?

SGLT2 inhibitors are a more recent hypoglycaemic agent, which inhibit the action of the SGLT2 proteins responsible for the reabsorption of the majority of the glucose that has been filtered. These proteins are situated at the proximal convoluted tubule. The action of these drugs is *via* the blockade of the respective low affinity and high capacity proteins. As a result of this mechanism of action these drugs cause glycosuria, consequently lowering the patients plasma glucose concentration in an insulin and incretin pathway independent manner (94–96). The commonly used drugs of this class are Canagliflozin, Dapagliflozin and Empaglifozin. Apart from the kidneys, the SGLT2 protein is also found to be expressed in other tissues including: adipose tissue, vascular tissue, such as endothelial cells, and the aortic wall (97–99). Therefore, SGLT2 inhibitors have been found to have pleotropic effects, most importantly cardio-protective effect along with their glucose lowering action.

Ortega et al. demonstrated that chronic oral Empagliflozin use reduced the Ag-II induced supra-renal AAA development in ApoE KO mice. The attenuation was a result of reduction in macrophage infiltration within the lesion and down-regulation of pro-inflammatory cytokines that was observed with Empagliflozin administration (100). SGLT2 inhibitors were additonaly seen to have an impact on lowering the levels of MMP-9 and MMP-2, along with reduced atherosclerosis, in ApoE KO mice. The authors also observed a marked reduction in vascular endothelial growth factor levels and neovascularisation in these Empagliflozin co-treated mice. This cotreatment was found to diminish Ag-II induced elastin degradation in immunohistochemistry analysis (100).

In-vitro studies in human aortic endothelial cells revealed that Empagliflozin decreased mononuclear-leucocyte endothelial cell interactions and endothelial production of chemokines induced by Ag-II (100). Kaji et al. (101) have also demonstrated *in-vitro* suppression of human endothelial cell proliferation and tubular formation by Canagliflozin. Thus, chronic oral administration of SGLT2 inhibitors show promise as novel glucose lowering agents, displaying pleotrophic effects on AAA. Further research in this field will add greater value to its therapeutic use in DM and beyond.

TABLE 1 | A brief outline of the mechanism by which various hypoglycaemic agents have a protective impact against AAs.

Hypoglycaemic agent	Mechanism of aortic aneurysm prevention
Biguanides–Metformin (14, 80–82)	• Resistance to AA through: reduced inflammation, elastin degradation and smooth muscle cell depletion
	• Combined with oral contraceptive pills, increased aortic elasticity is observed
PPAR gamma agonist–Thiazolidinediones (84–86, 88)	• Decreased expression of TNF-a, MMP-9, and IL-6 in AA wall but increased collagen production
	• Inhibition of JNK phosphorylation and down-regulation of TLR-4 expression associated with reduced proinflammatory chemokines
	• Reduced aortic expansion due to downregulation of osteopontin
Dipeptidyl peptidase inhibitors (89, 90)	• Dose dependent suppression of ROS
	• Reduced levels of MMP-9 and MMP-2
	• Reduced apoptosis in wall of the aorta and reduced macrophage infiltration
Sulfonylureas (91, 92)	• Associated with lower risk of AA development
	• Exact protective mechanism is not known
	• Proposed mechanism involves action of SUR-2 receptor on VSMC (9) wall.
GLP-1 receptor agonists-Lixisenatide (93)	• Reduction in ROS and macrophage infiltration
	• Inhibition of TNF-a, MMP-2 and MMP-9 gene expression in the aortic wall
SGLT2 inhibitors (94–100)	• Chronic use demonstrated reduced AAA development
	• SGLT2 Inhibitors have a pleotropic effect, with cardio-protective effects seen as well as just for DM treatment
Insulin therapy (41)	• Insulin therapy negates protective effects of oral hypoglycaemic agents

AA, aortic aneurysm; TNF-a, tumour necrosis factor-alpha; MMP, matrix metalloproteinase; IL, interleukin; JNK, C-Jun N-terminal kinase; TLR, toll-like receptor; ROS, reactive oxygen species; VSMC, vascular smooth muscle cell.

TABLE 2 | A summary of the key points from the review of the literature discussing the impact of DM on AA disease, and its role as a protective factor.

Summary table
AA and DM have a well-known significant disease burden
DM is a recognised risk factor for cardiovascular disease; however, literature suggests a protective role of DM in AA, thoracic and abdominal, with this association being observed with aortic dissection as well
There have been numerous mechanisms proposed for the protective role of AA in DM, these are related to: reduced wall stress, inflammation, neoangiogenesis, lower matrix metalloproteinases, and increased stimulation of transforming growth factor-beta providing protection for the vascular smooth muscle cell
Clinical and experimental studies have reported that the drugs used in the management of DM have a protective role against AA
Further research, including molecular and genetic studies, into the link between DM and AAs could help with individualising treatment strategies in the future

AA, aortic aneurysm; DM, diabetes mellitus.

What About Insulin Therapy?

The oral hypoglycaemic agents have shown to confer a protective effect on the incidence and progression of AA. Improvement of hyperglycemia by insulin therapy however, has been found to negate the protective effects (41).

FUTURE PERSPECTIVES

DM is an established cardiovascular risk factor and accelerates atherosclerosis. Experimental studies and data from epidemiological studies have shown DM to have a protective effect against the development, growth, expansion and rupture of AA. Human and animal studies have shown a spectrum of mechanisms by which DM could exert a protective effect on AA and dissection. Additionally, medications used in the management of hyperglycemia have shown to independently confer a protective effect on the formation and progression of AA.

These observations could help identify high risk groups to help in the primary prevention of AA. Understanding the pathogenesis involved helps in developing future prevention and management strategies both medically and surgically. The evidence of reduced expression of CDA-1 in the human AA walls and the protective effect of CDA-1 seen in experimental mice enables us to plan further involving CDA-1 as a potential therapeutic target in the prevention and management of AA. The downregulation of MMPs observed in animal models, as a potential mechanism involved in the protection observed in diabetes and with oral hypoglycaemic agents, could also act as a potential therapeutic target in future studies.

Further investigations are still needed to establish the mechanism implicated in the beneficial effect of diabetes on AD. Detailed studies into the cellular and molecular mechanisms and other genetic factors contributing to the aneurysm disease process would be required to individualise the treatment strategies in future.

CONCLUSION

DM has a significant impact on the healthcare of our society and has clearly been shown to be a risk factor for cardiovascular disease. However, our review of the literature has demonstrated the reported protective effects that DM

has in the development and progression of AA, as well as with AD.

The literature has reported various mechanisms by which hyperglycemia and presence of DM exerts its protective effects; however, it is important to note that there is yet to be a definitive consensus reached for all the proposed mechanisms. **Figure 1** illustrates these potential mechanisms against AA disease that we have covered in our review of the literature.

Building on the aforementioned, our review has highlighted the impact of oral hypoglycaemic agents themselves playing a role in the protection against AA disease. **Table 1** provides a detailed overview of the classes of drugs that we have discussed, as well as covering the negating action of insulin therapy on the protective effort by the discussed oral hypoglycaemic agents.

There is the need for further research into the association of DM and AA, investigating the molecular and genetic aspects with understanding of the natural history of these diseases. This will allow greater development of decision-making framework for management as we aim toward precision medicine for our patients (**Table 2**).

AUTHOR CONTRIBUTIONS

DA, WM, LS, RV, JR, MB, IW, BV, and MI have all collectively contributed to the intellectual property of this article, and have been involved in design, structure, data collection and revisions of this article. All authors contributed to the article and approved the submitted version.

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Incidence- and In-hospital Mortality-Related Risk Factors of Acute Kidney Injury Requiring Continuous Renal Replacement Therapy in Patients Undergoing Surgery for Acute Type a Aortic Dissection

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Background: Few studies on the risk factors for postoperative continuous renal replacement therapy (CRRT) in a homogeneous population of patients with acute type A aortic dissection (AAAD). This retrospective analysis aimed to investigate the risk factors for CRRT and in-hospital mortality in the patients undergoing AAAD surgery and to discuss the perioperative comorbidities and short-term outcomes.

Methods: The study collected electronic medical records and laboratory data from 432 patients undergoing surgery for AAAD between March 2009 and June 2021. All the patients were divided into CRRT and non-CRRT groups; those in the CRRT group were divided into the survivor and non-survivor groups. The univariable and multivariable analyses were used to identify the independent risk factors for CRRT and in-hospital mortality.

Results: The proportion of requiring CRRT and in-hospital mortality in the patients with CRRT was 14.6 and 46.0%, respectively. Baseline serum creatinine (SCr) [odds ratio (*OR*), 1.006], cystatin C (*OR*, 1.438), lung infection (*OR*, 2.292), second thoracotomy (*OR*, 5.185), diabetes mellitus (*OR*, 6.868), AKI stage 2–3 (*OR*, 22.901) were the independent risk factors for receiving CRRT. In-hospital mortality in the CRRT group (46%) was 4.6 times higher than in the non-CRRT group (10%). In the non-survivor ($n = 29$) and survivor ($n = 34$) groups, New York Heart Association (NYHA) class III-IV (*OR*, 10.272, $P = 0.019$), lactic acidosis (*OR*, 10.224, $P = 0.019$) were the independent risk factors for in-hospital mortality in patients receiving CRRT.

Conclusion: There was a high rate of CRRT requirement and high in-hospital mortality after AAAD surgery. The risk factors for CRRT and in-hospital mortality in the patients undergoing AAAD surgery were determined to help identify the high-risk patients and make appropriate clinical decisions. Further randomized controlled studies are urgently needed to establish the risk factors for CRRT and in-hospital mortality.

Keywords: acute type A aortic dissection, surgery, acute kidney injury, continuous renal replacement therapy, CRRT, risk factors

INTRODUCTION

Acute kidney injury (AKI) is one of the most common postoperative complications following cardiac surgery and is associated with increased morbidity and mortality (1). There is currently no consensus on the definition of cardiac surgery-associated AKI (CSA-AKI). The Kidney Disease: Improving Global Outcomes criteria (KDIGO) represent the current epidemiological and clinical standard for diagnosing AKI, including CSA-AKI (2, 3). Acute type A aortic dissection (AAAD) is the most dramatic emergency in cardiac surgery due to the high in-hospital mortality rate of ∼26% (4). Compared with other heart surgeries, the risk of AKI is higher after aortic dissection surgery (5, 6). Between 1999 and 2008, the incidence of AKI and AKI requiring dialysis (AKI-D) after cardiac surgery has increased from 30 and 5% to 47 and 14%, respectively (7). Continuous renal replacement therapy (CRRT) is widely used for hemodynamically unstable patients with considerable fluid accumulation (3, 8). However, the mortality of receiving CRRT after AKI is 40–70% (9), and second, the high cost of CRRT and the limited medical resources associated with CRRT impose a heavy social burden (10). Early identification of critically ill patients of high risk for CRRT and in-hospital mortality after cardiac surgery can be beneficial in improving the overall prognosis.

Few studies on the risk factors for postoperative CRRT in a homogeneous population of patients with AAAD. This retrospective analysis was designed to describe the incidence of AKI requiring CRRT in the patients undergoing AAAD surgery, evaluate the demographic and perioperative factors associated with the patients with AKI requiring CRRT, identify the association of CRRT with a duration of mechanical ventilation, in-hospital mortality, and 1-year readmission, and analyze the risk factors for CRRT and in-hospital mortality.

Abbreviations: AKI, acute kidney injury; CSA-AKI, cardiac surgery-associated acute kidney injury; AAAD, acute type A aortic dissection; KDIGO, Kidney Disease: Improving Global Outcomes; AKI-D, AKI incidence requiring dialysis; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; SD, standard deviations; IQR, interquartile range; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DHCA, Deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; ALB, albumin; BUN, blood urea nitrogen; UA, uric acid; Cys-C, cystatin C; MAP, mean arterial pressure; AMI, acute myocardial infarction; CVA, acute cerebrovascular accident; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy.

MATERIALS AND METHODS

Study Population

For this study, in **Figure 1**, we retrospectively collected the electronic medical records and laboratory results of 432 patients aged ≥18 years who underwent cardiac surgery for AAAD diagnosed by echocardiography or enhanced CT at the West China Hospital of Sichuan University (Sichuan, China) between March 2009 and June 2021. The exclusion criteria were as follows: (i) the patients who had received maintenance dialysis within the last month or were on dialysis before surgery ($n = 29$); (ii) the patients who had received kidney transplantation ($n = 5$); (iii) the patients who died within 24 h of admission to the hospital ($n = 23$); and (iv) the patients with incomplete data ($n = 59$). The present study was approved by the Ethics Committees of the West China Hospital of Sichuan University. Sichuan, China.

Data Collection

The data of the patients included in the present study, including the patient characteristics, perioperative factors, laboratory data, postoperative complications or comorbidities, and outcomes, were extracted from the electronic medical records system of our institution. The laboratory data of the CRRT group were obtained prior to the occurrence of AKI.

Measurements and Variable Definitions

Acute kidney injury was defined according to the KDIGO criteria (2) as follows: a serum creatinine (SCr) levels increase of ≥0.3 mg/dl within 48 h, or ≥1.5-fold the baseline level, which is known or hypothesized to have occurred within the prior 7 days, or urine output <0.5 ml/kg/h for 6 consecutive h. AKI severity was staged according to the following criteria (2) (**Table 1**).

In this retrospective analysis, the urine output criteria for defining AKI were not used, as 6- and 12-h urine outputs were not reliably recorded, and certain patients were treated with diuretics and CRRT. The decision for CRRT is determined by the assessment of the severity of AKI by the clinician and the comprehensive condition of patients. As some patients with AAAD were referred to our hospital from other hospitals, the lowest SCr level in the 2 days prior to admission was used as the baseline level if data were available; if not, we considered the first SCr available at admission as the baseline value. Drinking is defined as having consumed alcohol at least one time a week in the last year. CKD was defined by past medical history. Preoperative liver insufficiency was defined as a preoperative elevation of >80 U/L of aspartate aminotransferase (AST) or (and) alanine aminotransferase (ALT)

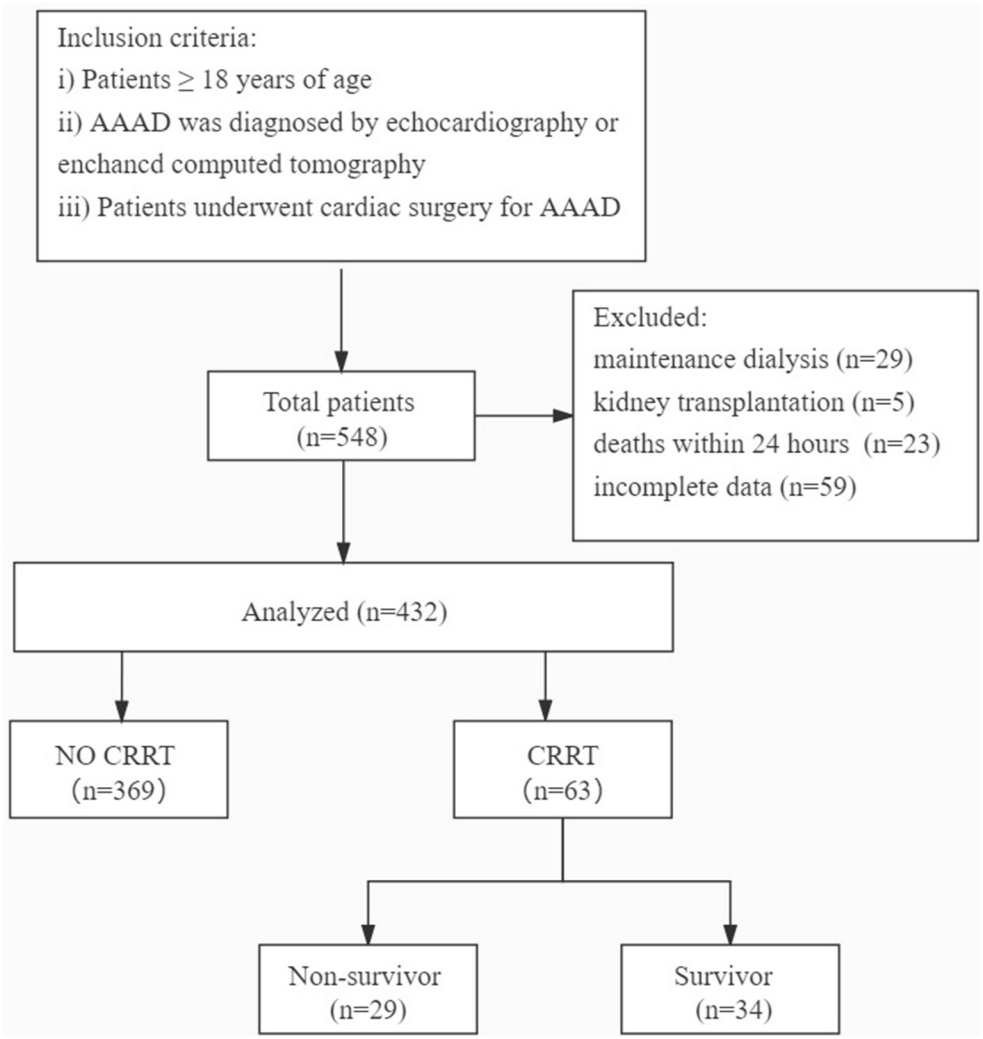

FIGURE 1 | Flow diagram of the study.

TABLE 1 | Kidney Disease: Improving Global Outcomes (KDIGO) stages of acute kidney injury (AKI) according to serum creatinine (SCr) levels and urine output.

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline	<0.5 ml/kg/h for 6–12 h
	Or ≥0.3 mg/dl (≥26.5 mmol/l) increase	
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline	<0.3 ml/kg/h for ≥24 h Or anuria for ≥12 h
	Or increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l)	
	Or initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	

KDIGO, Kidney Disease: Improving Global Outcomes; eGFR, estimated glomerular filtration rate.

in the patients. Deep hypothermic circulatory arrest (DHCA) is a measure to protect the brain by arresting extracorporeal circulation after cooling the brain temperature to 14.1–20°C in aortic arch replacement, for brain preservation. The diagnosis of postoperative acute myocardial infarction (AMI) was based on a history of typical chest pain, diagnostic ECG changes, serum cardiac biomarkers, and abnormalities on echocardiography and coronary angiography. Cerebral ischemia or hemorrhage resulting in complete or incomplete loss of brain function was defined as an acute cerebrovascular accident (CVA).

The patients were divided into the CRRT and non-CRRT groups according to whether they required CRRT or not; the patients in the CRRT group were divided into the survivor and non-survivor groups. The independent risk factors and perioperative complications and short-term outcomes were analyzed.

The primary outcomes were the occurrence of severe AKI, requiring CRRT, and in-hospital mortality. The secondary outcomes were the duration of mechanical ventilation, hospitalization costs, and 1-year re-admission.

Statistical Analysis

The baseline demographic and clinical data of patients were presented as numbers and percentages for categorical variables. The categorical variables were compared using chi-square tests. Data distribution normality was verified using the Kolmogorov–Smirnov test. The normally distributed continuous variables were presented as mean ± SD and the non-normally distributed continuous variables were represented as the median and interquartile range (IQR) and compared accordingly using independent samples *t*-test or Mann–Whitney *U*-test. A stepwise forward binary logistic regression analysis was applied to analyze the risk factors for patients receiving postoperative CRRT and in-hospital mortality. The omnibus tests of model coefficients were used to evaluate the multivariable binary logistic regression model, with $P < 0.05$ indicating that the binary logistic regression model was generally significant. Hosmer and Lemeshow test and −2 log likelihood (−2LL) provided an evaluation of the goodness

TABLE 2 | Demographics, preoperative factors, and laboratory data of 432 patients.

	ALL (*n* = 432)	No CRRT (*n* = 369)	CRRT (*n* = 63)	*P* value
Age, year, mean ± SD	48.19 ± 10.97	47.69 ± 10.59	51.10 ± 12.63	**0.023**
Gender, n (%)				**0.036**
Male	341 (78.9%)	285 (77.2%)	56 (88.9%)	
Female	91 (21.1%)	84 (22.8%)	7 (11.1%)	
BMI, kg/m^2, mean ± SD	24.85 ± 3.78	24.84 ± 3.65	24.89 ± 4.53	0.916
Smoking, n (%)	210 (48.6%)	181 (49.1%)	29 (46.0%)	0.658
Drinking, n (%)	136 (31.5%)	122 (33.1%)	14 (22.2%)	0.087
Medical history, n (%)				
Hypertension	250 (57.9%)	209 (56.6%)	41 (65.1%)	0.210
Poor blood pressure control	92 (21.3%)	72 (19.5%)	20 (31.7%)	**0.028**
A left ventricular ejection fraction of <35%	28 (6.5%)	22 (6.0%)	6 (9.5%)	0.289
Marfan syndrome	18 (4.2%)	14 (3.8%)	4 (6.3%)	0.348
Previous cardiac surgery	27 (6.3%)	23 (6.2%)	4 (6.3%)	0.972
Aortic regurgitation	176 (40.7%)	150 (40.7%)	26 (41.3%)	0.926
CKD	30 (6.9%)	22 (6.0%)	8 (12.7%)	0.052
COPD	28 (6.5%)	21 (5.7%)	7 (11.1%)	0.106
Diabetes mellitus	20 (4.6%)	11 (3.0%)	9 (14.3%)	**0.000**
Chronic liver disease	22 (5.1%)	18 (4.9%)	4 (6.3%)	0.624
Preoperative factors				
Hemorrhagic shock, n (%)	7 (1.6%)	4 (1.1%)	3 (4.8%)	0.094
Pericardial tamponade, n (%)	20 (4.6%)	17 (4.6%)	3 (4.8%)	0.957
NYHA class III-IV, n (%)	111 (25.7%)	85 (23.0%)	26 (41.3%)	**0.002**
Liver insufficiency, n (%)	51 (11.8%)	36 (9.8%)	15 (23.8%)	**0.001**
Renal artery involvement, n (%)	184 (42.6%)	154 (41.7%)	30 (47.6%)	0.383
Renal malperfusion, n (%)	103 (23.8%)	83 (22.5%)	20 (31.7%)	0.113
No renal malperfusion, n (%)	81 (18.8%)	71 (19.2%)	10 (15.9%)	0.527
Lab data (mean ± SD) or median (IQR)				
Baseline SCr, μmol/L	82 (65, 104)	79 (64, 99)	97 (83, 131)	**0.000**
BUN, mmol/L	6.32 (4.95, 8.60)	6.15 (4.90, 8.30)	7.50 (5.76, 11.41)	**0.000**
UA, umol/L	353 (280, 442)	349 (276, 430)	405 (301, 480)	**0.047**
Cys-C, mg/L	1.30 (0.92, 2.08)	1.2 (0.90, 1.73)	3.11 (1.54, 4.22)	**0.000**
ALB, g/L	37.90 (34.23, 41.10)	38.10 (34.35, 41.15)	36.10 (30.90, 40.30)	0.056
Proteinuria, n (%)	178 (41.2%)	142 (38.5%)	36 (57.1%)	**0.005**
Hematuria, n (%)	123 (28.5%)	104 (28.2%)	19 (30.2%)	0.748

The continuous variables that follow a normal distribution include age, and BMI which were expressed as mean ± SD. The continuous variables that do not follow a normal distribution were represented as median and IQR. The categorical variables were presented as numbers and percentages. Liver insufficiency was defined as a preoperative elevation of >80 U/L of aspartate aminotransferase (AST) or (and) alanine aminotransferase (ALT) in patients.

AKI, acute kidney injury; Scr, serum creatinine; SD, standard deviations; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DHCA, Deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; ALB, albumin; BUN, blood urea nitrogen; UA, uric acid; Cys-C, cystatin C; CRRT, continuous renal replacement therapy. Bold values represented P < 0.05.

TABLE 3 | Interoperative factors, postoperative comorbidities, and outcomes of 432 patients.

	ALL ($n = 432$)	Non-CRRT ($n = 369$)	CRRT ($n = 63$)	*P* value
Interoperative factors				
Total aortic arch replacement n (%)	319 (73.8%)	270 (73.2%)	49 (77.8%)	0.442
DHCA n (%)	105 (24.3%)	93 (25.2%)	12 (19.0%)	0.292
CPB duration ≥180 min n (%)	387 (89.6%)	336 (91.1%)	51 (81.0%)	**0.015**
RBC transfusion (units)	3.0 (1.0, 4.5)	3.0 (0.0, 4.0)	3.5 (2.0, 5.5)	0.150
Postoperative comorbidities, n (%)				
MAP within 2 h after surgery ≤65 mmHg	94 (21.8%)	67 (18.2%)	27 (42.9%)	**0.000**
Second thoracotomy	22 (5.1%)	11 (3.0%)	11 (17.5%)	**0.000**
AMI	14 (3.2%)	8 (2.2%)	6 (9.5%)	**0.002**
CVA	39 (9.0%)	32 (8.7%)	7 (11.1%)	0.532
Lung infection	132 (30.6%)	94 (25.5%)	38 (60.3%)	**0.000**
Lactic acidosis	104 (24.1%)	79 (21.4%)	25 (39.7%)	**0.002**
ARDS	65 (15.0%)	50 (13.6%)	15 (23.8%)	**0.035**
Hepatic failure	40 (9.3%)	29 (7.9%)	11 (17.5%)	**0.015**
AKI stage 2–3	207 (47.9%)	146 (39.6%)	61 (96.8%)	**0.000**
Outcomes				
Duration of mechanical ventilation, days	4 (2, 6)	3 (2, 5)	7 (5, 14)	**0.000**
Hospitalization costs, $	30410.21 (24734.17, 39734.99)	29635.79 (24052.40, 36689.51)	41147.65 (33731.50, 49527.07)	**0.000**
1-year re-admission n (%)	53 (12.3%)	46 (12.5%)	7 (11.1%)	0.762
In-hospital mortality n (%)	66 (15.3%)	37 (10.0%)	29 (46.0%)	**0.000**

The continuous variables and categorical variables were presented as mean ± SD, median and IQR, numbers and percentages, respectively. AKI, acute kidney injury; Scr, serum creatinine; SD, standard deviations; DHCA, deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; AMI, acute myocardial infarction; CVA, acute cerebrovascular accident; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy. Bold values represented P < 0.05. $Represents United States Dollar (USD).

of fit of the logistic regression model, and $P > 0.05$ would indicate a good fit. Only those variables found to be statistically significant in the univariable analysis and with a variance inflation factor (VIF) < 10 in the linear regression analysis were used in logistic regression analysis.

Statistical significance was set at $P \leq 0.05$. Statistical analysis was performed by the SPSS software package, version 26.0 (IBM Corp., Chicago, IL, USA) and GraphPad Prism 8.0 software (GraphPad Software, Inc., San Diego, CA, USA).

RESULTS

Demographic and Clinical Characteristics

A total of 432 patients with AAAD were included in the final sample. The demographic and clinical characteristics and laboratory data of patients hospitalized with AAAD are summarized in **Table 2**.

The mean age of all patients included in the study was 48.19 ± 10.97 years. The median body mass index (BMI) was 24.85 ± 3.78 kg/m^2. There were 250 (57.9%) patients with hypertension and 92 (21.3%) with poor blood pressure control. A small number of patients had chronic kidney injury (CKD, 6.9%), chronic obstructive pulmonary disease (COPD, 6.5%), diabetes (4.6%), chronic liver disease (5.1%), and other comorbidities. The median of baseline SCr level was 82 (65, 104) μmol/L. The median of cystatin C (Cys-C) level was 1.30 (0.92, 2.08) mg/L. According to aortic computed tomography angiography (CTA) findings, 184 patients were diagnosed with renal artery involvement, 103 of which had coexisting renal malperfusion.

Primary and Second Outcomes of Patients With AAAD

Among the recorded patients, 47.9% developed postoperative severe AKI (AKI stages 2–3). The total number of in-hospital mortality and requiring for CRRT was 66 (15.3%) and 63 (14.6%), respectively. In-hospital mortality in the CRRT group (46%) was 4.6 times higher than in the non-CRRT group (10%). Compared with the non-CRRT group, the CRRT group had a longer duration of mechanical ventilation and higher hospitalization costs. No statistical difference was observed in the 1-year readmission rate between the two groups ($P = 0.762$) (**Table 3**).

Risk Factors for Postoperative AKI With CRRT in Patients With AAAD

The multivariable analysis revealed baseline SCr [odds ratio (*OR*), 1.006; $P = 0.011$], Cys-C (*OR*, 1.438; $P = 0.001$), lung infection (*OR*, 2.292; $P = 0.017$), second thoracotomy (*OR*, 5.185; $P = 0.004$), diabetes mellitus (*OR*, 6.868; $P = 0.001$), AKI stage 2–3 (*OR*, 22.901; $P = 0.000$) were the independent risk factors for receiving CRRT (**Table 4**).

TABLE 4 | A multivariable analysis of risk factors associated with continuous renal replacement therapy (CRRT).

Variables	β	Odds ratio	95% confidence interval		*P* value
			Lower	Upper	
Baseline SCr	0.006	1.006	1.001	1.011	**0.011**
Cys-C	0.364	1.438	1.167	1.774	**0.001**
Lung infection	0.829	2.292	1.157	4.539	**0.017**
Second thoracotomy	1.646	5.185	1.700	15.814	**0.004**
Diabetes mellitus	1.927	6.868	2.182	21.621	**0.001**
AKI stage 2–3	3.131	22.901	5.220	100.466	**0.000**

Age, gender, poor blood pressure control, diabetes mellitus, NYHA class III–IV, liver insufficiency, baseline SCr, Cys-C, BUN, UA, proteinuria, MAP within 2 h after surgery ≤ 65 mmHg, second thoracotomy, AMI, lung infection, lactic acidosis, ARDS, hepatic failure, AKI stage 2–3 were included to establish a stepwise forward binary logistic regression (Omnibus tests of model coefficients: $X^2 = 137.693$, $P = 0.000$; Hosmer–Lemeshow goodness-of-fit test: $X^2 = 6.711$, $P = 0.568$; −2 log likelihood = 221.224). In the linear regression analysis of these variables, the variance inflation factor (VIF) was <10. Therefore, there were no problems of multicollinearity among these independent variables. The odds ratio (OR) and 95% CI were measured through binary logistic regression. The OR of the continuous variable represented that for a single unit increase, the probability of a positive event will increase by approximately OR-1 times.

NYHA, New York Heart Association; PLT, platelet; ALB, albumin; SCr, serum creatinine; Cys-C, cystatin C; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; AMI, acute myocardial infarction; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury. Bold values represented P < 0.05.

Risk Factors for In-hospital Mortality in Patients With CRRT After Surgery for AAAD

In this study, 63 patients with CRRT were divided into the survivor (34/63, 54.0%) and non-survivor groups (29/63, 46.0%). The characteristics, perioperative factors, laboratory data, and outcomes of the patients with CRRT are shown in **Table 5**. In the non-survivors and survivors groups, there were statistically significant differences in the history of drinking (41.4 vs. 5.9%), preoperative NYHA class III-IV (75.9 vs. 11.8%), cardiopulmonary bypass (CPB) duration ≥ 180 min (93.1 vs. 70.6%), duration of mechanical ventilation (16.5 vs. 10 days), MAP ≤ 65 mmHg within 2 h postoperatively (62.1 vs. 26.5%), hepatic failure (34.5 vs. 2.9%), acute respiratory distress syndrome (ARDS) (37.9 vs. 11.8%), lactic acidosis (62.1 vs. 20.6%), and CVA (20.7 vs. 2.9%).

In **Table 6**, the multivariable analysis showed that the independent risk factors for in-hospital mortality in the patients with CRRT included preoperative NYHA class III-IV (*OR*, 10.272; $P = 0.019$), lactic acidosis (*OR*, 10.224; $P = 0.019$). The patients with two or more predisposing factors including the history of drinking, CPB duration ≥ 180 min, MAP ≤ 65 mmHg within 2 h postoperatively, ARDS, hepatic failure, and acute cerebrovascular accident (CVA), were high-risk patients for in-hospital death in CRRT (*OR*, 19.816; $P = 0.002$).

DISCUSSION

This is the first study of independent risk factors for in-hospital mortality in patients with CRRT in a homogenous population of patients with AAAD.

In our study with 432 patients, the incidence of severe AKI (AKI stages 2–3), the overall in-hospital mortality, the proportion for requiring CRRT, and in-hospital mortality after CRRT, was 47.9, 15.3, 14.6, and 46.0%, respectively. Our findings revealed that diabetes, SCr, secondary thoracotomy, pulmonary infection, and severe AKI were the independent risk factors for CRRT. Preoperative severe heart failure, postoperative lactic acidosis, and a combination of any three or more risk factors were the independent risk factors for death in the patients with CRRT. The patients in the CRRT group had longer postoperative mechanical ventilation, higher hospitalization costs, and higher in-hospital mortality. This study supports evidence from the previous observations that 11–27% of patients undergoing surgery for aortic dissection required renal replacement therapy (RRT) (11–13) and the mortality for CRRT was between 40 and 70% (9, 14).

In this study, diabetes was found to be considered as an independent risk factor for CRRT that was consistent with the data published by The Japanese Society for Dialysis Therapy (JSDT), who found that diabetes has become the most common initial diagnosis for end-stage renal disease (ESRD) treated with dialysis (15). This is associated with hyperglycemia causing relative ischemia in the kidney, systemic endothelial cell dysfunction (16), podocyte injury (17), and sterile inflammation, leading to kidney injury and deterioration of kidney function (18).

Pulmonary infection was also an independent risk factor for CRRT. Sepsis (19), non-severe pneumonia (20), can give rise to the development and exacerbation of AKI and an increased risk of death due to the inflammatory response and organ crosstalk between lung and kidney (21).

Our findings were in accord with the recent studies indicating that the baseline SCr levels, second thoracotomy were considered as the independent risk factors for CRRT (11, 22, 23). Increased creatinine levels represent impaired kidney function (24). The second thoracotomy is performed when excessive bleeding occurs, which may cause hypovolemia (22). Perioperative hypotension or poor organ perfusion may lead to deterioration of renal function (25, 26).

Several reports have shown that serum cystatin C is a good indicator for identifying early renal impairment and predicting RRT requirements (27–30). Our study confirms that an elevated Cys-C is an independent risk factor for predicting the CRRT. Since serum cystatin C is not affected by diet, etiology of AKI, or urine output, it is a useful and highly diagnostic marker for AKI (27).

A severe and refractory AKI is an indication for CRRT, and early CRRT is recommended for patients with oliguria or fluid overload (31, 32). In our study, we found that AKI stage 2–3 was an independent risk factor for CRRT. CRRT can maintain water, electrolyte, acid-base balance, uremic solute homeostasis to prevent or delay the deterioration of renal function (32). The patients with AKI stage 2–3 had a 1-year survivability rate of 90% if the renal function was restored within 7 days (33, 34). It remains controversial as to the timing of initiation (35), dose, discontinuation (36), quality assessment indicators (37, 38) of RRT in patients with AKI. The clinicians must formulate and select individual treatment plans for their patients (39).

TABLE 5 | Demographics, perioperative factors, and outcomes of 63 patients with CRRT.

	ALL (*n* = 63)	**Non-survivor (*n* = 29)**	**Survivor (*n* = 34)**	***P* value**
Age, year, mean ± SD	51.10 ± 12.63	53.90 ± 12.48	48.71 ± 12.45	0.104
Gender, n (%)				0.326
Male	56 (88.9%)	27 (93.1%)	29 (85.3%)	
Female	7 (11.1%)	2 (6.9%)	5 (14.7%)	
BMI, kg/m^2, median (IQR)	25.06 (22.49, 27.17)	25.06 (22.49, 27.78)	24.86 (22.91, 26.45)	0.610
Smoking, n (%)	29 (46%)	14 (48.3%)	15 (44.1%)	0.741
Drinking	14 (22.2%)	12 (41.4%)	2 (5.9%)	**0.001**
Medical history, n (%)				
Hypertension	41 (65.1%)	19 (65.5%)	22 (64.7%)	0.946
Poor blood pressure control	20 (31.7%)	11 (37.9%)	9 (26.5%)	0.330
A left ventricular ejection fraction of <35%	6 (9.5%)	5 (17.2%)	1 (2.9%)	0.054
Marfan syndrome	4 (6.3%)	1 (3.4%)	3 (8.8%)	0.383
Previous cardiac surgery	4 (6.3%)	3 (10.3%)	1 (2.9%)	0.230
Aortic regurgitation	26 (41.3%)	8 (27.6%)	18 (52.9%)	**0.042**
CKD	8 (12.7%)	2 (6.9%)	6 (17.6%)	0.201
COPD	7 (11.1%)	4 (13.8%)	3 (8.8%)	0.532
Diabetes mellitus	9 (14.3%)	6 (20.7%)	3 (8.8%)	0.180
Chronic liver disease	4 (6.3%)	2 (6.9%)	2 (5.9%)	0.869
Preoperative factors				
Hemorrhagic shock, n (%)	3 (4.8%)	1 (3.4%)	2 (5.9%)	1.000
Pericardial tamponade, n (%)	3 (4.8%)	2 (6.9%)	1 (2.9%)	0.590
NYHA class III-IV n (%)	26 (41.3%)	22 (75.9%)	4 (11.8%)	**0.000**
Liver insufficiency, n (%)	15 (23.8%)	10 (34.5%)	5 (14.7%)	0.066
Renal artery involvement, n (%)	30 (42.7%)	13 (44.8%)	17 (50.0%)	0.682
Renal malperfusion, n (%)	20 (31.7%)	7 (24.1%)	13 (38.2%)	0.231
No renal malperfusion, n (%)	10 (15.9%)	6 (20.7%)	4 (11.8%)	0.492
Lab data (mean ± SD) or median (IQR)				
Baseline Scr, μmol/L	97 (83, 131)	97 (86, 111)	98 (72, 160)	0.720
BUN, mmol/L	7.5 (5.76, 11.41)	8.09 (5.92, 10.75)	7.40 (5.58, 11.70)	0.901
UA, umol/L	390.54 ± 129.90	380.25 ± 125.79	399.31 ± 134.55	0.566
Cys-C, mg/L	3.11 (1.54, 4.22)	2.95 (1.87, 4.15)	3.28 (1.09, 4.33)	0.940
ALB, g/L	36.10 (30.90, 40.30)	36.10 (30.70, 40.80)	36.10 (30.67, 40.23)	0.730
Proteinuria, n (%)	36 (57.1%)	14 (48.3%)	22 (64.7%)	0.189
Hematuria, n (%)	19 (30.2%)	9 (31.0%)	10 (29.4%)	0.889
Interoperative factors				
Total aortic arch replacement n (%)	49 (77.8%)	21 (72.4%)	28 (82.4%)	0.344
DHCA n (%)	12 (19.0%)	6 (20.7%)	6 (17.6%)	0.759
CPB duration ≥180 min n (%)	51 (81.0%)	27 (93.1%)	24 (70.6%)	**0.023**
RBC transfusion (units)	3.5 (3.0, 5.5)	3.0 (1.8, 5.5)	3.8 (2.0, 5.6)	0.527
Postoperative comorbidities, n (%)				
MAP within 2 h after surgery ≤ 65 mmHg	27 (42.9%)	18 (62.1%)	9 (26.5%)	**0.004**
Second thoracotomy	11 (17.5%)	5 (17.2%)	6 (17.6%)	0.966
AMI	6 (9.5%)	4 (13.8%)	2 (5.9%)	0.286
Lung infection	38 (60.3%)	21 (72.4%)	17 (50.0%)	0.070
Hepatic failure	11 (17.5%)	10 (34.5%)	1 (2.9%)	**0.001**
ARDS	15 (23.8%)	11 (37.9%)	4 (11.8%)	**0.015**
Lactic acidosis	25 (39.7%)	18 (62.1%)	7 (20.6%)	**0.001**
CVA	7 (11.1%)	6 (20.7%)	1 (2.9%)	**0.042**

(Continued)

TABLE 5 | Continued

	ALL ($n = 63$)	Non-survivor ($n = 29$)	Survivor ($n = 34$)	*P* value
Outcomes				
Hospitalization costs, $	41276.87 ± 14961.75	42604.69 ± 15729.64	40144.32 ± 14414.22	0.520
Duration of mechanical ventilation, days	7 (5, 14)	16.5 (9, 21)	10 (6, 20)	**0.049**

The continuous variables that follow a normal distribution include age, uric acid (UA), hospitalization costs were expressed as mean ± SD. The continuous variables that do not follow a normal distribution were represented as median and IQR. The categorical variables were presented as numbers and percentages. Liver insufficiency was defined as a preoperative elevation of >80 U/L of AST or (and) ALT in the patients.

AKI, acute kidney injury; Scr, serum creatinine; SD, standard deviations; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DHCA, Deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; ALB, albumin; BUN, blood urea nitrogen; UA, uric acid; Cys-C, cystatin C; CRRT, continuous renal replacement therapy; DHCA, Deep hypothermic circulatory arrest; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; AMI, acute myocardial infarction; CVA, acute cerebrovascular accident; ARDS, acute respiratory distress syndrome. Bold values represented $P < 0.05$.

[$] Represents United States Dollar (USD).

TABLE 6 | The multivariable analysis of risk factors associated with in-hospital mortality in the patients with CRRT.

Variables	β	Odds ratio	95% confidence interval		*P* value
			Lower	Upper	
Lactic acidosis	2.325	10.224	1.459	71.641	**0.019**
NYHA class III-IV	2.329	10.272	1.469	71.802	**0.019**
Risk factors ≥ 2 including Drinking CPB duration ≥180 min MAP within 2 h after surgery ≤65 mmHg Hepatic failure ARDS CVA	2.986	19.816	3.035	129.389	**0.002**

Drinking history, NYHA class III–IV, CPB duration ≥180 min, duration of mechanical ventilation, MAP within 2 h after surgery ≤ 65 mmHg, CVA, lactic acidosis, ARDS, and hepatic failure were included to establish a stepwise forward binary logistic regression (Omnibus tests of model coefficients: $X^2 = 48.417$, $P = 0.000$; Hosmer–Lemeshow goodness-of-fit test: $X^2 = 0.640$, $P = 0.726$; −2 log likelihood = 38.522). In the linear regression analysis of these variables, VIF was <10. There were no problems of multicollinearity among these independent variables. The OR and 95% CI were measured through binary logistic regression.

NYHA, New York Heart Association; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; ARDS, acute respiratory distress syndrome; CVA, acute cerebrovascular accident. Bold values represented $P < 0.05$.

The results of the current study showed that in-hospital mortality in the CRRT group was 4.6 times higher than in the non-CRRT group. It was reported that close to 40% of the patients in the dialysis mortality population died from the causes, such as heart failure, stroke, and myocardial infarction and infection (15), drinking (40), CPB duration (41, 42), hypotension (43), CVA (44), hepatic failure, and ARDS (45). Our findings were coherent with those of the previous studies. The kidney may induce distant organ crosstalk, including lung, heart, liver, or intestine. The prognosis in complicated AKI is poor when distant organ injury occurs (46, 47). Therefore, to reduce dialysis mortality, it is important to treat the distal organ crosstalk caused by AKI rather than focusing on the renal impairment alone (48).

Previous studies had shown that renal malperfusion was an independent risk factor for AKI, 30-day mortality, and poor prognosis in patients with AAAD (5, 49, 50). In our study, there was no significant increase in the incidence of renal malperfusion and renal artery involvement before surgery in the CRRT group and the post-CRRT in-hospital mortality group relative to the other groups. It is probably because that renal malperfusion improved before surgery or because timely treatment after the occurrence of AKI prevented the progression of AKI and thus reduced the usage of CRRT and in-hospital mortality.

Study Limitations

There were certain limitations to the present study: (i) data collected by different people over different periods may be affected by confounding factors, thereby affecting the conclusions; (ii) due to the lack of urine data, the creatinine level was used to define AKI; (iii) our study did not include long-term follow-up and did not clarify long-term outcomes, such as long-term mortality, whether the kidney function recovers after the CRRT or whether the condition progresses to chronic or end-stage renal disease after AAAD.

CONCLUSIONS

In the patients with post-operative AAAD, CRRT was in high demand and in-hospital mortality remained high. Diabetes, baseline SCr, Cys-C, lung infection, second thoracotomy, and

severe AKI were independent risk factors for CRRT. Severe cardiac failure and lactic acidosis were independent risk factors for in-hospital mortality in patients with CRRT. The risk factors for CRRT and in-hospital mortality in patients undergoing AAAD surgery were determined to help identify the high-risk patients and make appropriate clinical decisions. Further randomized-controlled studies are urgently needed to establish the risk factors for CRRT and in-hospital mortality.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committees of the West China Hospital of Sichuan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LY, XC, LJ, and JZ: research idea and study design. XC, LL, and TZ: data acquisition. XC, MF, JY, XW, and SW: statistical analysis. LY, JZ, and LJ: supervision or mentorship. All authors contributed to the article and approved the submitted version.

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ΔPCO_2 and $\Delta PCO_2/C_{(a-cv)}O_2$ Are Not Predictive of Organ Dysfunction After Cardiopulmonary Bypass

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Background: Cardiac surgery is associated with a substantial risk of major adverse events. Although carbon dioxide (CO_2)-derived variables such as venous-to-arterial CO_2 difference (ΔPCO_2), and PCO_2 gap to arterial–venous O_2 content difference ratio ($\Delta PCO_2/C_{(a-cv)}O_2$) have been successfully used to predict the prognosis of non-cardiac surgery, their prognostic value after cardiopulmonary bypass (CPB) remains controversial. This hospital-based study explored the relationship between ΔPCO_2, $\Delta PCO_2/C_{(a-cv)}O_2$ and organ dysfunction after CPB.

Methods: We prospectively enrolled 114 intensive care unit patients after elective cardiac surgery with CPB. Patients were divided into the organ dysfunction group (OI) and non-organ dysfunction group (n-OI) depending on whether organ dysfunction occurred or not at 48 h after CPB. ΔPCO_2 was defined as the difference between central venous and arterial CO_2 partial pressure.

Results: The OI group has 37 (32.5%) patients, 27 of which (23.7%) had one organ dysfunction and 10 (8.8%) had two or more organ dysfunctions. No statistical significance was found ($P = 0.84$) for ΔPCO_2 in the n-OI group at intensive care unit (ICU) admission (9.0, 7.0–11.0 mmHg), and at 4 (9.0, 7.0–11.0 mmHg), 8 (9.0, 7.0–11.0 mmHg), and 12 h post admission (9.0, 7.0–11.0 mmHg). In the OI group, ΔPCO_2 also showed the same trend [ICU admission (9.0, 8.0–12.8 mmHg) and 4 (10.0, 7.0–11.0 mmHg), 8 (10.0, 8.5–12.5 mmHg), and 12 h post admission (9.0, 7.3–11.0 mmHg), $P = 0.37$]. No statistical difference was found for $\Delta PCO_2/C_{(a-cv)}O_2$ in the n-OI group ($P = 0.46$) and OI group ($P = 0.39$). No difference was detected in ΔPCO_2, $\Delta PCO_2/C_{(a-cv)}O_2$ between groups during the first 12 h after admission ($P > 0.05$). Subgroup analysis of the patients with two or more failing organs compared to the n-OI group showed that the predictive performance of lactate and Base excess (BE) improved, but not of ΔPCO_2 and $\Delta PCO_2/C_{(a-cv)}O_2$. Regression analysis showed that the BE at 8 h after admission (odds ratio = 1.37, 95%CI: 1.08–1.74, $P = 0.009$) was a risk factor for organ dysfunction 48 h after CBP.

Conclusion : ΔPCO_2 and $\Delta PCO_2/C_{(a-cv)}O_2$ cannot be used as reliable indicators to predict the occurrence of organ dysfunction at 48 h after CBP due to the pathophysiological process that occurs after CBP.

Keywords: venous-to-arterial carbon dioxide difference, base excess, lactate, cardiopulmonary bypass, organ dysfunction

INTRODUCTION

Despite improvements in surgical technique, anesthesia, management, and postoperative care, cardiac surgery is still associated with a substantial risk of major adverse events (1). Early identification of risk factors and interventions reduce the occurrence of complications. Venous-to-arterial carbon dioxide (CO_2) difference (ΔPCO_2) is a parameter that reflects tissue hypoperfusion in critically ill patients who are insufficiently resuscitated (2). The PCO_2 gap to arterial–venous O_2 content difference ratio ($\Delta PCO_2/C_{(a-cv)}O_2$) has also been described as an indicator of the relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2) (3). Although they have been successfully used to guide fluid resuscitation in patients with sepsis (4, 5) and predict prognosis of non-cardiac surgery patients (6, 7), the predictive value of CO_2-derived variables after cardiopulmonary bypass surgery (CPB) is still controversial (8, 9). CO_2-derived variables may be unable to inform on tissue ischemia because they do not track VO_2 changes in cardiac surgical patients (10). Hyperlactatemia is related to tissue hypoxia but is also affected by factors such as catecholamines and metabolic rate. A previous study found that base excess (BE) is superior to lactate levels for the prediction of ICU mortality after cardiac surgery (11). Organ dysfunction is central to the pathogenesis of death and disability in critically ill patients, and the prognosis becomes worse as the number of failed organs increases. Therefore, it is more meaningful to use organ dysfunction as a clinical outcome variable because of the potential relationship. Although there are many studies on CO_2-derived variables and clinical outcome, few studies have explored the prognostic value of CO_2-derived variables basing on organ dysfunction. Organ dysfunction is considered to be an effective new outcome indicator in cardiac surgical patients, especially when the number of cases required is relatively small (12, 13).

The main objective of this study was to investigate relationship between CO_2-derived variables and organ dysfunction occurring during the early phases after elective cardiac surgery with CPB. The secondary objective was to compare these variables with BE and lactate, which are usually associated with tissue hypoperfusion.

Abbreviations: $\Delta PCO_2/C_{(a-cv)}O_2$, Arterial-venous O_2 content difference ratio; CO_2, carbon dioxide; CPB, cardiopulmonary bypass; Hb, hemoglobin; ICU, intensive care unit; n-OI, non-organ dysfunction group; OI, organ dysfunction group; ΔPCO_2, venous-to-arterial CO_2 difference.

MATERIALS AND METHODS

We conducted a prospective observational study in a 39-bed mixed intensive care unit (ICU) of a university-affiliated Hospital. Our clinical trial was registered in the China Clinical Trial Registry (registration number: ChiCTR-ROC-17010727). Ethics approval was obtained from the Ethics Committee of Taizhou Hospital, Zhejiang Province. Written informed consent was obtained from all patients. The clinical trial started in February 2017 and ended in August 2018.

Adults (≥18 years old) admitted to ICU immediately after CBP, were included if an arterial line and a central venous catheter (confirmed by X-ray) had been inserted. After initiation of the trial, we removed one of the eligibility criteria: "Factors affecting the accuracy of cardiac output monitoring: aortic regurgitation, atrial fibrillation, aortic balloon counter pulsation, high dose norepinephrine," because it was not necessary and would have reduced our sample size. The exclusion criteria were: emergency surgery, pregnancy, chronic renal insufficiency with dialysis, preoperative acute or chronic liver failure, hematologic diseases, misplacement of the central venous catheter, and death within 48 h.

Intraoperative and ICU management was conducted according to local protocols and international guidelines. Ventilator settings were as follows: control mode, tidal volume 6–8 mL/kg, positive end-expiratory pressure ≤5 cmH_2O, respirations 14–16 times/min, fraction of inspired oxygen 40%. Analgesia was achieved with continuous infusion of fentanyl (0.5–10 mg/kg/h) targeting Critical Care Pain Observation Tool scores of 0–2. Anesthesia was maintained with a continuous infusion of propofol (1–4 mg/kg/h) targeting Richmond Agitation-Sedation Scale scores of−2–0. Vasoactive drugs and fluid infusions were adjusted according to mean arterial pressure of 60–70 mmHg. Infusion of red blood cells was prescribed as needed to maintain hemoglobin (Hb) concentration ≥9.0 g/dL. Crystalloid solution (Lactated Ringer's solution or 0.9% saline) or 20% albumin was added for volume expansion if necessary.

We prospectively collected preoperative, intraoperative, and postoperative variables, including clinical characteristics, duration of surgery, CBP duration, vital signs, fluid balance, vasoactive-inotropic score, routine blood tests, blood gas results, and clinical biochemistry. The specific data collection time points were at ICU admission and 4 h (H4), 8 h (H8), 12 h (H12), 24 h (H24), and 48 h (H48) after ICU admission. White blood cell count, hemoglobin concentration, platelet count, clinical biochemistry, chest X-rays, or CT scans were reviewed to evaluate organ function at ICU admission, H24, and H48. The length of stay in ICU, length of ventilator use,

European System for Cardiac Operative Risk Evaluation II, Acute Physiology and Chronic Health Evaluation Score II (APACHE-II), and sequential organ failure score were recorded at ICU admission, H24, and H48. Paired arterial and central venous blood gases, arterial blood lactate, base excess (BE), and Hb levels were measured at ICU admission, H4, H8, and H12 using an automated analyzer (ABL800 Flex, Radiometer Medical Aps, Aakandevej 21, DK-2700 Bronshoj, Denmark).

Vasoactive-inotropic score (14) and CO_2-derived and O_2-derived variables were calculated as follows:

Vasoactive-inotropic score = dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 10 × milrinone (μg/kg/min)

+ 100 × epinephrine (μg/kg/min) + 100 × norepinephrine (μg/kg/min) + 10,000 × vasopressin (μg/kg/min)

$$\Delta PCO_2\ (mmHg) = P_{(cv-a)}CO_2 = P_{cv}CO_2 - P_aCO_2$$

$$C_aO_2(mL/L) = 1.34 \times S_aO_2 \times Hb$$

$$C_{cv}O_2(mL/L) = 1.34 \times S_{cv}O_2 \times Hb$$

$$C_{(a-cv)}O_2\ (mL/L) = C_aO_2 - C_{cv}O_2$$

$$\Delta PCO_2/C_{(a-cv)}O_2(mmHg/mL) = P_{(cv-a)}CO_2/C_{(a-cv)}O_2 = (P_{cv}CO_2 - P_aCO_2)/\ (C_aO_2 - C_{cv}O_2)$$

$$\text{Oxygen extraction ratio}(O_2ER)(\%) = 1 - S_{cv}O_2/S_aO_2$$

The primary outcome variable was organ dysfunction at H48. Briefly, H48 organ dysfunction included: acute respiratory distress syndrome (PaO_2/fraction of inspired oxygen <300 mmHg or PaO_2 <60 mmHg requiring non-invasive ventilation or invasive mechanical ventilation support), acute kidney injury [Kidney Disease Improving Global Outcomes (KDIGO) level ≥1], acute tissue hypoperfusion (presence of tachycardia and hypotension associated with a central venous oxygen saturation <65%, cardiac index ≤2.2 L/min/m^2), cardiac arrest (15) (cessation of cardiac mechanical activity, as confirmed by the absence of circulation signs), arrhythmia (15) (atrial fibrillation for ≥1 min was recorded, analyzed, and defined as "postoperative atrial fibrillation;" ventricular tachycardia and ventricular fibrillation were recorded by continuous ECG monitoring during the intensive care stay), acute neurologic dysfunction (stroke, seizure, persistent delirium, and Glasgow coma score below 12). According to the presence or absence of organ dysfunction at 48 h after CPB, the patients were divided into organ dysfunction group (OI) and non-organ dysfunction group (n-OI). The OI group was further divided into two subgroups: OI-1 including patients with one organ dysfunction, and OI-2 including patients with two or more organ dysfunctions.

Sample Size

GPower software version 3.0.10 was applied to estimate required sample size for this study. This study used repeated-measure, between factors for the analysis. The study effect size was set at 0.25, power was set at 90%, alpha value was set at 0.05, and four -time measurements. Based on these, a minimum total sample of 108 subjects is required.

Statistical Analysis

The statistical analysis was carried out using IBM SPSS 20 software. The Kolmogorov–Smirnoff test evaluated the normality of continuous variables and found that many continuous variables were non-normally distributed. Consequently, all continuous variables were expressed as median. The Mann–Whitney U test or Kruskal–Wallis test was used for group comparison, and repeated-measures ANOVA was used for intragroup comparison. Chi-square test (or Fisher's exact test, when appropriate) was used to compare categorical variables. GraphPad prism version 8.0.2 statistical software was used for boxplot charts.

According to the occurrence of organ dysfunction at H48, the patients were divided into n-OI and OI groups, with the OI group being further subdivided into OI-1 and OI-2 subgroups according to the number of organs with evidence of dysfunction at H48. Comparisons took place within the OI group, within the n-OI group, between the OI and n-OI groups, and between the n-OI and OI-2 subgroups. The ROC curve analysis was carried out to assess the predictive performance of the variables independently associated with H48 organ dysfunction. The area under the curve (AUC) was calculated based on their 95% confidence intervals (CIs).

In a subsequent analysis, variables were introduced into the logistic regression model if significantly associated with H48 organ dysfunction at the univariate analysis, when P-value was < 0.05. A Hosmer–Lemeshow test was used to assess the goodness of fit of the model.

RESULTS

Clinical Characteristics and Prognosis

A total of 139 patients who fulfilled the criteria were screened and 114 patients were included (**Figure 1**). A total of 77 (67.5%) patients formed the n-OI group, and 37 (32.5%) patients comprised the OI group, of which 23.7% (27/114) had one organ dysfunction, 8.8% (10/114) had two or more organ dysfunctions. Compared to the OI group, the n-OI group had shorter length of stay in hospital [10.0 (8.5–14.0) vs. 13.0 (10.0–18.0) days, P = 0.01], shorter length of ICU stay [42.0 (24.0–48.0) vs. 47.0 (27.0–66.5) h, P = 0.02], and lower H24 and H48 sequential organ failure scores [3 (2–5) vs. 5 (4–7), P = 0.01] and [4 (3–5) vs. 5 (3–6), P = 0.02, respectively]. No statistical difference in the duration of mechanical ventilation was detected between the two groups

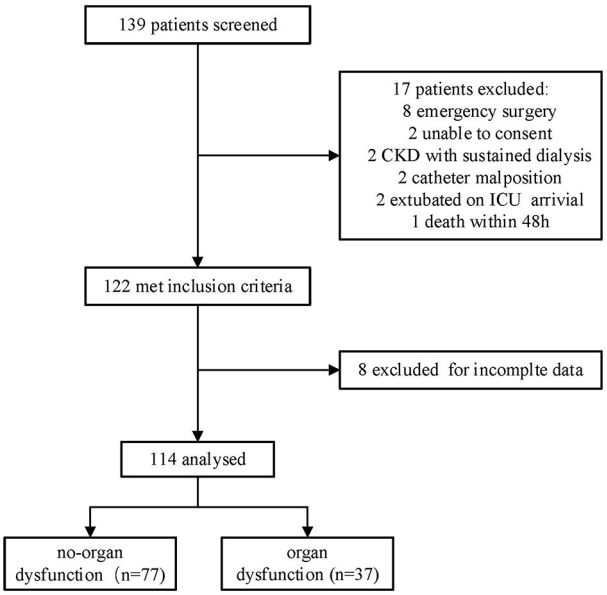

FIGURE 1 | Study flow-chart. CKD, chronic kidney disease.

of patients [19.0 (16.4–21.0) vs. 20.2 (18.5–22.8) h, $P = 0.07$] (**Table 1**).

Dynamic Changes in CO_2-Derived Variables in n-OI and OI Groups

The length of ventilator usage in all patients was 19.5 (range: 17.0–21.0) h. In order to reduce the influence of spontaneous breathing on CO_2-derived variables after weaning, ICU admission, H4, H8, and H12 time points were selected for analysis.

The ΔPCO_2 of the n-OI group at the four time points were 9.0 (7.0–11.0), 9.0 (7.0–11.0), 9.0 (7.0–11.0), and 9.0 (7.0–11.0) mmHg ($P = 0.84$), and those of the OI group were 9.0 (8.0–12.8), 10.0 (7.0–11.0), 10.0 (8.5–12.5), and 9.0 (7.3–11.0) mmHg ($P = 0.37$). The $\Delta PCO_2/C_{(a-cv)}O_2$ of the n-OI group at the four time points were 2.0 (1.6–2.7), 2.1 (1.7–2.8), 2.0 (1.5–2.3), and 2.0 (1.7–2.4) mmHg/mL ($P = 0.46$), and those of the OI group were 2.1 (1.7–2.9), 2.2 (1.8–2.5), 2.1 (1.8–2.6), and 1.8 (1.6–2.5) mmHg/mL ($P = 0.39$) (**Table 2**), respectively. There were no statistical differences in the CO_2-derived variables at any of the four time points ($P > 0.05$) between the n-OI and OI groups (**Figure 2**). Statistically significant differences were observed intragroup for pH, PO_2, BE, Hb concentration, fraction of inspired oxygen, lactate level, fluid balance, and body temperature at all four time points (**Table 2**).

The Prognostic Value of CO_2-Derived Variables

Regarding specific time point variables, ΔPCO_2, $\Delta PCO_2/C_{(a-cv)}O_2$, lactate and BE had no predictive value (**Table 3**). Comparison of the subgroup OI-2 to the n-OI group demonstrated that lactate and BE had limited predictive value (**Table 4**). After adjusting for age (median, ≤58, >58 years old) and gender, H8 BE (odds ratio = 1.37, 95% CI: 1.08–1.74, $P = 0.009$) was a risk factor for H48 organ dysfunction after CPB.

DISCUSSION

Clinical Implications

We found that the $\Delta PCO_2/C_{(a-cv)}O_2$ and ΔPCO_2 did not differ significantly between the two groups at different time points during the first 12 h after ICU admission. Elevated ΔPCO_2 and $\Delta PCO_2/C_{(a-cv)}O_2$ were common phenomena after CPB. The $\Delta PCO_2/C_{(a-cv)}O_2$ and ΔPCO_2 cannot be used to predict H48 organ dysfunction. The predictive performance of lactate and BE was significantly enhanced as the number of dysfunctioning organs increased, although it was limited.

To the best of our knowledge, this study is the first to analyze the association of both ΔPCO_2 and $\Delta PCO_2/C_{a-cv}O_2$ on 48 h-organ dysfunction after adult cardiac surgery. In our study, the ΔPCO_2 value, CPB time, aortic clamping time, and sequential organ failure score at ICU admission were similar to Guinot et al. study (16). They also found that ΔPCO_2 is not predictive of postoperative complications or mortality. Their research did not provide information on the tidal volume and pCO_2, which are thought to affect the accuracy of ΔPCO_2 (17). Our study has very specific ventilator settings, which make up for this deficiency. Additionally, we found that rewarming, Hb dilution, and pH change were universal after CPB, which might have affected the accuracy of our estimations (18, 19). According to the literature, pCO_2 may be elevated due to the accumulation of CO_2 in tissues caused by reperfusion after CPB (20). Another study with negative results was reported by Morel et al. (21), who believe that ΔPCO_2 is difficult to interpret due to the sudden variation of many parameters interfering with tissue perfusion. Such studies with negative results may have a common feature that outcomes may occur before measurement such as vasoplegia, heart failure, and acute renal failure. Furthermore, the complication itself may lead to an increased ΔPCO_2 and, according to the time of measurement, the arrow of causation could be reversed (22). In our study, the median sequential organ failure score was 5, 4, and 3 at ICU admission, and 24 and 48 h post admission, respectively. Therefore, some of the organ dysfunction was suspected to have occurred during surgery. However, we believe that outcomes to be reliable as organ dysfunction generally results in poor outcomes (prolonged ICU stay, prolonged hospital stay).

A review of the literature also found studies with positive results. Mukai et al. (23) found that the ΔPCO_2 at the end of cardiac surgery was a moderate predictor of postoperative complications (area under the curve [AUC]: 0.731; 95% confidence interval [CI] 0.588–0.874), at a 6.8 mmHg cut off with a sensitivity of 72.0% and specificity of 70.6%. Complications are defined as MMOM (major organ morbidity and mortality) (24), as follows: death, stroke requiring drug treatment, renal failure requiring dialysis, prolonged mechanical ventilation (more than 48 h postoperatively), re-operation, and deep sternal infection. It is worth noting that measurements were obtained at the end of surgery and the definition of complications were easy to identify.

TABLE 1 | Clinical characteristics and prognosis of patients in the n-OI and OI groups ($N = 114$).

	All ($N = 114$)	n-OI ($n = 77$)	OI ($n = 37$)	*P*-value
Age (years)	58 (50–66)	56 (47–64)	63 (55–68)	0.01*
Sex				0.32
Male	52	38	14	
Female	62	39	23	
BMI (kg/m^2)	22.7 (20.7–24.9)	22.2 (20.1–24.6)	23.4 (21.7–25.3)	0.048*
Type of surgery				0.58
Valve replacement (or plastic)	81	56	25	
CABG	3	1	2	
Combined surgery	13	8	5	
Other	17	12	5	
Duration of surgery (h)	4.3 (3.5–5.0)	4.0 (3.5–5.0)	4.5 (3.6–5.0)	0.31
CBP duration (min)	100 (78–135)	100 (80–135)	100 (75–145)	0.90
Aortic clamping duration (min)	65 (45–80)	65 (45–80)	60 (50–80)	0.94
Pacemaker (yes /no)	35/79	26/51	9/28	0.39
Comorbidities				0.38
Hypertension	45	27	18	
COPD	3	3	0	
Diabetes	8	3	5	
Stroke	6	4	2	
Chronic kidney disease	2	1	1	
Malignant cancer	2	0	2	
Gastrointestinal disease	4	3	1	
Coronary artery disease	1	0	1	
Vascular disease	3	2	1	
NYHA				0.93
I	8	5	3	
II	74	50	24	
III	30	21	9	
IV	2	1	1	
EuroSCORE	3 (2–5)	3 (1–4.5)	4 (1–5.5)	0.08
APACHEII (H24)	6 (4–8)	6 (4–7)	7 (4–10)	0.16
SOFA (H24)	4 (2–5)	3 (2–5)	5 (4–7)	0.01*
APACHEII (H48)	11 (9–15)	11 (9–14)	12 (9–16)	0.46
SOFA (H48)	3 (4-5)	4 (3–5)	5 (3–6)	0.02*
Length of ventilator (h)	19.5 (17.0–21.0)	19.0 (16.4–21.0)	20.2 (18.5–22.8)	0.07
LOS in ICU (h)	44.0 (24.9–48.5)	42.0 (24.0–48.0)	47.0 (27.0–66.5)	0.02*
LOS in hospital (days)	11.0 (9.0–15.0)	10.0 (8.5–14.0)	13.0 (10.0–18.0)	0.01*

*CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association functional classification; Euro SCORE, European system for cardiac operative risk evaluation; APACHE II, acute physiology and chronic health status score II; SOFA, sequential organ failure score; ICU admission, immediately after entering ICU; H24, 24 h after entering ICU; H48, 48 h after entering ICU. Continuous variables are represented by median (IQR). The Mann–Whitney U test was used for intergroup comparison. Categorical variables were used by Fisher's exact test; *P < 0.05.*

Hence, we cannot exclude that perioperative ΔPCO_2 could be predictive of outcome (21). A previous study reported that $\Delta PCO_2/C_{(a-cv)}O_2$ is not associated with respiratory quotient (25). In our study, $\Delta PCO_2/C_{(a-cv)}O_2$ was not associated with the existence of tissue hypoxia effectively because of its poor relationship with lactate (R^2 =0.067). $\Delta PCO_2/C_{(a-cv)}O_2$ was grouped according to whether it was ≥1.4 mmHg/mL, and no statistical significance were detected in the length of the ventilator, LOS in ICU, or the 24 h and 48 h sequential organ failure score (data not provided). That is probably largely because of the influence of CPB on the activation of inflammation *in vivo*, ischemia-reperfusion injury, myocardial suppression, and other factors, thus, a microcirculation disorder exists that can last for 72 h (26). From our research, we have observed many factors that affect CO_2-derived indicators after cardiac surgery in the real world, including CBP itself (27), translocation, endothelial dysfunction (28, 29), and microcirculation alterations (30) may directly or indirectly cause complications, making the interpretation of the results more complicated.

TABLE 2 | Clinical data on ICU admission and at H4, H8, H12 post admission in n-OI and OI groups.

	n-OI ($n = 77$)				*P*-value	OI ($n = 37$)				*P*-value
	ICU admission	**H4**	**H8**	**H12**		**ICU admission**	**H4**	**H8**	**H12**	
pH	7.40 (7.35–7.45)	7.37(7.31–7.43)*	7.38(7.32–7.43)	7.39 (7.35–7.42)	< 0.01	7.39 (7.31–7.43)	7.35(7.29–7.43)	7.37(7.30–7.41)	7.39 (7.33–7.44)†	0.02
P_aCO_2 (mmHg)	39.0 (35.0–43.0)	39.0 (35.0–43.0)	38.0 (34.5–41.5)	37.0 (34.0–41.0)	0.15	38.0 (35.0–43.0)	38.0 (35.0–43.5)	38.0 (33.5–41.0)	35.0 (32.5–40.0)	0.10
P_aO_2 (mmHg)	155 (113–186)	169 (150–190)	162 (145–181)	159 (141–180)	0.04	138 (102–163)	151 (127–175)	155 (123–179)	146 (115–170)	0.24
BE (mmol/L)	−0.3 (−2.2,−1.7)	−2.2 (−5.1,−0.7)*	−2.7 (−5.3,−0.8)**	−2.2 (−3.9,−0.7)¶	< 0.01	−1.0 (−4.2–0.5)	−2.6 (−6.8–0.8)*	−3.0 (−6.5,−1.6)	−2.2 (−5.3,−0.7)	0.01
Hemoglobin (g/L)	109.0 (101.0–124.0)	116.5 (105.0–128.8)*	112.0 (102.5–129.5)	112.0 (99.3–122.5)†	0.01	116.0 (103.0–125.0)	121.0(101.0–129.0)	115.0 (99.0–127.0)	107.0 (95.5–127.5)	0.17
FiO_2 (%)	50 (40–54)	43 (40–50)*	40 (40–50)**	40 (40–45)† ¶	< 0.01	50 (40–50)	40 (40–50)	40 (40–50)	40 (40–45)¶	< 0.01
S_aO_2 (%)	99 (99–100)	99 (99–100)	99 (99–100)	99 (99–100)	0.15	99 (98–100)	99 (98–99)	99 (98–100)	99 (99–100)	0.18
Lactate (mmol/L)	2.6 (1.7–3.7)	3.1 (2.0–5.1)*	3.5 (2.3–5.5)**	3.3 (2.5–5.3)¶	< 0.01	3.0 (1.9–5.1)	4.1 (2.0–6.1)	4.2 (2.6–7.0)**	3.9 (2.8–6.3)	< 0.01
$S_{cv}O_2$ (%)	71 (61–79)	72 (62–78)	69 (64–76)	71 (59–78)	0.80	68 (61–79)	70 (63–79)	68 (61–75)	68 (62–73)	0.57
ΔPCO_2 (mmHg)	9.0 (7.0–11.0)	9.0 (7.0–11.0)	9.0 (7.0–11.0)	9.0 (7.0–11.0)	0.84	9.0 (8.0–12.8)	10.0 (7.0–11.0)	10.0 (8.5–12.5)	9.0 (7.3–11.0)	0.37
S_aO_2–$S_{cv}O_2$ (%)	29 (20–38)	27 (21–35)	31 (23–36)	29 (21–39)	0.71	31 (22–40)	27 (20–38)	31 (21–39)	31 (26–38)	0.52
$C_{a\text{-}cv}O_2$ (mL/ L)	4.1 (3.1–5.4)	4.2 (3.0–5.5)	4.5 (3.7–5.4)	4.2 (3.2–5.8)	0.52	4.4 (3.8–5.5)	4.3 (3.3–5.5)	4.5 (3.4–5.9)	4.8 (3.8–5.3)	0.52
$\Delta PCO_2/C_{(a-cv)}O_2$ (mmHg/mL)	2.0 (1.6–2.7)	2.1 (1.7–2.8)	2.0 (1.5–2.3)	2.0 (1.7–2.4)	0.46	2.1 (1.7–2.9)	2.2 (1.8–2.5)	2.1 (1.8–2.6)	1.8 (1.6–2.5)	0.39
O_2ER (%)	29 (20–38)	27 (21–35)	31 (23–36)	29 (21–39)	0.70	31 (23–40)	27 (20–38)	31 (22–39)	40 (27–38)	0.53
Ventilator setting										
Tidal volume (mL)	453 (406–498)	448 (406–496)	450 (405–500)	459 (407–500)	0.54	454 (442–500)	462 (432–497)	461 (425–501)	466 (439–507)	0.56
Frequency (/min)	15.0 (15.0–16.0)	15.0 (15.0–16.0)	15.0 (15.0–16.0)	15.0 (15.0–16.0)	0.96	15.0 (15.0–16.0)	15.0 (15.0–16.0)	15.0 (15.0–16.0)	15.0 (15.0–16.0)	0.72
PEEP (cmH_2O)	5.0 (4.0–5.0)	5.0 (3.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.84	5.0 (4.0–5.0)	5.0 (5.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	0.78
Fluid challenge										
Intake (mL)	1845 (1500–2273)	640 (470–852)*	1130 (855–1483)‡**	1470 (1083–1883)¶†ξ	< 0.01	1651 (1275–2370)	530 (385–749)*	1045 (885–1248)‡**	1455 (1138–1828)†ξ	< 0.01
Output (mL)	1300 (1000–2000)	690 (530–893)*	1015 (818–1300)‡**	1285 (1040–1620)†ξ	< 0.01	1500 (1075–2275)	635 (490–968)*	955 (770–1349)‡**	1170 (990–1628)†ξ	< 0.01
Fluid balance (mL)	261 (-25–757)	−66 (-295–250)*	88 (-180–521)‡	140 (-182–541)†	< 0.01	350 (-230–900)	−90 (-398–112)*	15 (-298–327)‡	115 (-90–588)†ξ	< 0.01
VIS	4.0 (2.0–6.8)	4.0 (2.0–8.0)	4.0 (1.9–9.0)	4.0 (1.0–9.0)	0.36	4.0 (2.0–6.0)	5.3 (1.3–10.8)	5.5 (2.0–11.8)	5.0 (2.0–11.8)	0.10
Vital signs										
SBP (mmHg)	105 (100–121)	105 (93–112)	103 (96–112)	104 (98–113)	0.06	105 (92–116)	103 (94–114)	103 (95–113)	108 (102–115)	0.24
DBP (mmHg)	60 (54–68)	57 (53–63)	58 (54–64)	59 (54–64)	0.10	59 (54–66)	59 (55–65)	55 (51–64)	58 (51–66)	0.16
MAP (mmHg)	76 (68–85)	72 (68–79)	72 (69–78)	73 (67–79)	0.09	73 (66–80)	75 (68–79)	74 (65–80)	73 (70–81)	0.76
CVP (mmHg)	8 (7–11)	8 (7–10)	8 (6–10)	7 (6–10)	0.14	8 (5–10)	8 (6–9)	8 (6–10)	8 (6–11)	0.86
Temperature (°C)	37.0 (36.0–37.0)	36.7 (36.5–37.0)*	37.0(36.5–37.3)‡**	37.1 (36.6–37.4)¶†	< 0.01	37.0 (36.0–37.0)	36.5 (36.25–37.0)	36.8 (36.5–37.2)**	37.2 (37.0–37.6)¶†	< 0.01
Respiratory rate (/min)	15 (15–16)	15 (15–16)	15 (15–16)	15 (15–16)	0.89	15 (15–16)	15 (15–16)	15 (15–16)	15 (15–16)	0.75
Heart rate (/min)	85 (78–91)	83 (76–92)	83 (74–92)	81 (74–89)	0.22	89 (79–99)	86 (75–99)	84 (71–96)	84 (80–96)	0.42

*P_aCO_2, arterial partial pressure of carbon dioxide; P_aO_2, arterial partial pressure of oxygen; BE, base excess; FiO_2, fraction of inspiration O_2; S_aO_2, arterial oxygen saturation; $S_{cv}O_2$, central venous oxygen saturation; ΔPCO_2, central venous-to-arterial carbon dioxide difference; $\Delta PCO_2/C_{(a-cv)}O_2$, ΔPCO_2 to arterial-central venous oxygen content difference rate; O_2ER, oxygen extraction ratio; VIS, vasoactive-inotropic score; SBP, systolic pressure; DBP, diastolic pressure; MAP, mean arterial pressure; CVP, central venous pressure. Continuous variables are represented by median (IQR). Repeated-measures ANOVA was used for intragroup comparison. *$P < 0.05$ for groups H0 vs. H4, **$P < 0.05$ for groups H0 vs. H8, ¶$P < 0.05$ for groups H0 vs. H12, ‡ $P < 0.05$ for groups H4 vs. H8, $^{\dagger}P < 0.05$ for groups H4 vs. H12, ξ $P < 0.05$ for groups H8 vs. H12.*

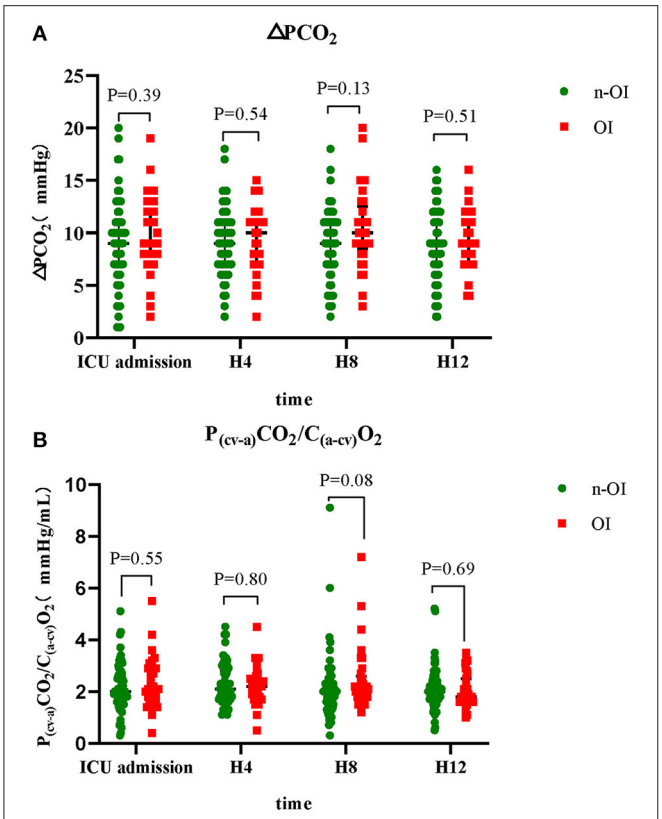

FIGURE 2 | Dynamic changes of carbon dioxide-derived variables of n-OI and OI groups at the four time points. **(A)** central venous-to-arterial carbon dioxide difference (ΔPCO_2) **(B)** ΔPCO_2 to arterial-central venous oxygen content difference rate ($\Delta PCO_2/C_{(a-cv)}O_2$). GraphPad prism version 8.0.2 statistical software was used to construct box charts (median with interquartile range). The Mann–Whitney U test was used for intergroup comparison.

TABLE 3 | Area under the ROC curve of variables grouped into n-OI and OI.

Variable	AUC	Standard error	*P*-value	95% CI
ICU admissionΔPCO_2	0.571	0.072	0.334	0.430–0.711
H4ΔPCO_2	0.514	0.076	0.843	0.366–0.663
H8ΔPCO_2	0.588	0.072	0.230	0.447–0.729
H12ΔPCO_2	0.566	0.070	0.366	0.429–0.704
ICU admission $\Delta PCO_2/C_{(a-cv)}O_2$	0.510	0.075	0.892	0.363–0.658
H4$\Delta PCO_2/C_{(a-cv)}O_2$	0.479	0.074	0.776	0.333–0.625
H8$\Delta PCO_2/C_{(a-cv)}O_2$	0.588	0.071	0.236	0.449–0.728
H12$\Delta PCO_2/C_{(a-cv)}O_2$	0.443	0.076	0.448	0.295–0.592
ICU admission Lactate	0.586	0.063	0.150	0.463–0.710
H4 Lactate	0.569	0.063	0.254	0.446–0.691
H8 Lactate	0.567	0.060	0.265	0.449–0.685
H12 Lactate	0.574	0.063	0.219	0.451–0.697
ICU admission Base excess	0.608	0.058	0.069	0.494–0.722
H4 Base excess	0.578	0.059	0.190	0.463–0.693
H8 Base excess	0.594	0.058	0.112	0.481–0.708
H12 Base excess	0.544	0.061	0.462	0.423–0.664

ΔPCO_2, central venous-to-arterial carbon dioxide difference; $\Delta PCO_2/C_{(a-cv)}O_2$, ΔPCO_2 to arterial-central venous oxygen content difference rate. SPSS 20 statistical software.

TABLE 4 | Area under the ROC curve of variables grouped into n-OI and OI-2.

Variable	AUC	Standard error	*P*-value	95% CI
ICU admissionΔPCO_2	0.538	0.105	0.713	0.333–0.744
H4ΔPCO_2	0.549	0.118	0.636	0.318–0.780
H8ΔPCO_2	0.591	0.118	0.380	0.360–0.822
H12ΔPCO_2	0.456	0.119	0.674	0.224–0.689
ICU admission $\Delta PCO_2/C_{(a-cv)}O_2$	0.562	0.109	0.550	0.348–0.777
H4$\Delta PCO_2/C_{(a-cv)}O_2$	0.670	0.100	0.104	0.473–0.866
H8$\Delta PCO_2/C_{(a-cv)}O_2$	0.700	0.104	0.055	0.497–0.903
H12$\Delta PCO_2/C_{(a-cv)}O_2$	0.557	0.119	0.581	0.324–0.791
ICU admission Lactate	0.635	0.103	0.195	0.434–0.837
H4 Lactate	0.634	0.098	0.198	0.442–0.826
H8 Lactate	0.715	0.099	0.039*	0.521–0.908
H12 Lactate	0.634	0.123	0.198	0.393–0.875
ICU admission Base excess	0.662	0.103	0.093	0.459–0.864
H4 Base excess	0.723	0.104	0.021*	0.519–0.926
H8 Base excess	0.831	0.061	0.001*	0.710–0.951
H12 Base excess	0.703	0.103	0.035*	0.501–0.904

*ΔPCO_2, central venous-to-arterial carbon dioxide difference; $\Delta PCO_2/C_{(a-cv)}O_2$, ΔPCO_2 to arterial-central venous oxygen content difference rate. SPSS 20 statistical software, *$P < 0.05$.*

Hyperlactatemia is common after cardiopulmonary bypass, and it can be influenced by many factors. Patients undergoing CPB are exposed to the "elution effect," i.e., the release of lactic acid from the lungs (31) and the liver due to organ malfunction associated with CPB (32). A recent study has demonstrated that hyperlactatemia may be also in relation to tissue metabolic uncoupling (33). Therefore, lactic acid does not always reflect tissue hypoxia. The predictive value of lactate after CPB surgery is limited. This study demonstrated that postoperative lactic acidemia is common, with progressively decreasing levels of lactic acid observed in both groups. After adjustment for confounding factors, compared to ΔPCO_2 and $\Delta PCO_2/C(a\text{-}cv)O_2$, lactic acid has a moderate ability to predict two or more organ dysfunction. In addition, BE is the amount of base in mmol required to titrate 1 L of whole arterial blood to a pH of 7.40, with the sample fully saturated with oxygen at 37°C and a P_aCO_2 of 40 mmHg. We also found that BE was a more robust predictor of H48 organ dysfunction than lactic acid, and H8 BE was a risk factor for dysfunction of two or more organs (odds ratio = 1.37), whereas lactic acid was not. A high negative value of BE may be associated with renal dysfunction, metabolic acidosis, and shock, but the factors associated with the reduced systemic BE in patients after cardiac surgery are yet to be clarified (34). We speculated that lactic acidosis might be one of the main

reasons leading to the high negative value of BE because a good correlation was established between BE and lactic acid ($R2 = 0.599$, $P < 0.05$), which could also explain the low susceptibility of BE to interference from other factors.

Methodological Considerations

This study has some limitations. First, this was a single-center study, and its results may not be generalizable. Second, the sample size was relatively small, and no deaths occurred among the study patients. Third, because the group classification was based solely on the occurrence of organ dysfunction, a misclassification bias may have occurred. However, our subgroup analysis was based on the number of failing organs and resulted in similar conclusions. Fourth, $P_{cv-a}CO_2/C_{(a-cv)}O_2$ cannot replace $P_{mv-a}CO_2/C_{(a-cv)}O_2$ (mv: mixed venous blood) and might have underestimated the CO_2 exchange from splanchnic circulation. Finally, it was not easy to detect when the outcome of interest, i.e., organ dysfunction, first occurred relative to the measurement. Continuous measurements or change over time may have more prognostic value than a single time point. However, the dynamic changes of ΔPCO_2 at t0 and T6 time points were not found to be associated with postoperative complications or mortality in children after CPB (16).

CONCLUSION

In conclusion, ΔPCO_2 and $\Delta PCO_2/C_{(a-cv)}O_2$ cannot be used as reliable indicators to predict the occurrence of organ dysfunction at 48 h after CBP, which is due to the complex pathophysiological processes after CBP.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Taizhou Hospital, Zhejiang Province. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SZ: data curation, investigation, resources, writing—original draft, validation, and funding acquisition. DZ: data curation, investigation, and methodology. X-QC: data curation, investigation, methodology, and software. Y-PJ, L-ZQ, W-YY, and W-YZ: data curation, investigation, and resources. C-GW: data curation and formal analysis. Q-MZ: data curation and resources. T-HT: design of the study and performed data synthesis of the revised stage. R-HL: conceptualization, data curation, formal analysis, funding acquisition, software, validation, writing—review, and editing. All authors have read and approved the manuscript.

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Performance of Sequential Organ Failure Assessment and Simplified Acute Physiology Score II for Post-Cardiac Surgery Patients in Intensive Care Unit

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Background: The aim of this study is to assess the performance of Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score (SAPS II) on outcomes of patients with cardiac surgery and identify the cutoff values to provide a reference for early intervention.

Methods: All data were extracted from MIMIC-III (Medical Information Mart for Intensive Care-III) database. Cutoff values were calculated by the receiver-operating characteristic curve and Youden indexes. Patients were grouped, respectively, according to the cutoff values of SOFA and SAPS II. A non-adjusted model and adjusted model were established to evaluate the prediction of risk. Comparison of clinical efficacy between two scoring systems was made by decision curve analysis (DCA). The primary outcomes of this study were in-hospital mortality, 28-day mortality, 90-day mortality, and 1-year mortality after cardiac surgery. The secondary outcomes included length of hospital stay and intensive care unit (ICU) stay and the incidence of acute kidney injury (AKI) within 7 days after ICU admission.

Results: A total of 6,122 patients were collected and divided into the H-SOFA group (SOFA $\geq$ 7) and L-SOFA group (SOFA $<$ 7) or H-SAPS II group (SAPS II $\geq$ 43) and L-SAPS II group (SAPS II $<$ 43). In-hospital mortality, 28-day mortality, 90-day mortality, and 1-year mortality were higher, the length of hospital and ICU stay were longer in the H-SOFA group than in the L-SOFA group ($p < 0.05$), while the incidence of AKI was not significantly different. In-hospital mortality, 28-day mortality, 90-day mortality, 1-year mortality, and the incidence of AKI were all significantly higher in the H-SAPS II group than in the L-SAPS II group ($p < 0.05$). Hospital stay and ICU stay were longer in the H-SAPS II group than in the L-SAPS II group ($p < 0.05$). According to DCA, the SAPS II scoring system had more net benefits on assessing the long-term mortality compared with the SOFA scoring system.

Conclusion: Exceeding the cutoff values of SOFA and SAPS II scores could lead to increased mortality and extended length of ICU and hospital stay. The SAPS II scoring

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system had a better discriminative performance of 90-day mortality and 1-year mortality in post-cardiac surgery patients than the SOFA scoring system. Emphasizing the critical value of the scoring system is of significance for timely treatment.

Keywords: post-cardiac surgery, SOFA, SAPS II, clinic outcome, intensive care unit

INTRODUCTION

Prognosis is a common challenge for patients after cardiac surgery. Although some progress has been achieved in the application of cardiac surgery procedures, the mortality rates after surgery remain high. Some scoring systems played an important role in the successful prediction of cardiac surgery-related mortality (1, 2). There was a preoperative risk stratification model, which had been widely accepted for mortality prediction of in-hospital mortality after cardiac surgery (3).

However, the scoring system focused on preoperative indicators without attention to intraoperative or postoperative conditions (4). The severity of surgical stress and inflammatory response to cardiopulmonary surgery could not be ignored (5) in cases that were associated with organ dysfunction and acute physiological changes. Previous studies reported that hyperlactatemia, bicarbonate, heart rate, and creatinine were essential for post-cardiac surgery patients as mortality-predictive variables (6–8). Recent studies had confirmed that the neutrophil/lymphocyte ratio of post 24 h after intensive care unit (ICU) admission is associated with postoperative mortality of cardiac surgery (9). Parameters and physiological indexes of post 24 h after ICU admission may provide a new way to improve prognosis early.

The Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score (SAPA II) were composed of organ function and biochemical indexes, which showed excellent predictive performance on many diseases in ICU (10, 11). There were few pieces of small sample literature that explored the role of SAPS II and SOFA scoring systems in predicting poor prognosis after cardiac surgery (12). The purpose of this study was to determine the critical values of the SAPS II and SOFA scoring system and to evaluate their performance in predicting the prognosis of patients undergoing cardiac surgery.

MATERIALS AND METHODS

Sources of Data

All data in this study were retrospectively extracted from MIMIC-III (Medical Information Mart for Intensive Care-III) database (13, 14). This is a freely open database for the public, which includes more than 40,000 critically ill patients from Beth Israel Deaconess Medical Center (Boston, Massachusetts, United States) between 2001 and 2012. The application of the database was approved by the institutional review committee of Beth Israel Deaconess Medical Center and Beth Israel Deacons Medical Center (Approval Code 10323541). Patient-related information in the database was anonymous, and personal informed consent was abandoned in this study.

Data Collection and Definitions

The structure query language (SQL) with code in MIMIC Code Repository (https://github.com/MIT-LCP/Mimic-Website) was used for extracting data. The whole variables involved basic characteristics (age, gender, body mass index), comorbidities (drug abuse, alcohol abuse, coagulopathy, liver disease, hypertension, hypothyroidism, congestive heart failure, diabetes, chronic lung disease, chronic kidney disease), laboratory tests (sodium, potassium, white blood cell counts, hemoglobin, platelet, lactate, creatinine, blood urea nitrogen, prothrombin time, international normalized ratio, glucose), and vital signs (heart rate, respiratory rate, body temperature, pulse oxygen saturation, diastolic pressure, systolic pressure, and mean arterial pressure). The SOFA score and SAPS II score were evaluated within the first 24 h after ICU admission. Variables were reported as the average value within 24 h admitted to ICU.

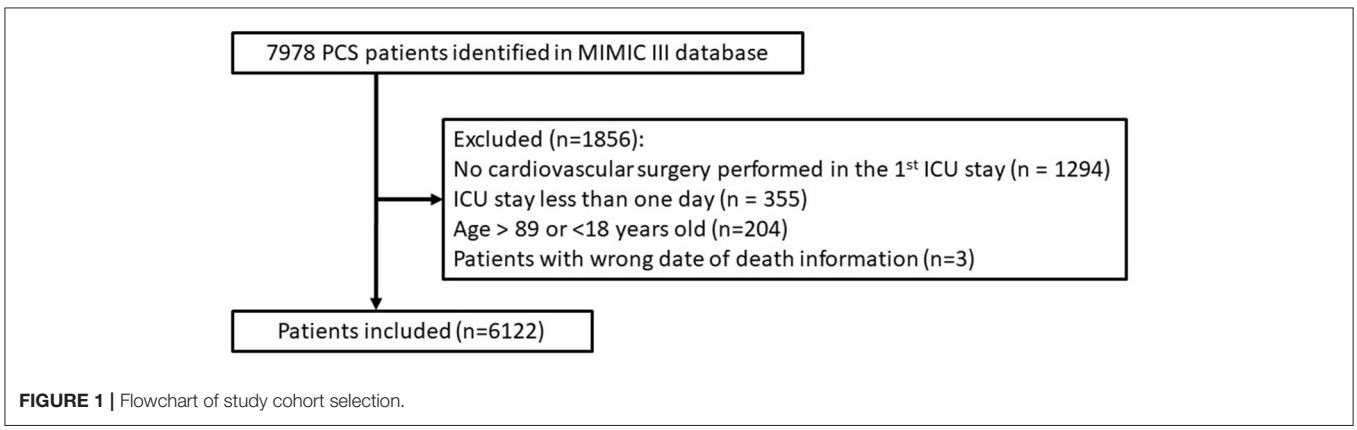

FIGURE 1 | Flowchart of study cohort selection.

TABLE 1 | Baseline clinical characteristics between survivors and non-survivors at 1 year.

Characteristics	Overall (n = 6,122)	Survivors (n = 4,516)	Non-survivors (n = 1,606)	p
Age, median (IQR)	66 (55, 76)	65.0 (54.0, 74.0)	69.0 (58.0, 79.0)	<0.001
Male gender, *n* (%)	3,704 (60.503)	2,790 (61.780)	914 (56.912)	<0.001
BMI, median (IQR)	27.84 (24.39, 31.84)	28.04 (24.67, 32.04)	27.06 (23.55, 31.24)	<0.001
Comorbidities				
Drug abuse, *n* (%)	208 (3.398)	156 (3.454)	52 (3.238)	0.681
Alcohol abuse, *n* (%)	474 (7.743)	331 (7.329)	143 (8.904)	0.043
Coagulopathy, *n* (%)	1,153 (18.834)	661 (14.637)	492 (30.635)	<0.001
Congestive heart failure, *n* (%)	816 (13.329)	384 (8.503)	432 (26.899)	<0.001
Liver disease, *n* (%)	463 (7.563)	250 (5.536)	213 (13.263)	<0.001
Renal failure, *n* (%)	869 (14.195)	526 (11.647)	343 (21.357)	<0.001
hypothyroidism, *n* (%)	617 (10.078)	460 (10.186)	157 (9.776)	0.639
Diabetes, *n* (%)	1,448 (23.652)	1,080 (23.915)	368 (22.914)	0.418
Chronic pulmonary, *n* (%)	1,179 (19.258)	818 (18.113)	361 (22.478)	<0.001
hypertension, *n* (%)	758 (12.382)	481 (10.651)	277 (17.248)	<0.001
Laboratory test				
WBC mean, median (IQR)	11.93 (8.9, 15.55)	11.85 (9.13, 15.2)	12.3 (8.1, 16.74)	0.347
BUN mean, median (IQR)	18.33 (13.0, 29.4)	16.5 (12.5, 23.5)	28.5 (18.0, 47.5)	<0.001
Sodium mean, median (IQR)	138.0 (136.0, 140.2)	138.0 (136.2, 140.0)	138.4 (135.33, 141.5)	0.002
PT mean, median (IQR)	14.65 (13.6, 16.2)	14.47 (13.5, 15.7)	15.6 (13.95, 18.6)	<0.001
INR mean, median (IQR)	1.3 (1.2, 1.5)	1.3 (1.2, 1.4)	1.43 (1.2, 1.8)	<0.001
Potassium mean, median (IQR)	4.19 (3.87, 4.5)	4.2 (3.9, 4.49)	4.15 (3.8, 4.6)	0.095
Platelet mean, median (IQR)	175.33 (130.33, 233.33)	176.33 (136.0, 228.5)	172.0 (109.67, 253.5)	0.007
Lactate mean, median (IQR)	1.93 (1.4, 2.7)	1.9 (1.4, 2.6)	2.0 (1.4, 3.1)	<0.001
Hemoglobin mean, median (IQR)	10.15 (9.15, 11.4)	10.2 (9.18, 11.4)	10.0 (9.05, 11.3)	0.001
Glucose mean, median (IQR)	130.57 (116.0, 150.89)	129.67 (116.43, 146.5)	135.25 (114.4, 166.86)	<0.001
Creatinine mean, median (IQR)	0.95 (0.72, 1.37)	0.9 (0.7, 1.18)	1.27 (0.83, 2.24)	<0.001
PH mean, median (IQR)	7.38 (7.34, 7.41)	7.38 (7.34, 7.41)	7.37 (7.31, 7.42)	<0.001
Vital sign				
SpO_2 mean, median (IQR)	97.77 (96.52, 98.81)	97.86 (96.72, 98.86)	97.47 (95.88, 98.7)	<0.001
BT mean, median (IQR)	36.81 (36.43, 37.24)	36.85 (36.47, 37.25)	36.74 (36.32, 37.21)	<0.001
Resp rate mean, median (IQR)	18.12 (16.08, 21.17)	17.7 (15.86, 20.25)	20.0 (17.19, 23.69)	<0.001
Mean bp mean, median (IQR)	75.11 (70.17, 81.36)	75.44 (70.79, 81.27)	74.02 (68.07, 81.73)	<0.001
Dias bp mean, median (IQR)	58.39 (53.15, 64.3)	58.64 (53.77, 64.37)	57.51 (51.26, 64.07)	<0.001
Sys bp mean, median (IQR)	112.86 (105.52, 122.26)	113.35 (106.45, 122.03)	111.22 (102.62, 123.08)	<0.001
Heartrate mean, median (IQR)	85.83 (77.53, 96.52)	84.77 (77.35, 94.74)	88.91 (78.05, 101.72)	<0.001
Score system				
SPAS II, median (IQR)	38 (30, 48)	35.0 (28.0, 44.0)	48.0 (38.0, 57.0)	<0.001
SOFA, median (IQR)	5 (3, 8)	5.0 (3.0, 7.0)	7.0 (4.0, 10.0)	<0.001
AKI 7-day, (%)	4,563 (74.534)	3,268 (72.365)	1,295 (80.635)	<0.001
Hospital stay ≥ 14 days, *n* (%)	2,092 (34.172)	1,359 (30.093)	733 (45.641)	<0.001
ICU stay ≥ 3 days, *n* (%)	3,422 (55.897)	2,265 (50.155)	1,157 (72.042)	<0.001
Survival time, median (IQR)	11.15 (6.26, 27.17)	9.89 (6.08, 19.68)	22.2 (8.08, 78.7)	<0.001

BMI, body mass index; WBC, white blood cell count; BUN, Blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; SOFA, sequential organ failure assessment; SPASII, simplified acute physiology score; AKI, acute kidney injury; ICU, the intensive care unit; SpO_2, pulse oxygen saturation; PH, potential of hydrogen; BT, body temperature; Data are represented as median (interquartile range) or n (%).

Patients with cardiac surgery whose diagnose code ranged from 33,010 to 37,799 were identified using current procedural terminology. Inclusion criteria were patients aged between 18 and 89 years, choosing the first hospitalization for analysis when admitted to hospital or ICU multiple times. Patients hospitalized in ICU <24 h were excluded. The primary outcomes were in-hospital mortality, 28-day mortality, 90-day mortality, and 1-year mortality after cardiac surgery. The secondary outcomes were the length of hospital stay, ICU stay, and the incidence of acute kidney injury (AKI) within 7 days after ICU admission.

The diagnosis of AKI referenced the improving global outcomes guideline (15).

Statistical Methods

Continuous variables of the study were non-normally distributed and reported as medians along with interquartile ranges (IQRs). Categorical variables were presented as numbers and percentages. Comparison of different groups was made using Kruskal–Wallis test or Mann–Whitney U-test for continuous variables, whereas chi-square or Fisher's exact tests were used for categorical variables. Non-adjusted models and adjusted models were established to investigate the association between scoring systems and outcomes in this study.

The cutoff values of SOFA and SAPS II scoring systems were obtained across receiver-operating characteristic (ROC) curve and Youden Indexes calculation. Based on different cutoff values, patients were divided into two groups. The clinical efficacy of scoring system models for poor outcomes was assessed by decision curve analysis (DCA), which was considered an appropriate method for estimating prognostic strategies (16). Kaplan–Meier curve was used to describe the difference in 1-year survival between different groups of the scoring system.

The SPSS software version 24.0 (IBM Corporation, Armonk, NY, United States) and the R software (version 4.0.3) were used for data processing, statistical analysis, and illustrations. Data missing 30% were removed and data missing <30% were processed by multiple imputations. Statistical differences were set at $p < 0.05$.

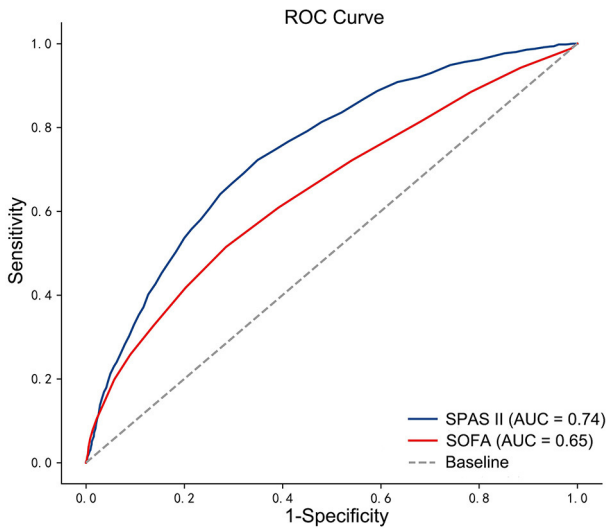

FIGURE 2 | The ROC curves for SOFA score and SAPS II score with 1-year postoperative mortality. ROC, receiver-operating characteristic.

RESULTS

Clinical Characteristics

A total of 6,122 patients admitted to ICU after cardiac surgery were enrolled retrospectively. The procedures and standards for data selection are shown in **Figure 1**. The clinical basic characteristics of the populations are shown in **Table 1**.

The AUC of SOFA and SAPS II scoring systems with 1-year postoperation mortality was 0.649 ($p < 0.001$) and 0.724 ($p < 0.001$), respectively (**Figure 2**). The cutoff value of the SOFA scoring system was 7, whereas the critical value of the SAPS II scoring system was 43. In the SOFA scoring system, the patients were divided into high SOFA group (H-SOFA group, SOFA ≥ 7, $N = 2{,}114$) and low SOFA group (L-SOFA group, SOFA < 7, $N =$

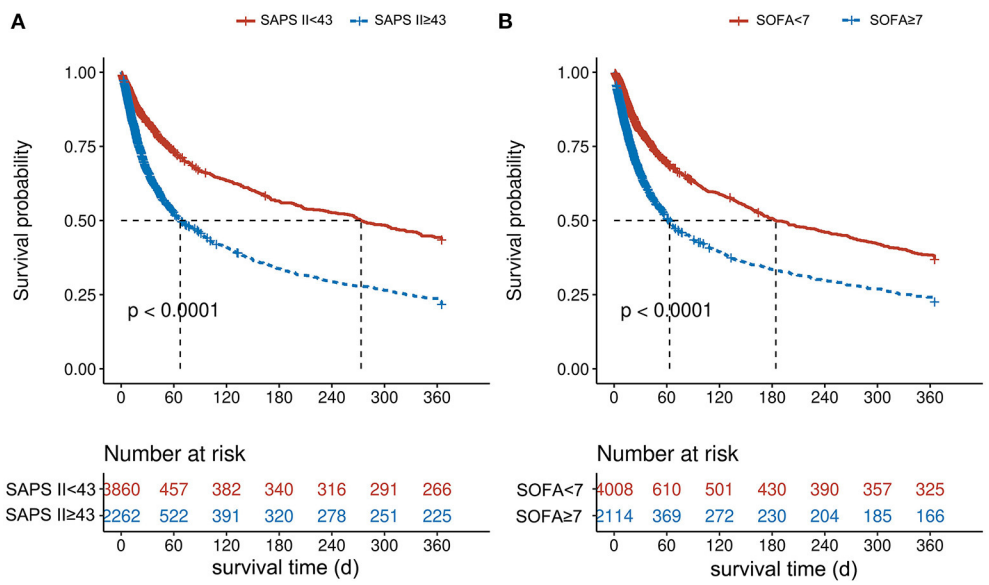

FIGURE 3 | Kaplan–Meier curves of 1-year mortality by scoring system groups. **(A)** For the SAPS II score, while **(B)** is for the SOFA score.

TABLE 2 | Basic characteristics of SOFA scoring system.

Characteristics	Overall (*n* = 6,122)	SOFA < 7 (*n* = 4,008)	SOFA≥7 (*n* = 2,114)	*p*
SOFA, median (IQR)	5 (3, 8)	4.0 (2.0, 5.0)	9.0 (8.0, 11.0)	<0.001
Age, median (IQR)	66 (55, 76)	66.0 (55.0, 76.0)	66.0 (55.0, 76.0)	0.793
Male gender, *n* (%)	3,704 (60.503)	2,385 (59.506)	1,319 (62.394)	0.028
BMI, median (IQR)	27.84 (24.39, 31.84)	27.62 (24.22, 31.59)	28.25 (24.69, 32.28)	<0.001
Comorbidities				
Drug abuse, *n* (%)	208 (3.398)	126 (3.144)	82 (3.879)	0.131
Alcohol abuse, *n* (%)	474 (7.743)	253 (6.312)	221 (10.454)	<0.001
coagulopathy, *n* (%)	1,153 (18.834)	464 (11.577)	689 (32.592)	<0.001
Liver disease, *n* (%)	463 (7.563)	193 (4.815)	270 (12.772)	<0.001
Renal failure, *n* (%)	869 (14.195)	405 (10.105)	464 (21.949)	<0.001
hypothyroidism, *n* (%)	617 (10.078)	417 (10.404)	200 (9.461)	0.244
diabetes, *n* (%)	1,448 (23.652)	934 (23.303)	514 (24.314)	0.376
Chronic pulmonary, *n* (%)	1,179 (19.258)	775 (19.336)	404 (19.111)	0.831
hypertension, *n* (%)	758 (12.382)	373 (9.306)	385 (18.212)	<0.001
Congestive heart failure, *n* (%)	816 (13.329)	449 (11.203)	367 (17.360)	<0.001
Laboratory test				
WBC mean, median (IQR)	11.93 (8.9, 15.55)	11.8 (9.1, 14.9)	12.23 (8.4, 16.93)	0.028
BUN mean, median (IQR)	18.33 (13.0, 29.4)	16.0 (12.0, 23.0)	25.5 (16.0, 44.0)	<0.001
Sodium mean, median (IQR)	138.0 (136.0, 140.2)	138.0 (136.0, 140.0)	138.0 (135.8, 140.5)	0.855
PT mean, median (IQR)	14.65 (13.6, 16.2)	14.35 (13.4, 15.55)	15.45 (14.1, 17.93)	<0.001
INR mean, median (IQR)	1.3 (1.2, 1.5)	1.27 (1.17, 1.4)	1.4 (1.25, 1.7)	<0.001
Potassium mean, median (IQR)	4.19 (3.87, 4.5)	4.15 (3.85, 4.45)	4.26 (3.9, 4.64)	<0.001
Platelet mean, median (IQR)	175.33 (130.33, 233.33)	188.67 (147.0, 245.5)	144.5 (100.5, 203.0)	<0.001
Lactate mean, median (IQR)	1.93 (1.4, 2.7)	1.8 (1.36, 2.43)	2.27 (1.6, 3.33)	<0.001
Hemoglobin mean, median (IQR)	10.15 (9.15, 11.4)	10.25 (9.23, 11.5)	9.95 (9.0, 11.1)	<0.001
PH mean, median (IQR)	7.38 (7.34, 7.41)	7.39 (7.35, 7.42)	7.35 (7.31, 7.4)	<0.001
Glucose mean, median (IQR)	130.57 (116.0, 150.89)	128.86 (115.67, 146.17)	134.57 (116.83, 158.67)	<0.001
Creatinine mean, median (IQR)	0.95 (0.72, 1.37)	0.85 (0.7, 1.1)	1.27 (0.88, 2.37)	<0.001
Vital sign				
SpO_2 mean, median (IQR)	97.77 (96.52, 98.81)	97.88 (96.72, 98.92)	97.54 (96.18, 98.62)	<0.001
BT mean, median (IQR)	36.81 (36.43, 37.24)	36.82 (36.44, 37.21)	36.81 (36.4, 37.3)	0.975
Resp rate mean, median (IQR)	18.12 (16.08, 21.17)	17.71 (15.85, 20.36)	19.21 (16.68, 22.73)	<0.001
Mean bp mean, median (IQR)	75.11 (70.17, 81.36)	76.04 (71.1, 82.55)	73.55 (68.4, 78.7)	<0.001
Dias bp mean, median (IQR)	58.39 (53.15, 64.3)	59.07 (53.88, 65.26)	56.97 (51.87, 62.63)	<0.001
Sys bp mean, median (IQR)	112.86 (105.52, 122.26)	114.87 (107.21, 124.73)	109.52 (102.82, 118.0)	<0.001
Heartrate mean, median (IQR)	85.83 (77.53, 96.52)	84.6 (76.96, 94.64)	88.25 (79.15, 100.26)	<0.001
Primary outcome				
Death in hospital, *n* (%)	925 (15.109)	396 (9.880)	529 (25.024)	<0.001
Death 28-day, *n* (%)	1,114 (18.197)	484 (12.076)	630 (29.801)	<0.001
Death 90-day, *n* (%)	1,301 (21.251)	585 (14.596)	716 (33.869)	<0.001
Death 1-year, *n* (%)	1,606 (26.233)	779 (19.436)	827 (39.120)	<0.001
Second outcome				
AKI 7-day, *n* (%)	4,563 (74.534)	2,726 (68.014)	1,837 (86.897)	<0.001
Hospital stay ≥ 14 days, *n* (%)	2,092 (34.172)	1,171 (29.217)	921 (43.567)	<0.001
ICU stay ≥ 3 days, *n* (%)	3,422 (55.897)	1,935 (48.278)	1,487 (70.341)	<0.001
Survival time, median (IQR)	11.15 (6.26, 27.17)	10.04 (5.95, 23.28)	14.47 (7.45, 34.13)	<0.001

BMI, body mass index; WBC, white blood cell count; BUN, Blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; SOFA, sequential organ failure assessment; SPASII, simplified acute physiology score; AKI, acute kidney injury; ICU, the intensive care unit; SPO2, pulse oxygen saturation; PH, potential of hydrogen; BT, body temperature; Data are represented as median (interquartile range) or n (%).

TABLE 3 | The logistics regression of SOFA scoring system.

Outcomes	Non-adjusted model			Adjusted model		
	OR	95% CL	*p*	OR	95% CL	*p*
In-hospital death	3.044	2.64, 3.514	<0.001	2.86	2.471, 3.312	<0.001
28-day mortality	3.091	2.707, 3.532	<0.001	2.897	2.528, 3.323	<0.001
90-day mortality	2.997	2.643, 3.399	<0.001	2.817	2.475, 3.208	<0.001
One-year mortality	2.664	2.369, 2,995	<0.001	2.479	2.195, 2.8	<0.001
AKI 7-day	1.392	1.229, 1.578	<0.001	1.122	0.981, 1.285	0.095
Hospital stay ≥ 14 days day	1.87	1.676, 2.087	<0.001	1.744	1.557, 1.954	<0.001
ICU stay ≥ 3 days	2.541	2.272, 2.843	<0.001	2.444	2.18, 2.743	<0.001

SOFA, sequential organ failure assessment; OR, odds ratio; CI, 95% confidence interval; AKI, acute kidney injury; ICU, intensive care unit; Adjusted for the confounders: resp rate mean, dias BP mean, sys BP mean, heart rate mean, bun mean, INR mean, potassium mean, lactate mean, hemoglobin mean, glucose mean, pH mean, SpO_2 mean, BMI, age, renal failure, liver disease, hypertension, alcohol abuse, coagulopathy, congestive heart failure, gender.

4,008). In the SAPS II scoring system, patients were divided into the high SAPS II group (H-SAPS II group, SAPS II ≥ 43, N = 2,262) and low SAPS II group (L-SAPS II group, SAPS II < 43, N = 3,860). Kaplan–Meier survival curves of scoring system groups were statistically different (log-rank $p < 0.001$, **Figure 3**).

Correlation Between SOFA Scoring System and Postoperative Outcomes

General comparative data of population are reported in **Table 2** and further explored in **Table 3**. Both short-term and long-term mortality rates were statistically significant in the comparison between SOFA scoring system groups. In-hospital mortality [odds ratio (OR) 2.86, 95% confidence interval (CI) 2.471, 3.312; $p < 0.001$], 28-day mortality (OR 2.897, 95% CI 2.528,3.323; $p < 0.001$), 90-day mortality (OR 2.817, 95% CI 2.475,3.208; $p < 0.001$), 1-year mortality (OR 2.479, 95% CI 2.195, 2.8; $p < 0.001$) all increased in the H-SOFA group compared with the L-SOFA group. In addition, length of in-hospital stay (OR 1.744, 95% CI 1.557, 1.954; $p < 0.001$) and ICU stay (OR 2.444, 95% CI 2.18, 2.743; $p < 0.001$) was extended in the H-SOFA group. However, there were no significant relationships in the incidence of acute renal failure (AKI) within 7 days after ICU admission ($p < 0.05$) between the two groups.

Correlation Between SAPS II Scoring System and Postoperative Outcomes

The basic general data are summarized in **Table 4** and deeply analyzed in **Table 5**. There were statistical differences between the groups of the SAPS II scoring system. The increased in-hospital mortality (OR 3.544, 95% CI 3.02, 4.164; $p < 0.001$), 28-day mortality (OR 3.92, 95% CI 3.376, 4.558; $p < 0.001$), 90-day mortality (OR 4.069, 95% CI 3.533, 4.693; $p < 0.001$) and 1-year mortality (OR 4.272, 95% CI 3.744, 4.879; $p < 0.001$) were obvious in the H-SAPS II group. The length of in-hospital stay (OR 2.912, 95% CI 2.581, 3.287; $p < 0.001$) and ICU stay (OR 2.997, 95% CI 2.651, 3.392; $p < 0.001$) was longer in the H-SAPS II group than the L-SAPS II group. The incidence of AKI within 7 days admitted to ICU was statistically significant (OR 1.464, 95% CI 1.258, 1.706; $p < 0.001$) in comparison.

Comparison of Decision Curves

As exhibited in **Figure 4**, the DCA curve of the SAPS II scoring system was higher than that of the SOFA scoring system in predicting 1-year mortality and 90-day mortality. Otherwise, the net benefit was not different between the two scoring systems in in-hospital mortality and 28-day mortality. This suggests that the SAPS-II scoring system is more meaningful than SOFA in assessing long-term mortality.

DISCUSSION

This retrospective study demonstrated that a score of 7 in the SOFA scoring system and a score of 43 in the SAPS II scoring system with the first 24 h after ICU admission were warning values for predicting the risk of outcomes. Exceeding the warning values of the SOFA score and SAPS II score was associated with elevated mortality, prolonged ICU interval, and hospital interval. Besides, the incidence of AKI was increased in the SAPS II scoring system but not in the SOFA scoring system.

After cardiac surgery, patients have the risk of organ dysfunction or even deterioration, which predicted a poorer prognosis. The aim of the SOFA score was to objectively and quantitatively evaluate the severity of six organ systems dysfunction over time. It consisted of respiratory, circulatory, renal, hematology, hepatic, and central nervous systems, which are related to the recovery of patients with cardiac surgery (17). Although its main role is to predict organ dysfunction, the association between quantification of SOFA score and survival was inevitable (18). A previous systematic review showed that the SOFA model based on 24 h after ICU admission could be used to predict mortality (19). Other types of patients were also effectively evaluated by SOFA score, including post-cardiac arrest syndrome (20), people requiring extracorporeal cardiopulmonary resuscitation (21), critically ill cirrhotic patients with acute decompensation (22), patients with acute respiratory failure in intensive care unit (23), contemporary cardiac intensive care unit population (24), critically ill elderly patients with acute infective endocarditis (25), extracorporeal membrane oxygenation (ECMO)-treated acute myocardial infarction (AMI) patients (26)—some of above

TABLE 4 | Basic characteristics of SAPS II scoring system.

Characteristics	Overall ($n = 6,122$)	SPAS II < 43 ($n = 3,860$)	SPAS II ≥ 43 ($n = 2,262$)	*p*
SPASII, median (IQR)	38 (30, 48)	32.0 (27.0, 37.0)	52.0 (47.0, 60.0)	<0.001
Age, median (IQR)	66 (55, 76)	63.0 (53.0, 73.0)	71.0 (61.0, 79.0)	<0.001
Male gender, *n* (%)	3,704 (60.503)	2,398 (62.124)	1,306 (57.737)	<0.001
BMI, median (IQR)	27.84 (24.39, 31.84)	27.9 (24.42, 31.98)	27.77 (24.29, 31.63)	0.303
Comorbidities				
Drug abuse, *n* (%)	208 (3.398)	152 (3.938)	56 (2.476)	0.002
Alcohol abuse, *n* (%)	474 (7.743)	301 (7.798)	173 (7.648)	0.832
Coagulopathy, *n* (%)	1,153 (18.834)	545 (14.119)	608 (26.879)	<0.001
Liver disease, *n* (%)	463 (7.563)	244 (6.321)	219 (9.682)	<0.001
Renal failure, *n* (%)	869 (14.195)	357 (9.249)	512 (22.635)	<0.001
Hypothyroidism, *n* (%)	617 (10.078)	372 (9.637)	245 (10.831)	0.134
Diabetes, *n* (%)	1,448 (23.652)	883 (22.876)	565 (24.978)	0.062
Chronic pulmonary, *n* (%)	1,179 (19.258)	714 (18.497)	465 (20.557)	0.049
Hypertension, *n* (%)	758 (12.382)	326 (8.446)	432 (19.098)	<0.001
Congestive heart failure, *n* (%)	816 (13.329)	353 (9.145)	463 (20.469)	<0.001
Laboratory test				
WBC mean, median (IQR)	11.93 (8.9, 15.55)	11.7 (9.0, 14.77)	12.43 (8.72, 17.1)	<0.001
Bun mean, median (IQR)	18.33 (13.0, 29.4)	15.67 (12.0, 21.5)	27.5 (17.0, 44.33)	<0.001
Sodium mean, median (IQR)	138.0 (136.0, 140.2)	138.0 (136.2, 140.0)	138.0 (135.67, 140.71)	0.720
INR mean, median (IQR)	1.3 (1.2, 1.5)	1.3 (1.2, 1.4)	1.4 (1.2, 1.7)	<0.001
PT mean, median (IQR)	14.65 (13.6, 16.2)	14.42 (13.4, 15.65)	15.25 (13.85, 17.6)	<0.001
Potassium mean, median (IQR)	4.19 (3.87, 4.5)	4.15 (3.85, 4.44)	4.24 (3.9, 4.65)	<0.001
Platelet mean, median (IQR)	175.33 (130.33, 233.33)	179.33 (137.0, 233.0)	168.5 (117.67, 234.0)	<0.001
Lactate mean, median (IQR)	1.93 (1.4, 2.7)	1.88 (1.4, 2.5)	2.12 (1.5, 3.15)	<0.001
Hemoglobin mean, median (IQR)	10.15 (9.15, 11.4)	10.3 (9.25, 11.5)	9.92 (9.0, 11.1)	<0.001
Glucose mean, median (IQR)	130.57 (116.0, 150.89)	128.5 (115.33, 145.22)	134.75 (117.6, 160.33)	<0.001
Creatinine mean, median (IQR)	0.95 (0.72, 1.37)	0.87 (0.7, 1.1)	1.23 (0.85, 2.25)	<0.001
PH mean, median (IQR)	7.38 (7.34, 7.41)	7.38 (7.35, 7.42)	7.36 (7.31, 7.4)	<0.001
Vital sign				
SpO_2 mean, median (IQR)	97.77 (96.52, 98.81)	97.82 (96.67, 98.82)	97.64 (96.28, 98.81)	<0.001
BT mean, median (IQR)	36.81 (36.43, 37.24)	36.84 (36.48, 37.24)	36.77 (36.35, 37.24)	<0.001
Res prate mean, median (IQR)	18.12 (16.08, 21.17)	17.72 (15.85, 20.41)	19.0 (16.57, 22.61)	<0.001
Mean bp mean, median (IQR)	75.11 (70.17, 81.36)	76.22 (71.22, 82.61)	73.4 (68.32, 78.79)	<0.001
Dias bp mean, median (IQR)	58.39 (53.15, 64.3)	59.56 (54.39, 65.59)	56.63 (51.14, 62.15)	<0.001
Sys bp mean, median (IQR)	112.86 (105.52, 122.26)	114.55 (107.05, 124.08)	110.26 (103.03, 119.36)	<0.001
Heart rate mean, median (IQR)	85.83 (77.53, 96.52)	84.89 (77.27, 94.66)	87.35 (78.06, 99.97)	<0.001
Primary outcome				
Death in-hospital, *n* (%)	925 (15.109)	293 (7.591)	632 (27.940)	<0.001
Death 28-day, *n* (%)	1,114 (18.197)	363 (9.404)	751 (33.201)	<0.001
Death 90-day, *n* (%)	1,301 (21.251)	446 (11.554)	855 (37.798)	<0.001
Death 1-year, *n* (%)	1,606 (26.233)	593 (15.363)	1,013 (44.783)	<0.001
Second outcome				
AKI 7-day, *n* (%)	4,563 (74.534)	2,621 (67.902)	1,942 (85.853)	<0.001
Hospital stay ≥ 14 days, *n* (%)	2,092 (34.172)	950 (24.611)	1,142 (50.486)	<0.001
ICU stay ≥ 3 days, *n* (%)	3,422 (55.897)	1,774 (45.959)	1,648 (72.856)	<0.001
Survival time, median (IQR)	11.15 (6.26, 27.17)	9.82 (5.86, 21.68)	15.3 (7.94, 41.25)	<0.001

BMI, body mass index; WBC, white blood cell count; BUN, Blood urea nitrogen; PT, prothrombin time; INR, international normalized ratio; SOFA, sequential organ failure assessment; SPASII, simplified acute physiology score; AKI, acute kidney injury; ICU, the intensive care unit; SPO_2, pulse oxygen saturation; PH,potential of hydrogen; BT,body temperature; Data are represented as median (interquartile range) or n (%).

TABLE 5 | The logistics regression of SAPSII scoring system.

Outcomes	Non-adjusted model			Adjusted model		
	OR	95% CL	*p*	OR	95% CL	*p*
In-hospital death	3.839	3.318, 4.45	<0.001	3.544	3.02, 4.164	<0.001
28-day mortality	4.292	3.744, 4.928	<0.001	3.92	3.376, 4.558	<0.001
90-day mortality	4.471	3.929, 5.093	<0.001	4.069	3.533, 4.693	<0.001
One-year mortality	4.748	4.208, 5.362	<0.001	4.272	3.744, 4.879	<0.001
AKI 7-day	2.869	2.502, 3.291	<0.001	1.464	1.258, 1.706	<0.001
Hospital stay ≥ 14 days	3.123	2.798, 3.488	<0.001	2.912	2.581, 3.287	<0.001
ICU stay ≥ 3 days	3.156	2.822, 3.533	<0.001	2.997	2.651,3.392	<0.001

SPASII, simplified acute physiology score; OR, odds ratio; CI, 95% confidence interval; AKI, acute kidney injury; ICU: the intensive care unit. Adjusted for the confounders: PT mean, INR mean, platelet mean, lactate mean, hemoglobin mean, glucose mean, creatinine mean, PH mean, SpO_2 mean, resp rate mean, mean BP mean, dias bp mean, BMI, congestive heart failure, drug abuse, coagulopathy, liver disease, renal failure, hypertension, gender.

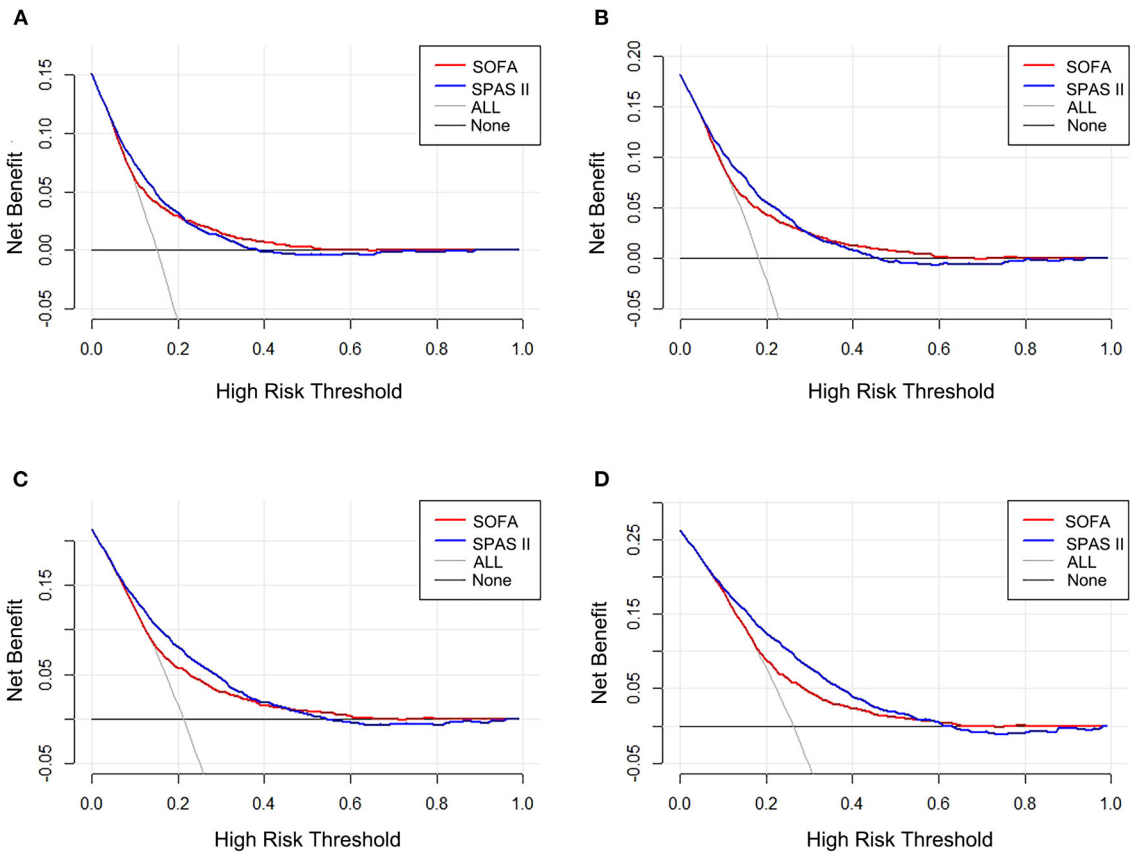

FIGURE 4 | Decision curve analysis (DCA) of the two scoring systems. **(A)** In-hospital mortality, **(B)** 28-day mortality, **(C)** 90-day mortality, and **(D)** 1-year mortality.

studies behaved even well. In the cardiac surgery population, the previous literature stated that SOFA score had good discriminative power for hospital mortality (27); the same observation was also confirmed in Ceriani et al.'s research (28). Doerr et al.'s study had found that SOFA score could predict 30-day mortality (29). In our study, we used a larger sample size to test the predictive effect of SOFA scores on short-term and long-term mortality. Results are remarkable on the performance of SOFA score as previous studies, especially above the cutoff value. The warning value of the SOFA scoring system is able to assess the risk of outcomes as a new valuable observation index in post-cardiac patients.

The SAPS II scoring system consisted of physiological variables, basic characteristics, and several complications, which could provide an estimate of the risk of death on the basis of large samples with the independence of primary diagnosis,

and also was developed for the evaluation of the efficiency of ICUs (30). Recent research established that the SAPS II score could predict the prognosis and in-hospital mortality in AMI patients treated with ECMO with a good performance (26). But it could not ser good predictor for discharged mortality in small sample size studies (31). The result of the previous study of more than 2,000 patients after cardiac surgery showed that the SAPS II score had good discrimination in-hospital mortality (27). The same role was confirmed in another post-cardiac surgery population (32). These researches were consistent with part of our findings. Moreover, previous literature had claimed that the SAPS II scoring system could be implemented reliably while mortality was closely related to the rater's scoring practice (33). This can be interpreted as the diversities of results. Although overestimates of mortality were reported by some researchers (34–37), the objective of our study was for early warning based on the threshold of the SAPS II scoring system.

Decision curve analysis is a method widely used to evaluate the clinical utility of specific models (38). The curve with the highest benefit score at a given threshold was determined to be the best choice (16). A recent study involving multiple scoring systems confirmed the superiority of the SAPS II scoring system in predicting mortality through DCA among sepsis patients (39). Besides, Abraham Schoe et al.'s research including more than 3,600 post-cardiac surgery patients has demonstrated that SOFA score and SAPS II score could predict hospital mortality, while SAPS II was better (32). This tendency is similar to our finding: The SAPS II scoring system had more net benefits on assessing the long-term mortality compared with the SOFA scoring system. As a comprehensive scoring system for postoperative multiple organ physiological function during post-cardiac surgery patients, the SAPS II scoring system may perform better in clinical application.

As for the complexity of progressing in disease, it is hard to find a perfect score of predicting risk comprehensively. The strength of this study lies in identifying warning values of the SOFA score and SAPS II score and giving new insight into the reference value of the SOFA and SAPS II scoring system. Moreover, it enriched the methods of early detecting the prognosis in patients with cardiac surgery and might be used as decision support for clinical intervention. The scoring system was tested in the discrimination of long-term mortality in a large sample of patients with cardiac surgery. However, it was a retrospective observational study which raised possible bias caused by heterogeneous factors. This study focuses on the whole group after cardiac surgery, but we believe that the changes in organ function after different cardiac surgery can also be reflected through the scoring system. Of course, it is also a perfect direction to further explore the differences in the scoring system in different types of cardiac surgery. Moreover, the collected data were from over 10 years ago, these conclusions may not be feasible nowadays with the improvement of surgical technology and ICU treatment level. In this large sample retrospective analysis, the short-term results are consistent with existing studies. There are still few longer-term results. These results can provide clinicians with a warning SOFA and SAPS II value, but the specific implementation should be treated with caution. More retrospective and prospective clinical studies are necessary for verification in the future.

CONCLUSION

This study suggested that exceeding the cutoff values of the SOFA score and SAPS II score could lead to increased mortality, prolonged length of ICU stay, and in-hospital stay. Score 7 in the SOFA scoring system and score 43 in the SAPS II scoring system with the first 24 h after ICU admission were warning values for worse outcomes. The SAPS II scoring system had a better discriminative performance of 90-day mortality and 1-year mortality in post-cardiac surgery patients than the SOFA scoring system. Focusing on the critical value of the scoring system is of significance for treatment in ICU.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession numbers can be found below: https://mimic.mit.edu/docs/iii/tables/.

ETHICS STATEMENT

Access to the database was reviewed and approved by the Institutional Review Committee of Beth Israel Deaconess Medical Center and Beth Israel deacons Medical Center (Approval Code 10323541). Written informed consent was not required for this study, in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

FX gathered and processed the data. FX, WL, and CZ prepared the results. FX, WL, and CZ contributed to writing the manuscript. FX and RC put forward the idea. RC revised the manuscript. All the authors read and approved the final manuscript.

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One-Stop Hybrid Coronary Revascularization Versus Off-Pump Coronary Artery Bypass Grafting in Patients With Multivessel Coronary Artery Disease

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Background: Data on one-stop hybrid coronary revascularization (HCR) are limited. This study aimed to compare the early and midterm outcomes of one-stop HCR with off-pump coronary artery bypass grafting (OPCAB) in patients with multivessel coronary artery disease.

Methods: From April 2018 to May 2021, 752 patients with multivessel coronary artery disease who underwent isolated one-stop HCR or OPCAB were retrospectively included in this analysis. After exclusion and propensity score matching, 151 patients who underwent HCR were matched with 151 patients who underwent OPCAB. The primary endpoints were midterm major adverse cardiovascular and cerebrovascular events (MACCE) after the procedure. The secondary endpoints were in-hospital complications and outcomes.

Results: The preprocedural characteristics were well balanced between the two groups after matching. The HCR group was associated with a lower rate of perioperative transfusion (23.8 vs. 53.0%, $p < 0.001$) and new-onset atrial fibrillation (AF) (5.3 vs. 15.2%, $p = 0.004$), shorter time of mechanical ventilation (h) [15 (16, 17) vs. 17 (16, 20), $p < 0.001$], and shorter length of stay (LOS) in the hospital (days) [19 (16, 24) vs. 22 (18, 27), $p = 0.001$]. Cumulated MACCE rates were similar between the two groups (15.9 vs. 14.0%, $p = 0.59$) during a median follow-up of 20 months.

Conclusions: One-stop HCR is safe and efficacious with less invasiveness and faster postoperative recovery in selected patients with multivessel coronary artery disease. Randomized controlled trials with larger sample sizes and long-term follow-up are warranted to confirm these findings.

Keywords: hybrid coronary revascularization (HCR), off-pump coronary artery bypass graft (OPCAB), percutaneous coronary intervention (PCI), minimally invasive direct coronary artery bypass (MIDCAB), major adverse cardiovascular and cerebrovascular events (MACCE)

INTRODUCTION

Coronary artery bypass grafting (CABG) remains the gold standard for the treatment of multivessel coronary artery disease (1–3). The left internal mammary artery (LIMA) to left anterior descending (LAD) graft provides most of the survival benefit of CABG due to its long-term patency rate, which can reach 90% at 10 years. However, the 10-year patency for saphenous vein graft (SVG) was only 60%, and conventional CABG is a relatively invasive and high-risk procedure via sternotomy (4–6). In-stent restenosis was <6% in patients undergoing percutaneous coronary intervention (PCI) with drug eluting stents (DESs) (7). However, the long-term outcomes of PCI were not superior to those of CABG in patients with intermediate or high SYNTAX scores (>22) (8, 9).

Hybrid coronary revascularization (HCR) was first introduced by Angelini in 1996 and consisted of LIMA-LAD anastomosis using a minimally invasive left thoracotomy approach and PCI procedure for non-LAD lesions (10). HCR combines the advantages of CABG and PCI, avoids their relative deficiencies, and achieves complete revascularization. The HYBRID trial and several observational studies have shown similar short and long-term outcomes compared with off-pump or on-pump CABG (11–14). Nevertheless, data comparing HCR and off-pump CABG (OPCAB) are still limited, and the safety and efficacy of HCR in multivessel coronary artery disease have not been completely indicated, especially for one-stop HCR patients, due to the majority composition of staged HCR in these studies. Considering the potentially different strengths and disadvantages between one-stop and staged HCR, the results of one-stop HCR need to be separately evaluated.

Therefore, we sought to investigate the early and midterm outcomes of one-stop HCR compared with OPCAB in patients with multivessel coronary artery disease to evaluate the safety and effectiveness of this procedure.

METHODS

Study Population

This was a retrospective single-center observational study conducted at Beijing Chaoyang Hospital, Capital Medical University. From April 2018 to May 2021, data from a total of 752 patients with multivessel coronary artery disease who underwent isolated one-stop HCR or OPCAB were collected. Patients with ST-segment elevation myocardial infarction within 30 days before the procedure, ejection fraction <30%, hemodynamic instability, and creatinine clearance <30 ml/min were excluded. Finally, 151 patients underwent one-stop HCR (HCR group), and 531 patients who received OPCAB (OPCAB group) were enrolled in this study. **Figure 1** shows the detailed flow of this study.

For the choice of revascularization strategies, all patients were reviewed and discussed preoperatively by the heart team of our center, which consisted of cardiac surgeons, interventional cardiologists, and anesthesiologists, to make the most appropriate decision regarding PCI, CABG, or HCR. The selection criteria of patients who underwent one-stop HCR were as follows: patients with multivessel disease in whom the LAD lesion was not suitable for PCI but was suitable for surgical revascularization and in whom the non-LAD lesions were amenable to PCI; and patients who were not good candidates for traditional CABG, such as poor right coronary or circumflex arteries for bypass, relative contraindication for sternotomy, porcelain aorta, lack of acceptable conduits, and patient desire for minimally invasive procedures.

Data Collection

Preoperative risk profile and demographic features, including age, sex, body mass index (BMI), hypertension, hyperlipoidemia, diabetes mellitus (DM), and smoking status, were retrospectively extracted for all patients from the database of Chaoyang Hospital. Intraoperative and postoperative variables were also collected. The SYNTAX score and EuroSCORE II were calculated based on the anatomy of the lesions and preoperative risk factors. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the local research ethics board of Chaoyang Hospital (No.: 2021-D-5), and individual consent for this retrospective analysis was waived.

Surgical Technique and Intervention

For the HCR group, all patients underwent one-stop HCR in the hybrid operating room. Surgical procedures were performed by minimally invasive direct coronary artery bypass (MIDCAB) or endoscopic assisted coronary artery bypass. LIMA was harvested as a pedicle directly through a small anterior thoracotomy (5–7 cm) at the fourth to fifth intercostal space using special retractors or via an endoscope to avoid chest wall retraction and rib spreading. Then, LIMA was hand sewn to the LAD territory via direct vision. All surgical procedures were performed by one experienced surgeon (Pixiong Su). A partial dose of protamine was administrated to neutralize heparin after LIMA-LAD anastomosis. Then, a loading dose of clopidogrel was administrated before closure of the thorax. The PCI procedures were performed according to practice guidelines and standard techniques (15). PCI for non-LAD lesions was performed through the femoral artery, and the femoral arterial sheath was placed before heparinization to avoid potential access site hematomas. The guidewire and stent selection were performed according to the interventionist's discretion. LIMA-LAD graft patency was immediately confirmed by angiography after chest closure. Then, DESs or drug-coated balloons (DCBs) were used to treat the non-LAD lesions.

For the OPCAB group, standard procedures described previously were followed (16). Aspirin was administered 100 mg daily after HCR and OPCAB procedures and then continued for life, while clopidogrel was administered at a dose of 75 mg/day for 12 months.

Follow-Up

All patients needed to return to the outpatient department for a postoperative review at 1 and 6 months after discharge from the hospital and then once a year after surgery. Patients who did not return for review visits were contacted via telephone during the study period by the research staff using standard procedures and forms.

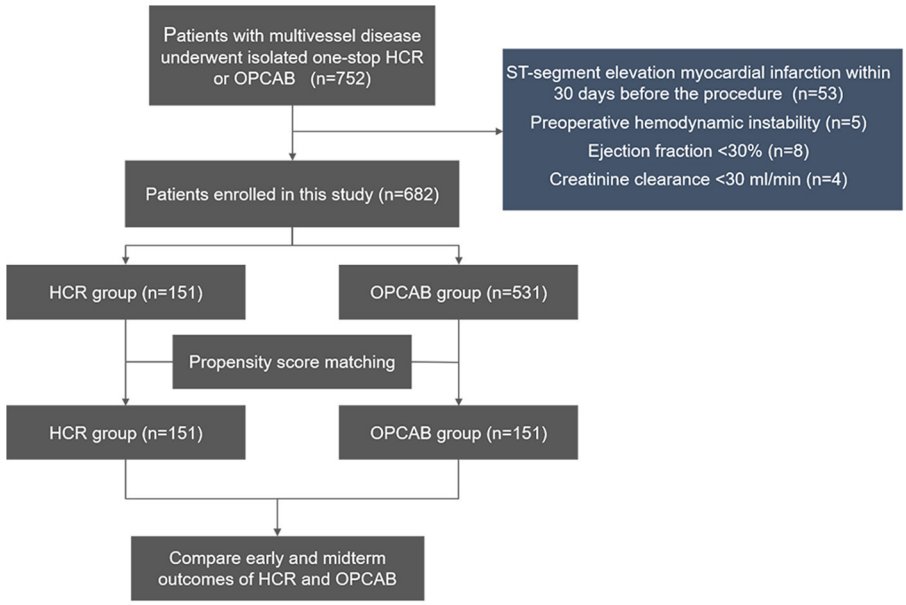

FIGURE 1 | Flow chart of the study. HCR, hybrid coronary revascularization; OPCAB, off-pump coronary artery bypass graft.

The primary endpoints of this study were midterm major adverse cardiovascular and cerebrovascular events (MACCE) after the procedure, including death, myocardial infarction (MI), stroke, and repeat revascularization (defined as any revascularization after the HCR procedure or isolated OPCAB procedure). The secondary endpoints were in-hospital complications and outcomes, defined as in-hospital death, MI, stroke, repeat revascularization, reoperation for bleeding, time of mechanical ventilation, mechanical ventilation (PMV), perioperative transfusion, renal failure requiring dialysis, new onset atrial fibrillation (AF), incision infection, intensive care unit (ICU) stay, and length of stay (LOS) in hospital (days).

Statistical Analysis

To reduce the impact of selection bias and potential confounding factors in this observational study, propensity score matching was performed using a logistic regression model. We chose nearest-neighbor caliper matching without a replacement, and the matching ratio was 1:1. Key variables and risk factors were involved in the matching. The standardized differences (SD) were calculated to assess the balance for the baseline characteristics before and after matching. SD values <10% indicated good matching. All matching procedures were performed by R (version 4.0.3).

Continuous variables were expressed as the means ± standard deviation or medians (the 25th percentile and the 75th percentile), and categorical data were summarized as a proportion. Comparisons of baseline characteristics and outcomes between the HCR group and OPCAB group were assessed by *t test* or Mann–Whitney *U* test for continuous variables and chi-square test or Fisher exact test for categorical variables before and after matching. Kaplan–Meier curves and log-rank tests were performed to compare cumulative events and MACCE rates between the two groups after matching. All statistical data analyses were performed by SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Before propensity score matching, there were significant differences in demographics and comorbidities between the two groups. The HCR group had a higher BMI, a higher proportion of hyperlipidemia patients, administration of statins, and better heart function. Additionally, there were significantly lower EuroSCORE II scores, a lower proportion of diabetes mellitus patients, previous MI, and preoperative intra-aortic balloon pump (IABP) insertion compared with the OPCAB group. Variables of the unmatched population are shown in **Table 1**.

There were 151 patients in each group after 1:1 propensity score matching, and the baseline characteristics were similar between the two groups (**Table 2**). In the HCR group, no patients required conversion to sternotomy or cardiopulmonary bypass (CPB), and the mean number of DESs or DCBs used in each patient was 2.3 ± 1.5. The LIMA-LAD anastomosis, mean graft flow (MGF), and pulsatility index (PI) were comparable between the two groups (**Table 3**).

In-Hospital Outcomes

The in-hospital outcomes are illustrated in **Table 4**. The incidences of in-hospital death, MI, stroke, and repeat

TABLE 1 | Preoperative characteristics of unmatched patients who underwent hybrid coronary revascularization (HCR) and off-pump coronary artery bypass (OPCAB).

Preoperative characteristics	HCR group, $N = 151$	OPCAB group, $N = 531$	SD	P
Age (years)	64.6 ± 9.4	63.6 ± 8.8	0.051	0.58
Male	75.5	77.0	0.036	0.70
BMI (kg/m2)	26.0 ± 3.3	25.3 ± 3.2	0.189	0.04
Hypertension	72.8	68.9	0.085	0.35
Hyperlipidemia	64.9	54.0	0.218	0.02
Diabetes mellitus	37.1	46.1	0.187	0.048
Smoker	55	50.1	0.098	0.29
COPD	1.3	2.3	0.063	0.75
Peripheral vascular disease	9.9	6.6	0.135	0.16
Preoperative arrhythmia	7.9	9.2	0.044	0.63
Previous stroke	19.9	21.7	0.043	0.64
Previous MI	16.6	45.6	0.583	< 0.001
Previous PCI	21.9	19.8	0.052	0.57
Acute coronary syndrome	98.7	96.2	0.128	0.19
Left main disease	41.7	36.9	0.100	0.28
LVEF (%)	63.6 ± 9.0	60.7 ± 11.0	0.265	0.001
LVEDD (mm)	48.0 ± 4.6	49.4 ± 5.8	0.235	0.003
Preoperative IABP	2.0	7.3	0.205	0.02
SYNTAX Score	30.1 ± 9.4	31.7 ± 8.0	0.195	0.07
EuroSCORE II	1.97 ± 1.67	2.93 ± 2.27	0.424	< 0.001
β blocker	64.9	70.1	0.113	0.23
ACEI/ARB	40.4	35.2	0.109	0.24
Statin	96.0	86.8	0.272	0.002

Values are presented as mean ± SD or %.
HCR, hybrid coronary revascularization; OPCAB, off pump coronary artery bypass grafting; SD, standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; IABP, intra-aortic balloon pump; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers.

TABLE 2 | Preoperative characteristics of matched patients who underwent HCR and OPCAB.

Preoperative characteristics	HCR group, $N = 151$	OPCAB group, $N = 151$	SD	P
Age (years)	64.6 ± 9.4	64.4 ± 8.6	0.011	0.92
Male	75.5	77.5	0.047	0.68
BMI (kg/m^2)	26.0 ± 3.3	25.3 ± 3.3	0.193	0.10
Hypertension	72.8	72.8	0.000	1.00
Hyperlipidemia	64.9	61.6	0.066	0.55
Diabetes mellitus	37.1	33.8	0.066	0.55
Smoker	55.0	51.7	0.066	0.56
COPD	1.3	2.0	0.045	1.00
Peripheral vascular disease	9.9	9.3	0.027	0.85
Preoperative arrhythmia	7.9	7.3	0.023	0.83
Previous stroke	19.9	19.9	0.000	1.00
Previous MI	16.6	16.6	0.000	1.00
Previous PCI	21.9	19.2	0.067	0.57
Acute coronary syndrome	98.7	98.7	0.000	1.00
Left main disease	41.7	43.7	0.041	0.73
LVEF (%)	63.6 ± 9.0	63.3 ± 9.2	0.021	0.83
LVEDD (mm)	48.0 ± 4.6	48.2 ± 5.4	0.028	0.78
Preoperative IABP	2.0	0.0	0.076	0.25
SYNTAX Score	30.1 ± 9.4	31.2 ± 7.4	0.081	0.51
EuroSCORE II	1.97 ± 1.67	2.36 ± 2.40	0.155	0.15
β blocker	64.9	65.6	0.015	0.90
ACEI/ARB	40.4	39.7	0.014	0.91
Statin	96.0	98.0	0.059	0.50

Values are presented as mean ± SD or %.
HCR, hybrid coronary revascularization; OPCAB, off pump coronary artery bypass grafting; SD, standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; IABP, intra-aortic balloon pump; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers.

revascularization were comparable between the two matched groups. Meanwhile, differences in the rate of reoperation for bleeding, PMV (≥48 h), renal failure requiring dialysis, incision infection, and length of ICU stay (h) were not statistically significant. The HCR group had a lower rate of perioperative transfusion (23.8 vs. 53.0%, $p < 0.001$) and new-onset AF (5.3 vs. 15.2%, $p = 0.004$), shorter time of mechanical ventilation (h) [15 (16, 17) vs. 17 (16, 20), $p < 0.001$], and shorter LOS in the hospital (days) [19 (16, 24) vs. 22 (18, 27), $p = 0.001$]. No patient developed vascular access complications under anticoagulation therapy. One patient developed postoperative stroke caused by atherosclerotic plaques detached from the left subclavian artery in selective LIMA angiography. For in-hospital death, one patient died of cardiogenic shock caused by postoperative MI, the other patient died of severe lung infection in the HCR group, and one patient died of stroke in the OPCAB group.

Midterm Outcomes

At a median follow-up time of 20 months (interquartile range: 10–30 months), the cumulative mortality in the HCR and OPCAB groups was 5.1 and 7.1%, respectively (log rank $p = 0.91$) (**Table 5**, **Figure 2**). Significant differences in the estimated rates of MI (4.3 vs. 4.3%, $p = 0.56$), stroke (4.0 vs. 4.5%, $p = 0.66$), repeat revascularization (4.7 vs. 5.0%, $p = 0.61$), and MACCE (15.9 vs. 14.0%, $p = 0.59$) were not observed for the HCR and CABG groups (**Table 5**, **Figure 3**).

DISCUSSION

Minimally invasive techniques for surgical myocardial revascularization have received much attention in recent years, especially the HCR technique (17). Compared with staged HCR, one-stop HCR can achieve complete revascularization in a single procedure, which avoids ischemic events during the

TABLE 3 | Intraoperative characteristics of matched patients who underwent HCR and OPCAB.

Intraoperative characteristics	HCR group, *N* = 151	OPCAB group, *N* = 151	*P*
Conversion to sternotomy	0	NA	NA
LIMA-LAD	98.7	95.4	0.17
MGF (ml/min)	23.5 ± 13.9	26.6 ± 19.7	0.11
PI	2.5 ± 1.4	2.4 ± 1.6	0.23
Number of DES/DCB	2.3 ± 1.5	NA	NA

Values are presented as mean ± SD or %.
HCR, hybrid coronary revascularization; OPCAB, off pump coronary artery bypass grafting; LIMA, left internal mammary artery; LAD, left anterior descending artery; MGF, mean graft flow; PI, pulsatility index; DES, drug-eluting stents; DCB, drug-coated balloon.

TABLE 4 | In-hospital outcomes of matched patients who underwent HCR and OPCAB.

Variables	HCR group, *N* = 151	OPCAB group, *N* = 151	*P*
In-hospital death	2 (1.3)	1 (0.7)	1.00
MI	3 (2.0)	4 (2.6)	1.00
Stroke	3 (2.0)	2 (1.3)	1.00
Repeat revascularization	0 (0.0)	1 (0.7)	1.00
Reoperation for bleeding	6 (4.0)	1 (0.7)	0.12
Time of mechanic ventilation (h)*	15 (16, 17)	17 (16,20)	< 0.001
PMV (≥ 48 h)	17 (11.3)	19 (12.6)	0.72
Perioperative transfusion	36 (23.8)	80 (53.0)	< 0.001
Renal failure needs dialysis	2 (1.3)	1 (0.7)	1.00
New onset AF	8 (5.3)	23 (15.2)	0.004
Incision infection	2 (1.3)	2 (1.3)	1.00
ICU stay (h)*	77 (66, 124)	95 (69, 140)	0.17
LOS in hospital (day)*	19 (16, 24)	22 (18, 27)	0.001

** Non-normal variables are presented as median (P25, P75).*
Categorical values are presented as n (%).
HCR, hybrid coronary revascularization; OPCAB, off pump coronary artery bypass grafting; MI, myocardial infarction; PMV, prolonged mechanic ventilation; AF, atrial fibrillation; ICU, intensive care unit; LOS, length of stay.

TABLE 5 | Midterm outcomes of matched patients who underwent HCR and OPCAB.

Variables	HCR group, *N* = 151	OPCAB group, *N* = 151	HR (95% CI)	*P*
Death	6 (5.1)	6 (7.1)	1.07 (0.34–3.30)	0.91
MI	4 (4.3)	6 (4.3)	0.69 (0.20–2.38)	0.56
Stroke	5 (4.0)	4 (4.5)	1.34 (0.36–4.95)	0.66
Repeat revascularization	4 (4.7)	6 (5.0)	0.72 (0.21–2.49)	0.61
MACCE	17 (15.9)	15 (14.0)	1.21 (0.60–2.41)	0.59

Events are presented as n (cumulative incidence rate%) after procedure.
HCR, hybrid coronary revascularization; OPCAB, off pump coronary artery bypass grafting; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; MACCE, major adverse cardiac and cerebrovascular events.

waiting period caused by incomplete revascularization in staged HCR. Furthermore, LIMA-LAD anastomosis can be evaluated by angiography immediately before PCI, and grafts can be revised if there are any major issues (18). Additionally, high-risk non-LAD PCI is performed with a protected LAD territory, and surgical bailout can be performed for any possible complication or unsuccessful PCI with a surgical team in a hybrid suite. Finally, this single-step procedure reduces hospital stay and readmission, provides convenience for patients, and improves patient satisfaction (19).

On the other hand, the simultaneous procedure requires a costly hybrid room featuring advanced surgical and interventional equipment. In addition, adopting an appropriate antiplatelet therapy strategy to balance the risk of bleeding and stent thrombosis is a major challenge (20).

To date, a series of published data comparing HCR with conventional CABG and OPCAB from different centers with variable surgical techniques and study methodologies have demonstrated limited conclusions (11, 12, 21, 22). Most of the patients involved in these studies underwent staged HCR, and the one-stop HCR approach accounted for only 15% of all HCR procedures in the United States (23). Outcomes of one-stop HCR should be proven, particularly due to their different natural attributes.

The present study compared early and midterm results between one-stop HCR and standard OPCAB, which revealed similar excellent in-hospital and midterm outcomes. In addition, the HCR group was associated with a lower rate of perioperative transfusion (23.8 vs. 53.0%), new-onset AF (5.3 vs. 15.2%), shorter time of mechanical ventilation, and LOS in the hospital. Consistent with our results, Reynolds et al. (24) evaluated a total of 4,260 patients (1,350 of whom underwent HCR) in a meta-analysis. They confirmed that HCR had a significantly lower rate of blood transfusion than CABG (22.8 vs. 46.1%) and a shorter time of mechanical ventilation and LOS in the hospital, but no significant differences were found in ICU stay, postoperative atrial fibrillation, renal failure, perioperative myocardial infarction, or death. Similar conclusions were also investigated by Sardar et al. (25). These findings indicated the advantages of minimally invasive and rapid recovery of HCR.

Another particular potential benefit of HCR procedures is completely avoiding manipulation of the aorta, which could theoretically reduce the risk of neurological events. However, in our study, the incidence of in-hospital stroke was low and was comparable between the two groups. Three (HCR group) and two (OPCAB group) patients developed stroke. Among the stroke patients in the HCR group, two patients had a history of cerebral infarction, and one stroke patient was caused by atherosclerotic plaques detached from the left subclavian artery in selective LIMA angiography. Meanwhile, in the OPCAB group, using proximal anastomosis devices (Heartstring or Enclose) was a routine procedure in our center. This surgical approach reduced aortic manipulation and was associated with a lower risk of perioperative stroke (26). Nevertheless, HCR is still an optimal strategy for patients with severe aortic atherosclerosis.

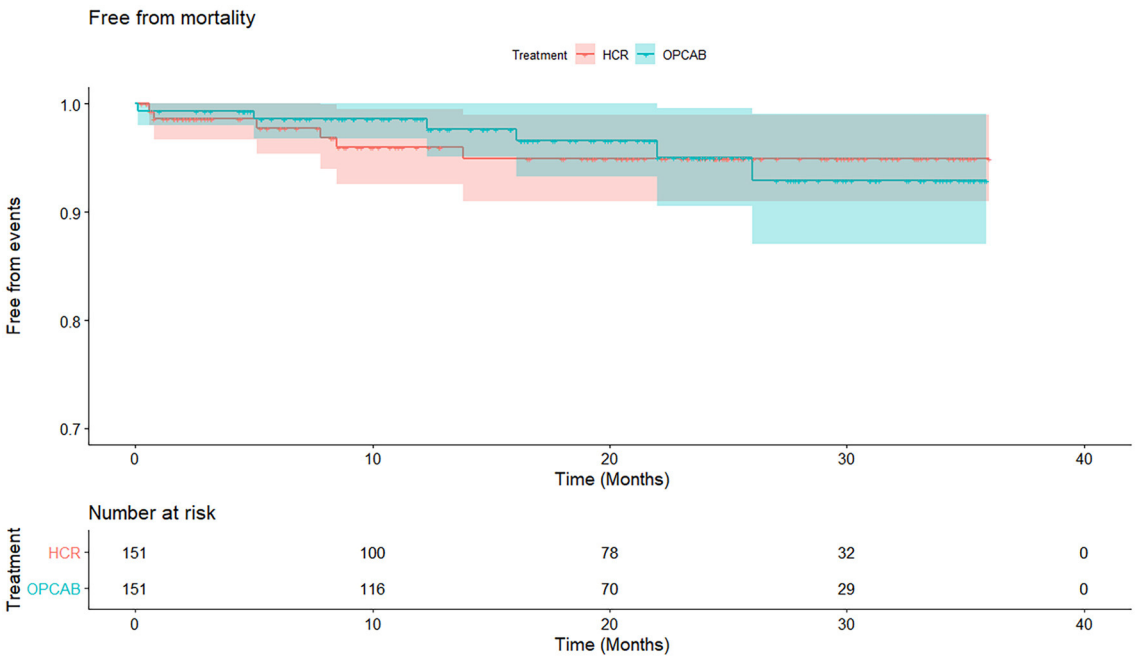

FIGURE 2 | Cumulative survival rate in hybrid coronary revascularization (HCR) and off-pump coronary artery bypass (OPCAB) group. Kaplan–Meier curve estimates similar cumulated survival rate in HCR and OPCAB groups (94.9 vs. 92.9%, $p = 0.91$) during the follow-up. HCR, hybrid coronary revascularization; OPCAB, off-pump coronary artery bypass graft.

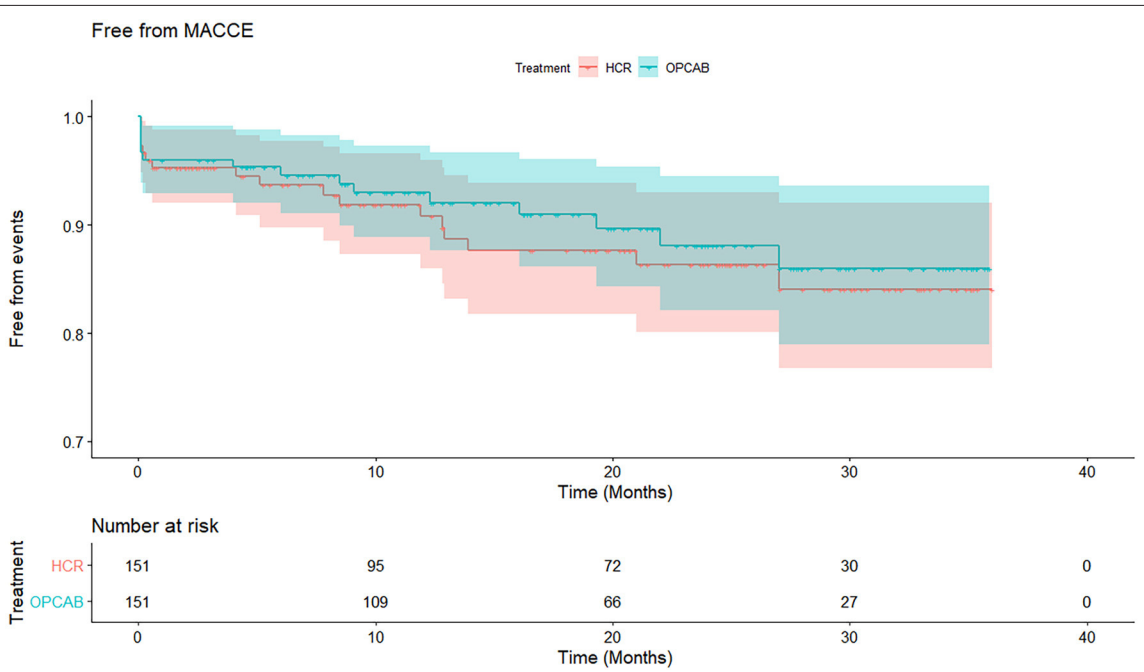

FIGURE 3 | Cumulative free from major adverse cardiovascular and cerebrovascular events (MACCE) rate in HCR and OPCAB group. Kaplan–Meier curve estimates similar cumulated free from MACCE rate in HCR and OPCAB groups (84.1 vs. 86%, $p = 0.59$) during the follow-up. MACCE, major adverse cardiovascular and cerebrovascular events; HCR, hybrid coronary revascularization; OPCAB, off-pump coronary artery bypass grafting.

Appropriate antiplatelet therapy to preserve stent patency and minimize the risk of postoperative bleeding is challenging in one-stop HCR procedures. Exposure to potent antiplatelet drugs may increase the risk of postoperative bleeding events. Coincidentally, in the present study, the reoperation rate for bleeding was higher in the HCR group (4.0 vs.0.7%), although the difference was not significant ($p = 0.12$), which is consistent with the rate of 3 to 6.8% reported by Zhao et al. and Harskamp et al. (18). Most of the reoperation cases occurred early after introducing one-stop HCR into our center, and the LIMA pedicle was harvested through direct vison at that time. Then, endoscopy was used in LIMA harvesting, which could reduce the trauma of the LIMA bed. We strengthened surgical hemostasis, such as by using the "LIMA bed closure" technique. As a consequence, few patients now develop major bleeding events requiring reoperation.

During midterm follow-up, we revealed no differences between the two groups in cumulative survival (94.9 vs. 92.9%, $p = 0.91$) or free from MACCE (84.1 vs. 86%, $p = 0.59$) after the procedure. These findings are consistent with recently published data. The HYBRID (POL-MIDES) trial (11), the largest prospective randomized study comparing HCR with conventional CABG, involved 98 HCR patients and 102 conventional CABG patients. The 5-year survival rates were 93.6% in the HCR group and 90.8% in the CABG group ($p = 0.69$), and the rates of freedom from MACCE were 45.2 and 53.4%, respectively ($p = 0.39$). No differences were found between the two groups. There were also no differences in the rates of MI, stroke, or repeat revascularization. Shen et al. (27) compared one-stop HCR, CABG, and PCI in an observational study. At the 3-year follow-up, actuarial survival was 99.3% in the HCR group and 97.2% in the CABG group, and the cumulative rate of freedom from MACCE was 93.6% after HCR and 86.5% after CABG ($p = 0.14$). In Shen's study, surgical revascularization was completed through a lower partial ministernotomy, which is different from the widely used technique through a small anterior thoracotomy.

In the present study, the rate of any repeat revascularization was comparable between the HCR and OPCAB groups (4.7 vs. 5.0%; OR.72; 95% CI.21–2.49; $p = 0.61$) during the follow-up. Hage et al. (12) compared HCR ($n = 147$, robotic-assisted minimally invasive direct CABG) and OPCAB ($n = 216$) using inverse-probability weighting. The HCR was associated with a higher in-hospital reintervention rate (HCR 3.4% vs. CABG 0%, $p = 0.03$). For long-term follow-up, freedom from any form of revascularization was similar between the two groups (91 vs. 92%; $p = 0.80$), which is consistent with our results. In contrast, a meta-analysis from Nolan et al. (28) found that HCR was also associated with a higher risk of long-term repeat target vessel revascularization (TVR) than CABG.

Several limitations need to be addressed. First, this study was a single-center retrospective study, and the risk of selection bias was inevitable despite the benefits of propensity score matching. Second, the sample size was limited. Finally, the follow-up time was short, and long-term follow-up to verify the effectiveness of one-stop HCR is warranted.

CONCLUSIONS

One-stop HCR is safe and efficacious with less invasiveness and faster postoperative recovery in selected patients with multivessel coronary artery disease. Compared with OPCAB, one-stop HCR is associated with a lower rate of perioperative transfusion and new-onset AF, shorter time of mechanical ventilation and LOS in the hospital, and excellent similar midterm outcomes. Randomized controlled trials with larger sample sizes and long-term follow-up are warranted to confirm these findings.

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 authors.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

DL, PS, and JG: conception and design. YL, JZ, and PS: administrative support. DL, JG, YGu, XA, and XZ: provision of study materials or patients. DL and YGa: collection and assembly of data. DL, JG, and SG: data analysis and interpretation. DL: manuscript writing. All authors read and approved the final manuscript.

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Incidence, Risk Factors and Outcomes of Postoperative Headache After Stanford Type a Acute Aortic Dissection Surgery

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Background: Postoperative headache (POH) is common in clinical practice, however, no studies about POH after Stanford type A acute aortic dissection surgery (AADS) exist. This study aims to describe the incidence, risk factors and outcomes of POH after AADS, and to construct two prediction models.

Methods: Adults who underwent AADS from 2016 to 2020 in four tertiary hospitals were enrolled. Training and validation sets were randomly assigned according to a 7:3 ratio. Risk factors were identified by univariate and multivariate logistic regression analysis. Nomograms were constructed and validated on the basis of independent predictors.

Results: POH developed in 380 of the 1,476 included patients (25.7%). Poorer outcomes were observed in patients with POH. Eight independent predictors for POH after AADS were identified when both preoperative and intraoperative variables were analyzed, including younger age, female sex, smoking history, chronic headache history, cerebrovascular disease, use of deep hypothermic circulatory arrest, more blood transfusion, and longer cardiopulmonary bypass time. White blood cell and platelet count were also identified as significant predictors when intraoperative variables were excluded from the multivariate analysis. A full nomogram and a preoperative nomogram were constructed based on these independent predictors, both demonstrating good discrimination, calibration, clinical usefulness, and were well validated. Risk stratification was performed and three risk intervals were defined based on the full nomogram and clinical practice.

Conclusions: POH was common after AADS, portending poorer outcomes. Two nomograms predicting POH were developed and validated, which may have clinical utility in risk evaluation, early prevention, and doctor-patient communication.

Keywords: headache, cardiac surgery, Stanford type A acute aortic dissection, risk factor, nomogram

INTRODUCTION

Stanford type A acute aortic dissection is a life-threatening cardiovascular disease related to significant risk of morbidity and mortality (1). Although great improvement has been made in diagnostic techniques and initial management over the past decades, prompt surgical interventions remain the standard treatment (2). However, survival after Stanford type A acute aortic dissection surgery (AADS) is still suboptimal and a considerable proportion of patients develop various postoperative complications (1).

Postoperative headache (POH) is one of the most common surgical complications, which is associated with decreased quality of life, poorer outcomes, and additional economic burden (3–7). At present, many studies describing the incidence and outcomes of POH have been conducted and several independent risk factors for POH have been reported in the literature (7–12). Nevertheless, none of these studies were carried out in patients undergoing AADS and available information is still lacking in this population.

In the present study, we aimed to investigate the incidence, risk factors and outcomes of POH in adult patients who underwent AADS, and to construct and validate two nomogram models for POH after AADS to provide help for risk assessment and early prevention.

MATERIALS AND METHODS

Ethical Statement

This study was conducted according to the ethical statement of the Declaration of Helsinki. The Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IORG No. IORG0003571) approved this study. Written informed consent was waived due to its observational, retrospective nature.

Study Population

This was a multicenter, observational, retrospective study. Consecutive adult patients (older than 18 years) who underwent AADS in four tertiary care centers between 2016 and 2020 were enrolled. Patients with the following conditions were excluded from the study: (1) intraoperative death or postoperative unconsciousness, and (2) records with missing data.

Data Collection and Variables

We collected clinical data using the hospital's electronic medical record management systems. Pre-, intra-, and post-operative variables were collected and analyzed. Preoperative variables included sex, age, body mass index, smoking, drinking, diabetes mellitus, hypertension, cerebrovascular disease, chronic headache history, chronic obstructive pulmonary disease, gastrointestinal tract disease, peripheral vascular disease, atrial fibrillation, left ventricular ejection fraction, cardiac function, pulmonary artery hypertension, pericardial effusion, general surgery history, cardiac surgery history, red blood cell (RBC) count, white blood cell (WBC) count, platelet count, hemoglobin, serum creatinine, urea nitrogen, uric acid, albumin, and globulin levels. Intraoperative variables included cardiopulmonary bypass (CPB) time, aortic cross clamp time, use of deep hypothermic circulatory arrest (DHCA), and transfusion of RBC. Postoperative variables included readmission to intensive care unit (ICU), reintubation, tracheotomy, mortality, ICU duration, and hospital stay.

Definitions of Important Variables

In this study, POH was diagnosed on the basis of a self-reported or recorded headache identified in the electronic medical records. Body mass index was calculated on the basis of height and body weight. Smoking history referred to current or previous daily smoking. Chronic obstructive pulmonary disease was defined in accordance with previous diagnosis, self-report, or FEV1/FVC ≤ 0.7. Chronic headache history referred to recorded or self-reported migraine or other kinds of recurrent headaches. Cerebrovascular disease referred to a history of carotid artery surgery, transient ischemic attack, cerebral infarction, cerebral hemorrhage or stroke. Diabetes mellitus referred to fasting glucose $\geq$ 7.0 mmol/L, random glucose $\geq$ 11.1 mmol/L, or previous diagnosis of diabetes mellitus. Hypertension referred to previous diagnosis of hypertension or blood pressure $>$ 140/90 mmHg.

Statistical Analysis

Patients were divided into the training set and the validation set by 7:3 ratio. The development and internal validation of the model was performed using the training set and the external validation of the model was performed using the independent validation set. Normally distributed continuous variables were presented as means with standard deviations. Non-normally distributed continuous variables were presented as medians with inter-quartile ranges. Categorical variables were presented as frequencies with percentages. We first performed univariate logistic regression analysis to screen possible risk factors. Factors with $P < 0.1$ or considered to be clinically significant were further entered into a forward stepwise multivariate logistic regression analysis to identify independent risk factors. A nomogram based on these independent risk factors was then constructed.

We performed internal validation by bootstrap method using 1,000 replicates in the training set and external validation in the validation set. The area under the receiver operating characteristic (ROC) curve (AUC) was used to assess the discrimination. Both Hosmer-Lemeshow goodness-of-fit test and visual inspection were used to assess the calibration. Decision curves and clinical impact curves were used to assess the clinical usefulness. The Delong method was used to compare the AUCs between the training and the validation sets (13).

Statistical analyses were performed using SPSS (IBM SPSS Statistics 26.0, SPSS Inc., Chicago, IL) and R software (version 4.0.5, www.R-project.org/). A two-tailed P-value < 0.05 was deemed statistically significant.

Abbreviations: AADS, Stanford type A acute aortic dissection surgery; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ICU, intensive care unit; OR, odds ratio; POH, postoperative headache; RBC, red blood cell; ROC, receiver operating characteristic; WBC, white blood cell.

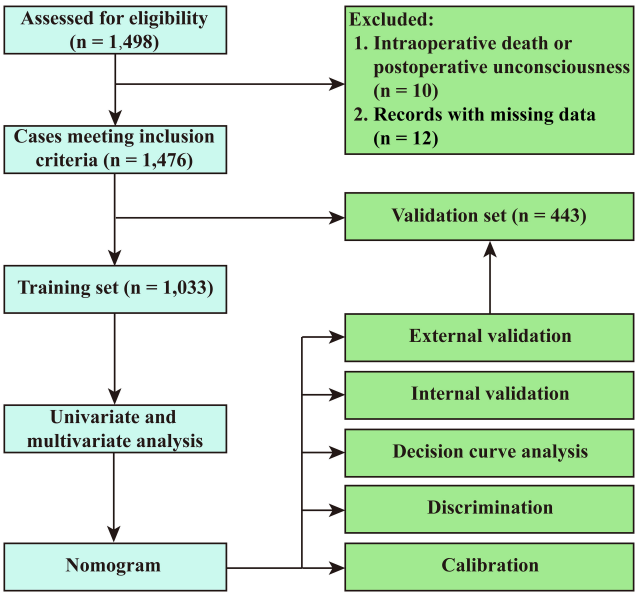

FIGURE 1 | Flow chart of the study.

RESULTS

Demographic Characteristics

Among the 1,498 adults who underwent AADS, 10 patients died intraoperatively or lapsed into unconsciousness postoperatively, and 12 patients had missing data in the medical records (**Figure 1**). The remaining 1,476 patients meeting the inclusion criteria were divided into two groups based on if one or two episodes of headache developed during their postoperative hospitalization and were further analyzed. The mean age of these included patients was 50.83 ± 11.35 years, 75.6% were men. The overall morbidity of POH after AADS was 25.7%.

There were multiple comorbidities and underlying conditions in this study population, in which smoking history existed in 43.9% of the patients, drinking history in 35.8%, hypertension in 68.1%, diabetes mellitus in 4.3%, cerebrovascular disease in 17.8%, chronic headache history in 11.4%, peripheral vascular disease in 13.6%, gastrointestinal tract disease in 8.5%, chronic obstructive pulmonary disease in 1.0%, atrial fibrillation in 0.8%, general surgery history in 20.5%, cardiac surgery history in 6.5%, pulmonary artery hypertension in 2.8%, pericardial effusion in 27.0%. The median CPB time was 204 (166, 247) min, aortic cross clamp time was 116 (94, 143) min, intraoperative RBC transfusion was 4.0 (2.5, 6.0) units, and DHCA was used in 58.9% of the patients. No significant difference was observed with regard to baseline conditions and operative variables between the training set and the validation set (**Table 1**).

Development of the Full Nomogram

The results of the univariate analysis conducted in the training set are presented in **Table 2**. Factors with $P < 0.1$ or considered to be clinically significant were further entered into a forward stepwise multivariate logistic regression analysis to identify independent risk factors. Co-linearity of covariates were assessed and highly collinear covariates were removed from the model. Finally, eight independent risk factors were identified in the full model, including younger age, female sex, smoking history, cerebrovascular disease, chronic headache history, the use of DHCA, CPB time, and intraoperative RBC transfusion (**Table 3**). A full nomogram used to predict the probability of POH after AADS was then constructed based on these preoperative and intraoperative predictors (**Figure 2**). The nomogram scaled each regression coefficient to a scale of 0–100 points, which demonstrated their relative importance. We also created an interactive web-based dynamic nomogram which is available online (https://xinlingdu.shinyapps.io/dynnomapp/).

The probability range of POH after AADS predicted by the nomogram was large. The personalized risk can be directly and easily assessed by summing the points of all the predictors. Young females who had a history of smoking, cerebrovascular disease, chronic headache, longer CPB time, more intraoperative RBC transfusion, and experienced DHCA may obtain more points and thus at a higher risk of POH. A concrete case is illustrated in **Figure 2**. For the online predictive system, press the "Quit" button in the bottom-left corner to exit the application and reload the procedure. Fill in the information of a concrete patients and click the "Predict" button, the predicted probability of POH after AADS was presented in the "Graphical summary" area on the right. The information of the patient and the model can also be acquired by clicking the "Numerical summary" and "Model summary" (**Supplementary Figure 1**).

Validation and Assessment of the Full Nomogram

The nomogram was well validated by both internal and external validations. By visual inspection, the calibration curves showed good consistency between estimated and actual probabilities. This was in agreement with the results of the goodness-of-fit test, with Hosmer-Lemeshow chi-square statistics of 5.226 ($P = 0.733$, **Figure 3A**) and 3.134 ($P = 0.926$, **Figure 3B**) in the training and validation sets. ROC curves were plotted to assess the discrimination, and the AUCs were 0.842 [95% confidence interval (CI), 0.815–0.869] and 0.847 (95% CI, 0.806–0.888) in the training and validation sets (**Figure 3C**), both indicating excellent predictive capability. There was no significant difference between the two AUCs ($P = 0.83$). Decision curve analysis was carried out to evaluate the clinical usefulness of the nomogram. The decision curves indicated that the nomogram could obtain more net benefits across a wide range of threshold probabilities than either the treat-none scheme or the treat-all-patients scheme both in the training and validation sets (**Figure 3D**). The clinical impact curves also revealed that the nomogram was clinically useful (**Figures 3E,F**).

Development, Validation, and Assessment of the Preoperative Nomogram

The above nomogram model was established using both preoperative and intraoperative variables. To facilitate early

TABLE 1 | Comparison of characteristics between the training and validation sets.

Characteristics	Training set $n = 1,033$ (%)	Validation set $n = 443$ (%)	*P* value
Demographics			
Male	787 (76.2)	329 (74.3)	0.431
Age (years)	50.62 ± 11.56	51.29 ± 10.85	0.299
Body mass index (kg/m^2)	25.29 ± 3.65	25.62 ± 3.62	0.112
Smoking history	470 (45.5)	178 (40.2)	0.059
Drinking history	367 (35.5)	161 (36.3)	0.764
Underlying conditions			
Hypertension	696 (67.4)	309 (69.8)	0.370
Diabetes mellitus	42 (4.1)	21 (4.7)	0.557
Chronic obstructive pulmonary disease	13 (1.3)	2 (0.5)	0.157
Cerebrovascular disease	184 (17.8)	79 (17.8)	0.992
Peripheral vascular disease	137 (13.3)	64 (14.4)	0.543
Gastrointestinal tract disease	88 (8.5)	38 (8.6)	0.970
Atrial fibrillation	10 (1.0)	2 (0.5)	0.311
Cardiac surgery history	70 (6.8)	26 (5.9)	0.517
General surgery history	207 (20.0)	96 (21.7)	0.477
Pulmonary artery hypertension	28 (2.7)	14 (3.2)	0.634
Pericardial effusion	271 (26.2)	128 (28.9)	0.292
NYHA class III-IV	87 (8.4)	36 (8.1)	0.851
Left ventricular ejection fraction (%)	62 (59, 65)	61 (59, 65)	0.460
Laboratory values			
White blood cell count ($\times 10^9$/L)	10.09 (7.57, 12.89)	10.24 (7.43, 12.85)	0.802
Red blood cell count ($\times 10^{12}$/L)	4.28 (3.85, 4.63)	4.25 (3.81, 4.62)	0.930
Hemoglobin (g/l)	129 (116, 140)	130 (116, 140)	0.881
Platelet count ($\times 10^9$/L)	160 (128, 206)	159 (128, 205)	0.480
Serum creatinine (μmol/L)	80.7 (65.5, 110.8)	81.5 (66.8, 114)	0.437
Urea nitrogen (mmol/L)	6.20 (4.99, 7.91)	6.31 (5.20, 8.00)	0.149
Uric acid (μmol/L)	369.2 (287.2, 456.5)	366.9 (279.8, 467.8)	0.936
Serum albumin (g/L)	37.9 (35.0, 40.9)	37.7 (34.7, 40.7)	0.284
Serum globulin (g/L)	25.3 (22.6, 28.3)	26.0 (22.9, 28.3)	0.295
Operative variables			
Cardiopulmonary bypass time (minutes)	205 (167, 248)	202 (165, 246)	0.527
Aortic cross clamp time (minutes)	116 (95, 145)	116 (91, 141)	0.168
Deep hypothermic circulatory arrest	611 (59.1)	259 (58.5)	0.807
Transfusion of red blood cells (units)	4 (2, 6)	4 (3, 6)	0.272

preoperative prediction, we further established a preoperative nomogram using only preoperative factors. Seven independent predictors were identified by multivariate logistic regression analysis in the training set, including lower platelet count, higher WBC count, and the five preoperative predictors mentioned above (**Table 4**). Then, a preoperative nomogram was constructed on the basis of these predictors (**Figure 4A**).

This nomogram was also well validated by both internal validation using bootstrap method in the training set and external validation in the independent validation set. The model fitted well by visual inspection of the calibration curves and goodness-of-fit test, with Hosmer-Lemeshow chi-square statistics of 7.998 ($P = 0.434$, **Figure 4B**) and 10.148 ($P = 0.255$, **Figure 4C**) in the training and validation sets, respectively. The AUCs were respectively 0.740 (95% CI, 0.704–0.775) and 0.760 (95% CI, 0.705–0.814) in the training and validation sets, indicating no significant difference ($P = 0.55$, **Figure 4D**). The decision and clinical impact curves also demonstrated that the nomogram may have usefulness in clinical practice.

Risk Stratification

We further performed a risk stratification on the basis of the full nomogram and clinical practice (**Table 5**). We selected predicted probabilities of 0.1 and 0.4 as the cutoff values and defined three risk groups as low, medium, and high risk groups, corresponding to the scores of <388 points, 388–435 points, and >435 points on the graphical nomogram. In this study, more than one-third of the patients were classified into the low risk

TABLE 2 | Univariate analysis of possible risk factors for POH after AADS in the training set.

Characteristics	Without POH $n = 756$ (%)	With POH $n = 277$ (%)	*P* value
Demographics			
Male	581 (76.9)	206 (74.4)	0.406
Age (years)	51.92 ± 11.33	47.09 ± 11.46	<0.001
Body mass index (kg/m^2)	25.34 ± 3.58	25.13 ± 3.84	0.409
Smoking history	309 (40.9)	161 (58.1)	<0.001
Drinking history	254 (33.6)	113 (40.8)	0.032
Underlying conditions			
Hypertension	534 (70.6)	162 (58.5)	<0.001
Diabetes mellitus	29 (3.8)	13 (4.7)	0.537
Chronic headache history	68 (9.0)	63 (22.7)	<0.001
Chronic obstructive pulmonary disease	12 (1.6)	1 (0.4)	0.117
Cerebrovascular disease	115 (15.2)	69 (24.9)	<0.001
Peripheral vascular disease	103 (13.6)	34 (12.3)	0.571
Gastrointestinal tract disease	63 (8.3)	25 (9.0)	0.724
Atrial fibrillation	9 (1.2)	1 (0.4)	0.228
Cardiac surgery history	42 (5.6)	28 (10.1)	0.010
General surgery history	156 (20.6)	51 (18.4)	0.429
Pulmonary artery hypertension	21 (2.8)	7 (2.5)	0.826
Pericardial effusion	191 (25.3)	80 (28.9)	0.242
NYHA class III-IV	65 (8.6)	22 (7.9)	0.737
Left ventricular ejection fraction (%)	62 (59, 65)	61 (59, 65)	0.336
Laboratory values			
White blood cell count ($\times 10^9$/L)	9.97 (7.42, 12.37)	10.45 (7.92, 14.24)	0.002
Red blood cell count ($\times 10^{12}$/L)	4.29 (3.86, 4.63)	4.22 (3.77, 4.62)	0.506
Hemoglobin (g/l)	130 (116, 140)	128 (114, 141)	0.272
Platelet count ($\times 10^9$/L)	165 (130, 211)	153 (125, 194)	0.007
Serum creatinine (μmol/L)	80.9 (66.7, 108.3)	79.5 (63.7, 121.4)	0.880
Urea nitrogen (mmol/L)	6.26 (5.04, 7.80)	6.20 (4.88, 8.65)	0.860
Uric acid (μmol/L)	365.6 (287.6, 444.4)	375.0 (283.3, 496.6)	0.275
Serum albumin (g/L)	38.1 (35.0, 41.0)	37.4 (34.4, 40.2)	0.017
Serum globulin (g/L)	25.4 (22.9, 28.3)	25.0 (22.5, 28.2)	0.350
Operative variables			
Cardiopulmonary bypass time (minutes)	193 (159, 234)	243 (198, 288)	<0.001
Aortic cross clamp time (minutes)	112 (92, 137)	138 (111, 168)	<0.001
Deep hypothermic circulatory arrest	392 (51.9)	219 (79.1)	0.807
Transfusion of red blood cells (units)	4 (2, 5)	6 (3, 7)	<0.001

AADS, Stanford type A acute aortic dissection surgery; POH, postoperative headache.

group, about two-fifths into the medium risk group, and about a quarter into the high risk group. We compared the predicted probabilities and the observed probabilities in the training and validation sets between the three risk groups (**Figure 5**). No significant difference was observed between the predicted and actual probabilities in the same risk interval ($P > 0.05$) and it differed significantly between different risk intervals ($P < 0.05$), which indicated good consistency and reasonable division.

Outcomes

The overall mortality rate of the included patients was 8.7%, with a rate of 6.6% in patients without POH vs. 15.0% in those with POH [odds ratio (OR) = 2.510, 95% CI, 1.735–3.631; $P < 0.001$). We also observed significantly higher probabilities of readmission to ICU, reintubation and tracheotomy, and significantly longer postoperative ICU and hospital stay in patients with POH. Details of the comparison in patients with and without POH after AADS are presented in **Table 6**.

DISCUSSION

POH has been reported to be an indicator of increased risk of mortality and averse outcomes (3, 5, 6), which was consistent with the present study. The overall incidence of POH after AADS

TABLE 3 | Multivariate analysis of independent risk factors for POH after AADS.

Characteristics	Coefficient	Standard error	OR (95% CI)	*P* value
Female sex	1.082	0.247	2.951 (1.817–4.792)	<0.001
Age (years)	−0.052	0.008	0.950 (0.935–0.965)	<0.001
Smoking history	1.163	0.210	3.201 (2.121–4.831)	<0.001
Chronic headache history	1.235	0.239	3.437 (2.150–5.495)	<0.001
Cerebrovascular disease	0.956	0.222	2.602 (1.685–4.019)	<0.001
Cardiopulmonary bypass time (min)	0.011	0.002	1.011 (1.008–1.014)	<0.001
Intraoperative transfusion of RBC (units)	0.248	0.042	1.281 (1.181–1.390)	<0.001
Deep hypothermic circulatory arrest	1.283	0.195	3.607 (2.459–5.290)	<0.001
Constant	−4.134	0.559	0.016	<0.001

AADS, Stanford type A acute aortic dissection surgery; CI, confidence interval; OR, odds ratio; POH, postoperative headache; RBC, red blood cell.

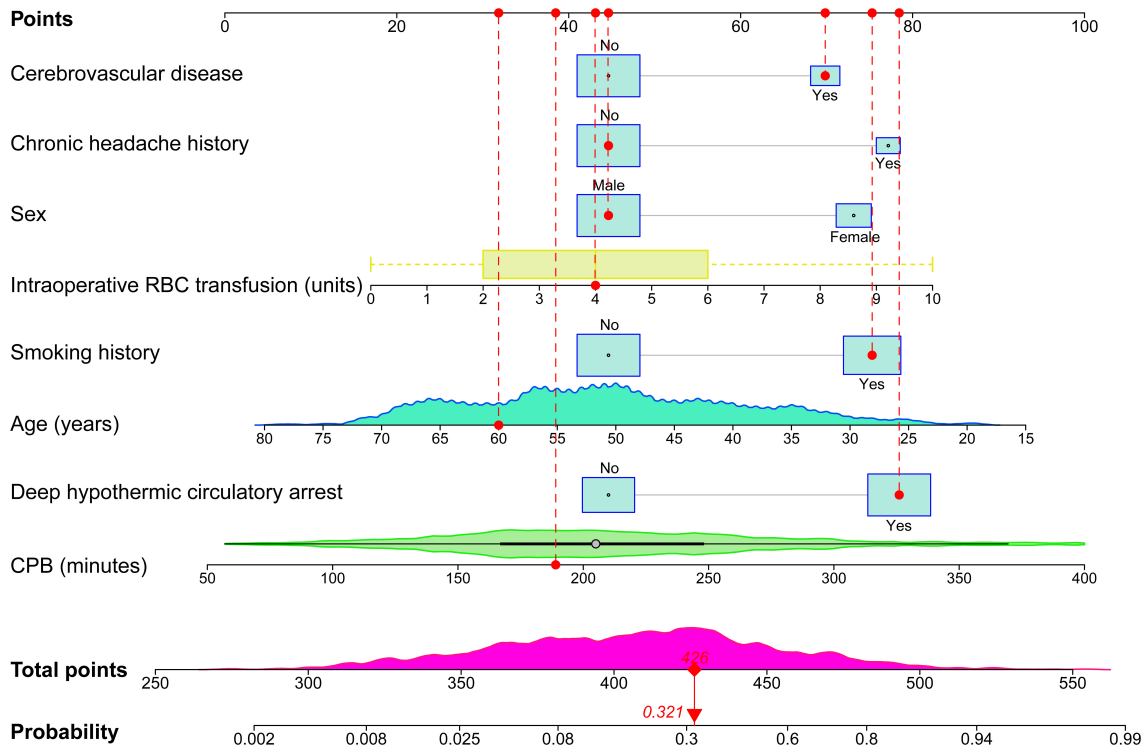

FIGURE 2 | Full nomogram for the prediction of POH after AADS. A concrete case is presented to show how to use the nomogram. This was a 60-year-old male patient who had a history of smoking and cerebrovascular disease, but did not have a chronic headache history. He experienced DHCA, and the duration of CPB was 189 min and the transfused RBC was 4 units. The individual item score corresponding to each factor was presented at the top, and the total points were obtained from the sum of the scores corresponding to each factor by a red dot. Given values of the 8 predictors, the patient can be intuitively mapped onto the nomogram. It can be clearly seen from the nomogram that the total points of this patient was 426 points and the corresponding probability of POH was 0.321. AADS, Stanford type A acute aortic dissection surgery; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; POH, postoperative headache; RBC, red blood cell.

was 25.7% and the mortality was 8.7%. However, compared with patients without POH, the mortality was significantly higher in patients who suffered from POH. Moreover, we observed significantly higher probability of other adverse outcomes such as tracheotomy and reintubation in these patients. The higher risk of adverse outcomes and mortality stressed the need of identifying independent risk factors and high-risk patients of POH after AADS.

Globally, various studies focused on identifying predictors for POH have been carried out in patients undergoing other surgeries (6, 8–10, 12), however, studies conducted in patients undergoing AADS are still lacking. To our knowledge, our work is the first report that describes the incidence, predictors, and outcomes of POH after AADS, and is the first attempt to construct and validate clinical prediction models in this area worldwide. In this study,

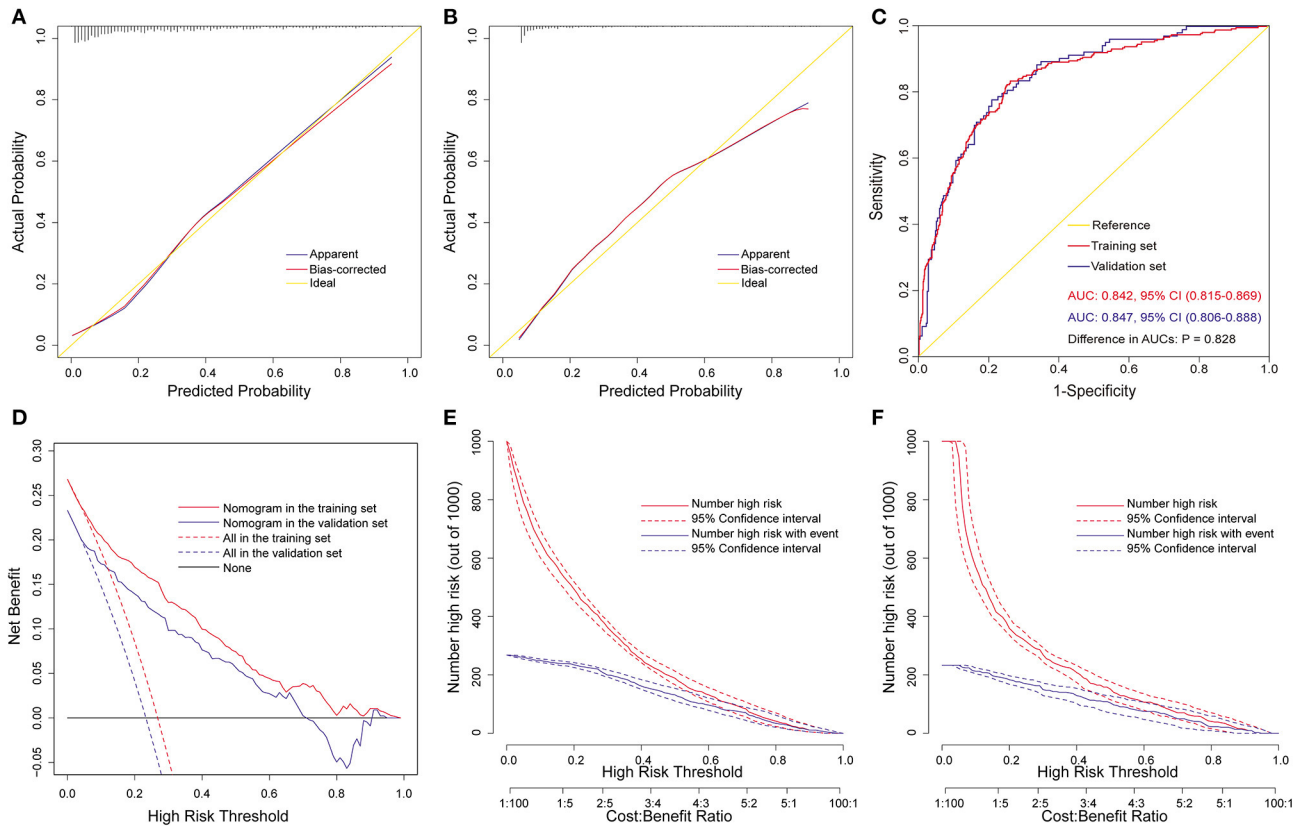

FIGURE 3 | Assessment of the full nomogram model for POH after AADS. Calibration plots in the training set **(A)** and the validation set **(B)**, ROC curves in the two sets **(C)**, decision curves in the two sets **(D)**, and clinical impact curves in the training set **(E)** and the validation set **(F)**. AADS, Stanford type A acute aortic dissection surgery; AUC, area under the receiver operating characteristic curve; CI, confidence interval; POH, postoperative headache; ROC, receiver operating characteristic curve.

TABLE 4 | Multivariate analysis of preoperative independent risk factors for POH after AADS.

Characteristics	Coefficient	Standard error	OR (95% CI)	*P* value
Platelet count ($\times 10^9$/L)	−0.004	0.001	0.996 (0.994–0.998)	0.002
Female sex	1.332	0.228	3.789 (2.423–5.927)	<0.001
Age (years)	−0.045	0.007	0.956 (0.942–0.969)	<0.001
Smoking history	1.291	0.194	3.636 (2.488–5.313)	<0.001
Cerebrovascular disease	0.949	0.198	2.584 (1.753–3.808)	<0.001
Chronic headache history	1.060	0.217	2.888 (1.888–4.418)	<0.001
White blood cell count ($\times 10^9$/L)	0.084	0.020	1.087 (1.045–1.132)	<0.001
Constant	−1.610	0.625	0.200	0.010

AADS, Stanford type A acute aortic dissection surgery; CI, confidence interval; OR, odds ratio; POH, postoperative headache.

we developed and validated a full nomogram model and a preoperative nomogram model using clinical data of 1,476 patients who underwent AADS in four tertiary care centers. The former was constructed based on five preoperative and three intraoperative predictors and the latter was based on seven preoperative predictors. Both nomogram models indicated good calibration, discrimination, and clinical usefulness. Three risk groups were finally divided to facilitate clinical application based on the full nomogram model and clinical practice.

Younger age and female sex have been reported to be associated with the development of POH in various surgeries (8, 9, 11, 14–16), which was consistent with our results. Droby and colleagues conducted a prospective study in patients who experienced post-lumbar puncture and found that compared to participants who did not develop a POH, patients that developed a POH were younger ($P = 0.033$) (17). Bitargil and colleagues conducted a respective study in patients undergoing endothermal ablation of the greater saphenous vein under spinal anesthesia and reported that female patients suffered from significantly more headaches than males (27 vs. 10%, $P = 0.013$) (9). Takenaka and colleagues conducted a large-scale study in patients who underwent primary lumbar spine surgery and reported that POH were more frequently observed in females than in males (OR = 2.70, $P = 0.001$) and advanced age was a significant protective factor for POH (OR = 0.70, $P < 0.001$) (14).

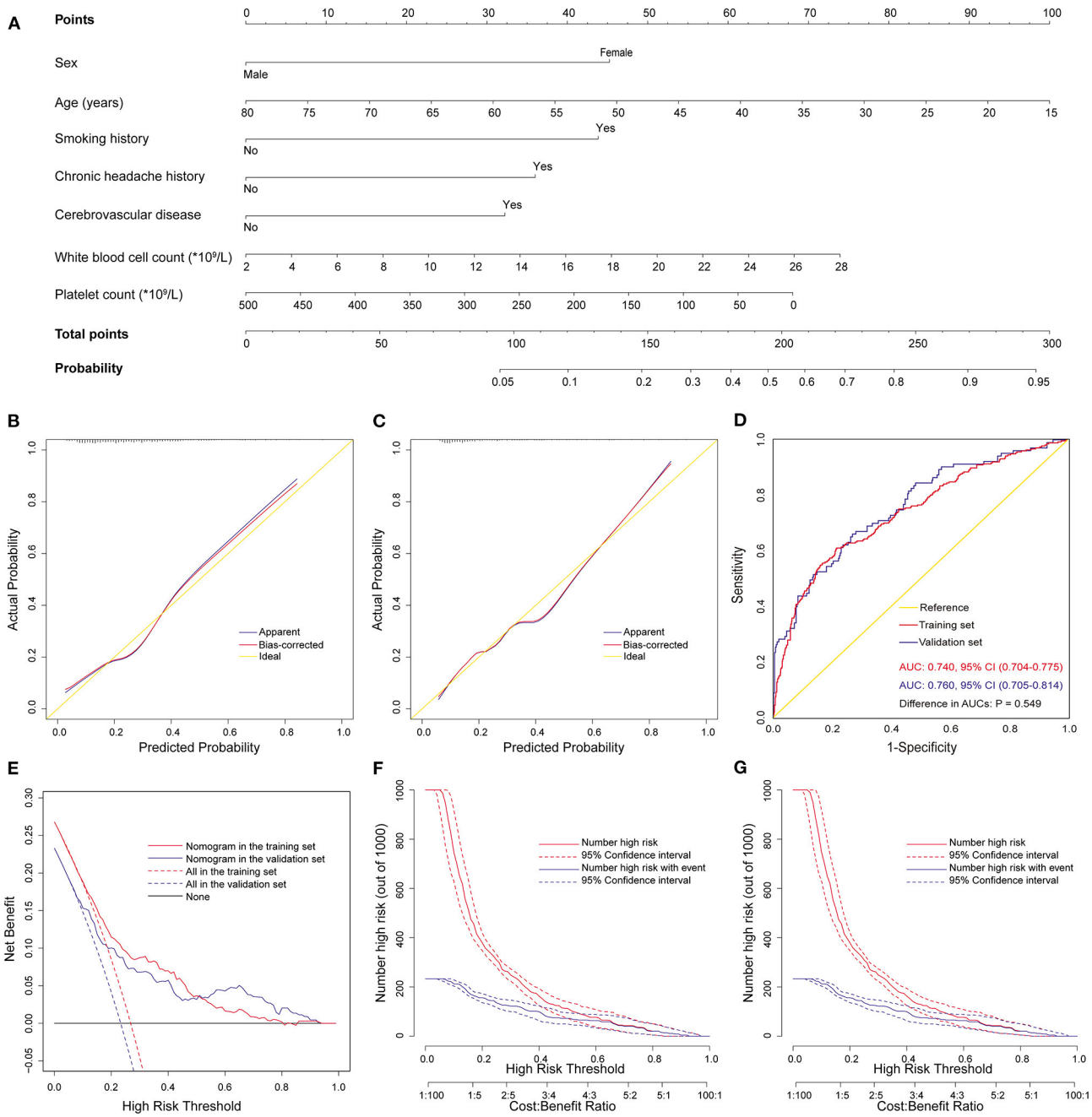

FIGURE 4 | Development, validation, and assessment of the preoperative nomogram for POH after AADS. The construction of the preoperative nomogram for POH after AADS **(A)**, calibration plots in the training set **(B)** and the validation set **(C)**, ROC curves in the two sets **(D)**, decision curves in the two sets **(E)**, and clinical impact curves in the training set **(F)** and the validation set **(G)**. AADS, Stanford type A acute aortic dissection surgery; AUC, area under the receiver operating characteristic curve; CI, confidence interval; POH, postoperative headache; ROC, receiver operating characteristic curve.

The sex- and age-related difference in POH are likely multifactorial. Recently, several potential mechanisms have been posited such as hormones influence, pain perception, and psychosocial factors (18). Fluctuating hormone levels during the menstrual cycle and hormone-related differences in cerebrovascular reactivity have long been blamed for the development of kinds of headaches (19–21). In terms of pain perception, it is believed that females and younger patients are more sensitive than males and older patients (22). In addition, compared to males and older patients, females and younger patients prefer to interpret, recall and report physical discomforts as symptoms such as pain, which may be due to the fact that

TABLE 5 | Risk intervals of POH based on the nomogram.

Risk intervals	Low risk (<388 points)	Medium risk (388–435 points)	High risk (>435 points)
Estimated probability (%)	<10	10–40	>40
Observed probability, % (95% CI)	4.7 (2.8–6.5)	21.2 (17.9–24.5)	62.7 (57.7–67.6)
No. of patients (%)	515 (34.9)	594 (40.2)	367 (24.9)

CI, confidence interval; POH, postoperative headache.

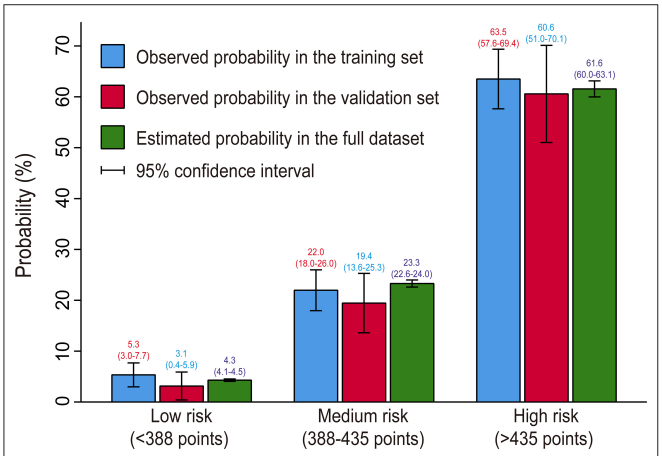

FIGURE 5 | Bar chart showing the consistency between predicted and observed probabilities. No significant difference was observed between the predicted and actual probabilities in the same risk interval ($P > 0.05$) and it differed significantly between different risk intervals ($P < 0.05$), indicating good consistency and reasonable division.

TABLE 6 | Postoperative variables in patients with and without POH after AADS.

Variables	All patients $n = 1,476$ (%)	Without POH $n = 1,096$ (%)	With POH $n = 380$ (%)	*P* value
Reintubation	216 (14.6)	122 (11.1)	94 (24.7)	<0.001
Tracheotomy	165 (11.2)	88 (8.0)	77 (20.3)	<0.001
Readmission to ICU	132 (8.9)	84 (7.7)	48 (12.6)	0.003
ICU stay (days)	7 (5, 11)	6 (5, 9)	9 (6, 15)	<0.001
Hospital stay (days)	21 (17, 27)	20 (16, 26)	24 (19, 31)	<0.001
Mortality	129 (8.7)	72 (6.6)	57 (15.0)	<0.001

AADS, Stanford type A acute aortic dissection surgery; ICU, intensive care unit; POH, postoperative headache.

it is more socially acceptable to express such emotions in those patients (16).

Chronic headache history was identified as an independent predictor for POH after AADS by multivariate analysis, which was in agreement with previous results in the literature (12, 15, 23, 24). Valentinis and colleagues conducted a prospective cohort study in patients who were operated on for intracranial tumors and reported that a longstanding headache history was the only significant independent intrapersonal predictor for POH (OR = 3.07, $P = 0.01$) (23). Ryzenman and colleagues conducted a large prospective cohort study in patients undergoing acoustic neuroma surgery to investigate the incidence and risk factors of POH and its effects on physical and psychosocial function (15). They found that preoperative headache was independently associated with the development of POH (OR = 1.4, $P < 0.01$) and patients who suffered from preoperative headache had more multiple occurrences of POH daily. Furthermore, Yabuki and colleagues reported that patients with preoperative headache had higher pain levels, higher neuropathic pain symptoms, and poorer quality of life (25). Hence, we believe that it may be an appropriate option to take prophylactic drugs to reduce the risk of POH for patients who had a chronic headache history (26).

Several other preoperative independent predictors for POH were also identified in our analysis, including cerebrovascular disease, smoking, WBC and platelet count. Headaches are common accompanying symptoms of cerebrovascular diseases and headaches attributed to ischemic strokes and transient ischemic attacks occur frequently. Oliveira and colleagues reported that the prevalence of headaches attributed to transient ischemic attacks and ischemic strokes were respectively 7.4–34% and 26–36% (27). A prospective study conducted by Matsota and colleagues indicated that smoking history was independently associated with the development of POH in patients undergoing elective surgery patients (OR = 1.74, $P = 0.006$) (8). Although the exact linkage between smoking and headache remains to unknown at present, it is undeniable that tobacco exposure is in some manner related to cluster headache (28). Given numerous negative health effects, decreased tobacco exposure and smoking cessation should be recommended in hopes of reducing disability and improving functionality (29).

The elevation of WBC count as a predictor for POH has been identified in previous study, which may relate to the acute phase systemic inflammatory response (24). Yazar and colleagues carried out a prospective study to investigate the role of inflammation and oxidative stress in the etiology of migraine (30). They found that the neutrophil, neutrophil/lymphocyte, monocyte/lymphocyte and platelet/lymphocyte ratios were higher in patients with migraine than patients without that ($P < 0.05$). The serum C-reactive protein, neutrophil, neutrophil/lymphocyte, monocyte/lymphocyte, and C-reactive protein /albumin ratios were higher during migraine attack periods ($P < 0.05$). Guo and colleagues conducted a retrospective study to explore prognostic factors for permanent neurological dysfunction after total aortic arch replacement with regional cerebral oxygen saturation monitoring. By multiple logistic regression analysis, they found that preoperative low platelet count was an independent predictor for postoperative neurological complications, which may be associated with platelet consumption coagulopathy (31). Siewert and colleagues conducted a genetic correlation analysis to explore risk factors for migraine headache using cross-trait linkage disequilibrium score regression and tested for potential causality between migraine and those phenotypes using Mendelian randomization (32). They found that migraine headache had genetic correlations with various traits including cardiovascular disease, smoking status, WBC count and platelet count.

Besides the preoperative predictors mentioned above, three intraoperative predictors for POH after AADS were also identified in this study, including RBC transfusion, CPB time and the use of DHCA. Although RBC transfusion can be lifesaving during cardiovascular surgery, massive transfusion has been confirmed to relate to various adverse events (33, 34). Arngrim and colleagues conducted a MRI spectroscopy and angiography study finding that experimental hypoxia was associated with headache attacks (35). Accordingly, we hypothesize that the reduced capacity of oxygen-carrying of the transfused RBCs which may lead to insufficient oxygen supply to the brain may be one of the responsible causes of POH. Furthermore, massive transfusion of RBC is often due to massive blood loss, which may also result in insufficient oxygen supply due to blood dilution and the reduction of active RBC and hemoglobin. Recently, a restrictive blood transfusion strategy has been especially recommended in clinical practice guidelines to prevent the development of various adverse events (36, 37).

It can be easily understood that CPB time is independently associated with the development of POH after AADS. On the one hand, longer duration of CPB often indicates longer duration of the whole surgery, longer forced position, and more intake of anesthetic agents, which have been reported to be significantly related to the development of POH (8, 38). On the other hand, the CPB process itself can result in brain injury and POH in many ways, including cerebral edema, embolism, hemodilution, and hypoxia (39–41). A systematic review conducted by Caldas and colleagues indicated that the development of neurological complications in patients who underwent cardiac surgery may be partially caused by the damage of cerebral autoregulation during CPB (40). Therefore, it may be effective to decrease the incidence of POH and other neurological complications through better brain protection strategy during CPB (41).

The use of DHCA has long been considered to be the standard neuroprotection strategy in patients undergoing AADS, however, this technique remains related to significant risk of brain damage and complications (42), which was again confirmed by this study. To reduce the risk of brain damage, continuous cerebral perfusion techniques have been proposed these years, including antegrade cerebral perfusion via the right subclavian artery only or with selective perfusion of both the carotid arteries and retrograde cerebral perfusion via the venous system. Using the UK National Adult Cardiac Surgical Audit, Benedetto and colleagues investigated the association between neuroprotective strategies and clinical outcomes in patients undergoing AADS (43). They found that compared to DHCA, the use of unilateral and bilateral antegrade cerebral perfusion was related to a decreased risk of death and cerebrovascular accident. Nonetheless, no consensus has been reached on which neuroprotective strategy should be preferred and there exists significant variation in clinical practice (44–47).

The nomograms may be helpful for risk evaluation, early prevention, surgeon-patient communication, and clinical decision-making. Taking appropriate strategies based on the nomograms may obtain more clinical net benefits. Besides preoperative precautions, preventive efforts during operations also make sense. Bezov and colleagues concluded that operator experience was a modifiable risk factors for POH (18). Benedetto and colleagues reported that high-volume surgeons, cardiac centers, and intraoperative factors were strong determinants of clinical outcomes after AADS (1).

There are several limitations in this study. First, the study was retrospectively designed and POH was diagnosed on the basis of medical records. Thus, we cannot assure that all the patients with POH were recorded in the database, which may result in an underestimation of the true morbidity. Second, some factors that may significantly relate to POH were not available in our analysis, such as operator experience. Nevertheless, the nomograms had reasonable performance in predictive capability, calibration, and clinical usefulness. Third, POH was the primary endpoint, but the evaluation of the types and severity of POH was not available because of the retrospective limitations. Prospective studies with more explicit classification of the types and severity of POH may make more sense in future work.

CONCLUSIONS

To our knowledge, this is the first study describing the incidence, risk factors and outcomes of POH in patients undergoing AADS. POH was prevalent in our results, and the mortality and other adverse outcomes increased significantly in patients with POH. We constructed a full nomogram using five preoperative and three intraoperative predictors and a preoperative nomogram using seven preoperative predictors. Both nomograms demonstrated good calibration, discrimination, and clinical utility. We further defined three risk groups to facilitate clinical application. These findings may be helpful for risk evaluation, surgeon-patient communication, clinical decision-making, and early prevention.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of patient confidentiality. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IORG No. IORG0003571). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XD, XH, PY, and AZ: conception and design. XD, PY, HW, and SL: administrative support. XD, XH, HW, and AZ: provision of study materials or patients. DW, JW, FX, XL, SL, RL, YS, PY, and JL: collection and assembly of

data. DW, SL, and XH: data analysis and interpretation. All authors: manuscript writing and final approval of manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.781137/full#supplementary-material

Supplementary Figure 1 | Screenshots of the interactive web-based dynamic nomogram created for the full predictive model of POH after AADS. Squares represent the point estimates for a given set of conditions, and the bars surrounding them reflect the 95% CIs. In the screenshots, we present the probabilities and corresponding 95% CIs of POH of 10 different patients **(A)**; when click the square, the information of the patient and corresponding risk are presented **(B)**; all the information of the patients can be acquired by clicking the "Numerical Summary" **(C)**; and the information of the model can be acquired by clicking the "Model Summary" **(D)**.

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REVIEW
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Benefits and Pitfalls of the Perceval Sutureless Bioprosthesis

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Objective: To highlight the main target points covered by clinical studies on the Perceval sutureless valve for surgical aortic valve replacement (SAVR) and raise a point of discussion for further expansion of its use when compared with stented bioprostheses (SB) and transcatheter aortic valve replacement (TAVR).

Methods: We reviewed clinical trials and retrospective studies published up to date and compared the outcomes in terms of mortality, myocardial infarction (MI) stroke, paravalvular leak (PVL), permanent pacemaker implantation (PPI), bleeding and long-term outcomes.

Results: Clinical studies showed that 30-day mortality ranged from 0–4% for Perceval and 2.9–7% for TAVR. The incidence of PVL (Perceval 1.9–19.4 vs. TAVR 9–53.5%), PPI (Perceval 2–11.2 vs. TAVR 4.9–25.5%), stroke (Perceval 0 vs. TAVR 0–2.8%), MI (Perceval 0 vs. TAVR 0–3.5%), were all higher in the TAVR group. Compared to other SB, mortality ranged from 0–6.4% for Perceval and 0–5.9% for SB. The incidence of PVR (Perceval 1–19.4 vs. SB 0–1%), PPI (Perceval 2–10.7 vs. SB 1.8–8.5%), stroke (Perceval 0–3.7 vs. SB 1.8–7.3%) and MI (Perceval 0–7.8 vs. SB 0–4.3%) were comparable among the groups. In patients with a bicuspid aortic valve, mortality rate was (0–4%) and PVL incidence was (0–2.3%). However, there was a high incidence of PPI (0–20%), and stroke (0–8%). Long-term survival ranged between 96.7–98.6%.

Conclusions: The Perceval bioprosthesis has proved to be a reliable prosthesis for surgical aortic valve replacement due to its implantation speed, the reduced cardiopulmonary bypass time, the reduced aortic cross-clamp time and the shorter intensive care unit and hospital length of stay.

Keywords: benefits, pitfalls, Perceval, sutureless, review, sutureless valve replacement

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INTRODUCTION

Surgical aortic valve replacement (SAVR) with the sutureless self-expanding Perceval aortic bioprosthesis (LivaNova Group, Milan, Italy) was developed to combine the advantages of the transcatheter aortic valve replacement (TAVR) procedure, allowing for a fast implantation with no need for suturing, with the benefits of a conventional surgical approach owing to the possibility of

removing the native valve along with the calcifications. The valve has grown in popularity mostly due to the reduced cardiopulmonary bypass (CPB) time (1), the improved myocardial recovery time and its application in minimally invasive cardiac surgery (MICS) procedures (2). In addition, the three PARTNER clinical trials' (3–5), the SURTAVI trial (6) and other observational cohort studies (7, 8) have evidenced the non-inferiority of TAVR vs. SAVR. In this context, some reports of successful valve-in-valve TAVR in bioprostheses with structural valve deterioration (SVD) have generated enthusiasm particularly for future applications (9, 10). In addition, other outcomes of the valve include improved hemodynamics, a self-expanding radial force, usage in hostile roots, enhanced surgical and recovery speed, and enabling minimally invasive cardiac surgery procedures. However, many points deserve to be highlighted such as the impact of permanent pacemaker implantation (PPI) after SAVR, the application of the sutureless bioprostheses in patients with bicuspid aortic valves (BAV), the impact of thrombocytopenia on the survival rate and the implantation of this bioprostheses in patients with small aortic annuli.

The goal of this review is to highlight the main target points covered by clinical studies and raise a point of discussion for further expansion of the use of Perceval.

MATERIALS AND METHODS

Inclusion Criteria

Studies were included if any of the following criteria were met: (1) reported outcomes of Perceval compared with other heart valve prostheses or procedures; (2) reported analysis of complications using the Perceval; (3) reported off-label experience; (4) reported learning curve analysis; (5) reported one or more case of SAVR with Perceval.

Exclusion Criteria

Studies were excluded if any of the following criteria were met: (1) reported outcomes of exclusively other sutureless valves; (2) grouped outcomes of Perceval with other prostheses in the same cohort; (3) not published in the English language; (4) not published in a peer-reviewed journal; and (5) was a conference abstract.

Data Collection

The data collection was done on August 31, 2021. One author (AD) screened the articles and reviewed it three times. The final results were reviewed by another investigator (MPS). The primary reported outcomes of the study included (a) the surgical technique; (b) clinical trials investigating the Perceval valve; (c) the sutureless vs. TAVR; (d) the sutureless vs. other stented bioprostheses (e) Perceval in mini-SAVR; (f) Perceval and bicuspid aortic valves; (g) long-term outcomes of the Perceval valve (valve durability); (h) the incidence of thrombocytopenia after Perceval implantation; (i) the ideal candidate for the prosthesis implantation (**Figure 1**).

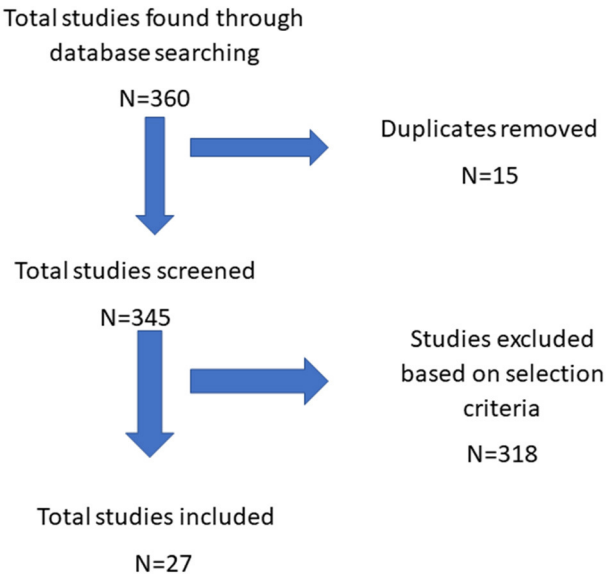

FIGURE 1 | Flowchart study selection process.

THE MOST APPROPRIATE SURGICAL TECHNIQUE FOR VALVE IMPLANTATION

The aortic incision is performed at the distal portion at the sinotubular junction to preserve a segment of ascending aorta above the prosthetic valve. The aortic valve should be excised at a position corresponding to the incision line of the native leaflets and the aortic annulus should be decalcified to prepare the implant site. A complete decalcification of the aortic annulus is not necessary. To ensure the correct positioning and orientation of the prosthesis, three guiding sutures are placed to act as reference for accurate alignment of the inflow portion of the prosthesis with the insertion plane of the native leaflets. For each valve sinus, one stitch is positioned immediately 2–3 mm below the lowest portion of the native leaflet resection line. On the prosthesis, each guiding suture is passed into a dedicated thread loop located at the midlevel of the inflow ring and aligned to the median part of the prosthetic sinuses. Once the prosthesis is connected to the three guiding suture, the release device is introduced into the aorta (11). In this context, the Perceval Livanova company recommend placing the guiding sutures 2–3 mm below the leaflet insertion line. Using this technique, Yanagawa et al. (12) found a PPI rate of 28%. Therefore, they modified the technique by placing the guiding sutures at the nadir of each cusp and not 2 to 3 mm below. After the modification, the PPI rate dropped to 0%. Nguyen et al. (13), recommend performing the transverse aortotomy ∼3.5 cm above the level of the aortic annulus, and 0.5 cm above the sinotubular junction, to leave a free edge for closure of the aortotomy. In bicuspid aortic valves, the surgeon must recreate 3 nadirs that are positioned

Abbreviations: TAVR, transcatheter aortic valve replacement; CPB, cardiopulmonary bypass; PPI, permanent pacemaker implantation; BAV, bicuspid aortic valve; MI, myocardial infarction; PVL, paravalvular leak; SAVR, surgical aortic valve replacement; MS, mini-sternotomy; RAT, right anterior thoracotomy.

at ∼120° to better manage the asymmetry of each cusp. To achieve this, the surgeon can use a commercial sizer with 120° markings to recreate a normal nadir. In addition, a dedicated balloon should be inserted into the prosthesis and inflated at a pressure of 4 atm for 30 sec.

CLINICAL TRIALS

The "PERCEVAL TRIAL—Perceval S valve pilot study was performed in 30 high-risk patients who were scheduled for isolated SAVR due to severe aortic stenosis (14). This prospective analysis was undertaken at three European Centers from April 2007 to February 2008 and concentrated on perioperative and 1-year outcomes. Operative mortality was 3.3% and moderate paravalvular leak (PVL) was present in two patients. The PERCEVAL-AVR clinical trial evidenced the non-inferiority for the sutureless vs. stented for major adverse cerebral and cardiovascular events at 1 year, whereas aortic valve hemodynamics improved equally in both groups. Perceval significantly reduced surgical times (mean CPB: 71.0 ± 34.1 vs. 87.8 ± 33.9 mins; mean aortic cross-clamp times: 48.5 ± 24.7 vs. 65.2 ± 23.6; both p-values <0.001), but resulted in a higher rate of permanent pacemaker implantation (PPI – 11.1 vs. 3.6% at 1 year). Incidences of PVL and central leak were similar.

The CAVALIER clinical trial (15) reported a mean cross-clamp time of 41.5 ± 20.3 mins and a mean CPB time of 39.0 ± 12.5 mins while the mean hospital length of stay was 12.0 ± 7.4 days. There were three reported cardiac valve-related deaths, and eight cases were cardiac related but not valve related. There were five early explanted valves 13.8 days post-implant due to PVL discovered at follow-up.

PERCEVAL VS. TAVR. WHEN ENEMIES BECOME ALLIES

SVD has been reported in many case series and the treatment in these patients has successfully been delivered through valve-in-valve TAVR using both the Evolut Pro and the Corevalve (16) (**Figure 2**). With respect to Perceval vs. TAVR, the SURTAVI trial (6) showed that TAVR with the self-expanding CoreValve was non-inferior to SAVR for the primary endpoint at 2 years for the treatment of severe aortic stenosis in intermediate-risk patients (STS-PROM, 3–15%; median 4.5%). The Perceval valve benefits, may render ViV-TAVR second procedure easier and safer. This includes a self-expanding nitinol stage, a radio-opaque frame, and sinusoidal struts that "push" coronary ostia and sinuses away from prosthesis leaflets. In addition, eight retrospective clinical studies showed that 30-day mortality was higher in the TAVR group which may be explained with the higher preoperative risk in this population (16–24). The most used prosthesis in TAVR were the Corevalve, Sapien, Lotus and Portico. The CPB and aortic cross-clamp time for the Perceval ranged between 54 and 73.4/SD = 23.1–25 mins and 32–43.4/SD = 13.4–17, respectively. Mortality ranged from 0 to 4% for Perceval and 2.9–7% for TAVR. The incidence of PVL (Perceval 1.9–19.4 vs. TAVR 9–53.5%), PPI (Perceval 2–11.2 vs. TAVR 4.9–25.5%), stroke (Perceval 0 vs. TAVR 0–2.8%), and myocardial infarction (MI) (Perceval 0 vs. TAVR 0–3.5%), were all higher in the TAVR group (**Table 1**).

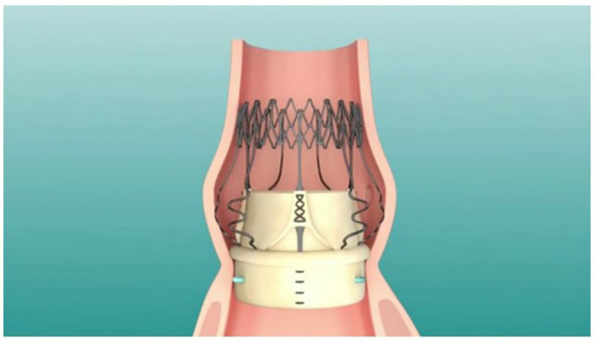

FIGURE 2 | Sutureless aortic valve in the aortic annulus.

PERCEVAL VS. OTHER STENTED BIOPROSTHESES. NEW GENERATION VS. OLD STYLE

Compared to other stented bioprostheses (SB), the Perceval valve had similar outcomes. Four prospective and four retrospective clinical studies showed that 30-day mortality was higher in the Perceval group which may be explained with the higher preoperative risk in this population (24–31). Mortality ranged from 0 to 6.4% for Perceval and 0–5.9% for SB. The aortic cross-clamp time in minutes (Perceval 30.8–65.3/SD = 13.6–29.1 vs. SB 59–90/SD = 23–30.3) and CPB time in minutes (Perceval 47–88/SD = 11–34.9 vs. SB 87.8–120/SD = 20.4–37.9) were all significantly higher in the SB group ($p < 0.05$). The incidence of PVL (Perceval 1–19.4 vs. SB 0–1%), PM (Perceval 2–10.7 vs. SB 1.8–8.5%), stroke (Perceval 0–3.7 vs. SB 1.8–7.3%), MI (Perceval 0–7.8 vs. SB 0–4.3%), were comparable among the groups (**Table 2**). The most used stented valves were the CE Perimount, Magna Ease and Triflecta valves.

PERCEVAL FOR MICS AND MINI-SAVR

One of the benefits of the Perceval bioprosthesis is its widespread usage in mini-SAVR. Perceval has been developed in order to combine the best of two worlds, as they could facilitate the implantation while maintaining the benefits of SAVR. Currently, the upper ministernotomy (MS) and the right anterior thoracotomy (RAT) are the most common approaches for (mini-SAVR). Bonacchi et al. (32) evidenced the benefits of the valve in both MS and RAT. In addition, the international prospective registry (33) comparing MS with RAT showed an aortic cross-clamp time of 43 vs. 55 mins ($p < 0.01$), cardiopulmonary bypass time of 67 vs. 89 mins ($p < 0.01$) and a prosthesis implantation time of 15.5 vs. 12 mins ($p = 0.014$), respectively. In this context, the Sutureless and Rapid Deployment International Registry (34), pointed out the efficacy of the Perceval bioprosthesis in redo

TABLE 1 | Sutureless aortic valve replacement vs. transcatheter aortic valve replacement.

Study author	Biancari et al.		Muneretto et al.		D'Onofrio et al.		Santarpino et al.		Miceli et al.		Muneretto et al.		Repossini et al.		Gerfer et al.	
Type of clinical study	**Retrospective**		**Retrospective**		**Retrospective**		**Retrospective**		**Retrospective**		**Retrospective**		**Retrospective**		**Retrospective**	
Valve types and nr. of patients	**Perceval *N* = 144**	**TAVR *N* = 144**	**Perceval *N* = 53**	**TAVR *N* = 55**	**Perceval *N* = 31**	**TAVR *N* = 143**	**Perceval *N* = 443**	**TAVR *N* = 1,002**	**Perceval *N* = 37**	**TAVR *N* = 37**	**Perceval *N* = 288**	**TAVR = 367**	**Perceval = 158**	**TAVR = 158**	**Perceval = 59**	**TAVR = 59**
30-day Mortality (%)	1.4	6.9	0	1.8	0	7	4	2.9	0	3	5.8	9.8	1.9	5.8	5.1	1.7
Bleeding (%)	4.2	0	7.5	0	NR	NR	NR	NR	1	1	4.9	1.9	NR	NR	NR	NR
Paravalvular leak (%)	2.8	53.5	1.9	9	19.4	28.7	NR	NR	2	30	4	18	0.5	4.3	0	6.8
Stroke (%)	0	2.1	0	0	0	2.8	NR	NR	0	2	1.5	5.8	NR	NR	1.7	0
Myocardial Infarction (%)	0	0	0	1.8	0	3.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Permanent pacemaker implantation (%)	11.2	15.4	2	25.5	3.2	4.9	5.8	11.6	2	0	9.8	14.7	5.4	11.9	10.2	8.5
Aortic cross-clamp time in minutes ± SD	42 ± 17	NA	32 ± 14	NA	NR	NA	43.4 ± 13.4	NA	NR	NA	32.8 ± 12.6	NA	NR	NR	49 ± 22	NA
Cardiopulmonary bypass time in minutes ± SD	71 ± 24	NA	54 ± 25	NA	NR	NA	73.4 ± 23.1	NA	NR	NA	50 ± 11.5	NA	NR	NR	83 ± 32	NA
TAVR types	NA	CoreValve Sapien Lotus Portico	NA	NR	NA	NR	NA	Sapien	NA	Sapien	NA	Corevalve, Sapien XT, Accurate TA	NA	NR	NA	Accurate NEO

TAVR, transcatheter aortic valve replacement; SD, standard deviation; NR, not reported; NA, not applicable.

TABLE 2 | Sutureless aortic valve replacement vs. other stented bioprostheses.

Study author	Muneretto et al.		Gilmanov et al.		Pollari et al.		D'Onofrio et al.		Vaquero et al.		Fischlein et al.		Dalen et al.		Forcillo et al.	
Type of clinical study	**Prospective**		**Retrospective**		**Prospective**		**Retrospective**		**Prospective**		**Prospective**		**Retrospective**		**Retrospective**	
Valves and patients	**Perceval *N* = 53**	**Stented *N* = 55**	**Perceval *N* = 133**	**Stented *N* = 133**	**Perceval *N* = 88**	**Stented *N* = 88**	**Perceval *N* = 31**	**Stented *N* = 112**	**Perceval *N* = 140**	**Stented *N* = 409**	**Perceval *N* = 447**	**Stented *N* = 449**	**Perceval = 171**	**Stented = 171**	**Perceval = 76**	**Stented = 319**
30-day Mortality (%)	0	0	0.8	1.5	2.4	3.7	0	1.8	6.4	5.9	1	1	1.8	2.3	5	6
Bleeding (%)	7.5	10.5	6.8	3.8	2.4	6.1	NR	NR	NR	NR	4.4	6.3	4.1	6,4	8	8
Paravalvular leak (%)	1.9	0	NR	NR	NR	NR	19.4	1	3.6	0.5	1	0	0	1.2	0	0
Stroke (%)	0	1.8	NR	NR	3.7	7.3	0	0	2.9	2.7	1.5	1.9	2.3	1.2	0	5
Myocardial infarction (%)	0	0	1.5	0	NR	NR	0	0.9	7.8	4.3	1	1.5	NR	NR	0	0
Permanent pacemaker implantation (%)	2	1.8	NR	NR	6.1	8.5	3.2	0.9	10.7	2	10.6	3.2	9.9	2.9	17	8
Aortic cross-clamp time in minutes/SD	30.8 ± 13.6	65.3 ± 27.7	56	90	47 ± 16	59 ± 23	NR	NR	65.3 ± 29.1	77.2 ± 30.3	48.5 ± 24.7	65.2 ± 23.6	40 ± 15	65 ± 15	46	68
Cardiopulmonary bypass time in minutes/SD	47 ± 18.5	89.4 ± 20.4	88	120	71 ± 11	92 ± 33	NR	NR	81.3 ± 34.9	95.7 ± 37.9	71.0 ± 34.1	87.8 ± 33.9	69 ± 20	87 ± 20	60	85
Type of stented valves	NA	Perimount, Edwards	NA	CE Edwards, Medtronic, CE standard	NA	NR	NA	NR	NA	Triflecta	NA	NR	NA	CE Perimount	NA	CE, Medtronic, Mitroflow, St. Jude epic, St. Jude Biocor

NA, not applicable; SD, standard deviation; NR, not reported.

operations showing a mean cardiopulmonary bypass time of 95 ± 34.3 mins, an aortic cross-clamp time 57.8 ± 23.2 mins with 0% in hospital mortality, a 3.6% incidence of new PPI and 2.5% incidence of PVL. Recent technological developments have led to endoscopic aortic valve replacement. Vola et al. (35) reported the endoscopic SAVR with Perceval. Exposure was provided by four ports in the second, third, and fifth intercostal spaces with femfem CPB. Perceval was implanted with an aortic cross-clamp and CPB time of 80 and 166 mins, respectively. At 5-month follow-up, echocardiography was satisfactory. Balkhy et al. (36) reported the first in human robotic SAVR with Perceval. The patient was a 76-year-old male who underwent a combined procedure of coronary artery bypass surgery and SAVR. Two 8-mm arm ports were placed in the 1st and 3rd intercostal space at the midclavivular line. Aortic cross clamp lasted 86 mins. The patient was discharged on postoperative day 2 and at 6-month follow-up the patient was in good health.

BICUSPID AORTIC VALVES AND PERCEVAL

This topic remains controversial among surgeons. Many clinical studies, including the PERSIST-AVR clinical trial (37), excluded patients with a congenital bicuspid aortic valve. Some reports suggested that the sutureless valves may increase the risk of PVL and/or potential dislocation related to BAV aortic root asymmetry (38). Nguyen et al. (13) emphasized that the most crucial point during surgery is to recreate three natural nadirs points positioned at 120° with the aim of recreating a circular annulus. Four retrospective clinical studies (13, 34, 39, 40) with a small population ranging between 11 and 88 patients evidenced a low mortality rate (0–4%) and PVL incidence (0–2.3%). However, there was a high incidence of PPI (0–20%), and stroke (0–8%) (**Table 3**). The mean aortic cross clamp time in minutes (39–55/SD = 3.1–14) and CPB time in minutes (54.5–80/SD = 4.4–22) were higher compared to non BAV procedures. These outcomes mean that despite recent surgical technique developments, PPI remain a hurdle for BAV patients undergoing SAVR with sutureless bioprostheses.

THROMBOCYTOPENIA. DO WE REALLY NEED TO CORRECT IT?

Several causes of platelet dysfunction have been speculated: (1) the detoxification process with homocysteic acid and the storage aldehyde-free solution; (2) the naked alloy stent; and (3) mechanical stress and turbulence, especially in small valve sizes (41). At the end of the day, Vendramin and Bortolotti correctly pose the following questions: Do we really need to solve it and why should we still be worried (42)? In this context, Stegmeier et al. (43) showed that Perceval, when compared to other prostheses, is more prone to causing thrombocytopenia, however, no detrimental clinical effect of this phenomenon was found. The mean minimum platelets count was 47,000 μm and upon discharge the platelets level was 166,000 μm. Can medical therapy have an impact on thrombocytopenia? The result from the study showed a non-significant difference among patients on aspirin and dual antiplatelet medical therapy. In addition, there was no significant change in platelets and red blood cells transfusion. However, the reoperation for bleeding rate (20%) was higher than in the other two groups (Labcor TLPB-A = 4% and Hancock valve = 8%). Moreover, a sub-analysis of the PERSIST-AVR clinical trial evidenced that the Perceval group had a higher platelet reduction than the control group (46 vs. 32%) (44). The phenomenon was transient in both groups, with a slow recovery of the platelet count by hospital discharge. No differences were observed between groups regarding need of transfusions, blood loss, major bleeding and stroke events. While comparing the Intuity valve with its Perceval counterpart, Jiritano et al. (41) found that no risk factors that may have predisposed to platelet dysfunction were found in either group. More red blood cell transfusions were given to the Perceval group as compared with the Intuity group (10 vs. 7 units, $p = 0.012$) as well as platelets (4 vs. 0 units, $P < 0.01$). Platelet count at discharge for Perceval was 102.18 ± 29.34 μm. In addition, mean platelet volume was significantly larger in the Perceval group on postoperative days 1, 3, and 5 ($P = 0.04$, $P = 0.001$, $P = 0.015$), whereas platelet distribution width was significantly larger in the Perceval group on postoperative days 3 and 5 ($P = 0.018$, $P = 0.026$). Looking at the clinical studies outcomes the answer to Vendramin and Bortolotti is the following: "no, we do not need to correct the transient thrombocytopenia, but we should be cautious."

HEMODYNAMIC CHANGES, VENTRICULAR MASS REGRESSION, AND PORCELAIN AORTA

We found nine clinical studies but only eight were reporting data with standard deviations. Six of the studies were retrospective observational cohort studies and two were prospective non-randomized clinical trials (**Table 4**) (11, 21–23, 35, 36). The effective orifice area (EOA) ranged between 1.5 and 1.7 cm^2/SD = 0.3–0.5 since discharge up to 2 years of follow-up. The mean transvalvular gradient ranged between 10.1 and 14 mmHg/ SD = 4.3–6.4 at discharge, 8.9 mmHg/ SD = 3.2–4.2 at 6 months, 8.7–9.9 mmHg/SD = 3.7–5 at 1 year and 8–9 mmHg/SD = 3.4–4.1 at 2 years follow-up. The peak transvalvular gradient was 19.4–27 mmHg/SD = 8.1–11 at discharge, 16.8–19.6 mmHg/SD = 6.7–7.6 at 6 months, 17.1–20.9 mmHg/SD 7.6–9.2 at 1 year, 16.6–18.3 mmHg/SD 5.6–7.2 mmHg at 2 years follow-up. With respect to the ventricular mass regression, Santarpino et al. (45) found that the mean ± SD left ventricular mass index decreased from 148.4 ± 48.4 g/m^2 to 119.7 ± 38.5 g/m^2 (P = 0.002) whereas interventricular septum and posterior wall thickness decreased from 13.9 ± 2.3 mm to 12.1 ± 2.8 mm ($P = 0.02$) and 12.1 ± 1.6 mm to 11.3 ± 1.3 mm (P = 0.04) at follow-up. In addition, there have been sporadic reports of the implantation of the Perceval in porcelain aortas. Santarpino et al. (46) reported a 72-year-old woman with severe AS, coronary artery disease, and porcelain aorta. The patient underwent CABG, removal of the ascending aorta, and implantation of a 23-mm Perceval

TABLE 3 | Clinical outcomes of bicuspid aortic valve stenosis treated with sutureless valve.

Study author	Durdu et al. (mean ± SD)	Nguyen et al. (mean ± SD)	Szecel et al. (mean ± SD)	Miceli et al. (mean ± SD)
Number of patients	***N* = 13 patients**	***N* = 25 patients**	***N* = 11 patients**	***N* = 88 patients**
Type of clinical study	Retrospective	Retrospective	Retrospective	Retrospective
30-day mortality (%)	0	4	0	1.6
Bleeding (%)	7.6	1	NR	3.1
Paravalvular leak (%)	0	0	0	2.3
Stroke (%)	7.6	8	0	4.2
Myocardial infarction (%)	0	0	0	NR
Permanent pacemaker implantation (%)	7.6	20	0	5.7
Aortic cross-clamping time in minutes/SD	40.3 ± 3.1	45.9 ± 14.0	39 ± 13	55
Cardiopulmonary bypass time in minutes/SD	54.5 ± 4.4	56.1 ± 14.9	66 ± 22	80

NR, not reported; SD, standard deviation.

TABLE 4 | Hemodynamic outcomes.

Endpoints	Santarpino et al. *N* = 658 (mean ± SD)	Rubino et al. *N* = 314 (mean ± SD)	Mazine et al. *N* = 215 (mean ± SD)	Folliguet et al. *N* = 208 (mean ± SD)	Shrestha et al. *N* = 30 (mean ± SD)	Shrestha et al. *N* = 243 (mean ± SD)	Miceli et al. *N* = 37 (Mean ± SD)	Repossini et al. *N* = 158
Type of clinical study	Prospective	Retrospective	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective
EOA (cm^2) at discharge	1.5 ± 0.4	NR	1.56 ± 0.37	1.4 ± 0.4	NR	1.5 ± 0.4	NR	NR
EOA (cm^2) at 6 months	1.5 ± 0.3	NR	NR	1.5 ± 0.4	NR	1.5 ± 0.4	NR	NR
EOA (cm^2) at 1 year	1.5 ± 0.4	NR	NR	1.5 ± 0.3	1.55 ± 0.35	1.6 ± 0.4	NR	NR
EOA (cm^2) at 2 years	NR	NR	NR	NR	1.51 ± 0.26	1.7 ± 0.5	NR	NR
Mean gradient (mmHg) at discharge	10.3 ± 4.5	14 ± 6	13.3 ± 6.4	10.4 ± 4.3	NR	10.1 ± 4.7	11.4 ± 3.7	10.9 ± 5.4
Mean gradient (mmHg) at 6 months	8.9 ± 4.1	NR	NR	8.9 ± 3.2	NR	8.9 ± 4.2	NR	NR
Mean gradient (mmHg) at 1 year	9.2 ± 5	NR	NR	8.7 ± 3.7	9.9 ± 4.6	8.9 ± 4.6	NR	NR
Mean gradient (mmHg) at 2 years	NR	NR	NR	NR	8 ± 4.1	9 ± 3.4	NR	NR
Peak gradient (mmHg) at discharge	19.4 ± 8.1	27 ± 11	24.5 ± 10.8	21.3 ± 8.6	NR	20.3 ± 9.9	19.2 ± 6.9	18.7 ± 9.1
Peak gradient (mmHg) at 6 months	16.8 ± 7	NR	NR	19.6 ± 6.7	NR	18 ± 7.6	NR	NR
Peak gradient (mmHg) at 1 year	17.1 ± 8.7	NR	NR	18.8 ± 7.6	20.9 ± 9.2	17.5 ± 8.2	NR	NR
Peak gradient (mmHg) at 2 years	NR	NR	NR	NR	16.6 ± 7.2	18.3 ± 5.6	NR	NR

EOA, effective orifice area; SD, standard deviation; NR, not reported.

and FlowWeave Bioseal 24-mm prosthesis (Jotec, Hechingen, Germany). Gatti et al. (47) reported the use of Perceval in four patients with porcelain aorta. All patients were discharged within postoperative day 20 and, at 1 to 6-month, were alive with improvements in symptoms.

LONG-TERM OUTCOMES OF THE PERCEVAL VALVE

The Perceval aortic valve has proven to be a reliable bioprosthesis with excellent early and midterm outcomes. However, the long-term outcomes of the valve have not been studied and results are coming from some clinical studies. Our literature research found one retrospective study and one clinical trial with a 5-year follow-up period (**Table 5**). Shrestha et al. (48) reported the outcomes of 720 patients evidencing a 1.4% of cardiac deaths, 1,5% of valve explants, 1% of major paravalvular leak, 1.4% of A-V block III and 0.8% of stroke. The 5-year outcomes of a prospective clinical trial (14) with only 30 patients evidenced a cardiac mortality of 3.3%, an A-V block type III of 3.3% but no stroke, paravalvular leak, valve thrombosis or structural valve deterioration was noticed. The echocardiographic outcomes at 3, 4, and 5-year follow-up evidenced an EOA of 1.64–1.68 (SD 0.4–0.42), 1.68 (SD 0.43), 1.69–1.8 (SD 0.3–0.42), respectively. In addition, the mean transvalvular gradient across the valve at 3, 4,

TABLE 5 | Long-term outcomes of the Perceval bioprosthesis.

Late events> 30 days.studies	Shrestha et al. *N* = 729 patients	Meuris et al. *N* = 30 patients
Type of study	Retrospective	Prospective clinical trial
Follow-up duration	5 years	5 years
Deaths (%)	7	28.7
Cardiac deaths (%)	1.4	3.3
Valve explants (%)	1.5	0
Major paravalvular leak (%)	1	0
Endocarditis (%)	1.6	6.6
Structural valve deterioration (%)	0	0
Valve thrombosis (%)	0	0
AV block III (%)	1.4	3.3
Stroke	0.8	0

TABLE 6 | Long-term echocardiographic outcomes (5-year follow-up) of the Perceval bioprosthesis.

Study	Shrestha et al. *N* = 729 patients (mean ± SD)	Meuris et al. *N* = 30 (mean ± SD)
LVEF at 3 years (%)	67 ± 9	NR
LVEF at 4 years (%)	66.1 ± 9.1	NR
LVEF at 5 years (%)	65.8 ± 7.7	NR
Mean transvalvular gradient at 3 years mmHg	7.7 ± 2.8	8.3 ± 2.5
Mean transvalvular gradient at 4 years mmHg	7.8 ± 3.8	7.6 ± 3.6
Mean transvalvular gradient at 5 years mmHg	8.8 ± 4.6	9.3 ± 5.5
Peak transvalvular gradient at 3 years mmHg	16 ± 5.2	16.6 ± 6.2
Peak transvalvular gradient at 4 years mmHg	17.8 ± 8.1	17.5 ± 7.8
Peak transvalvular gradients at 5 years mmHg	21.1 ± 9.7	21.4 ± 11.5
EOA at 3 years (cm^2)	1.64 ± 0.42	1.68 ± 0.4
EOA at 4 years (cm^2)	1.68 ± 0.43	1.68 ± 0.43
EOA at 5 years (cm^2)	1.8 ± 0.3	1.69 ± 0.42

and 5 years was 7.7–8.3 mmHg (SD 2.5–2.8), 7.6–7.8 mmHg (SD 3.6–3.8), 8.8–9.3 mmHg (SD 4.6–5.5), respectively. These results once more confirm the usefulness of the Perceval valve (**Table 6**).

THE IDEAL CANDIDATE FOR SUTURELESS AORTIC VALVE REPLACEMENT

Many studies have evidenced the benefits of Perceval aortic bioprosthesis, especially in the following three situations:

(a) High-risk patients undergoing a combined surgical procedure
(b) Hostile aortic root
(c) A small aortic annulus.

In the first situation, the use of sutureless and rapid-deployment valves allows economy of precious CPB time by alleviating the need to place and tie sutures around the aortic annulus, while still allowing native valve excision and annular decalcification. In a systematic review and meta-analysis that included 12 observational studies, Phan et al. (49) demonstrated that the pooled durations of cardiopulmonary bypass and aortic cross-clamp for isolated SAVR were 57 and 33 min, respectively. These values are nearly half of those reported in the Society of Thoracic Surgeons National Database[1] for conventional SAVR.

In hostile aortic roots and redo operations, Perceval may become the bioprosthesis of choice. In addition to the time-saving procedure and to the non-necessity of complete annular decalcification, it allows valve replacement after graft infection. In the last scenario, the benefits include less foreign material used (pledgets/sutures), less manipulation of friable tissues, and radial force of Perceval solidifies root repair. During reoperations and extensive decalcification of the annulus, clefts in the mitral valve/left atrium can form. In this situation, the Perceval valve can be easily compressed and removed (without the necessity of removing all the sutures as in the stented valves), the cleft repaired, and the valve redeployed again (50). However, neither the CAVALIER nor the PERSISTENT-AVR clinical trials mentioned the hostile aortic root.

Finally, in case of a small aortic annulus, an aortic root enlargement should be performed to implant an adequately sized bioprosthesis. However, this is not always feasible as newly minted surgeons do not have sufficient technical experience to perform these procedures. In this scenario, the sutureless prosthesis have shown good outcomes when implanted with low post-procedural transvalvular gradients (45). In addition, Perceval is a proven option for high-risk patients and for those at risk of prosthesis-patient mismatch (51).

Contraindications for the prosthesis implantation are (a) subjects with aortic root enlargement, where the ratio between observed and expected diameters (calculated as a function of age and patient body surface area) is $\geq$1.3; (b) subjects with known hypersensitivity to nickel alloys, (c) subjects with aneurysmal dilation or dissection of the ascending aortic wall needing surgical correction.

POTENTIAL PITFALLS OF PERCEVAL

Limitations and drawbacks of the Perceval bioprosthesis are the following;

(a) PVL.
(b) Acquired conduction disorders and PPI.
(c) SVD and need for reintervention.

PVL has shown an increased incidence in the TAVR and the sutureless bioprostheses with the latter being the highest (52). Surgeons came to understand that the Achilles heel of these

[1]https://publicreporting.sts.org/

bioprostheses is the non-coronary sinus which is slightly lower compared to the left and right sinuses. During the deployment phase, the valve must be positioned in a lower angle of 15–30° at the level of the non-coronary sinus, on the side of the surgeon. When the valve is accurately positioned, and no gap exists on visual inspection than it should be deployed. This technique avoids the incidence of PVL. However, it has been shown that these results are related to a learning curve and experienced surgeons tend to have a lower incidence of PVL (53).

The PPI trend has shown a slow but steadily decrease since the introduction by Yanagawa et al. (12) of their modification of the implantation height. They found that a higher implantation of the valve (2–3 mm) decreases the incidence of conduction abnormalities requiring a pacemaker. This is in contrast with the first prescription given from the company to implant the valve below the annular plane. SVD happens continuously and Perceval is not exempt from it.

CONCLUSIONS

The Perceval bioprosthesis has proved to be a reliable prosthesis for conventional SAVR and mini-SAVR due to its implantation speed, the reduced CPB time, the reduced aortic cross-clamp time and the shorter intensive care unit and hospital length of stay. In addition, its adoption in hostile roots, and the usage in reinterventions coupled with the low profile render it a formidable tool in the surgical armamentarium.

AUTHOR CONTRIBUTIONS

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

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Lysophosphatidic Acid May Be a Novel Biomarker for Early Acute Aortic Dissection

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Background: Misdiagnosis and delayed diagnosis of acute aortic dissection (AAD) significantly increase mortality. Lysophosphatidic acid (LPA) is a biomarker related to coagulation cascade and cardiovascular-injury. The extent of LPA elevation in AAD and whether it can discriminate sudden-onset of acute chest pain are currently unclear.

Methods: We measured the plasma concentration of LPA in a cohort of 174 patients with suspected AAD chest pain and 30 healthy participants. Measures to discriminate AAD from other acute-onset thoracalgia were compared and calculated.

Results: LPA was significantly higher in AAD than in the AMI, PE, and the healthy (344.69 ± 59.99 vs. 286.79 ± 43.01 vs. 286.61 ± 43.32 vs. 96.08 ± 11.93, $P < 0.01$) within 48 h of symptom onset. LPA level peaked at 12 h after symptom onset, then gradually decreased from 12 to 48 h in AAD. LPA had an AUC of 0.85 (0.80–0.90), diagnosis threshold of 298.98 mg/dl, a sensitivity of 0.81, specificity of 0.77, and the negative predictive value of 0.85. The ROC curve of LPA is better than D-dimer ($P = 0.041$, Delong test). The decision curve showed that LPA had excellent standardized net benefits.

Conclusion: LPA showed superior overall diagnostic performance to D-dimer in early AAD diagnosis may be a potential biomarker, but additional studies are needed to determine the rapid and cost-effective diagnostic tests in the emergency department.

Keywords: aortic dissection, biomarker, lysophosphatidic acid, diagnosis, chest pain

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INTRODUCTION

Aortic dissection is a life-threatening cardiovascular disease that causes ∼10,000 deaths in the United States each year (21% before admission and 32% in-hospital) (1, 2). Recently, Sweden indicated that the incidence has increased about 7.2/100,000 (3). However, the early identification and diagnosis of high-risk chest pain as acute aortic dissection (AAD) is the major challenge. Treatment measures include coronary angiography and thrombolytic drugs, which may cause poor prognosis in 24.8% of AAD, who are misdiagnosed as acute myocardial infarction (AMI) or acute pulmonary embolism (PE) (4–6). Not only that, chest CT or MRI is time-money-consuming and limited by emergency room conditions compared to biomarkers for the diagnosis of AAD (7, 8).

Several researches have investigated AAD potential biomarkers for faster and more accurate clinical treatment, such as smooth muscle myosin (9), calcium binding protein (10), soluble elastin fragments (11), soluble ST2 (5), and D-dimer (12). While increased values for D-dimers raise suspicion for AAD (4), it is difficult to use it to desciminate AAD from PE in daily practice, and there are nine (2.43%) exhibited negative D-dimer results in 370 AAD patients according to our previous studies (13). Moreover, the younger and smaller thrombosis groups have low specificity. A valuable diagnostic marker should provide information for early identification or elimination to improve the clinical treatment of AAD (12).

Lysophosphatidic acid (LPA) is a small and simple glycerophospholipid (1-acyl-2-hydroxy-3-phosphoglycerol structure) (14), which is an early molecular marker of coagulation cascade activation and cardiovascular-injury (15, 16). Previous researches have shown that lysophosphatidylcholine (LPC) was also involved in aortic aneurysm formation and decreased substantially in AAD, which is hydrolyzed to produce LPA (17, 18). The LPA may be produced earlier than D-dimer, or have a better diagnostic performance than D-dimer and AAD risk scoring system (19, 20), but the relationship between LPA and AAD is unclear. The plasma LPA levels of patients with acute chest pain (AAD, AMI, PE) and healthy participants were measured and compared to evaluate the diagnostic performance in distinguishing AAD from other chest pains.

METHODS

Research Sample

This is a single-center retrospective cohort including patients with suspected AAD within 48 h of onset and healthy participants, who came from the emergency department and medical examination center of the Second Xiangya Hospital of Central South University (Changsha, China) between May 2020 and January 2021. All suspected AAD patients were examined for medical imaging and D-dimer for the final diagnosis (19, 21). The exclusion criteria are shown in **Supplementary Table 1**.

About 3–5 ml of whole blood was taken from the brachial vein and placed in a sodium citrate anticoagulant tube immediately after hospital admission. The samples were centrifuged at 1000 r/min for 15 min to process into plasma, and stored at −80°C. All sample processing methods are similar.

The Ethics Committee of the Second Xiangya Hospital of Central South University approved this study. Informed consent was obtained from all patients. However, consent was obtained from a family member in a case of sudden death after admission or during autopsy.

Outcome

All patients with AAD, characterized by symptoms onset-time within 48 h, had image information from aortic computed tomography to confirm the final diagnosis. AMI diagnosis criteria were: (1) chest pain lasting >20 min, (2) Serial ECG changes with new pathological Q waves or ST-segment and T-wave changes, and (3) a plasma creatine kinase-myocardial band elevation (more than twice the normal level or cardiac troponin I (cTnI) level > 0.1 ng/ml). A positive pulmonary artery computed tomography scan was for PE diagnosis.

Measurement of LPA

The processed serum was measured by the human lysophosphatidic acid kit (Wuhan Huamei Bioengineering Co., Ltd.), and D-dimer was detected by the TOP700 automatic coagulation analyzer.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (IQR). ANOVA and Kruskal-Wallis test

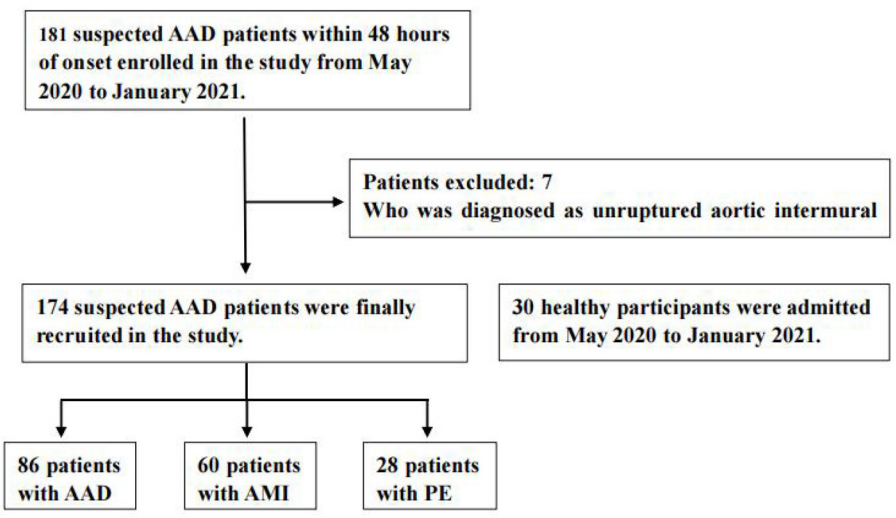

FIGURE 1 | Flow diagram of exclusion and enrollment of study patients. Describes the exclusion and enrollment of study patients. AAD, acute aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism.

were used for parametric and non-parametric data in multiple groups, *T*-test and Mann-Whitney U-test were used as a *post-hoc* analysis. Categorical variables were expressed as frequencies and compared using Fisher's precision probability test or Chi-square analysis. Logistic regression analysis was also used. $P = 0.05$ was considered statistically significant. Pearson correlation and delong test (22) were used to compare the relationship and ROC curve between LPA and D-dimer. The decision curve for a theoretical distribution was given to describe expected net benefit (23, 24).

The R (https://www.r-project.org/), The R Foundation, and EmpowerStats (http://www.empowerstats.com), X&Y Solutions Inc, Boston, MA were used for all statistical analyses.

RESULTS

A total of 204 patients, including 86 AAD patients, 60 AMI patients, 28 PE patients, and 30 healthy participants (Normal), were selected (**Figure 1**). The patient characteristics after 48 h of onset are shown in **Table 1** and **Supplementary Table 2**. AAD patients were mostly younger males with no significant difference in symptom onset time in all groups than non-AAD patients (**Supplementary Table 3**). The D-dimer and LPA levels were significantly higher in AAD patients than in non-AAD patients on the whole (**Supplementary Table 2**). LPA level (344.69 ± 59.99) was significantly different from AMI, PE, and Normal. However, AMI and PE were not statistically different (**Figure 2A**). D-dimer levels in AAD and PE were

TABLE 1 | Baseline characteristics of chest pain patients with AAD vs. other groups.

	AAD	AMI	PE	Normal	*P*-value
No. of participates	86	60	28	30	
Gender, male	58 (67.44)$^{\#}$	32 (53.33)	12 (42.86)†	16 (53.33)	0.087
Age, year	53.60 ± 11.46$^{※}$	57.30 ± 5.34†	55.36 ± 5.15	54.67 ± 4.33	0.077
Onset time to hospital, hours	11.45 ± 5.12	10.00 ± 4.43	11.32 ± 3.84	-	0.168
HR,/min	81.33 ± 18.22	79.57 ± 10.57	81.57 ± 10.82	78.37 ± 11.38	0.722
SBP, mmHg					
Left-S	141.21 ± 38.62	136.25 ± 15.99	136.32 ± 12.58	135.07 ± 15.03	0.608
Right-S	135.58 ± 36.93	135.40 ± 15.71	136.32 ± 13.21	135.50 ± 14.39	0.998
Difference-S	18.00 (7.00–31.00)$^{※\#*}$	3.00 (2.00–5.00)†	2.00 (2.00–4.00)†	3.00 (2.00–4.00)†	<0.001
DBP, mmHg					
Left-D	79.90 ± 22.31	83.42 ± 11.87	84.25 ± 9.60	79.83 ± 13.53	0.473
Right-D	76.94 ± 20.02$^{※}$	83.83 ± 12.06†	84.96 ± 11.35	81.63 ± 13.25	0.030
Difference-D	10.00 (4.00–13.75)$^{※\#*}$	3.00 (2.00–4.25)†	3.00 (1.75–6.00)†	3.00 (2.00–5.00)†	<0.001
History of					
Hypertension, %	72 (83.72)$^{※\#*}$	25 (41.67)$^{\dagger\#*}$	7 (25.00)$^{\dagger※}$	5 (16.67)$^{\dagger※\#}$	<0.001
Diabetes, %	5 (5.81)$^{※\#}$	17 (28.33)$^{\dagger\#*}$	5 (17.86)†	3 (10.00)$^{※}$	0.002
Stroke, %	6 (6.98)	4 (6.67)	2 (7.14)	0 (0)	0.530
Chronic kidney disease, %	12 (13.95)	12 (20.00)$^{\#}$	3 (10.71)*	0 (0)	0.067
OSAS, %	26 (30.23)$^{※*}$	0 (0)$^{\dagger\#}$	7 (25.00)$^{※*}$	0 (0)$^{\dagger\#}$	<0.001
COPD, %	5 (5.81)	2 (3.33)	3 (10.71)	0 (0)	0.257
Marfan, %	2 (2.33)	0 (0)	0 (0)	0 (0)	0.428
CAD, %	10 (11.63)$^{※*}$	26 (43.33)$^{\dagger\#*}$	5 (17.86)$^{※*}$	0 (0)$^{\dagger※\#}$	<0.001
Valvular heart disease, %	2 (2.33)$^{※\#}$	8 (13.33)†*	3 (10.71)†*	0 (0)$^{※\#}$	0.017
Smoking, %	49 (56.98)$^{\#*}$	27 (45.00)$^{\#*}$	4 (14.29)$^{\dagger※}$	7 (23.33)$^{\dagger※}$	<0.001
Drinking, %	21 (24.42)$^{\#}$	11 (18.33)	3 (10.71)†*	6 (20.00)$^{\#}$	0.056
Medication history					
Aspirin, %	12 (13.95)*	11 (18.33)	5 (17.86)	0 (0)	0.100
Clopidogrel, %	7 (8.14)*	9 (15.00)	3 (10.71)	0 (0)	0.134
Statin, %	16 (18.60)*	10 (16.67)	3 (10.71)	0 (0)	0.075
Hormone, %	3 (3.49)*	2 (3.33)	1 (3.57)	0 (0)	0.784
D-dimer, ug/ml	7.58 ± 4.80$^{※*}$	3.14 ± 2.11$^{\dagger\#*}$	8.49 ± 5.22$^{※*}$	0.59 ± 0.43$^{\dagger※\#}$	<0.001
LPA, mg/dl	344.69 ± 59.99$^{※\#*}$	286.79 ± 43.01†*	286.61 ± 43.32†*	96.08 ± 11.93$^{\dagger※\#}$	<0.001

AAD, acute aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism; SBP, systolic blood pressure; DBP, diastolic blood pressure; OSAS, obstructive sleep apnea syndrome; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; LPA, lysophosphatidic acid. $P < 0.05$, statistically different. †Significance vs. "AAD," $^{※}$Significance vs. "AMI," $^{\#}$Significance vs. "PE," *Significance vs. "Normal."

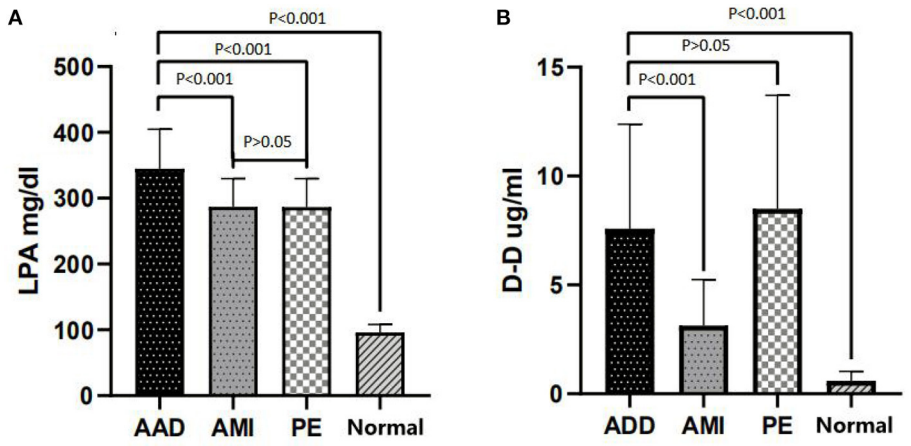

FIGURE 2 | LPA and D-dimer levels in chest pain patients with AAD vs. other groups. **(A)** LPA distribution (Mean ± standard deviation) in AAD, AMI, PE, and Normal. **(B)** D-dimer distribution (Mean ± standard deviation) in AAD, AMI, PE, and Normal. LPA, lysophosphatidic acid; AAD, acute aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism; Normal, healthy participants.

TABLE 2 | Multivariate regression analysis for AAD diagnosis.

Exposure	Univariate analysis			Multi-factor analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Difference-S, mmHg	1.56	1.33, 1.84	<0.001	1.42	1.13, 1.78	0.003
Difference-D, mmHg	1.41	1.26, 1.57	<0.001	1.20	0.87, 1.67	0.272
Right-D, mmHg	0.97	0.96, 0.99	0.005	0.93	0.87, 1.00	0.047
Hypertension, %	11.26	5.64, 22.49	<0.001	9.67	1.93, 48.32	0.006
Diabetes, %	0.23	0.08, 0.63	0.004	0.04	0.00, 0.48	0.011
CAD, %	0.37	0.17, 0.80	0.012	0.15	0.01, 2.32	0.176
Valvular heart disease, %	0.23	0.05, 1.07	0.062	0.67	0.07, 6.97	0.740
Smoking, %	2.79	1.57, 4.96	0.001	0.41	0.07, 2.48	0.334
Drinking, %	2.40	1.14, 5.05	0.021	0.96	0.18, 5.10	0.962
D-dimer, ug/ml	1.03	1.02, 1.03	<0.001	1.02	1.01, 1.03	0.043
LPA, mg/dl	1.23	1.13, 1.30	<0.001	1.21	1.06, 1.43	0.007

AAD, acute aortic dissection; Difference-S, difference of systolic blood pressure; Difference-D, difference of diastolic blood pressure; Right-D, the right diastolic blood pressure; CAD, coronary artery disease; LPA, lysophosphatidic acid. P < 0.05, Statistically different.

TABLE 3 | Diagnostic performance of AAD patients vs. others using LPA compared with D-Dimer.

	AUC	95% CI	Threshold	Sensitivity	Specificity	PLR	NLR	PPV	NPV
D-D, ug/ml	0.76	0.70–0.82	1.87	0.90	0.55	1.82	0.11	0.57	0.91
LPA, mg/dl	0.86	0.80–0.90	298.98	0.81	0.77	3.56	0.24	0.72	0.85
P for compare	0.041	-	-	-	-	-	-	-	-

D-D, d-dimer; LPA, lysophosphatidic acid. P < 0.05, Statistically different (Delong test).

higher but no statistical difference between the two (**Figure 2B**). Logistic multiple regression analysis showed that the blood pressure differences, hypertension history, D-dimer, and LPA were independently associated with AAD ($P < 0.001$) (**Table 2**).

Pearson analysis showed that LPA level was positively associated with D-dimer, $p < 0.05$) (coefficient of 0.17 in AAD, 0.15 in AMI, and 0.24 in PE). There was no significant correlation in Normal (**Supplementary Figure 2**).

LPA Distribution

The box plots were used to analyze LPA levels in AAD patient plasma at different onset times (**Supplementary Figure 3**).

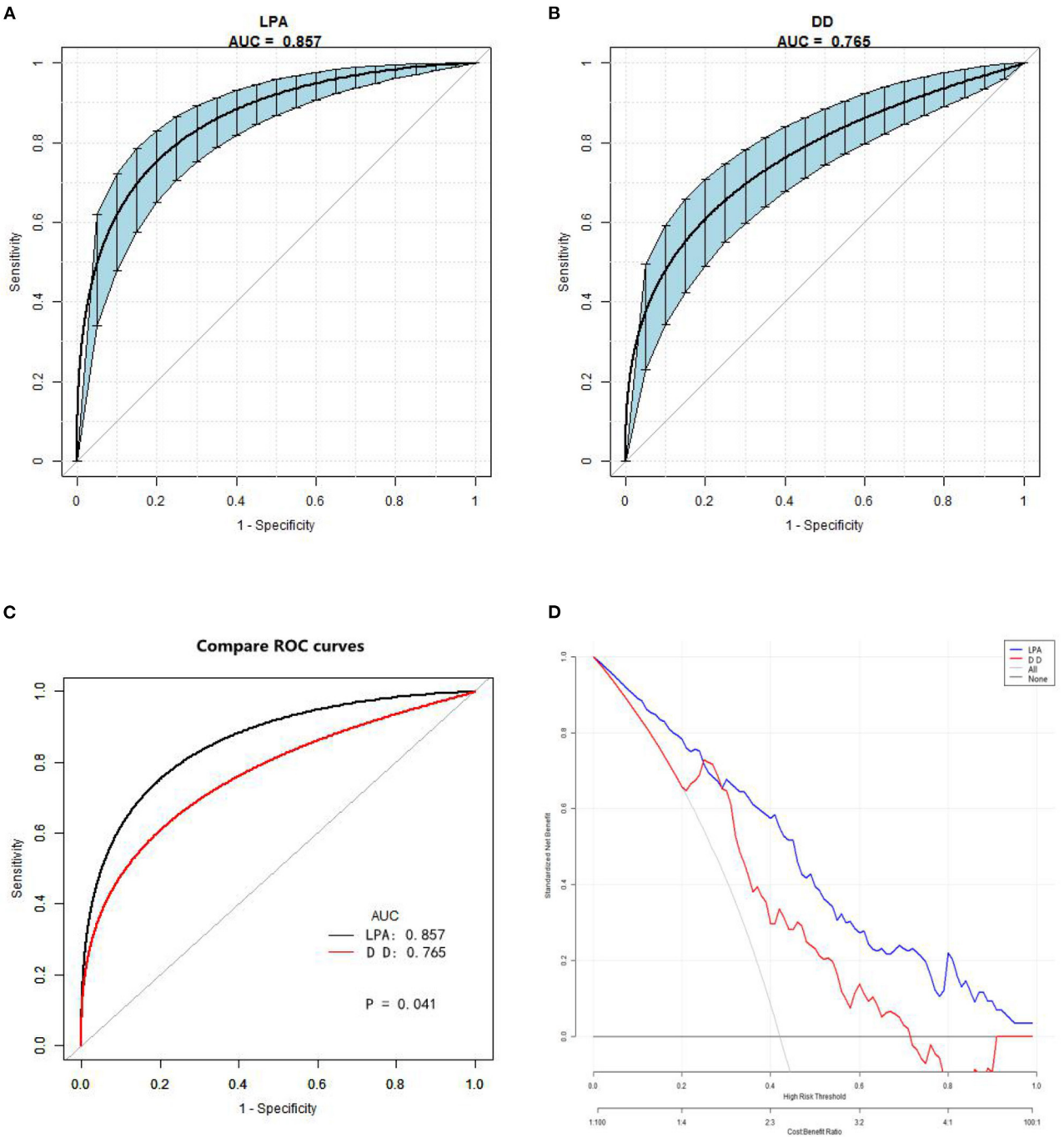

FIGURE 3 | Receiver operating characteristic and decision curve. **(A)** The AUC value of LPA predicting AAD. **(B)** The AUC value of D-dimer predicting AAD. Blue shading shows the bootstrap estimated 95% CI with AUC. **(C)** Comparison of ROC curves between D-dimer and LPA. The ROC curve of LPA is better than D-dimer (Delong test). **(D)** Decision curve for a theoretical distribution. Solid line: prediction model, LPA = blue, DD = red. Thin gray line: assume all patients have AAD. Black bottom line: assume no patients have AAD. The vertical axis displays standardized net benefit. The two horizontal axes show the correspondence between risk threshold and cost:benefit ratio. The graph gives the expected net benefit per patient associated with LPA and DD, with LPA performing better. LPA, lysophosphatidic acid; AAD, acute aortic dissection; AUC, area under the curve.

Based on the different onsets of symptoms in AAD patients, LPA seems to peak at 12 h and gradually decreased after 12 h, easing after 24 h ($P < 0.05$). The number of chest pain patients at different symptoms onset-time was not statistically significant ($P = 0.148$) (**Supplementary Table 3**).

Diagnostic Performance for Discriminating AAD

The ROC analysis results indicated that D-dimer had an AUC of 0.76 (0.70–0.82), diagnosis threshold of 1.87 ug/ml, a sensitivity of 0.90, specificity of 0.55, and the negative predictive value of 0.91. LPA had an AUC of 0.85 (0.80–0.90), diagnosis threshold of 298.98 mg/dl, a sensitivity of 0.81, specificity of 0.77, and the negative predictive value of 0.85 (**Table 3**; **Figures 3A,B**). The ROC curve of LPA is better than D-dimer ($P = 0.041$, Delong test) (**Figure 3C**). The decision curve for a theoretical distribution showed that LPA had excellent standardized net benefits (**Figure 3D**).

DISCUSSION

This study, which included 174 suspected AAD patients and 30 healthy participants, found that LPA may be used for the clinical diagnosis of AAD. LPA, mainly produced by activated platelets, may be an early biomarker of the initiation of thrombosis and coagulation. Researches have shown that coagulation cascade activates platelets to release a large amount of lysophospholipids and autotaxin with phospholipase D activity stored in alpha particles at the same time. The two substances undergo a biochemical reaction to produce LPA, which increases the plasma concentration (14, 25, 26). LPA binding to its receptors (LPA1-6) on platelet surface activates platelets and forms a positive feedback reaction, alters platelet in morphology, promotes aggregation and thrombus stability (27–29). Moreover, LPA activates LPA1 and LPA3 expressed in vascular endothelial cells (30), promotes immune response and aggravate endothelial cell damage via Gαi-RhoA-ROCK-NF-κB dependent pathways (31). LPA also increases the expression of intracellular matrix metalloproteinase-2, which will remodel the extracellular matrix and reduce the aggregation of endothelial cells to promote the migration and aggregation of inflammatory cells, thereby damaging endothelial cells to activate the coagulation cascade (32).

We found that the magnitude of elevated LPA can distinguish patients with AAD from patients with AMI, PE, and the healthy within 48 h after symptom onset. AAD is a disease with high mortality due to severe damage to the aortic structure. There are also some biomarkers showing clinical prognosis including CRP (33), NT-pro BNP (34) and cardiac troponin (35). When aortic dissection occurs, disruption to the aortic media immediately changes aorta hemodynamics, then intramural hematoma expand (especially when the intimal layer is also disrupted) as the blood flow inside media (5). The tissue coagulation factor III directly exposed to the blood in the arterial smooth muscle activates the exogenous coagulation pathway and promotes the coagulation cascade (13). Platelets, an indispensable role in the coagulation cascade, are continuously activated by the LPC-ATX-LPA pathway to produce more LPA before the aortic dissection is surgically repaired (14, 36). Although some studies speculate that the half-life of LPA is only 2–3 min under the action of LPPs, the continuous existence of disruption to the aortic media and positive feedback may be a reasonable explanation for the increase in plasma LPA in AAD patients (37, 38).

Our results suggested that the degree of the elevation of LPA levels is associated with the different magnitudes of vascular injury among AAD, AMI, and PE. Although LPA level in PE and AMI patients was higher than the healthy, there were still lower than AAD in our study. Substantial aortic hemodynamic changes significantly increased the circulating LPA level in the aorta (largest artery) compared with the small and medium blood vessels of pulmonary embolism and acute coronary syndrome. Studies have shown that LPA level is associated with the release location, releasing LPA directly and quickly to the aortic circulation may be another reason for the higher degree of AAD patients (39).

In addition, we speculated that LPA peaks at 12 h according to the symptoms of AAD patients, and our results also found that the threshold of LPA is 298.98 mg/dl, the specificity and AUC are 0.77 and 0.857, respectively, which are better than D-dimer ($P < 0.05$, Delong test). This means that as a marker of platelet activation, LPA $\geq$ 300 mg/dl indicates a high risk of AAD, and may be earlier than D-dimer. However, D-dimer has higher sensitivity and negative predictive value compared to LPA. As a fibrin degradation product in the circulation after thrombolytic fibrinolysis, D-dimer has been found to increase similarly in many diseases, including PE and AAD. In fact, D-dimer aids clinical diagnosis for PE only as a rule-out tool when the test result is negative (5).

To the best of our knowledge, this is the first study showing that LPA is associated with aortic dissection and could be a novel AAD biomarker. However, this study has some limitations. It is still unclear how LPA changes over time in AAD patients, a large-scale prospective multicenter study is needed to confirm the generalizability of the findings, the diagnostic validity, and the accuracy of this novel detection method since this was a single-center study. Second, the assay method used could provide an inconsistent absolute value for the LPA concentration, influencing the recommended cut-off level. Therefore, various detection methods should be accurately calibrated. Thirdly, this study did not include all undifferentiated chest pain patients, hence, patient selection could be biased. Finally, LPA < 300 mg/dl is difficult to rule out AAD in daily practice, and other diseases (ovarian cancer) (40) can also increase LPA levels. Therefore, further confirmatory diagnosis based on medical images is essential to prevent misdiagnosis in clinical practice.

CONCLUSION

LPA showed superior overall diagnostic performance to D-dimer in early AAD diagnosis may be a potential biomarker, but additional studies are needed to determine the rapid and cost-effective diagnostic tests in the emergency department.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: We are deeply sorry for this, because there

is still some research in progress for the time being. In order not to affect the following research, it is not convenient to disclose the data. Requests to access these datasets should be directed to 188212324@csu.edu.cn.

ETHICS STATEMENT

The hospital institutional review board of the Second Xiangya Hospital approved the study. The data collection and analysis followed the Ethics Committee of the institution and the Declaration of Helsinki. The Ethics Committee of the institution reviewed the patient consents, and the data were used only for research purposes.

AUTHOR CONTRIBUTIONS

XP and XC: drafted, revised, and reviewed the article. YZ and GY: conducted statistical analysis. ZH, HZ, ZP, WP, and ND: reviewed and revised the manuscripts. TG and MZ: organized the database. All authors significantly contributed to the conception, study design, execution, data acquisition, analysis, interpretation, approved the final version, agreed on the journal, and are responsible for this study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.789992/full#supplementary-material

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Nitric Oxide in Selective Cerebral Perfusion Could Enhance Neuroprotection During Aortic Arch Surgery

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Background: Hypothermic circulatory arrest (HCA) in aortic arch surgery has a significant risk of neurological injury despite the newest protective techniques and strategies. Nitric oxide (NO) could exert a protective role, reduce infarct area and increase cerebral perfusion. This study aims to investigate the possible neuroprotective effects of NO administered in the oxygenator of selective antegrade cerebral perfusion (SCP) during HCA.

Methods: Thirty male SD adult rats (450–550 g) underwent cardiopulmonary bypass (CPB), cooling to 22°C body core temperature followed by 30 min of HCA. Rats were randomized to receive SCP or SCP added with NO (20 ppm) administered through the oxygenator (SCP-NO). All animals underwent CPB-assisted rewarming to a target temperature of 35°C in 60 min. At the end of the experiment, rats were sacrificed, and brain collected. Immunofluorescence analysis was performed in blind conditions.

Results: Neuroinflammation assessed by allograft inflammatory factor 1 or ionized calcium-binding adapter molecule 1 expression, a microglia activation marker was lower in SCP-NO compared to SCP (4.11 ± 0.59 vs. 6.02 ± 0.18%; $p < 0.05$). Oxidative stress measured by 8oxodG, was reduced in SCP-NO (0.37 ± 0.01 vs. 1.03 ± 0.16%; $p < 0.05$). Brain hypoxic area extent, analyzed by thiols oxidation was attenuated in SCP-NO (1.85 ± 0.10 vs. 2.74 ± 0.19%; $p < 0.05$). Furthermore, the apoptotic marker caspases 3 was significantly reduced in SCP-NO (10.64 ± 0.37 vs. 12.61 ± 0.88%; $p < 0.05$).

Conclusions: Nitric oxide administration in the oxygenator during SCP and HCA improves neuroprotection by decreasing neuroinflammation, optimizing oxygen delivery by reducing oxidative stress and hypoxic areas, finally decreasing apoptosis.

Keywords: hypothermic circulatory arrest (HCA), nitric oxide (NO), selective cerebral perfusion, neuroprotection, aortic arch surgery/hemiarch repair

INTRODUCTION

Hypothermic circulatory arrest (HCA) is required during aortic arch surgery (1). Since the 1990's, selective brain perfusion (SCP) techniques have become increasingly common (2, 3). Despite these advancements, neurological damage of different severity develops in 5–20% of patients, mainly in urgent interventions for aortic dissection (4).

Neurological damage comprises permanent neurological dysfunction (PND) and temporary neurological dysfunction (TND). These two types of damage differ for etiopathogenesis, histological and clinical manifestation. PND manifests itself clinically as a neurological deficit secondary to perfusion deficit (embolism, vascular occlusion, and absence of blood flow). Risk factors for PND include an atheromatous disease and vasculopathy of the epiaortic vessels and the cerebral circulation (5, 6). TND is a reversible and widespread lesion attributed primarily to a global brain ischemic lesion consequence of inadequate brain protection (7).

Although techniques advancements and developments have reduced PND, the percentage of patients with TND is still exceedingly high (8). A combination of hypothermia and SCP could expose the brain to an excess of oxygen delivery related to reduced demand during hypothermia (9). This could impair cerebral microvascular autoregulation with the production of reactive oxygen species (ROS), oxidative stress, and inflammation that could contribute to TND development (**Figure 1**).

Nitric oxide (NO) has been recognized for its cardioprotective and neuroprotective effects (10). Since constitutive NO synthase (cNOS) is impaired during hypothermia (11), NO administration could effectively optimize cerebral microvascular blood flow, attenuating ischemia-reperfusion injury, neuroinflammation, and neuronal death (12). This preclinical study aims to investigate the neuroprotective effects of NO administered through SCP in HCA.

METHODS

All experiments were performed according to the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1996). The experimental protocol was validated by the scientific committee for experimental research of the University of Verona and approved by the National Ministry of Health (Ministerial Authorization Number 568/2020-PR, Protocol Number 56DC9.54).

A total of 30 male Sprague Dawley rats weighing 450 ± 50 g, aged 6–7 months, were used for the experiments.

Abbreviations: CPB, Cardiopulmonary bypass; DAPI, 4′,6-Diamidine-2′-phenylindole dihydrochloride; HCA, Hypothermic circulatory arrest; Iba1, Allograft inflammatory factor 1 or ionized calcium-binding adapter molecule 1; NO, Nitric oxide; NOS, Nitric oxide synthase; PND, Permanent neurological dysfunction; ROS, Reactive oxygen species; SCP, Selective cerebral perfusion; TND, Temporary neurological dysfunction.

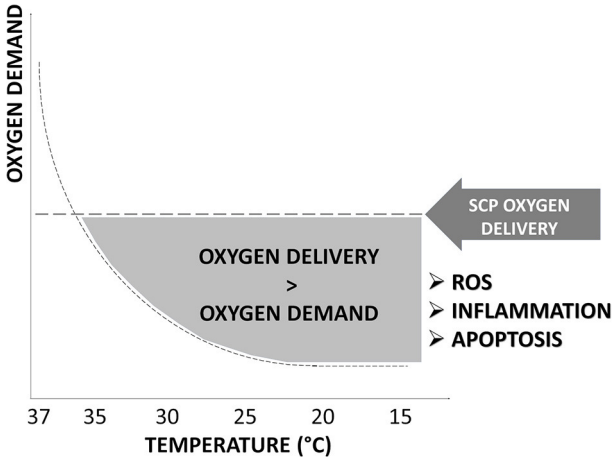

FIGURE 1 | Oxygen delivery in hypothermia. The excess of oxygen delivered by selective cerebral perfusion (SCP) compared to decreased oxygen demand at the different grades of hypothermia is represented by the gray area under "SCP oxygen dysfunction." An excess in oxygen delivery increases reactive oxygen species (ROS), oxidative stress, inflammation, and apoptosis and promotes temporary neurologic deficit (TND) development. SCP flow rate, oxygen content, temperature, and blood gas management of the perfusate have not been clearly defined and vary considerably among centers.

Surgical Procedure

Anesthesia was induced with Sevoflurane 6% (Forene; Abbott, Baar, Switzerland), rats were orotracheal intubated and ventilated by mechanical respirator for rodents (Harvard Model 687, Harvard Apparatus, Holliston, MA, USA). Tidal volume was 10 ml/kg and respiratory frequency 70 breaths per minute, animals were kept sedated with a mixture of oxygen and sevoflurane 2%, ketoprofen 2 mg/kg was injected subcutaneously to maintain analgesia, and 2 mg/kg of pancuronium-bromide was infused through the right femoral vein to obtain muscle relaxation. Electrocardiogram and body temperature through a rectal probe were monitored throughout the entire experiment. Furthermore, a miniaturized 2-Fr-diameter catheter (model SPR 838, Millar Instruments, Houston, TX, USA) was inserted into the right femoral artery to monitor systemic arterial pressure.

Animals were surgically prepared for cardiopulmonary bypass (CPB). Rat CPB model was previously described in detail (13–15). The circuit was modified to permit selective cerebral perfusion. After right external jugular isolation, a 5-Fr-diameter cannula was inserted and advanced in the right atrium, and 500 IU/kg of heparin was administered. The left common carotid artery was cannulated with a 24 G catheter advanced to the aortic arch, and another 26 G catheter was inserted in the upper left carotid artery and directed to the brain. The two cannulas were connected through a three-way stopcock to the arterial perfusion line.

The extracorporeal circulation circuit was constituted by an outflow tube connected to the right jugular vein, a venous reservoir connected to vacuum (maintained between −40 and −60 cmH_2O), a connection tube that runs through a roller pump (Stockert SIII, Sorin, Germany) and ends in a hollow

fiber oxygenator with industrial standard characteristics (Sorin, Mirandola, MO, Italy), and an inflow tube connected through a three-way stopcock to upper and lower left carotid artery. The total length of the extracorporeal circuit was 90 cm, outflow tube had 2 mm inside diameter whereas the remaining circuit had 1.6 mm inside diameter; total filling volume was 6.5 ml and constituted by 50% lactated Ringer's solution and 50% colloid solution (Voluven, Fresenius Kabi Italia Srl, VR, Italy). The oxygenator exchange surface area was 450 cm^2. A flow rate of 110–130 ml/kg/min and a range of mean arterial pressure of 70–80 mmHg was assured. The temperature was adjusted by a heat exchanger (Sarns cardioplegic set, Terumo Cardiovascular System Corp., Ann Arbor, MI, USA) incorporated in the circuit, and it was modulated upon rectal temperature monitoring.

Experimental Protocol

Hypothermia (22°C) was induced in 25 min. CPB was conducted with the total assisted flow (110–130 ml/kg). When the temperature was 22 ± 1°C, the aorta was clamped, and rats were left in a state of HCA. Immediately the three-way stopcock on the arterial line was turned to direct the oxygenated blood flow only to the cannula inserted in the upper left carotid and, therefore, to the brain. In its gaseous form, NO could be administered to the patient through the CPB, connecting the NO delivery system directly to the oxygenator (16, 17).

Animals were randomized to receive unilateral SCP (10 ml/kg/min) with oxygenated blood (group SCP; $n = 15$) or with the addition of NO (20 ppm) using a gas delivery system (iNOmax, Mallinckrodt Staines-upon-Thames, United Kingdom) connected directly to the oxygenator (group SCP-NO; $n = 15$).

The experimental model has been evaluated in preliminary experiments to measure the blood flow through the cannula inserted in the superior left carotid artery, the cerebral electrical activity measured by continuous EEG, and methemoglobin production on right jugular vein blood samples.

The dose regimen of 20 ppm of NO has been selected considering the highest dosage with a cumulative methemoglobin production minor or equal to 4% in pilot experiments. After 30 min, the aortic clamp was removed, and total CPB was re-established. After 60 min of reperfusion and rewarming to 35°C, the animals were weaned from CPB (**Figure 2**).

Arterial Blood Gas Analysis

Arterial samples were collected for blood gas analysis (pH, pO_2, pCO_2, hematocrit, and lactate) before the procedure (T0), before HCA (T1), after HCA (T2), and at the end of the experiment (T3).

Tissue Analysis

After injection of a lethal bolus of KCl, phosphate-buffered saline (PBS 1X, 10 ml) was injected in the cannula inserted in the upper left carotid, followed by 10 ml paraformaldehyde 4% (PFA)-4% sucrose. A posterior craniotomy was performed, and the whole brain was removed and placed in PFA 4–4% sucrose overnight. The next day brains were placed in 30% sucrose solution and kept at 4°C. About 70 slides were prepared for each sample, each with 4–5 slices (35-μm-thick) and stored at −20°C. Cryosections were incubated overnight at 4°C in the primary antibody solution. The following day, slides were left in incubation with the secondary antibody conjugated with fluorophores. Slides were kept in the dark to avoid the photobleaching of the fluorophore.

Ionized calcium binding adapter molecule 1 (Iba1) (Wako Chemicals, USA) is specific for microglia cells and macrophages that are determinants of the central nervous system's first and primary immune defense (18–20). To analyze the degree of oxidative stress and apoptosis, we evaluate the expression of 8-oxo-2′-deoxyguanosine (8oxodG) (ABCAM, UK) and caspases 3 (Cell Signaling, USA) (21–23).

After incubation with the primary and secondary antibody solution, slides were incubated with DAPI (4′,6-diamidine-2′-phenylindole dihydrochloride, molecular probes—Thermo Fisher Scientific, 1:3,000) for nucleus staining.

To detect hypoxic regions in the brain, reduced thiols were labeled (24). After perfusion with a solution containing N-ethylmaleimide (NEM) and iodoacetic acid (IAA) to block free thiols, brains were fixed with 4% PFA containing NEM and IAA. Finally, brains were dissected and kept overnight in the same solution and then processed for cryosectioning as described before. After cryosectioning, samples were washed with a solution containing tris(2-carboxyethyl) phosphine hydrochloride in PBS to reduce free disulfides. Samples were then labeled with 0.1% CPM (7-diethylamino-3-(4'-maleimidylphenyl)-4-methylcoumarin) and mounted with DABCO (1,4-diazabicyclo[2.2.2]octane).

Slides were examined with a fluorescence microscope (Eclipse Ti, Nikon, objective 20X); images obtained for each region considered were then transferred to a computer for analysis using a custom-designed ImageJ macro (US National Institutes of Health) in blind conditions.

Statistical Analysis

Data analysis was performed using SPSS software version 21 (SPSS Inc., Chicago, Illinois), mean ± SD was calculated for all the measurements. The average percentage of cells positive for specific markers: Iba1, 8oxodG, and caspases 3 expressions were quantified in randomly selected brain regions comprising the sensory-motor cortex. The number of marker positive cells (Iba1, 8oxodG, and caspases 3) was normalized to the total number of nuclei of the regions considered (429 images were quantified across the different conditions, each image was acquired as a single image). For the hypoxic area analysis, the sensory-motor cortex was delimited, and hypoxic areas were quantified as the percentage of the mean gray level of each brain slice. The percentage of positive pixels for the hypoxic areas were normalized for the total pixel in the region considered (121 images were quantified across the different conditions, each image was acquired as a large image constituted by 6 × 20 fields).

Student *t*-test or Mann–Whitney non-parametric tests were applied to compare the immunofluorescent analysis and the blood gas values of the two groups; $p < 0.05$ was considered statistically significant.

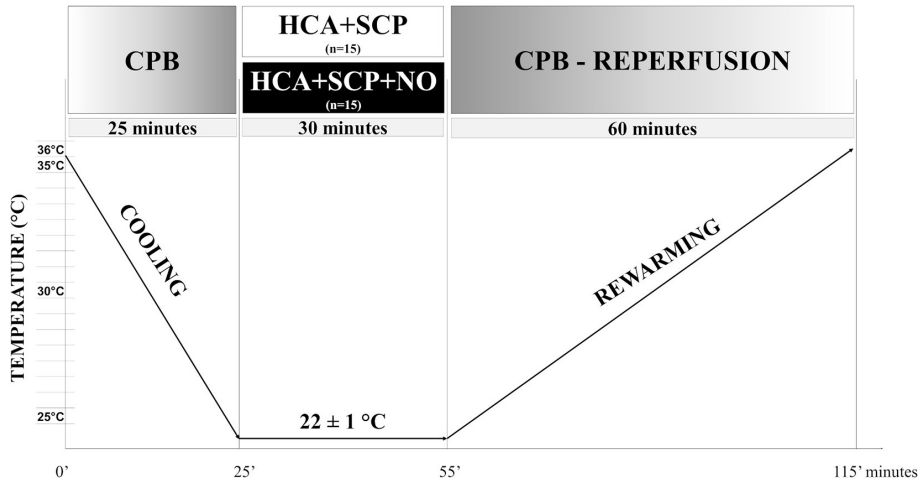

FIGURE 2 | Experimental protocol. Timeline of the experimental protocol. CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; SCP, selective cerebral perfusion.

RESULTS

Arterial Blood Gas Analysis

Blood gas analysis showed an increase in lactates during HCA, followed by a gradual normalization during rewarming. The pH returned normal during rewarming after the development of acidosis in the circulatory arrest phase. No significant differences were identified between SCP and SCP-NO groups (**Table 1**).

Inflammation

Ionized calcium binding adapter molecule 1 (Iba1) expression is specific for microglia cells and macrophages and indicates an inflammatory activation, and its amount correlates with the degree of neuroinflammation. Expression of Iba1 in different brain areas of the sensory-motor cortex in the SCP-NO group was lower compared to SCP (4.11 $\pm$ 0.59 vs. 6.02 $\pm$ 0.18%; $p < 0.05$), indicating decreased microglia activation and neuroinflammation (**Figure 3**).

Oxidative Stress

Hypothermic circulatory arrest (HCA) and SCP contribute to ROS production and oxidative stress, which determine cell death by lipid peroxidation and DNA oxidation. The latter is associated with the conversion of the deoxyguanosine into 8-oxo-2'-deoxyguanosine (8oxoDG) that is recognized as a marker of oxidative stress. In the SCP-NO group, the 8oxoDG content was lower compared to SCP (0.37 $\pm$ 0.01 vs. 1.03 $\pm$ 0.16%; $p < 0.05$), indicating attenuated oxidative stress (**Figure 4**).

Hypoxia

Thiols are a functional group of cysteine amino acids, which on the base of the oxidoreductive state could exist either as a reduced form of free thiols (-SH) or an oxidized form (-S-S-). In states of higher tissue oxygenation, thiols exist as oxidized disulfides; on the contrary, lower oxygen tissue oxygenation (hypoxia condition) leads to an increased free thiols presence. The latter indicate hypoxic brain areas, which were lower in SCP-NO compared to SCP (1.85 $\pm$ 0.10 vs. 2.74 $\pm$ 0.19%; $p < 0.01$), indicating a beneficial effect on NO in promoting the oxygen delivery counteracting impaired cerebral microcirculation (**Figure 5**).

Apoptosis

The expression of caspases 3 identifies cells where the apoptotic process is initiated. The apoptotic index (% of apoptotic cells) was lower in SCP-NO compared to SCP (10.64 $\pm$ 0.37 vs. 12.61 $\pm$ 0.88%; $p < 0.05$), demonstrating an attenuated cell death (**Figure 6**).

DISCUSSION

Hypothermic circulatory arrest (HCA) is still necessary to safely perform aortic arch surgery. Nowadays, SCP is the primary technique for brain protection in large aortic centers, while the HCA temperature has been rising progressively over the last few years (25, 26). There is a certain degree of consensus in the use of SCP and HCA; however, the temperatures and flow of perfusion vary from center to center, and there are no consensus statements, no clinical guidelines (4). Although HCA reduces brain metabolism and assures neuroprotection while permitting intervention in a clear surgical field, it can induce oxidative stress, inflammatory response, endothelial swelling, cerebral edema, and vasospasm (27). The critical role of reperfusion and simultaneous rewarming should not be underestimated since they have been demonstrated to be the main responsible for neuroinflammation and neuronal apoptosis, resulting in TND and cognitive dysfunction (28, 29).

To maximize the neurological outcome, efforts to identify possible neuroprotective agents combined with SCP should be pursued similarly to what has been done for cardioplegic solutions. The ideal pharmacological agent to add to SCP should improve perfusion distribution overcoming impaired cerebral autoregulation during hypothermia. Moreover, it

TABLE 1 | Blood gas parameters.

			SCP	SCP-NO	SCP	SCP-NO
	T0 (35°C)	**T1 (22°C)**	**T2 (22°C)**	**T2 (22°C)**	**T3 (35°C)**	**T3 (35°C)**
pH	7.40 ± 0.05	7.36 ± 0.04	7.23 ± 0.10	7.22 ± 0.12	7.38 ± 0.03	7.38 ± 0.05
pCO_2 (mmHg)	39 ± 2.5	32 ± 3	48 ± 5.3	48 ± 3.7	32 ± 4.3	30 ± 5.8
pO_2 (mmHg)	140 ± 10	305 ± 20	90 ± 15	87 ± 12	210 ± 33	213 ± 43
Hematocrit (%)	45 ± 2.5	47.6 ± 2.3	31 ± 2.5	32 ± 2.5	29 ± 2.8	30 ± 2.8
Lactate (mmol/l)	1.0 ± 0.2	2.5 ± 0.5	8.5 ± 2.5	8.3 ± 2.4	4.1 ± 1.6	4.6 ± 2

SCP, selective cerebral perfusion; SCP-NO, selective cerebral perfusion plus nitric oxide. T0, baseline; T1, before hypothermic circulatory arrest (HCA); T2, after HCA; T3, end of reperfusion.

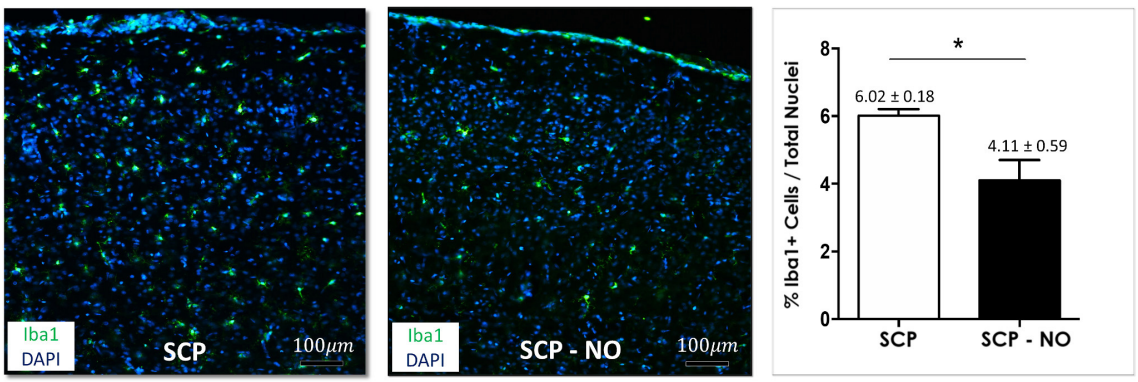

FIGURE 3 | Inflammation: Iba1. Representative images of Iba1 expression at the cortical level, between the selective cerebral perfusion (SCP) group compared to selective cerebral perfusion with nitric oxide 20 ppm (SCP-NO). In the graph, blind quantification was performed to calculate the average percentage of Iba1 expression in the brain regions considered (*$p < 0.05$). The average percentage of Iba1 positive cells was normalized to the total number of nuclei in the regions of interest considered (170 images quantified across the different conditions) (magnification ×20). Iba1, ionized calcium-binding adapter molecule 1; DAPI, 4′,6-diamidine-2′-phenylindole dihydrochloride.

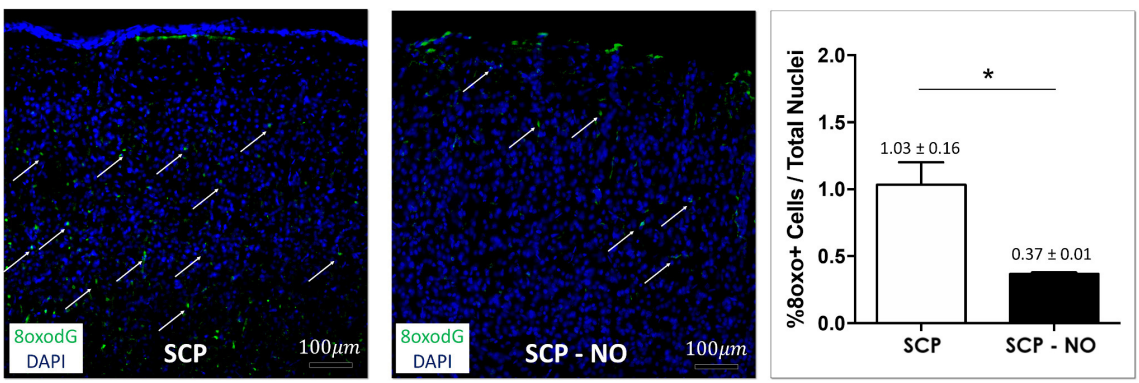

FIGURE 4 | Oxidative stress: 8oxodG. Representative images of 8oxodG expression at the cortical level (arrows), in selective cerebral perfusion (SCP) group compared to selective cerebral perfusion with nitric oxide 20 ppm (SCP-NO). In the graph, blind quantification was performed to calculate the average percentage of 8oxodG expression in the brain regions considered (*$p < 0.05$). The average percentage of 8oxodG positive cells was normalized to the total number of nuclei in the regions of interest considered (85 images quantified across the different conditions) (magnification ×20). 8oxodG, 8-oxo-2'-deoxyguanosine. DAPI, 4′,6-diamidine-2′-phenylindole dihydrochloride.

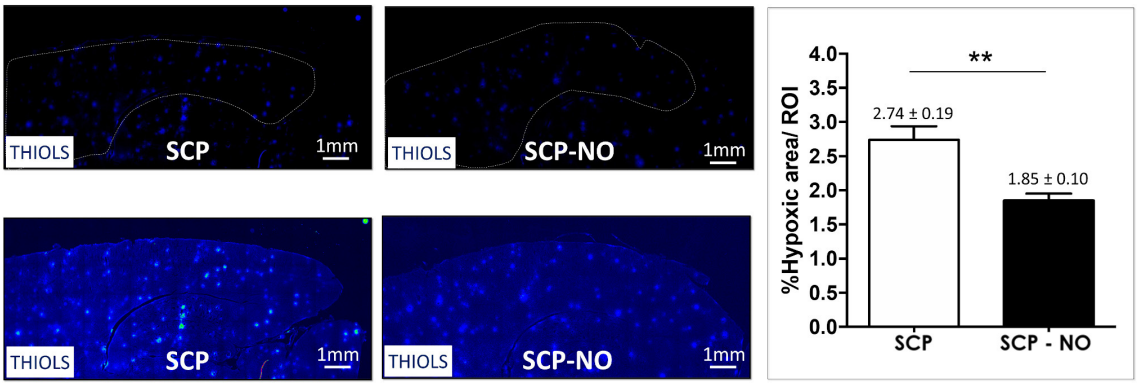

FIGURE 5 | Hypoxia: thiols. Representative images of hypoxic areas at the cortical level, in selective cerebral perfusion (SCP) group compared to selective cerebral perfusion with nitric oxide 20 ppm (SCP-NO). In the graph, blind quantification was performed to calculate the average percentage of the hypoxic area extension in the brain regions considered (**$p < 0.01$). The average percentage of the positive pixels for the hypoxic area was normalized to the total number of pixels of the regions of interest considered (121 images quantified across the different conditions) (magnification ×20). DAPI, 4′,6-diamidine-2′-phenylindole dihydrochloride.

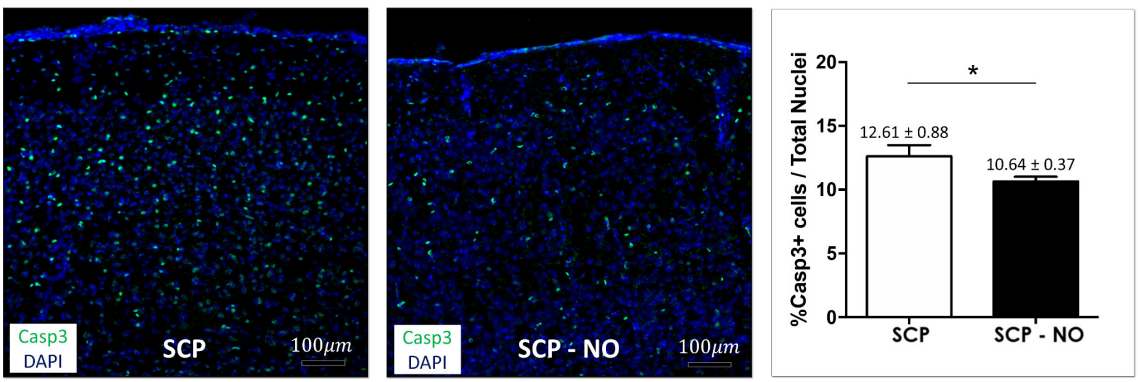

FIGURE 6 | Apoptosis: caspases 3. Representative images of caspase 3 expression at the cortical level, in selective cerebral perfusion (SCP) group compared to selective cerebral perfusion with nitric oxide 20 ppm (SCP-NO). In the graph, blind quantification was performed to calculate the average percentage of caspase 3 expression in the brain regions considered (*$p < 0.05$). The average percentage of caspase 3 positive cells was normalized to the total number of nuclei in the regions of interest considered (174 images quantified across the different conditions) (magnification ×20). Casp3, caspases 3. DAPI, 4′,6-diamidine-2′-phenylindole dihydrochloride.

should minimize ischemia-reperfusion injury responsible for neuroinflammation and apoptosis (30).

Nitric oxide (NO) administration has been studied after focal cerebral ischemia and has been demonstrated to decrease nuclear factor kappa B activation, oxidative and nitrosative stress, inflammation, and apoptosis, resulting in reduced infarct size and increased cerebral blood flow. The basal concentration is mainly due to constitutive isoforms of NO synthase (eNOS and nNOS). It is essential for regulating cerebrovascular hemodynamic and protecting endothelium integrity from inflammatory, oxidative, and procoagulant stimuli. Total suppression of eNOS activity in knockout mice makes them hypertensive and more susceptible to ischemia-reperfusion injury, with larger infarcts than in controls and severe reduction in cerebral blood flow. Conversely, nNOS gene deficiencies or nNOS inhibition decrease infarct volume and neuronal death (12).

During ischemia and hypothermia, the production of NO by constitutive NO synthase decreases. This is followed by a late burst of NO produced by inducible NO synthase (iNOS) that further increases its concentration to toxic concentrations (10). The primary sources of iNOS include microglia, astrocytes, and endothelial cells, infiltrating leukocytes, and can influence the evolution of brain damage after an ischemic injury. To the same extent microglia and macrophages express Iba1 when activated by a proinflammatory stimulus or by hypothermia (20, 31).

In this study, NO administration in SCP resulted in a reduced expression of Iba1, corresponding to lower neuroinflammation. Indeed, less activation of microglia leads to lower production of inflammatory cytokines, and prevents the expression of iNOS, thus attenuating cell damage resulting from inflammatory activation (32). This is consistent with the results obtained investigating the effects of inhaled NO on microglia after deep HCA (33).

In this study, NO administration during circulatory arrest reduced oxidative stress, as shown by the lower 8oxodG content. Cerebrovascular ischemia induces an inflammatory response and associated increased cytokine release and iNOS activity. NO, generated mainly by iNOS, reacts with superoxide and forms peroxynitrite. Peroxynitrite causes cellular necrosis with other ROS by lipid peroxidation, DNA damaging, disrupting mitochondrial respiratory chain, and ATP production (10).

Changes in eNOS expression, increased ROS production, and eNOS uncoupling are the principal reasons behind endothelial dysfunction. NADPH oxidase catalyzes the transfer of electrons from NADPH to oxygen to produce superoxide. The mitochondrial electron transport chain is another important source of superoxide in the cerebral vasculature. Oxidative stress and related cytotoxicity result in mitochondrial dysfunction, further accelerating superoxide production and neuronal death (12).

Nitric oxide (NO) administration reduces iNOS activation and eNOS uncoupling (10). In this situation, the production of peroxynitrite and superoxide is lowered, and oxidative stress on neuronal cells decreases.

In addition to the reduced neuroinflammation and oxidative stress, the reduction in hypoxic areas in animals treated with NO-enriched SCP could contribute to neuronal cell survival. Thiols groups are oxidized more uniformly, and the hypoxic area extension, detected by reduced thiols, decreases. The reduction of oxidative stress and hypoxic areas are indicative of preserved coupling between oxygen delivery and consumption. Administration of NO downregulates neuronal apoptosis by inhibiting increased phosphorylation of JNK, c-Jun, and Bcl-2. Furthermore, NO can nytrosilate caspases 3 directly and prevent the activation of apoptosis (12). These effects, along with an increase in cerebral blood flow, reduce brain damage after the ischemia-reperfusion event (21).

All these elements with an attenuated inflammatory milieu explain the reduced apoptosis index demonstrated in brains perfused by SCP added with NO. Indeed, NO significantly decreased caspases 3 positive cells, demonstrating a positive effect of NO administration on cell survival.

A possible limitation of this study is that it was performed on a small animal model constituted of healthy rats and with data collected in an early phase (1 h) after hypothermic circulatory arrest.

However, the protocol is clinically relevant and assured continuous SCP during 30-min HCA. The two groups studied were equivalent, and there were no vascular alterations; the consequence was diffuse and non-focal brain damage. The latter was measured by immunofluorescence analysis, and it is not possible to diagnose through current clinical techniques. Clinical manifestations can range from a slow awakening after anesthesia to delirium and psychomotor agitation resulting in TND. This study aimed to address this type of neurological damage, which negatively impacts neurologic outcomes and prognosis after aortic arch surgery.

The results of this study could inspire prospective randomized clinical studies to investigate NO application as a neuroprotective agent during SCP and HCA.

CONCLUSIONS

Nitric oxide (NO) administration in the oxygenator during SCP and HCA may improve neuroprotection decreasing neuroinflammation, optimize oxygen delivery by reducing oxidative stress and hypoxic areas finally decrease apoptosis.

Further experiments are needed to investigate the effects on neurological 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 animal study was reviewed and approved by the Scientific Committee for Experimental Research of the University of Verona and approved by the National Ministry of Health (Ministerial Authorization Number 568/2020-PR, Protocol Number 56DC9.54).

AUTHOR CONTRIBUTIONS

DL: conceptualization, methodology, investigation, and writing-original draft. AR: conceptualization project administration, writing-review, and editing. GF and GL: funding acquisition and supervision. LG: resources acquisition (nitric oxide). SM and MT: methodology and investigation (cardiopulmonary bypass technician). ID, LM, and SD: formal analysis (immunofluorescence). AM and RM: methodology, investigation, and experiment execution. All authors contributed to the article and approved the submitted version.

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Clinical and Surgical Evaluations of Reoperation After Mechanical Mitral Valve Replacement Due to Different Etiologies

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Background: This study aimed to evaluate the clinical and surgical characteristics of patients who required reoperation after mechanical mitral valve replacement (MVR).

Methods: We retrospectively identified 204 consecutive patients who underwent reoperation after mechanical MVR between 2009 and 2018. Patients were categorized according the reason for reoperation (perivalvular leakage, thrombus formation, or pannus formation). The patients' medical and surgical records were studied carefully and the rates of in-hospital complications were calculated.

Results: The mean age was 51±12 years and 44% of the patients were male. The reasons for reoperation were perivalvular leakage (117 patients), thrombus formation (35 patients), and pannus formation (52 patients). The most common positions for perivalvular leakage were at the 6–10 o'clock positions (proportions of ≥25% for each hour position). Most patients had an interval of >10 years between the original MVR and reoperation. The most common reoperation procedure was re-do MVR (157 patients), and 155 of these patients underwent concomitant cardiac procedures. There were 10 in-hospital deaths and 32 patients experienced complications. The 10-year survival rate was 82.2 ± 3.9% in general, and the group of lowest rate was patients with PVL (77.5 ± 5.2%). The independent risk factors were "male" (4.62, 95% CI 1.57–13.58, $P = 0.005$) and "Hb<9g/dL before redo MV operation" (3.45, 95% CI 1.13–10.49, $P = 0.029$).

Conclusion: Perivalvular leakage was the most common reason for reoperation after mechanical MVR, with a low survival rate in long term follow-up relatively.

Keywords: prosthesis malfunction, mitral valve replacement, perivalvular leakage, thrombus, pannus

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INTRODUCTION

Mechanical prosthesis replacement is a valuable treatment option for mitral valve lesions. It offers a much longer life expectancy than a biological prosthesis. However, a few patients require secondary operation after mechanical mitral valve replacement (MVR). In such cases, the most common pathogeneses include perivalvular leakage (PVL), thrombus, or pannus formation. Although coupled with low prevalence (6.5% for 10 years follow-up, or 1,000–2,000 cases per year in Japan or the US), (1–4) the redo operation remains a significant challenge to clinicians and patients.

Several studies and reviews have examined the therapies and prognosis of redo operations after mechanical MVR, especially for patients with PVL (5–7). However, cases of thrombus or pannus were insufficient. In contrast, it was also worth comprehensively analyzing the operative techniques and their impacts on patients by different etiologies. Therefore, the current study aims to report the clinical features, operative techniques, and complications in-hospital of redo operations after mechanical MVR in our medical center.

MATERIALS AND METHODS

Patients Selection

More than 2,000 mitral valve surgeries have been completed in recent years in our hospital; (8) however, only a few of these patients underwent secondary operations. This retrospective study evaluated patients undergoing reoperation after mechanical MVR from January 2009 to December 2018. Medical records, including echocardiographic, clinical, operative, and in-hospital outcomes, were collected. For inclusion, patients were also required to have undergone transthoracic Doppler echocardiography and preoperative coronary angiography if older than 45. The cause of redo MVR was attributed to perivalvular leakage, thrombogenesis, and pannus formation. Patients were categorized into groups correspondingly. For patients of PVL, because of the variances of mitral annular, a novel item, "summed points of PVL," was used to evaluate the severity of perivalvular leakage, representing the overall points of a lesion by clock position. The medical records were reviewed carefully to confirm the cause of the operation. The details of lesions were affirmed by the surgery records in cases of inconsistencies with echocardiography or other imaging.

The primary endpoint was defined as the death in the follow-up. The secondary endpoint was defined as the complications in-hospital, including mortality in hospital, bleeding reoperation, continuous renal replacement therapy (CRRT), Intra-Aortic Balloon Pump (IABP), tracheotomy, stroke, ventilator usage $\geq$96 h, and ICU Stay $\geq$7 days.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation, and categoric variables were represented as percentages. Comparisons were performed by the χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test

TABLE 1 | Preoperative characteristics of the study patients.

	PVL* (*n* = 117)	Thrombus (*n* = 35)	Pannus (*n* = 52)	Overall (*n* = 204)	*P*-value†
Age (y)	51 ± 13	47 ± 13	52 ± 10	51 ± 12	0.10
Male (%)	69 (59%)	9 (26%)	11 (21%)	89 (44%)	< 0.01
BSA (m^2)	1.5 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	1.3 ± 0.4	< 0.01
BMI§(kg/m^2)	22 ± 3	23 ± 3	23 ± 4	22 ± 3	0.02
Risk factors, *n* (%)					
Atrial fibrillation**	69 (59%)	21 (60%)	36 (69%)	126 (62%)	0.44
Tricuspid regurgitation	74 (63%)	16 (46%)	32 (62%)	122 (60%)	0.17
Pulmonary hypertension	45 (39%)	20 (57%)	25 (48%)	90 (44%)	0.12
Hypertension	17 (15%)	4 (11%)	3 (6%)	24 (12%)	0.26
Diabetes mellitus	6 (5%)	3 (9%)	3 (6%)	12 (6%)	0.75
History of stroke	6 (5%)	1 (3%)	10 (19%)	17 (8%)	< 0.01
NYHA III/IV	69 (59%)	22 (63%)	29 (56%)	120 (59%)	0.80
History of AVR	42 (36%)	9 (28%)	12 (23%)	63 (31%)	0.19
Echocardiology					
LVEF, (%)††	60 ± 12	52 ± 22	56 ± 15	57 ± 15	0.07
< 50%, n (%)	5 (4%)	1 (3%)	6 (12%)	12 (6%)	0.13
LVEDD	56 ± 13	40 ± 17	45 ± 11	53 ± 10	< 0.01
≥55mm, *n* (%)	74 (63%)	8 (23%)	11 (21%)	93 (46%)	< 0.01
MVPG§§	9 ± 5	14 ± 9	11 ± 6	10 ± 6	< 0.01
Hemoglobin (g/dL)	118 ± 23	128 ± 21	120 ± 22	120 ± 23	0.08
Intervals of operations (y)	11 ± 8	9 ± 7	15 ± 8	12 ± 8	< 0.01
≥10y, *n* (%)	61 (52%)	19 (54%)	40 (77%)	120 (59%)	0.01

PVL, Perivalvular Leakage.
† *Comparisons among PVL, thrombus or pannus.*
BSA, Body Surface Area.
§*BMI, Body Mass Index.*
**Atrial fibrillation, Atrial fibrillation before redo MV operation.*
†† *LVEF, Left Ventricular Ejection Fraction.*
LVEDD, Left Ventricular End Diastolic Diameter.
§§*MVPG, Mitral Valve Pressure Gradient.*
P value < 0.05, with significant difference in statistics.

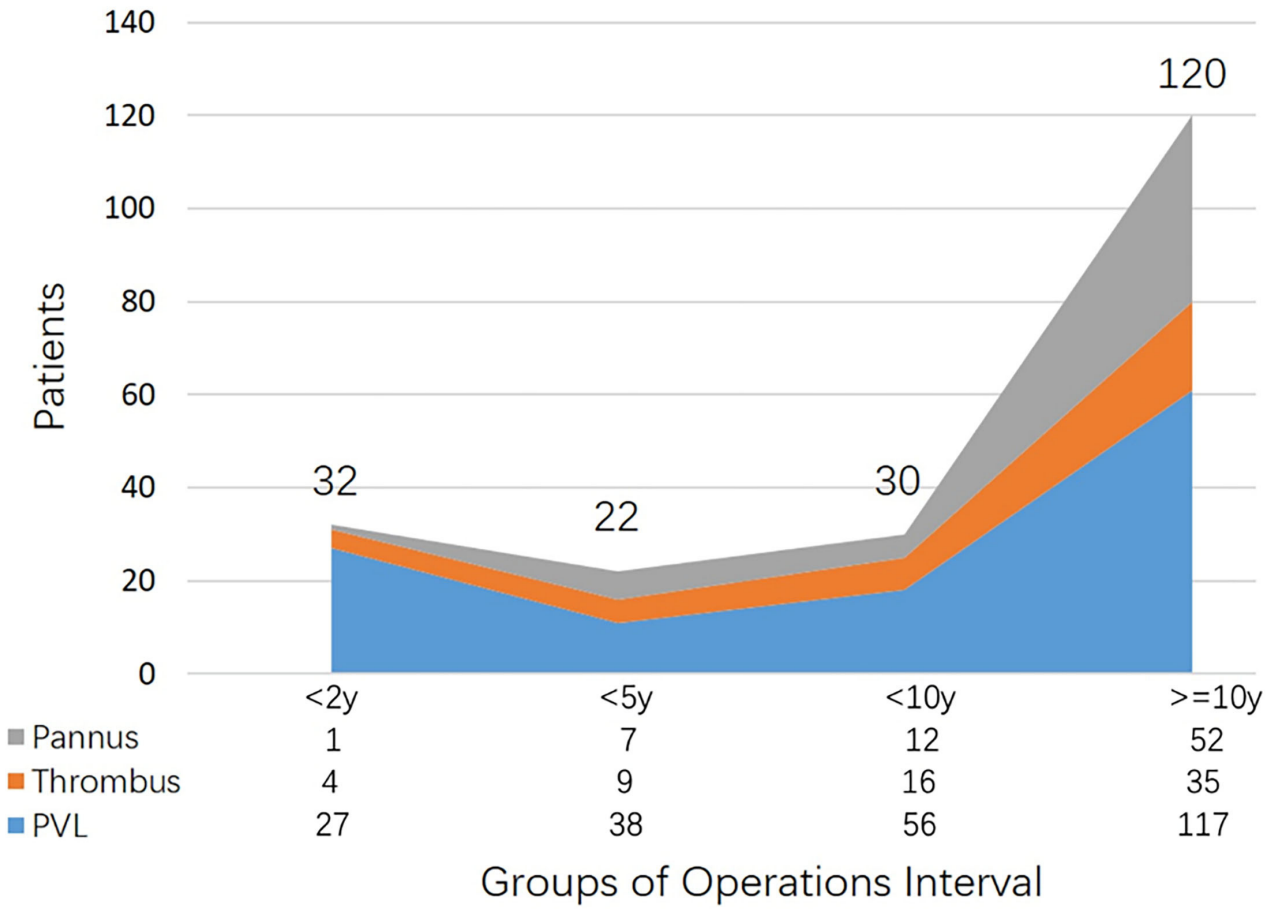

FIGURE 1 | Patient distributions of etiologies categorized by operations interval.

for continuous variables. Multiple logistic regression models were used to assess associations with the in-hospital outcomes. As appropriate, survival rates were compared between groups, using the log-rank test or Breslow's test. Predictors or risk factors were analyzed by Cox regression. All variables were included in the univariate analysis. Those with a probability value of <0.1 were included in the multivariate regression. In terms of the Cox multivariate model, missing values were replaced by multiple imputation, and predictor selection using backward stepwise regression with Akaike information criterion (AIC) was performed on all imputed datasets. All statistical tests were two-sided, and a probability value of <0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS software (version 19.0; IBM Corp., Armonk, NY, USA).

RESULTS

Characteristics of Patients With Redo Operations After Mechanical MVR

Two hundred and four patients underwent redo operation after mechanical MVR. Their average height was 1.64 ± 0.1 m, and average weight was 61 ± 11 kg, average age was 51 ± 12 years old, and 50 patients (24.5%) were older than 60. Groups were categorized by etiologies: perivalvular leakage (n = 117), thrombus (n = 35), and pannus (n = 52). The baseline and clinical data of patients enrolled are summarized in **Table 1**.

Most baseline characteristics among the patients showed no difference in statistical terms. Patients with perivalvular leakage had more proportion of males (n = 69, 59%), with the highest BSA (1.5 ± 0.4 m^2) and the lowest BMI (22 ± 3 kg/m^2). The pannus group had the longest interval of operations (15 ± 8 years, $p = 0.001$). Group PVL had the largest left ventricular end-diastolic diameter (LVEDD, 56 ± 13 mm, $p < 0.001$), and group thrombus had the greatest mitral valve pressure gradient (MVPG, 14 ± 9 mmHg, $p = 0.004$).

As displayed in **Figure 1**, more than half of the patients had more than 10 years gap between operations. Especially for patients with pannus, the average interval was 15 ± 8 years, and few of them underwent redo operations <10 years after primary surgery. The majority of PVL patients were in the group "< 2 years" (n = 27, 84.4%). Moreover, among patients with thrombus, the morbidity of redo surgery appeared to be similar in the entire cohort.

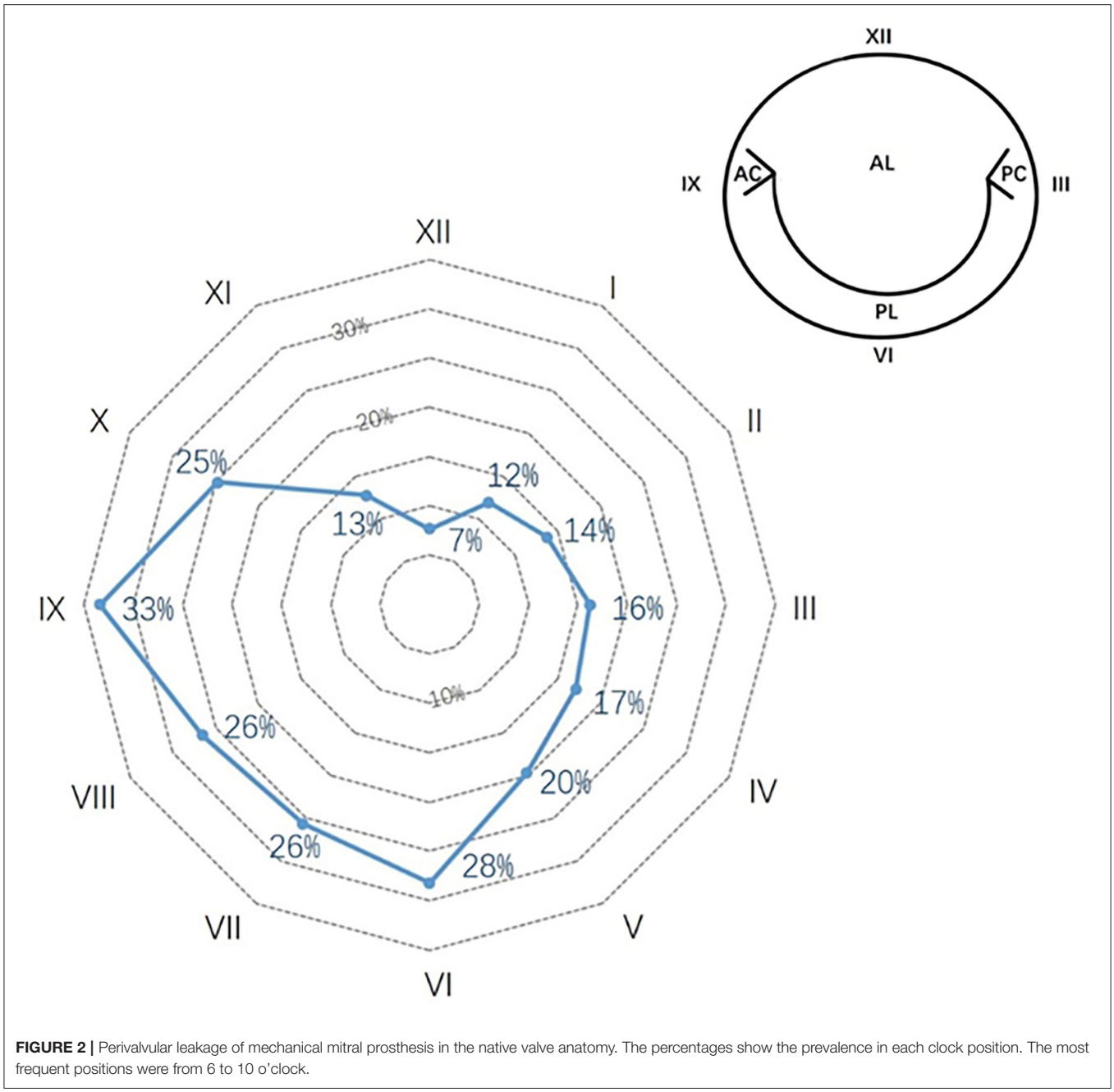

FIGURE 2 | Perivalvular leakage of mechanical mitral prosthesis in the native valve anatomy. The percentages show the prevalence in each clock position. The most frequent positions were from 6 to 10 o'clock.

Detailed documentation of perivalvular leakage was available for 109 (93% of PVL group). **Figure 2** illustrates the distribution of perivalvular leakage illustrated by the clock position on a radar chart. Eighty-one patients (74% of PVL records) had more than one point of lesion. The most susceptible regions appeared from six to ten o'clock, with a prevalence of no <25%.

We used a novel item, "summed points of PVL," to evaluate the severity of perivalvular leakage, representing the lesion's overall points by clock position. Generally, patients were found to have 2.6 ± 1.4 points (**Figure 3**), and it had no relationship with the interval of operations ($r = 0.06$, $p = 0.56$). Furthermore, we analyzed the PVL patients combined with AVR simultaneously and found no relationship between "summed points of PVL" and "aortic valve replacement" (eight of one point, eight of two summed points, and seven of more than two points, $p = 0.797$).

Characteristics of Redo Operations After Mechanical MVR

One hundred and fifty-seven patients underwent repeat MVR, with 147 mechanical prostheses (94% of re-MVR) implanted. Forty patients of perivalvular leakage (34% of PVL group) underwent PVL repair, and seven patients (14% of pannus group) underwent pannus clearance only.

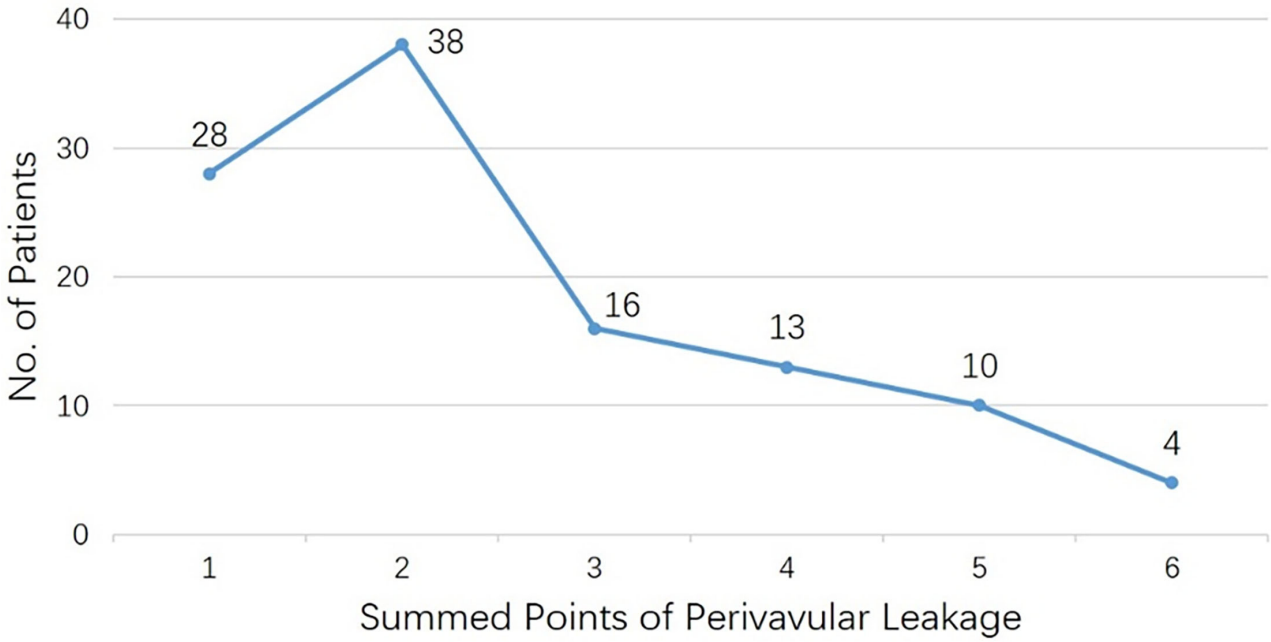

FIGURE 3 | Patients number for each subgroup with summed points of perivalvular leakage.

One hundred and fifty-five patients underwent concomitant heart procedures, including 131 tricuspid valve repairs and 54 aortic valve replacements (AVR) (**Table 2**). The operation time was 327 ± 104 min, and the aortic cross-clamping (ACC) time was 103 ± 48 min. Operations in the PVL group had a shorter ACC time than non-PVL groups (min: 96 ± 46: 112 ± 50, $p = 0.01$). We had recorded 10 deaths (mortality of 4.9%) in the hospital. And as shown in **Table 3**, there was no difference among the three groups in terms of complications in general or in detail.

Follow-Up of Redo Operations After Mechanical MVR

The overall survival rate at 10 years was 82.2 ± 3.9%. As shown in **Figure 4**, there was no difference among the three groups in terms of etiologies (log-rank test, $P = 0.18$). However, differences could be observed after categorizing patients into the PVL group and Others group (non-PVL group) (log-rank test, $P = 0.06$). Univariate and multivariate Cox regression analyses (**Table 4**) revealed that "Male" (4.62, 95% CI 1.57–13.58, $P = 0.005$) and "Hb<9g/dL before secondary MV operation" (3.45, 95% CI 1.13–10.49, $P = 0.029$) were the independent risk factors in patients undergoing redo operations after mechanical MVR. Additionally, LVEF might influence the late outcomes of patients after the redo MV operation (1.07, 95% CI 1–1.14, $P = 0.061$).

DISCUSSION

Patients by Different Etiologies of Redo Operations After Mechanical MVR

In the present study, perivalvular leakage was the most important pathogenesis leading to a secondary operation after mechanical MVR. Patients with perivalvular leakage had a longer diameter of left ventricular end-diastole, and the percentage of left ventricular dilation (LVEDD ≥55 mm) was up to 63%. This could be attributed to the fact that the pathophysiology was similar to mitral regurgitation, which also led to a shorter interval between operations than patients with pannus or thrombus (years: 11 ± 8: 13 ± 8, $p = 0.058$). These findings were in line with Botta et al. report (mean: 130 months) (9). Most studies proposed that patients require intervention only with the moderate-severe PVL or coupled with symptoms; mild PVL without symptoms usually had a benign course and could be managed in follow-up carefully (10). However, the surgeries peaked slightly in PVL patients during the first 2 years. This spike in the extremely short interval might be attributed to the surgical techniques being used. Meanwhile, patient numbers in other groups increased gradually with time in 10 years, after former mechanical MVR from our study.

In the current investigation, the perivalvular leakage in the mitral position was predominantly at six to ten o'clock position (≥25% in each point), which was mirror-symmetric to Bouhout et al. study (from two to six o'clock, ≥35% for each point) (6). Meanwhile, another important assessment was the severity of PVL. Because of the different sizes of mitral prostheses, it might be unreasonable to compare them by length or width directly. We analyzed the item, "summed points of PVL" (2.6 ± 1.4 points), which represented the overall leakage points by clock position. These data could benefit further analysis.

Patients with pannus had the greatest MVPG in the cohort (14 ± 9 mmHg, $p = 0.004$). This was in line with previous studies and reports on pannus and thrombus (11, 12). The current consensus showed that pannus always formed as circular mass curved along the ring, and thrombus tended to infest into the prosthesis,

TABLE 2 | Blood transfusion and operative characteristics of the study patients.

	PVL*** ($n = 117$)	Thrombus ($n = 35$)	Pannus ($n = 52$)	Overall ($n = 204$)	*P*-value†††
Operative techniques					
PVL-repairing	40 (34%)	-	-	40 (20%)	-
Pannus clearance	-	-	7 (14%)	7 (3%)	-
Mitral valve replacement	77 (66%)	35 (100%)	45 (87%)	157 (77%)	<0.01
Mechanical prosthesis§§§	76	30	41	147	0.02
Size of prosthesis (mm)	27 ± 2	26 ± 1	26 ± 1	26 ± 2	<0.01
Concomitant procedure, n****	87 (74%)	24 (69%)	44 (85%)	155 (76%)	0.19
Aortic valve replacement	26 (22%)	7 (20%)	21 (40%)	54 (27%)	0.03
Tricuspid valve repairing	76 (65%)	20 (57%)	35 (67%)	131 (64%)	0.61
Operation time (mins)	330 ± 107	321 ± 114	325 ± 98	327 ± 104	0.93
CPB time††††	149 ± 72	157 ± 71	161 ± 65	153 ± 70	0.56
ACC time	96 ± 46	105 ± 45	117 ± 53	103 ± 48	0.02
P-ACC time§§§§	30 ± 22	33 ± 30	40 ± 52	33 ± 34	0.89
P-ACC: ACC	0.36 ± 0.27	0.34 ± 0.29	0.36 ± 0.38	0.35 ± 0.30	0.33
Length of hospital stay (d)	26 ± 18	15 ± 7	18 ± 10	22 ± 15	<0.01
Postoperative stay (d)	13 ± 11	11 ± 6	10 ± 6	12 ± 9	0.08
ICU stay (h)	101 ± 147	94 ± 116	83 ± 99	95 ± 131	0.76
Ventilator usage (h)	48 ± 87	46 ± 76	37 ± 39	45 ± 75	0.38
Blood Transfusion					
Red blood cell (u)	8 ± 7	9 ± 14	6 ± 5	8 ± 8	0.49
Plasma (ml)	917 ± 780	1,216 ± 2,229	741 ± 572	939 ± 1163	0.63
Platelet (u)	1.6 ± 1.5	1.5 ± 0.8	1.5 ± 1.6	2.0 ± 3.5	0.89

***PVL, Perivalvular Leakage.
††† Comparisons among PVL, thrombus or pannus.
Values are n (%), or median (interquartile range).
§§§Comparisons (PVL, Thrombus, & Pannus) in patients received redo MV replacement.
****No. of patients received concomitant procedures.
†††† CPB, Cardio-Pulmonary Bypass.
ACC, Aortic Cross Clamping.
§§§§P-ACC, CPB time of Post ACC.
P value < 0.05, with significant difference in statistics.

which further restricted leaflet motion and caused a malfunction. Moreover, patients with pannus had the most prolonged interval of operations (15 ± 8 years, $p = 0.001$). The development of pannus that can affect the hemodynamics of artificial prostheses requires a significant amount of time (13). In contrast, thrombi always give rise to acute symptoms, leading to shorter intervals (9 ± 7 years), similar to our study. These findings were consistent with Separham et al. report (14).

Techniques and Details of Redo Operations

Thirty-three percent of PVL patients underwent perivalvular leakage repair, with shorter aortic cross-clamping time than redo MVR in the same group (min: 78 ± 45: 105 ± 44, $p = 0.002$). However, this procedure did not cut down the operation time and Cardio-Pulmonary Bypass (CPB) time in general. Moreover, CPB time after ACC was not significantly different between the three etiology groups. Thus, it could be recognized that the operative techniques would not impact the difficulty of surgery.

The most common type of operative technique was the repeated replacement of mitral prosthesis (re-MVR), received by 66% of patients of PVL in our cohort. However, Bouhout et al. study showed that 76% of patients underwent PVL repair, who also reported the opposite distribution of PVL points mentioned above (6). PVL patients also had a larger prosthesis size than patients with thrombus or pannus in our hospital. All re-MVRs implanted artifacts had a size similar to the previous operation. The mechanical prosthesis was the mainstream choice for surgeons, even for patients aged more than 65 years. There were 11 cases of 14 implantations (three bioprosthetic valves). For these cases, there were four with small aortic annulus (size 19 or 21), two with endocarditis, one with Behcet's disease, and one with patient preference. These results might differ from Fukunaga et al. findings, which suggested that 75% of patients aged 50–69 years had received biological prostheses (15). However, the composition of their cohort was significantly different from ours, as there were only 6.8% cases of PVL in the mechanical MVR group.

Among patients undergoing concomitant operations, 22% (54 patients) had AVR, of which 31 patients underwent secondary replacement. The most common lesion of the aortic prosthesis was pannus formation ($n = 16$), and there were eight patients with a mean aortic valve pressure gradient >30 mmHg at rest. In our cohort, secondary AVR was more common among patients with a history of AVR [OR 3.54, 95%CI (1.84, 6.81), $p < 0.01$].

Meanwhile, in the present study, there were seven patients who underwent pannus removal through the transaortic route.

TABLE 3 | Complications of redo operations after mechanical MVR*.

	PVL† (*n* = 117)	Thrombus (*n* = 35)	Pannus (*n* = 52)	Overall (*n* = 204)	*P*-value
Complications, n (%)§	19 (16%)	6 (17%)	7 (13%)	32 (16%)	0.87
ICU stay ≥ 7d	12 (10%)	3 (9%)	2 (4%)	17 (8%)	0.38
Ventilator usage ≥ 96 h	7 (6%)	3 (9%)	4 (8%)	14 (7%)	0.84
Mortality in hospital	4 (3%)	3 (9%)	3 (6%)	10 (5%)	0.44
CRRT**	8 (7%)	3 (9%)	1 (2%)	12 (6%)	0.35
Tracheotomy	5 (4%)	1 (3%)	1 (2%)	7 (3%)	0.73
Bleeding reoperation	5 (4%)	2 (6%)	4 (8%)	11 (5%)	0.66

Complications: mortality in hospital, bleeding reoperation, CRRT, IABP, tracheotomy, stroke, ventilator usage ≥ 96 h, ICU Stay ≥ 7 d;

† *PVL, Perivalvular Leakage.*

Comparisons among PVL, thrombus or pannus.

§*No. of patients with complications after redo MV operation.*

***CRRT, Continuous Renal Replacement Therapy.*

TABLE 4 | Univariate/multivariate cox regression of redo operations after mechanical MVR.

Variables	Univariate regression HR (95% CI)	*P*-value	Multivariate regression HR (95% CI)	*P*-value
Age	1.02 (0.98, 1.06)	0.256		
Male	4.62 (1.69, 12.63)	0.003	4.62 (1.57, 13.58)	0.005
BMI[xxii]	1.02 (0.90, 1.16)	0.728		
Etiologies[xxiii]	0.54 (0.26, 1.11)	0.093	0.84 (0.41, 1.76)	0.649
NYHA III/IV	1.41 (0.57, 3.50)	0.457		
PH[xxiv]	0.91 (0.38, 2.20)	0.839		
Atrial fibrillation[xxv]	1.19 (0.48, 2.94)	0.712		
Hb<9g/dL	3.67 (1.22, 11.06)	0.021	3.45 (1.13, 10.49)	0.029
MVR[xxvi]	0.60 (0.24, 1.49)	0.269		
Multi-Operation[xxvii]	3.12 (0.73, 13.38)	0.126		
LVEDD[xxviii]	1.01 (0.97, 1.05)	0.770		
LVEF[xxix]	1.06 (1, 1.13)	0.063	1.07 (1, 1.14)	0.061

[xxii] *BMI, Body Mass Index.*

[xxiii] *Etiologies, PVL, thrombus, pannus.*

[xxiv] *PH, Pulmonary Hypertension.*

[xxv] *Atrial fibrillation, Atrial fibrillation before redo MV operation.*

[xxvi] *MVR, Patients receiving MVR finally during the redo MV operation.*

[xxvii] *Multi-Operation, Multi-cardiac operations performed simultaneously during the redo MV operation.*

[xxviii] *LVEDD, Left Ventricular End Diastolic Diameter.*

[xxix] *LVEF, Left Ventricular Ejection Fraction.*

Their MVPG was 5 ± 1 mmHg, compared to 11 ± 7 mmHg ($p = 0.001$). Park et al. (16) found that patients with MVPG <5 mmHg could not benefit from the pannus clearance. Our findings were in line with their report.

Endpoints After Redo Operations

Complications during the perioperative period have already been outlined in the Results section. The in-hospital mortality in our cohort was relatively low in our study compared to previous reports (2, 7, 17). The prevalence of dialysis and postoperative stroke (one case) was at an extremely low level, (18, 19) and the morbidity of bleeding during reoperation in our study was similar to a previous study (20). However, the ICU stay time and length of hospital stay after the operation was longer in our study than that reported earlier (19).

The overall survival rate at 10 years for our study participants was 82.2 ± 3.9%, similar to that reported by Fukunaga et al. (survival rate: 79.2%) (21). In our study cohorts, the PVL group had an outcome of 77.5 ± 5.2% after a 10-year follow-up which was the worst among the three groups. This might be due to the larger LVEDD than other groups (percentage of LVEDD>65 mm; PVL: Thrombus: Pannus; 63: 23: 21%). Patients with PVL always had worse outcomes than those patients with thrombus or pannus (1, 7, 14, 21). However, the survival rate of PVL patients in our study was still higher than in some studies, such as Bouhout et al. (57 ± 6%) (6). This may be attributed to the inclusion of relatively older adults in their group and a higher proportion of patients with NYHA III/IV. Furthermore, Botta et al. reported a survival rate at 5 years similar to our study (88.8: 84.0%) (9). However, these studies had different outcomes after

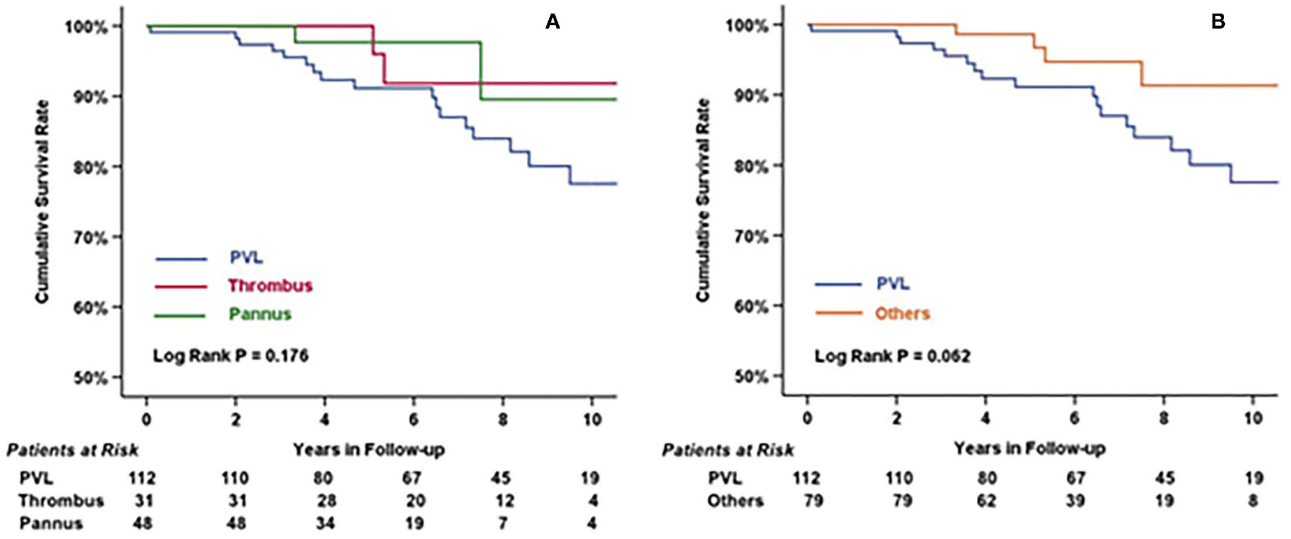

FIGURE 4 | Cumulative survival rate of patients categorized by etiologies **(A)** and by PVL/Others **(B)**. There was no statistical difference among three groups (log rank $P = 0.176$), but had significant difference between patients with or without perivalvular leakage before redo MV operation (log rank = 0.062).

Cox regression analysis. Our research had found that "male" and "Hb <9g/dL before secondary MV operation" were independent risk factors affecting long-term prognosis.

Patients with thrombus in our study had a 10 years survival rate of 91.8 ± 5.5%, which was mildly lower than that reported by Raman et al. (97.4 ± 1.2%) (22). Furthermore, those with pannus had a moderate survival rate (89.5%) compared with the thrombus group and PVL group, similar to findings reported by Park et al. (87.6%) (23). This suggests that patients with mechanical mitral valve dysfunction would have a good prognosis if they underwent a proper redo procedure.

Limitations of the Study

There were some limitations to our study. First, due to insufficient or missing clinical data, the insights drawn based on the surgical and patient history might not be fully valid and acceptable. Many patients did not undergo echocardiography in recent 2–3 years, making it further challenging to analyze the functioning of mechanical prostheses.

CONCLUSION

Despite the low prevalence, reoperation after mechanical mitral valve replacement remains a key challenge. In our study, perivalvular leakage might be the possible cause of operation, which might lead to a low survival rate in the long-term follow-up relatively. Male patients with low hemoglobin (Hb <9g/dL) before the redo MV operation might have a worse outcome during the long-term follow-up compared to other patient subgroups.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital, National Center for Cardiovascular Disease. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

SW, HS, JX, and CD: main surgeons of operations. JL, MS, and QY: statistics. JL and SW: writing. SW: general responsibility. All authors contributed to the article and approved the submitted version.

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Does a Small Body Have a Negative Impact on Minimally Invasive Mitral Valve Surgery?

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Backgrounds: Minimally invasive mitral valve surgery (MIMVS) in patients with a small body presents surgeons with a technically difficult surgical maneuver. We hypothesized that physique might negatively influence the safety and technical complexity of MIMVS.

Methods: One hundred and twenty-one patients underwent MIMVS in our institution between May 2014 and April 2020. These patients were categorized into two groups. The first group was the small physique group ($n = 20$) consisting of patients with a stature <150 cm. The second group was the normal physique group ($n = 101$) consisting of patients with a stature >150 cm. The primary endpoint was freedom from death and major adverse cardiovascular and cerebrovascular events (MACCE). The secondary endpoint was freedom from moderate or severe mitral regurgitation.

Results: Cardiopulmonary bypass time (130 ± 29 vs. 156 ± 55 min, $p = 0.02$) and aortic cross-clamp time (75 ± 27 vs. 95 ± 39 min, $p = 0.03$) were significantly shorter in the small physique group. Both in the early and midterm periods, there was no significant difference in the mortality (early, 5.0 vs. 1.0%, $p = 0.30$. midterm, 5.0 vs. 1.0%, $p = 0.09$), MACCE (early, 5.0 vs. 6.9%, $p = 0.65$. midterm, 5.0 vs. 5.9%, $p = 0.93$) and the residual MR (early, 0 vs. 1.0%, $p = 0.66$. midterm, 5.0 vs. 4.9%, $p = 0.93$) between the two groups.

Conclusions: Small physique is not a hurdle for MIMVS in terms of the safety of the operation.

Keywords: mitral valve surgery, minimally invasive cardiac surgery, physique, small body, safety

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INTRODUCTION

Previously, the primary candidates for minimally invasive cardiac surgery (MICS) were young patients who were socially active and had low risk and who expected excellent cosmesis (1). However, the indication for this method has recently expanded to relatively elderly people expecting faster recovery brought about by the preservation of their sternum (2). In the future, other good candidates for MICS will be children or adolescents who are seeking a fast return to social activities and better cosmesis.

Preliminary reports in relation to MICS in congenital cardiac surgery have focused on the clinical success of the operation for atrial septal defect (ASD), ventricular septal defect (VSD), and

atrioventricular septal defect *via* right thoracotomy (3, 4). For example, Yoshimura et al. reported excellent operative results for patients with ASD (mean age 7 years, mean body weight 23.9 kg). Mishaly et al. performed ASD or VSD closure and mitral valve repair on young patients, including 60 infants (mean age 9 years, mean body weight 20 kg), and concluded that the establishment of cardiopulmonary bypass (CPB) or the maintenance of good exposure in congenital cardiac surgery *via* right thoracotomy could be achieved in children with a body weight >9 kg.

One of the biggest concerns with MICS in patients with a small body is leg ischemia (5) due to the relatively small vascular diameter required for cannulation and the likelihood of spasticity, especially in young patients. Another concern is the technical difficulty in performing surgical maneuvers in a small pleural cavity (6). These concerns might be the primary reasons for the delay in the introduction of recent technological advances in MICS for congenital heart surgery.

Historically, among all variables with an influence on surgical outcome, body weight and body mass index or body surface area (BSA) have also been investigated (7, 8) to determine whether they significantly influence the outcome. However, in previously published reports, full sternotomy was performed in all documented cases, and none of the studies provided information on the impact of quantitative preoperative variables, such as body height, vascular diameter for cannulation, and the vertical or cross diameter of the pleural cavity on the operative results. Thus, elucidation of the negative factors for the completion of MICS would be of great value.

In this study, the patients who underwent mitral valve surgery were categorized into two groups using the MICS approach (MIMVS), namely, patients with a small physique and those with a normal physique, and the patient characteristics and clinical outcomes between the two groups were compared to elucidate the validity of MIMVS for individuals with a small body.

METHODS

The institutional review board of Asahikawa Medical University Hospital approved this retrospective study and waived the need for written patient consent (IRB number: 19083).

Patient Demographics

A total of 121 patients underwent MIMVS in our institution between May 2014 and April 2020. **Figure 1** shows the distribution of body mass index [BMI, 1-(A)], body surface area [BSA, 1-(B)] and height [1-(C)] in these patients. Mean BMI, BSA, and height in male/ female were 22.5 ± 3.1/21.2 ± 3.6 kg/m^2, 1.7 ± 0.2/1.5 ± 0.2 m^2, and 167 ± 7.2/153 ± 8.3 cm, respectively.

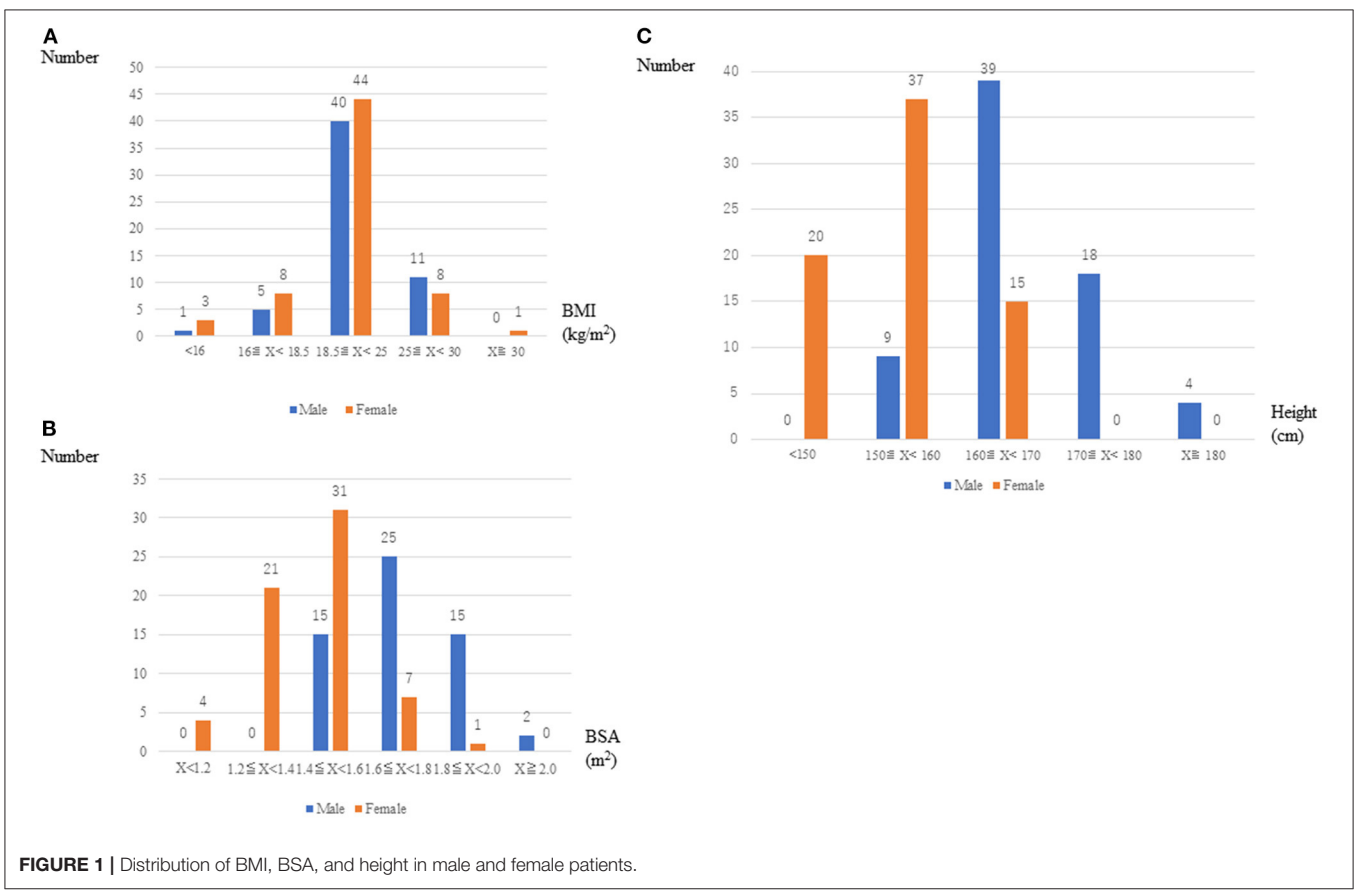

FIGURE 1 | Distribution of BMI, BSA, and height in male and female patients.

We categorized these patients into two groups: the small physique group ($n = 20$), which consisted of patients with a stature <150 cm, and the normal physique group ($n = 101$), which consisted of patients with a stature >150 cm.

Table 1 presents the patient demographics of the two groups. A significant difference in age (79 ± 7 vs. 62 ± 15 years, $p < 0.001$), gender ($p < 0.001$), height (143 ± 4.5 vs. 163 ± 8 cm, $p < 0.001$), body weight (42 ± 7.5 vs. 59 ± 10.7 kg, $p < 0.001$), BSA (1.3 ± 0.1 vs. 1.6 ± 0.1, $p < 0.001$), and the diastolic or systolic dimensions of the left ventricle (LVDd, 49 ± 5 vs. 54 ± 8.0 mm, $p = 0.01$. LVDs, 31 ± 6 vs. 35 ± 8.2 mm, $p = 0.02$) was observed between these two groups. Preoperative computed tomography revealed a significant difference in the axial length of the pleural cavity between the two groups (220 ± 10.6 vs. 242 ± 21.7 mm, $p < 0.001$) but none in the vertebra–sternum distance (97 ± 11.7 vs. 102 ± 196 mm, $p = 0.21$) or diameter of the femoral artery (10 ± 1.6 vs. 11 ± 2.0 mm, $p = 0.15$). Our exclusion criteria for MIMVS are as follows: 1. The existence of calcified or atherothrombotic ascending aorta. 2. The existence of significant coronary artery disease. 3. Severe mitral annular calcification. 4. Very obese patient (BMI ≧ 35) or critical emaciation (BMI ≦ 15). 5. Poor femoral or iliac access.

TABLE 1 | Patient demographics.

Variable	Small physique ($n = 20$)	Normal physique ($n = 101$)	*p*-value
Age, y	79 ± 7	62 ± 15	<0.001*
Gender, male	0	57	<0.001*
Height, cm	143 ± 4.5	163 ± 8	<0.001*
Body weight, kg	42 ± 7.5	59 ± 10.7	<0.001*
BMI, kg/ m²	20.6 ± 3.3	22.0 ± 3.4	0.22
BSA, m²	1.3 ± 0.1	1.6 ± 0.1	<0.001*
NYHA class			
0/I/II/III/IV	5/10/5/0	37/39/20/5	–
≧III	5	25	0.98
Preoperative TTE			
LVDd, mm	49 ± 5	54 ± 8.0	0.01*
LVDs, mm	31 ± 6	35 ± 8.2	0.02*
EF, %	66 ± 8.1	63 ± 10.2	0.23
MR grade			
0/I/II/III/IV	0/1/0/0/19	0/3/1/4/93	
AR grade			
0/I/II/III/IV	4/7/7/1/0	59/19/23/0/0	
Etiology of mitral valve			
Degenerative	18	88	0.73
MS, rheumatic	1	6	0.75
IE	1	7	0.85
Detail of MR	19	101	
Type I/II/III	3/15/1	14/76/5	
Atrial functional MR	3	14	0.89
Preoperative CT			
Vertebra–sternum distance, mm	97 ± 11.7	102 ± 19.6	0.21
Axial length of the pleural cavity, mm	220 ± 10.6	242 ± 21.7	<0.001*
Diameter of the femoral artery, mm	10 ± 1.6	11 ± 2.0	0.15

BMI, body mass index; BSA, body surface area; CT, computed tomography; EF, ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; TTE, transesophageal echocardiography.
**Means the existence of significant difference of p-value.*

Operative Procedure of MICS Mitral Surgery

In this study, 2 surgeons performed MIMVS. In our unit, MIMVS was performed under direct vision with the assistance of thoracoscope routinely for the surgery. Femoral cannulation was performed in surgical cut down technique using a one-stage arterial cannula [PCKC-A 16 French (Fr), 18 Fr, Toyobo, Osaka, Japan] and a single venous cannula (QuickDraw, 25 Fr, Edwards Lifesciences, Irvine, CA, USA) or a two-stage venous cannula (RAP FV cannula 22–25 Fr, LivaNova, Milan, Italy) inserted through the right atrium into the superior vena cava. During CPB, carbon dioxide insufflation of 3 L/min was employed for de-airing of the heart. A 5- to 7-cm right thoracotomy was performed *via* the fourth intercostal space. After establishing a full CPB flow, pericardiotomy was performed. Body temperature was decreased to mild hypothermia of 30–32°C. After aortic cross-clamp using a Cygnet flexible clamp (Vitalitec International, Inc., Plymouth, MA, USA), initial cardioplegia was delivered in an antegrade fashion, followed by left atriotomy with intermittent delivery of blood cardioplegia performed every 30 min.

The left atrium (LA) was exposed by the gentle retraction of the ascending aorta by LA retractor (Adams-Yozu Mini-Valve System, Geister, Tuttlingen, Germany). After mitral valve surgery was completed, LA was closed in a single-layer fashion followed by declamp without terminal hot-shot of cardioplegia. RV pacing lead was placed before routinely releasing the cross-clamp.

Postoperative Anticoagulation

Postoperative oral anticoagulation was administered. Irrespective of the rhythm pattern, warfarin was routinely administered to all patients, and the prothrombin time–international normalized ratio was controlled between 1.8 and 3.0. If sinus rhythm was stable for longer than 3 months, warfarin therapy was discontinued, except in cases of mitral valve replacement with a mechanical valve.

Endpoint

The primary endpoint was freedom from death and major cardiac and cerebrovascular event (MACCE). The secondary endpoint was freedom from moderate or severe mitral regurgitation.

Statistical Analysis

Preoperative, intraoperative, and postoperative data were recorded and retrospectively reviewed. Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as either absolute numbers or percentages.

Baseline patient characteristics, operative data, postoperative complications, and outcome rates were compared using Pearson's chi-squared test or Fisher's exact test for categorical

TABLE 2 | The details of operative procedures.

Variable	Small physique ($n = 20$)	Normal physique ($n = 101$)	p-value
Operative time	177 ± 45	210 ± 60	0.02*
CPB time	130 ± 29	156 ± 55	0.02*
ACC time	75 ± 27	95 ± 39	0.03*
Second run of CPB	0	6	0.54
Operative procedures			
Mitral valve	20	101	–
Isolated mitral valve surgery	16	69	0.42
Annuloplasty	18	88	0.72
Ring	9	41	0.81
Band	9	47	0.90
Valve repair	16	69	0.98
Triangular resection	4	28	0.59
Folding plasty	5	22	0.77
Indentation closure	2	20	0.52
Artificial chordae	3	23	0.56
Chordal transplantation	0	3	0.44
Central edge to edge	0	1	0.66
Commissural closure	3	7	0.37
Patch augmentation	0	3	0.44
Valve replacement	2	10	0.98
Tricuspid valve repair	4	32	0.42
Surgical maze procedure	2	28	0.15

ACC, aortic cross-clamp; CPB, cardiopulmonary bypass.

TABLE 3 | Operative outcomes in the early and midterm periods.

Variable (percentage)	Small physique ($n = 20$)	Normal physique ($n = 101$)	p-value
30-day mortality	1 (5.0)	1 (1.0)	0.30
In-hospital mortality	1 (5.0)	1 (1.0)	0.30
MACCE (including death)	1 (5.0)	7 (6.9)	0.65
Reexploration for bleeding	1 (5.0)	2 (2.0)	0.42
Reexpansion pulmonary edema	0	0	–
Pulmonary herniation	0	2 (2.0)	0.53
Stroke	0	0	–
SSI	0	0	–
Reoperation within 12 months	0	3 (3.0)	0.44
Readmission due to HF	0	0	–
Postoperative TTE at discharge			
≧Moderate MR	0	1 (1.0)	0.66
Mean PG bw LA-LV, mm Hg	2.5 ± 1.1	2.8 ± 1.4	0.38
Latest postoperative TTE			
Follow-up periods, years	2.1 ± 1.4	2.9 ± 1.8	0.09
≧Moderate MR	1 (5.0)	5 (4.9)	0.93
All-cause death	1 (5.0)	1 (1.0)	0.09
MACCE (including death)	1 (5.0)	6 (5.9)	0.93
Reoperation	0	5 (4.9)	0.31

SSI, surgical site infection; HF, heart failure; MR, mitral regurgitation; TTE, transesophageal echocardiography.

variables or Student's t-test or the Wilcoxon rank-sum test for continuous variables. The significance level was set at $p < 0.05$. For the time-to-event analysis, we employed log-rank tests and the Kaplan–Meier method. The Kaplan–Meier method was employed to demonstrate overall survival, freedom from MACCE and freedom from significant MR defined as moderate or severe MR. Statistical analyses were conducted using STATA version 15.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Operative time, cardiopulmonary time, and aortic cross-clamp time were significantly shorter in the small physique group than in the normal physique group (operative time, 177 ± 45 vs. 201 ± 60 min, $p = 0.02$; cardiopulmonary time, 130 ± 29 vs. 156 ± 55 min, $p = 0.02$; aortic cross-clamp time, 75 ± 27 vs. 95 ± 39 min, $p = 0.03$; **Table 2**), despite the fact that the percentages of isolated mitral valve surgery in both groups were not significantly different ($p = 0.42$; **Table 2**).

In relation to the details of the operative procedures, no significant difference was observed between the group in the use of materials for mitral annuloplasty ($p = 0.72$), frequency of valve repair ($p = 0.98$), concomitant tricuspid valve repair ($p = 0.42$), and antiarrhythmic operation ($p = 0.15$) (**Table 2**).

In the early postoperative periods, one patient in poor preoperative condition both in the small and normal physique groups died, respectively (30 days mortality, 5.0 vs. 1.0%, $p = 0.30$). There was no significant difference in the rate of MACCE and significant residual MR between two groups (MACCE, 5.0 vs. 6.9%, $p = 0.65$. ≧Moderate MR, 0 vs. 1.0%, $p = 0.66$; **Table 3**).

The postoperative follow-up periods were 2.1 ± 1.4 vs. 2.9 ± 1.8 year, respectively ($p = 0.09$). In the midterm, no significant difference was observed in the rate of overall death (5.0 vs. 1.0%, $p = 0.09$), MACCE (5.0 vs. 5.9%, $p = 0.93$), postoperative significant mitral regurgitation (5.0 vs. 4.9%, $p = 0.93$), and reoperation (0 vs. 4.9%, $p = 0.31$) between the two groups. Kaplan-Meyer curve in relation to overall survival, freedom from MACCE, and freedom from significant MR were not significantly different between the two groups ($p = 0.09$, 0.93, and 0.93, respectively; **Figures 2**–**4**).

DISCUSSION

In general, MICS requires performing surgical maneuvers using long-shafted instruments in small spaces, which is not easy due to the technical aspects. Therefore, appropriate patient selection is important, taking into consideration the safety of the procedure, the surgeon's level of comfort performing the surgical maneuvers, and whether the clinical outcome is promising and not compromised as compared with conventional open-heart surgery.

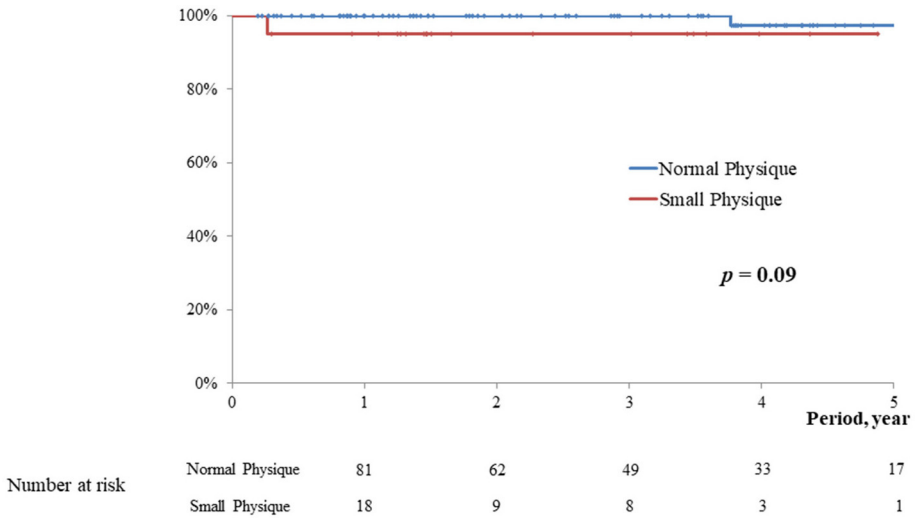

FIGURE 2 | Survival.

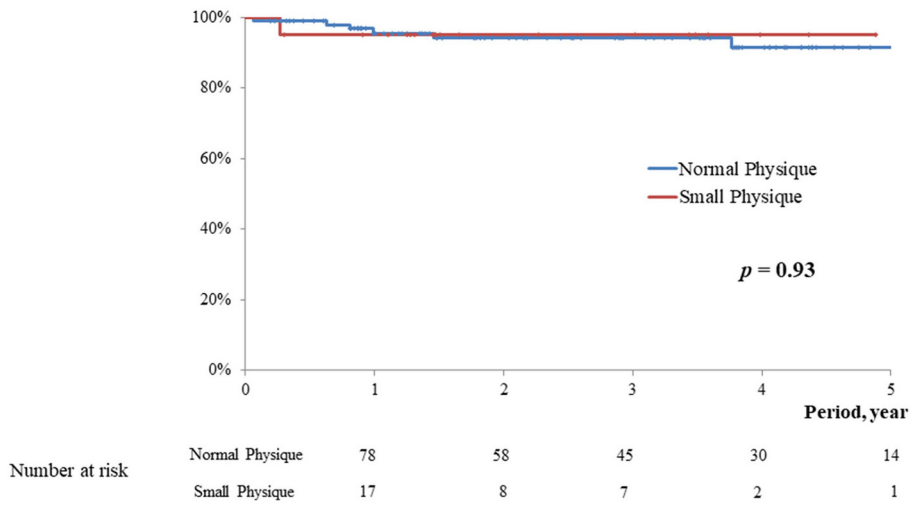

FIGURE 3 | Freedom from MACCE.

We hypothesized that a small physique might have an influence on the safety or technical complexity of MICS. However, the findings of this study suggest that CPB and aortic cross-clamp time as well as operative time in the small physique group was not longer than that in the normal physique group, although 75% in the small physique group underwent isolated MVP while 64% in the normal physique group and this might be related to the result that CPB and cross clamp time were shorter in the small physique group.

The definition of small stature may vary based on the patient's race. Short stature is defined as an adult height greater than two standard deviations below the mean for age and gender, which corresponds to the shortest 2.3% of individuals (9). Typically, in developed countries, this includes adult men shorter than 158 cm and adult women shorter than 149 cm. A recent national health and nutrition survey in Japan (10) revealed that the mean height of adult men and women in Japan was 168 ± 7.1 and 154.5 ± 7.0 cm, respectively. Taking this into consideration, the definition of small physique in this study was defined as a height <150 cm.

Historically, researchers have discussed how the difference in body size influences the outcomes of cardiac surgery. In their multiple regression analysis, Tarui et al. found significant associations among BMI, cannula size, and operation time and an increase in postoperative creatinine phosphorus kinase (11). Several reports have elucidated the strong association between large BSA or BMI (7, 8, 12) and the inferiority in clinical outcome, indicating that obese individuals typically

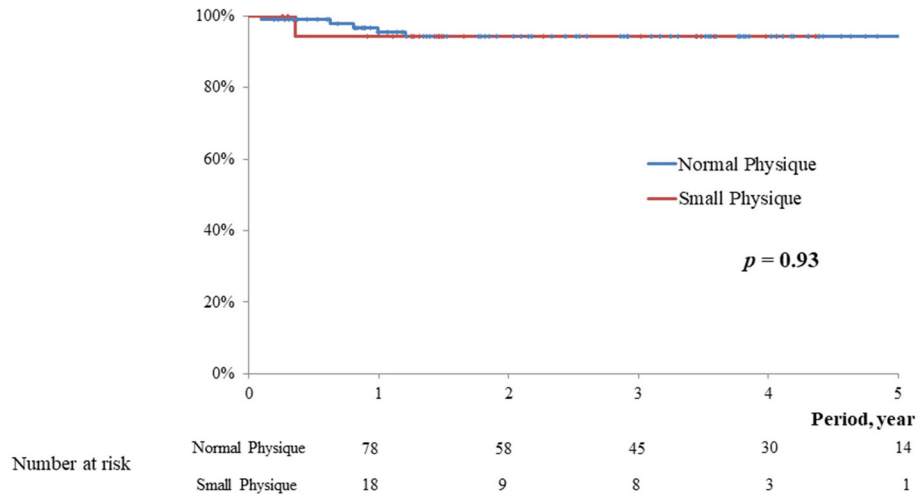

FIGURE 4 | Freedom from ≧ moderate MR.

have multicomorbidities, such as diabetes, hypertension, and impaired respiratory function. However, all of these studies precluded only conventional cardiac surgery *via* full sternotomy and did not discuss the influence of this factor on the technical complexity in MICS. To the best of our knowledge, this is the first report elucidating whether there is a significant association between small body size and clinical outcome in MIMVS.

Stable perfusion is important in open-heart surgery, especially in MICS. The most typical venous drainage setup in MICS is femoral vein cannulation (13). Poor venous drainage leads to a bad exposure of the mitral valve, making the surgery itself uncomfortable. In addition, venous back pressure results in the washout of cardioplegia, diminishing its cardioprotective effects, which may result in perioperative ventricular dysfunction (14). In the present study, we used low-profile venous cannulas (22 or 25 Fr); thus, we rarely experienced any difficulty in cannulation or in setting the position of the tip of the venous cannula appropriate to the drain under the guidance of intraoperative transesophageal echocardiography, even in patients with small physique. With regard to arterial cannulation in MICS, the common femoral artery (CFA) is the most commonly adopted site. The CFA diameter steadily increases throughout life, and it is significantly correlated with height, weight, and BSA. In addition, the CFA diameter is larger in men than in women (15). Limited to our study, all the patents in the small physique group were elderly women, and the mean diameter of the femoral artery in the two groups was not significantly different from that in the normal physique group. This feature of the current study might have influenced the outcome, which was different from our hypothesis.

As an indicator for the estimation of the actual surgical space in MICS mitral value surgery, the distance between the vertebrae and sternum is regarded as quite important for determining whether the MICS approach is optimal. This distance should preferably be 80 mm or greater for direct vision MICS (6). In fact, in our small physique group, this variable was beyond this threshold. Moreover, none of the patients in the small physique group demonstrated a funnel chest or thorax deformity.

The finding in this study, namely, that physique has no impact on the surgical outcome in MIMVS, contributes to the extension of the indication for the MICS approach in mitral valve surgery to small elderly people or young patients in adolescence who expect a quick recovery *via* preservation of their sternum and subsequent fast return to their daily lives.

Study Limitations

This study had some limitations. Namely, this was a retrospective study, and the sample size of the two groups was quite small. Patients' selection referred by our exclusion criteria was unavoidable especially early in the series in terms of patient safety.

In this study, small physique group was constituted only by women unexpectedly. It was because that we set the threshold of statue for small physique as 150 cm referring to the national database about physique in Japanese people. We intentionally set only a single parameter (height) as an influencer of the body shape itself on surgical outcome. However, various factors such as BSA or BMI may influence to the clinical outcome of surgery in real practice. Actually, the number of very obese patient whose BMI over 30 was only 1, and that of very slim or skinny patients whose BMI under 16 was 4 in this series (**Figure 1**). Similarly, the number of the patient whose BSA was over 2.0 was only 2 people, and whose BSA under 1.2 was only 4 in this series (**Figure 1**). Moreover, all of them got well soon after MICS uneventfully. So, it is difficult to elucidate the power of very high or low BMI on the clinical outcome in MICS in this study.

Despite these limitations, the strengths of this study include the quite conclusive findings, with complete clinical

follow-up examinations performed for all patients, including late echocardiographic follow-up findings.

Our results reconfirm the feasibility of the MICS approach in patients with a small body.

In conclusion, a small physique is not a contraindication for MIMVS.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Asahikawa Medical University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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

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ORIGINAL RESEARCH
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Percutaneous Cementoplasty to Treat Sternal Instability After Cardiac Surgery

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Introduction: Although rare, sternal pseudarthrosis is encountered after cardiac surgery and impacts the quality of life by triggering motion-dependent chest pain. We thought to describe its treatment by percutaneous cementoplasty and report the clinical follow-up of patients treated in our institution.

Methods: This case series is a retrospective study based on five patients who benefited from a sternal cementoplasty as a treatment for symptomatic pseudarthrosis after cardiac surgery. The progression of the symptoms was assessed during clinical follow-up using the Quebec back pain disability (QBPD) scale and Visual Analog Scale (VAS).

Results: None of the patients presented evidence of local complications or neurological disorders. The intra- et post-operative images show no major leak of the cement, no embolism and no damage to the internal mammary artery or the heart. All patients described an improved quality of life due to reduced pain in all-day clinical activities. The QBPD scores improved from 54.8 ± 29.3 to 30.0 ± 17.4 ($p = 0.02$) and the VAS from 7.0 ± 2.8 to 1.6 ± 1.6 ($p = 0.01$). Furthermore, three out of five patients could completely stop taking analgesics.

Conclusion: Sternal pseudarthrosis is a debilitating affliction that may complicate sternotomy after cardiac surgery. This series demonstrates that a more conservative approach such as cementoplasty can be successful in terms of reducing pain, and constitutes a promising technique in selected cases.

Keywords: sternotomy, sternal non-union, percutaneous cementoplasty, heart surgery complications, coronary artery bypass graft (CABG)

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INTRODUCTION

Median sternotomy is the most common approach for cardiac surgery. This technique is considered safe but pertains a complication rate of 0.5 to 5% (1–3). Sternal instability is the most frequent complication encountered. During the first 2 weeks after surgery, sternal instability is named dehiscence. After 3 months, it is named pseudarthosis (4). Sternal pseudarthrosis (SPA) is defined as a defect of consolidation with no sign of healing and is characterized by sternal instability. This is characterized by sternal clicking, excessive motion discomfort (4), and pain in the absence of infection (5). The incomplete sternal union might be due to scarce sternal stability because of intensified thoracic motions, an exaggerated fibrous tissue covering the osteotomy line, and/or an impaired healing capacity. Patient (diabetes mellitus,

obesity, chronic obstructive pulmonary disease, smoking) and procedural (cardiopulmonary bypass, excessive use of bone wax, bilateral internal mammary artery harvesting) risk factors have been considered (1, 4, 6–9). Sternal pseudarthrosis (SPA) significantly impacts the quality of life of suffering patients and increases their risk of pneumonia and mediastinitis (2, 4, 10).

The pain found in SPA is due to the friction of the bone with fibrous tissue. The cement acts in two ways: it reduces the mechanical stress and heats up to 70°C during its polymerisation leading to the destruction of the nerve endings. It already reaches 70% of its solid-state within 20–25 min after injection and is completely compact after 4 h. In SPA, the cement decreases micro-movements and stimulates subsequent bone consolidation. The cement's bridges have good resistance to axial forces, and the remaining sternal wires ensure vertical stability.

We describe hereby the characteristics of five patients suffering from SPA and who underwent percutaneous cementoplasty in our center.

PATIENTS AND METHODS

All patients treated for SPA in 2017 were included. A *sternal instability scale* (SIS) was used to assess SPA (11). The assessor evaluates the instability by placing two fingers on each side of the incision while the patient performs unilateral and bilateral shoulder flexion and abduction, trunk rotation and lateral flexion, cough and profound inspiration. Indeed, upper limbs' mobilization causes longitudinal shear, whereas cough and deep inspiration put the sternum through lateral and transverse shear (8, 12). Those three distraction forces, particularly lateral shear, are responsible for sternal split (2). The SIS grading ranges from 0 to 4, ranging from no detectable motion to complete instability with up to >1 ½ finger space (11).

The baseline clinical and procedural characteristics were obtained by reviewing the hospital electronic database. Once SPA was considered, its characterization was performed by computed tomography (CT) imaging to delineate the extent of the malunion and the presence or absence of bone bridges.

TABLE 1 | Patient's characteristics.

Patients	Gender	Age (years)	Time from operation to cementoplasty (months)	Obesity (> 30 kg/m²)	Diabetes	COPD	Smoking (pack-years)
#1	M	77	11	−	−	−	Never
#2	F	74	33	−	−	−	Former, 60 p-y
#3	M	67	60	+	+	−	Former, 50 p-y
#4	F	69	30	+	+	+	Former, 45 p-y
#5	F	78	23	+	+	−	Current, 100 p-y

+, present; −, absent.

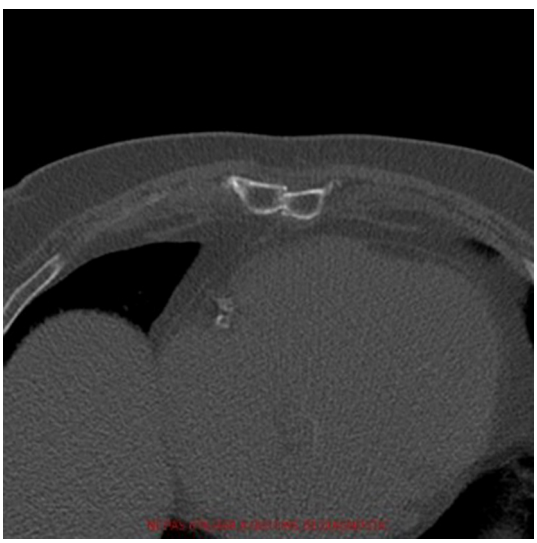

FIGURE 1 | Pre-operative axial computed-tomography image of patient 1. The diagnosis of pseudarthrosis is clear as we can't see any bone bridges between the two halves.

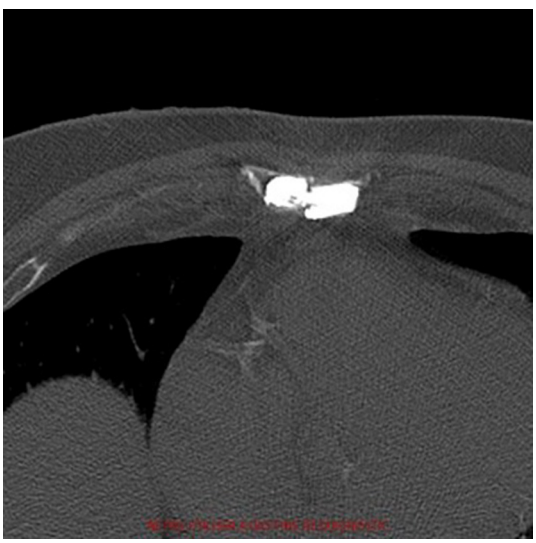

FIGURE 2 | Post-operative axial computed-tomography image of patient 1. The radiopaque cement fills the pseudathrosic parts of the sternum to reduce the pain and a bridge is created for a better stabilization.

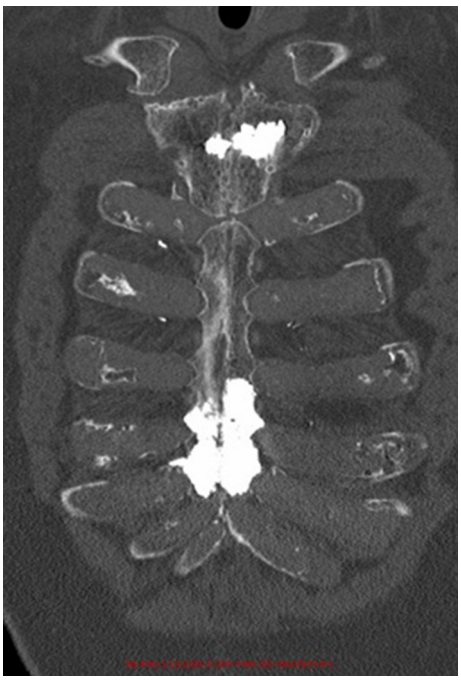

FIGURE 3 | Post-operative coronal computed-tomography image of patient 1.

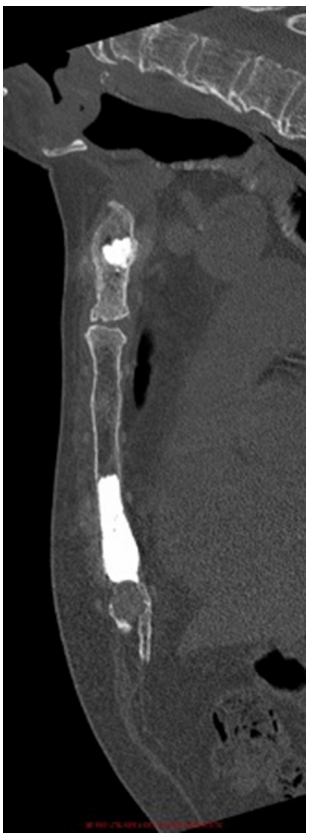

FIGURE 4 | Post-operative sagittal computed-tomography image of patient 1.

Cementoplasty Technique

After performing local anesthesia with lidocaine, the procedure is executed under sedation-analgesia with morphium, midazolam and intravenous paracetamol. Antibiotic prophylaxis is made with 1.5 g intravenous cefuroxime. The intervention is achieved under CT-scan imaging to verify the correct placement of the needles and the spreading of cement. All CT-guided injections are performed with one 64-channel multidetector CT scanner (Somatom Definition AS; Siemens Healthineers, Erlangen, Germany). A monoplanar CT scout view was obtained in the lateral projection (tube current: 60 mAs, peak voltage: 120 kVp), followed by a spiral CT scan (tube current: 50 mAs, peak voltage: 100 kVp), as preparation for the injection. The pre-injection CT images is limited to the sternal segments of interest to minimize the radiation exposure. The needle puncture site on the skin is selected on the initial spiral CT scan sections.

Spinal Confidence™ combines a highly viscous cement with a hydraulic distribution system. The ultra-viscous radiopaque cement CONFIDENCE™ (DePuy Synthes, Johnson&Johnson) reaches a pasty phase immediately after the cement components have been mixed, thus limiting the risk of intravascular embolization. The amount of cement spread is let at the discretion of the in-charge radiologist. Bedrest is then taken for 4 h to allow the cement to consolidate.

Follow-Up

As the intervention is made under CT-scan and the cement is almost stiff when the procedure ends, there is no need for a radiological follow-up unless the patient presents new symptoms. One month after the cementoplasty, a clinical appointment is scheduled during which the patient fills the QBPD scale and VAS and some exercises from the sternal instability scale are performed.

RESULTS

Patient Demographics

Three women and two men (age 72 ± 4yo; range: 67–77) suffering from non-infected SPA were treated by percutaneous cementoplasty (**Table 1**). Three of them had a metabolic syndrome with obesity (BMI >30 kg/m^2), type-2 diabetes mellitus and dyslipidaemia. One patient suffered from chronic obstructive pulmonary disease (COPD). Four patients were smokers (64 ± 25 pack-years; range: 45–100). All patients underwent coronary artery bypass surgery with left internal mammary artery grafting and three had bilateral internal mammary artery grafting. Two patients suffered from sternal infection after CABG surgery and one patient had a redo operation. SPA was localized in three patients (manubrium $n = 1$; body $n = 2$) and generalized in two.

Cementoplasty Procedures

The procedure time was 27 ± 12 minutes. The radiation exposure was 0.13 ± 0.04 mGy. During the procedure, 3 ± 3 mL of cement were injected. **Figures 1–4** depict example of pre- and postinterventional CT findings.

TABLE 2 | Patients' scores from the Quebec back pain disability scale before and after the intervention.

Patients	QBPD scores before cementoplasty	QBPD scores after cementoplasty	Sites of injection (Manubrium (M) and/or body (B))
1	64	46	M + B
2	5	1	B
3	56	33	M
4	68	40	B
5	81	30	M + B

No immediate or short-term complication happened. The intra- and post-operative images show no major leak of the cement, no embolism and no damage to the internal mammary artery or the heart.

Clinical Follow-Up

At one-month follow-up, no patients presented evidence of complications or neurological sensorimotor disorder. Every patient described an improvement in their daily activities and quality of life. The Quebec back pain disability scale score (**Table 2**) improved from 54.8 ± 29.3 to 30.0 ± 17.4 ($p = 0.03$) and concerning the visual analog pain scale, we noted an improvement from 7.0 ± 2.8 to 1.6 ± 1.6 ($p = 0.01$). Furthermore, three out of five patients completely stopped taking painkillers whereas two additional significantly decreased the dose.

DISCUSSION

Percutaneous cementoplasty was developed for vertebroplasty in 1984 as a treatment for vertebral hemangioma. Its indication has been extended to vertebral fracture due to its capability to tolerate compressive pressures. Here, we report for the first time the possibility of using percutaneous cementoplasty to treat SPA. We demonstrate the feasibility, the safety and the efficacy of this novel and minimally invasive alternative technique to surgery. We are convinced that percutaneous cementoplasty can be used in all type of SPA regardless of its cause.

Postoperative sternal wound infection is found in 0.5–8.4% of cases (13) and could lead to SPA. The classical risk factors for SPA are smoking, metabolic syndrome and COPD (6). In addition to increasing the odds of sternal dehiscence by 3.9 times, obesity seems to be the most critical risk factor for postoperative sternal infection (9). Moreover, Seyfer et al. noted that bilateral mammary artery grafting is at greater risk since every mammary artery harvesting is associated with a 90% drop of the ipsilateral sternal blood flow (14). Therefore, smoking, metabolic syndrome, obesity, COPD and bilateral mammary artery grafting are associated with SPA (1, 15). To limit the incidence of SPA, the modifiable components of these risk factors should be tightly controlled, and the use of steroids and non-steroidal anti-inflammatory drugs minimized during the few weeks before CABG (5). Considering that the separation of the sternal edges usually begins in the caudal third due to the concentration of distraction forces and low blood supply, adding wires at the lower end is an efficient way to lower its incidence (2, 4, 9).

When SPA occurs, a careful physical examination is mandatory during the first year since a large part of non-infectious SPA will resolve spontaneously over time. If not, a CT scan of the sternum should be done. In these patients, surgical closure or percutaneous cementoplasty will be discussed on a case-by-case basis with the in-charge surgeon. In the case of a poor surgical candidate, percutaneous cementoplasty appears to be associated with encouraging preliminary results.

Limitations

The present study is limited in size with possible selection bias. Given the uncertainty around point estimations, extrapolations should be drawn with caution. The fact that it was performed in a single center with cementoplasty performed by a single experienced operator with uniform procedural strategies makes generalizations to other centers limited.

CONCLUSION

SPA is a debilitating affliction that may complicate sternotomy after cardiac surgery. Percutaneous cementoplasty constitutes a promising technique in selected cases.

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by La Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD). The patients/participants provided their written informed consent to participate in this study. All patients gave their written informed consent to the procedure and the work has been performed under the general approval by the Local Ethics Committee (FR-339-14).

AUTHOR CONTRIBUTIONS

TP: collected the informations in patients' files, interviewed NT, and wrote the article. SC: patients' cardiologist, direct supervisor of TP, and corrected the temporary versions of the article. GK: performed the CABG and corrected the final version of the article. NT: performed the percutaneous cementoplasty and corrected the final version of the article. All authors contributed to the article and approved the submitted version.

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Blood Urea Nitrogen-to-Albumin Ratio in Predicting Long-Term Mortality in Patients Following Coronary Artery Bypass Grafting: An Analysis of the MIMIC-III Database

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Background: This study examined the role of blood urea nitrogen-to-albumin ratio (BAR) in predicting long-term mortality in patients undergoing coronary artery bypass grafting (CABG).

Methods: In this retrospective cohort study, patients undergoing CABG were enrolled from the Medical Information Mart for Intensive Care III (MIMIC III) database. Patients were divided into the three groups according to the optimal cutoff values of BAR determined by X-tile software. The survival curve was constructed by the Kaplan–Meier method and multivariate Cox regression analysis was performed to explore the independent prognostic factors of 1- and 4-year mortality after CABG. The receiver operating characteristic (ROC) curves and the areas under the ROC curves (AUCs) were calculated to estimate the accuracy of BAR in predicting the outcomes. Subgroup analyses were also carried out.

Results: A total of 1,462 patients at 4-year follow-up were included, of which 933, 293, and 236 patients were categorized into the group 1 (≤6.45 mg/g), group 2 (>6.45 and ≤10.23 mg/g), and group 3 (>10.23 mg/g), respectively. Non-survivors showed an increased level of BAR at both 1- ($p < 0.001$) and 4-year ($p < 0.001$) follow-up compared with the survivors. The patients with a higher BAR had a higher risk of 1- and 4-year mortality following CABG (33.05 vs. 14.33 vs. 5.14%, $p < 0.001$ and 52.97 vs. 30.72 vs. 13.08%, $p < 0.001$, respectively). Cox proportional hazards regression model suggested a higher BAR as an independent risk factor of 1-year mortality (HR 3.904; 95% CI 2.559–5.956; $P < 0.001$) and 4-year mortality (HR 2.895; 95% CI 2.138–3.921; $P < 0.001$) after adjusting for confounders. Besides, the receiver operating characteristic (ROC) curves showed the better predictive ability of BAR compared to other grading scores at both 1- (0.7383, 95% CI: 0.6966–0.7800) and 4-year mortality (0.7189, 95% CI: 0.6872–0.7506). Subgroup analysis demonstrated no heterogeneous results of BAR in 4-year mortality in particular groups of patient.

Conclusion: This report provided evidence of an independent association between 1- and 4-year mortality after CABG and BAR. A higher BAR was associated with a higher risk of long-term mortality and could serve as a prognostic predictor in patients following CABG.

Keywords: coronary artery bypass grafting, blood urea nitrogen, albumin, mortality, MIMIC III database

INTRODUCTION

Coronary artery bypass grafting (CABG) has long been recognized as the most effective myocardial revascularization procedure for patients with advanced coronary artery disease (CAD) (1). This procedure has been performed for more than 40 years to alleviate symptoms and reduce the risk of death in ischemic heart disease (2). While a substantial reported literature on risk assessment following CABG has mainly focused on short- and midterm mortality, few studies have examined predictive indicators for long-term postoperative mortality (3, 4).

Blood urea nitrogen (BUN) is an interesting biomarker that reflects the glomerular filtration rate (GFR) and correlates with postoperative prognosis after cardiac surgery including CABG (4–7). Serum albumin is well-documented for its multiple

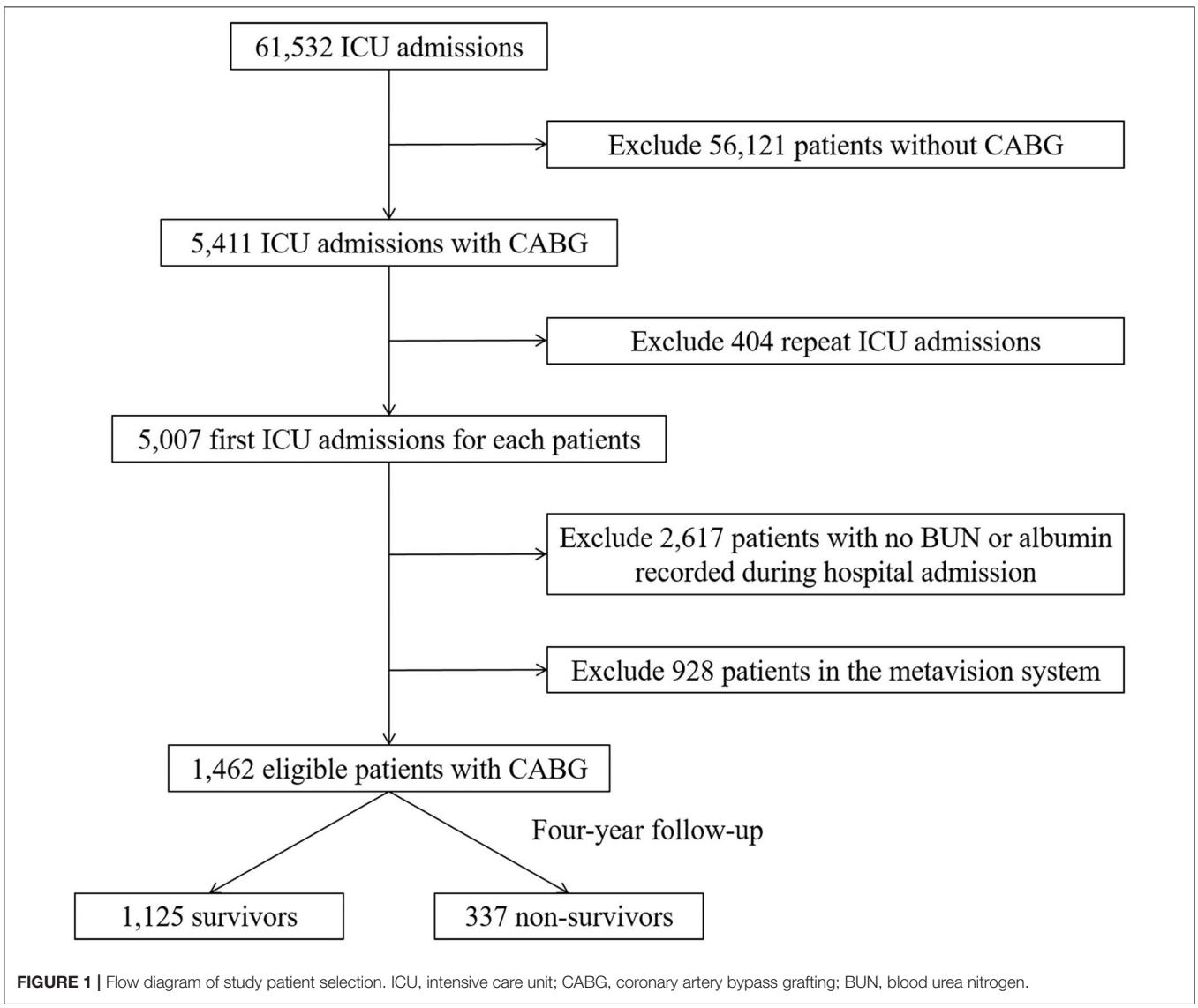

FIGURE 1 | Flow diagram of study patient selection. ICU, intensive care unit; CABG, coronary artery bypass grafting; BUN, blood urea nitrogen.

TABLE 1 | Patient characteristics of survivors and non-survivors at 4-year follow-up.

Characteristics	Survivors (n = 1,125)	Non-survivors (n = 337)	p
Age (years)	69.18 (60.47, 77.10)	76.92 (69.03, 82.65)	<0.001
Male, *n* (%)	808 (71.82%)	212 (62.91%)	0.002
Body mass index (kg/m^2)	27.66 (25.07, 31.39)	27.02 (23.38, 30.97)	0.001
Vital signs			
Heart Rate (beats/minute)	84.95 (78.86, 90.93)	84.95 (78.01, 89.81)	0.664
SBP (mmHg)	112.14 (106.02, 119.36)	112.15 (105.59, 121.29)	0.592
DBP (mmHg)	56.56 (52.98, 61.32)	54.75 (50.41, 59.81)	<0.001
Respiratory Rate (beats/minute)	16.84 (15.20, 19.12)	16.81 (14.86, 19.12)	0.599
SpO_2 (%)	98.20 (97.23, 98.97)	98.16 (97.18, 99.01)	0.776
Comorbidities, *n* (%)			
Hypertension	725 (64.44%)	149 (44.21%)	<0.001
Chronic pulmonary disease	141(12.53%)	61 (18.10%)	0.009
Diabetes	420 (37.33%)	139 (41.25%)	0.195
Hyperlipidemia	597 (53.07%)	117 (34.72%)	<0.001
Cerebrovascular disease	73 (6.49%)	29 (8.61%)	0.181
Chronic kidney disease	57 (5.07%)	38 (11.28%)	<0.001
Atrial fibrillation	451 (40.09%)	180 (53.41%)	<0.001
Laboratory parameters			
BUN (mg/dL)	18.00 (14.00, 24.00)	26.00 (17.00, 38.00)	<0.001
Albumin (g/dL)	3.70 (3.20, 4.00)	3.40 (2.90, 3.70)	<0.001
White blood cell (K/μL)	8.50 (6.80, 11.10)	9.30 (7.10, 12.35)	0.006
Hematocrit (%)	36.40 (32.50, 40.10)	33.70 (30.45, 37.20)	<0.001
Hemoglobin (g/dL)	12.60 (11.30, 14.00)	11.40 (10.40, 12.70)	<0.001
Platelet (K/uL)	213.00 (171.00, 260.00)	210.00 (167.00, 263.50)	0.666
Glucose (mg/dL)	121.00 (100.00, 156.00)	124.00 (103.00, 167.00)	0.188
Creatinine (mg/dL)	1.00 (0.80, 1.20)	1.20 (0.90, 1.70)	<0.001
Sodium (mmol/L)	139.00 (137.00, 141.00)	139.00 (136.00, 141.00)	0.043
Potassium (mmol/L)	4.10 (3.80, 4.40)	4.20 (3.90, 4.60)	0.001
Bicarbonate (mmol/L)	4.20 (3.90, 4.50)	4.20 (3.90, 4.60)	0.031
Scoring systems			
SOFA scores	4.00 (3.00, 6.00)	6.00 (3.00, 8.00)	<0.001
APS III scores	34.00 (27.00, 43.00)	44.00 (34.00, 57.00)	<0.001
SIRS scores	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.794
Vasoactive use, *n* (%)	462 (41.07%)	125 (37.09%)	0.192
BAR (mg/g)	5.00 (3.85, 6.79)	7.80 (5.31, 12.83)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; SOFA, sequential organ failure assessment; APS III, Acute Physiology Score III; SIRS, systemic inflammatory response syndrome; BAR, blood urea nitrogen-to-albumin ratio.

physiological effects and is widely used during and after cardiac surgery (8). Low-perioperative serum albumin level in patients undergoing cardiac surgery is associated with the increased risk of mortality following surgery and greater incidence of postoperative morbidity, even in the long-term scenario (8–11).

Although both BUN and albumin have been individually applied as predictors of prognosis following cardiac surgery (5, 12, 13), the literature does not contain data investigating the relationship between BAR and long-term mortality after CABG. This retrospective cohort study aimed to explore the role of BAR in predicting long-term mortality in patients following CABG by an analysis of the MIMIC-III database.

MATERIALS AND METHODS

Database Source and Study Population

This retrospective cohort study analyzed the data extracted from the Medical Information Mart for Intensive Care III (MIMIC III) database. This large, publicly available critical care database includes >60,000 patients admitted to the Beth Israel Deaconess Medical Center (BIDMC) from 2001 to 2012 (14). An online training course, Data or Specimens Only Research, was completed by authors to obtain the certification (Record ID: 36309330) for getting access to the database.

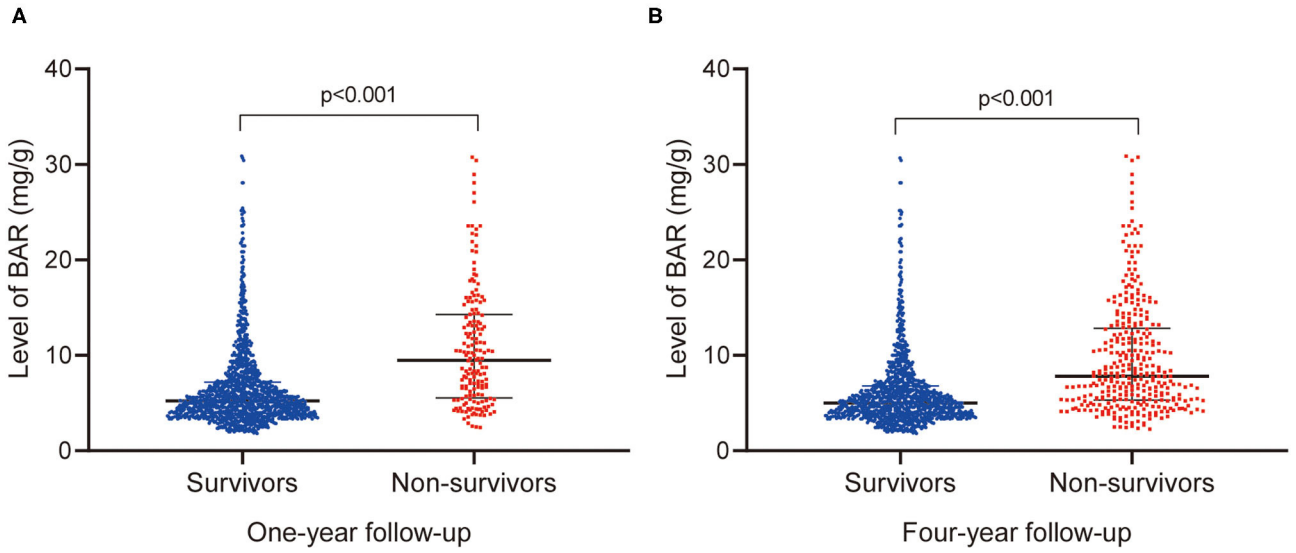

FIGURE 2 | Comparison of BAR levels between survivors and nonsurvivors at 1- **(A)** and 4-year **(B)** follow-up. BAR, blood urea nitrogen-to-albumin ratio.

A total of 5,411 patients from MIMIC-III database were included who underwent CABG according to ICD-9 code. The exclusion criteria were as follows: (1) patients with more than one ICU admissions ($n = 404$); (2) either BUN or albumin values were absent at admission ($n = 2{,}617$); (3) patients in the metavision system ($n = 928$). Finally, a total of 1,462 patients who were followed for at least 4-year were included in the study population.

Data Extraction

The Structure Query Language (SQL) with PostgreSQL (version 9.6) was applied for extracting relevant data from MIMIC-III database including: (1) demographics: age, gender, height, weight; (2) vital signs: heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, temperature and SpO_2; (3) comorbidities: hypertension, chronic pulmonary disease, diabetes, hyperlipidemia, cerebrovascular disease, chronic liver disease, chronic kidney disease (CKD) and atrial fibrillation (AF); (4) laboratory parameters: BUN, albumin, white blood cell (WBC), hemoglobin, hematocrit, platelet, glucose, creatinine, sodium, potassium and bicarbonate; (5) scoring systems: sequential organ failure assessment (SOFA), acute physiology score III (APS III) and systemic inflammatory response syndrome (SIRS); (6) vasoactive medications: dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, vasopressin. The laboratory parameters from the first laboratory results were used for analysis. The BAR was calculated by dividing the BUN by the albumin. Postoperative 4-year all-cause mortality was the primary endpoint and 1-year mortality was the secondary endpoint.

Statistical Analysis

In this study, the optimal cutoff values of BAR for 4-year all-cause mortality were selected with the help of X-tile (version 3.6.1, Yale University School of Medicine, New Haven, Connecticut, USA) software. The Shapiro–Wilk tests were employed for assessing the distribution of variables. Continuous variables were presented as mean ± SD or median and interquartile range (IQR). Categorical variables were presented as numbers and percentages. An ANOVA test or Kruskal–Wallis H-test and the chi-squared test or Fisher's exact test were used to test any significant differences as appropriate. The Kaplan–Meier method with log-rank tests was applied to describe the difference of survival. The univariate and multivariate Cox proportional hazard models were employed for the univariate and multivariate analyses. Variables with a $p < 0.1$ in the univariate model were selected into the multivariable model and the results were presented as hazard ratios (HRs) with 95% CIs. The ROC curves were constructed to evaluate the prognostic efficiency. Subgroup analysis was performed to further verify the role of BAR on the endpoints in subsets of participants using a stratified Cox proportional-hazards regression model. All the statistical analyses were performed using STATA V.14.0, RStudio software (version 1.2.5001), GraphPad Prism 8, and SPSS Statistics 25 (IBM Incorporation, Chicago, Illinois, USA). A two-sided $p < 0.05$ was considered as statistically significant.

RESULTS

Patient Characteristics

Initially, 61,532 intensive care unit (ICU) admissions were extracted from MIMIC III database. According to the ICD-9 code, 5,007 patients who underwent CABG with first ICU admission were screened. After excluding the patients with either missing BUN or albumin values ($n = 2{,}617$) and data from the metavision system ($n = 928$), 1,462 eligible patients were finally enrolled for analysis and categorized into a survived group ($n = 1{,}125$) and the non-survived group ($n = 337$) after 4-year

follow-up. Flow diagram of exclusion and enrollment of study patients is given in **Figure 1**.

The patient characteristics of survivors and non-survivors stratified on 4-year mortality were depicted in **Table 1**. Non-survivors are older compared to survivors ($p < 0.001$). Besides, a higher proportion of chronic pulmonary disease ($p = 0.009$), CKD ($p < 0.001$), AF ($p < 0.001$) and also a higher level of BUN ($p < 0.001$), WBC ($p = 0.006$), creatinine ($p < 0.001$), potassium ($p = 0.001$), SOFA scores ($p < 0.001$), and APS III scores ($p < 0.001$), was observed among non-survivors. The patient characteristics were grouped on 1-year mortality in **Supplementary Table 1**. Of note, the non-survivors presented an increased level of BAR at both 1-year ($p < 0.001$) and 4-year ($p < 0.001$) follow-up compared with survivors (**Figure 2**).

Association Between BAR and 1- and 4-Year Mortality After CABG

All the patients were divided into the three groups as group 1 (BAR $\leq$ 6.45 mg/g, $n = 933$), group 2 (6.45 $<$ BAR $\leq$ 10.23

TABLE 2 | Clinical characteristics of patients classified by BAR.

Characteristics	BAR levels (mg/g)			*p*
	Group 1: ≤ 6.45 (*n* = 933)	Group 2: > 6.45, ≤ 10.23 (*n* = 293)	Group 3: > 10.23 (*n* = 236)	
Age (years)	69.13 (60.09, 77.16)	74.66 (66.16, 80.98)	73.80 (64.91, 80.38)	<0.001
Male, *n* (%)	675 (72.35%)	192 (65.53%)	153 (64.83%)	0.017
Body mass index (kg/m^2)	27.66 (24.87, 31.04)	27.70 (24.63, 31.47)	27.66 (24.54, 32.28)	0.590
Vital signs				
Heart Rate (beats/minute)	85.09 (78.94, 91.27)	84.33 (78.73, 89.27)	84.82 (77.33, 90.83)	0.291
SBP (mmHg)	111.92 (105.98, 119.08)	112.93 (105.88, 121.60)	112.14 (105.68, 119.75)	0.328
DBP (mmHg)	56.92 (52.97, 61.57)	55.58 (52.24, 60.43)	54.13 (50.54, 59.22)	<0.001
Respiratory Rate (beats/minute)	16.83 (15.17, 19.06)	17.16 (15.40, 19.44)	16.68 (14.37, 19.02)	0.046
SpO_2 (%)	98.20 (97.23, 98.98)	98.20 (97.13, 98.92)	98.20 (97.18, 99.11)	0.797
Comorbidities, *n* (%)				
Hypertension	638 (68.38%)	164 (55.97%)	72 (30.51%)	<0.001
Chronic pulmonary disease	127 (13.61%)	42 (14.33%)	33 (13.98%)	0.949
Diabetes	300 (32.15%)	124 (42.32%)	135 (57.20%)	<0.001
Hyperlipidemia	514 (55.09%)	126 (43.00%)	74 (31.36%)	<0.001
Cerebrovascular disease	59 (6.32%)	22 (7.51%)	21 (8.90%)	0.353
Chronic kidney disease	15 (1.61%)	32 (10.92%)	48 (20.34%)	<0.001
Atrial fibrillation	374 (40.09%)	142 (48.46%)	115 (48.73%)	0.007
Laboratory parameters				
BUN (mmol/L)	16.00 (13.00, 19.00)	26.00 (23.00, 29.00)	43.00 (35.00, 57.00)	<0.001
Albumin (g/dL)	3.80 (3.40, 4.00)	3.40 (2.95, 3.75)	3.10 (2.50, 3.50)	<0.001
White blood cell (K/μL)	8.40 (6.80, 10.90)	8.80 (6.95, 11.75)	9.40 (7.20, 13.18)	<0.001
Hematocrit (%)	37.10 (33.45, 40.60)	34.10 (31.20, 37.40)	32.40 (29.13, 36.08)	<0.001
Hemoglobin (g/dL)	13.00 (11.60, 14.15)	11.70 (10.70, 12.90)	11.00 (9.90, 12.18)	<0.001
Platelet (K/uL)	216.00 (174.00, 260.00)	204.00 (162.00, 257.00)	208.50 (168.50, 270.50)	0.228
Glucose (mg/dL)	119.00 (99.00, 150.00)	125.00 (105.00, 171.00)	133.00 (103.00, 195.75)	<0.001
Creatinine (mg/dL)	0.90 (0.80, 1.10)	1.20 (1.00, 1.45)	1.90 (1.40, 3.00)	<0.001
Sodium (mmol/L)	139.00 (137.00, 141.00)	139.00 (137.00, 141.00)	138.00 (136.00, 140.00)	<0.001
Potassium (mmol/L)	4.10 (3.80, 4.30)	4.10 (3.90, 4.50)	4.40 (4.00, 4.90)	<0.001
Bicarbonate (mmol/L)	4.10 (3.90, 4.40)	4.20 (3.90, 4.55)	4.40 (3.90, 4.80)	<0.001
Scoring systems				
SOFA scores	4.00 (3.00, 6.00)	5.00 (3.00, 7.00)	6.00 (4.00, 8.00)	<0.001
APS III scores	33.00 (25.00, 40.00)	40.00 (33.00, 47.50)	51.00 (41.00, 59.00)	<0.001
SIRS scores	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.828
Vasoactive use, *n* (%)	388 (41.59%)	117 (39.93%)	82 (34.75%)	0.159
Clinical outcomes, *n* (%)				
1-year mortality	48 (5.14%)	42 (14.33%)	78 (33.05%)	<0.001
4-year mortality	122 (13.08%)	90 (30.72%)	125 (52.97%)	<0.001

BAR, blood urea nitrogen-to-albumin ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; SOFA, sequential organ failure assessment; APS III, Acute Physiology Score III; SIRS, systemic inflammatory response syndrome.

mg/g, $n = 293$), and group 3 (BAR > 10.23 mg/g, $n = 236$) according to the cutoff values determined by the X-tile software. The patient characteristics among different groups are given in **Table 2**. A higher proportion of diabetes, CKD, and AF, along with higher levels of BUN, WBC, glucose, creatinine, potassium, bicarbonate, the SOFA scores, and APS III scores was noticed in group 3. At 1-year follow-up, the mortality in the group 3 was significantly higher compared to the other two groups (33.05 vs. 14.33 vs. 5.14%, $p < 0.001$) (**Figure 3A**). The result was similar at 4-year follow-up (52.97 vs. 30.72 vs. 13.08%, $p < 0.001$) (**Figure 3A**). The association between BAR values and postoperative survival was shown with the Kaplan–Meier curves in **Figure 3B**, indicating that a higher BAR was related to an increased risk of postoperative mortality after CABG ($p < 0.001$).

The Cox proportional hazards regression model was applied to determine the potential independent association between BAR and 1- and 4-year mortality following CABG (**Supplementary Table 2** and **Table 3**). In the univariate model, the risk of 1- and 4-year mortality was higher in the patients with a higher BAR (p for trend <0.001 and <0.001, respectively). In the multivariate model, the values of BAR remained independently correlated with the risk of 4-year mortality (p for trend < 0.001). A consistent result was obtained between BAR and 1-year mortality (p for trend < 0.001).

Prognostic Efficiency of BAR in 1- and 4-Year Mortality After CABG

Furthermore, the prognostic efficiency of BAR and other grading scores (SOFA score, APS III score, and SIRS score) predicting long-term outcomes were compared using ROC curves. For 1-year mortality, the AUC was 0.7383 (95% CI: 0.6966–0.7800) for BAR, 0.6258 (95% CI: 0.5764–0.6751) for SOFA score, 0.6820 (95% CI: 0.6387–0.7253) for APS III score, and 0.5029 (95% CI: 0.4567–0.5490) for SIRS score (**Figure 4A**). For 4-year mortality, the AUC was 0.7189 (95% CI: 0.6872–0.7506) for BAR, 0.6166 (95% CI: 0.5807–0.6525) for SOFA score, 0.6624 (95% CI: 0.6291–0.6956) for APS III score, and 0.5044 (95% CI: 0.4691–0.5397) for SIRS score, suggesting a better predictive ability of BAR in long-term mortality after CABG (**Figure 4B**). By incorporating the variables screened out by the multivariate Cox regression, model 1 and model 2 were constructed to predict 1- and 4-year mortality and the ROC curves were constructed to evaluate the prognostic efficiency of BAR and two models. As shown in **Figure 5A**, the AUC of model 1 for 1-year mortality was 0.7983 (95% CI: 0.7643–0.8323). The AUC of the 4-year mortality of patients with CABG predicted by model 2 was 0.7770 (95% CI: 0.7495–0.8045) (**Figure 5B**). Besides, the AUCs (95% CIs) of the BAR and model 2 were stable over time (**Figure 5C**), and the discrimination of outcome was higher for model 2 than for BAR.

Subgroup Analysis of BAR and 4-Year Mortality After CABG

As shown in **Table 4**, subgroup analysis was carried out to investigate the heterogeneous results of BAR in 4-year mortality in the particular patient groups. The test for interactions were not statistically significant for age, sex, vasoactive medication, and most comorbidities, including hypertension, chronic pulmonary disease, diabetes, hyperlipidemia, CKD, AF (p for interaction = 0.746, 0.108, 0.862, 0.902, 0.557, 0.111, 0.052, 0.351, and 0.316).

DISCUSSION

This study for the first time showed that BAR is independently associated with long-term mortality following CABG. Currently, there is no consensus widely accepted regarding a standardized evaluation tool for predicting long-term mortality following coronary revascularization. Establishing a prognostic model including demographical and clinical parameters to predict

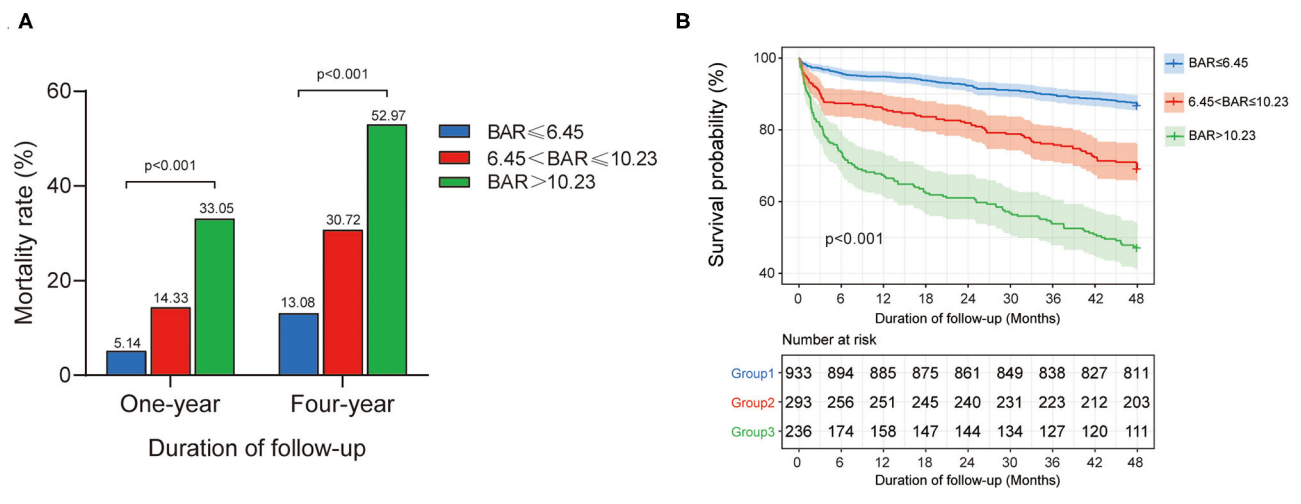

FIGURE 3 | Relationship between BAR and all-cause mortality in patients after CABG: **(A)** the mortality rate in each endpoint according to BAR levels, **(B)** The Kaplan–Meier survival curve of survival probability in patients with different BAR levels. *P*-value was calculated by log-rank test and indicated in the plot. BAR, blood urea nitrogen-to-albumin ratio; CABG, coronary artery bypass grafting.

TABLE 3 | Cox proportional hazard models exploring the association of BAR with 4-year mortality.

Variables	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	***P***	**Hazard ratio (95% CI)**	***P***
Age (years)				
≤65	Reference	–	Reference	–
>65	2.610 (2.055–3.314)	<0.001	1.999 (1.567–2.551)	<0.001
Male	0.698 (0.560–0.871)	0.001	Not selected	–
Body mass index	0.967 (0.946–0.988)	0.002	0.973 (0.952–0.993)	0.010
Vital signs				
Heart Rate	1.001 (0.992–1.011)	0.782	–	–
SBP	1.003 (0.993–1.013)	0.564	–	–
DBP	0.961 (0.946–0.977)	<0.001	Not selected	–
Respiratory Rate	0.991 (0.956–1.027)	0.614	–	–
SPO_2	0.949 (0.872–1.032)	0.221	–	–
Comorbidities				
Hypertension	0.474 (0.382–0.588)	<0.001	0.777 (0.614–0.983)	0.035
Chronic pulmonary disease	1.446 (1.095–1.908)	0.009	1.446 (1.093–1.913)	0.010
Diabetes	1.146 (0.923–1.424)	0.217	–	–
Hyperlipidemia	0.504 (0.403–0.631)	<0.001	0.771 (0.607–0.980)	0.034
Cerebrovascular disease	1.329 (0.908–1.945)	0.143	–	–
Chronic kidney disease	2.062 (1.471–2.890)	<0.001	Not selected	–
Atrial fibrillation	1.596 (1.288–1.977)	<0.001	Not selected	–
Laboratory parameters				
BUN	1.035 (1.029–1.040)	<0.001	Not selected	–
Albumin	0.478 (0.407–0.561)	<0.001	0.792 (0.658–0.954)	0.014
White blood cell	1.042 (1.019–1.065)	<0.001	Not selected	–
Hematocrit	0.944 (0.27–0.961)	<0.001	1.049 (1.008–1.092)	0.020
Hemoglobin	0.794 (0.752–0.838)	<0.001	0.809 (0.721–0.909)	<0.001
Platelet	1.000 (0.998–1.001)	0.773	–	–
Glucose	1.002 (1.000–1.004)	0.058	Not selected	–
Creatinine	1.412 (1.317–1.513)	<0.001	Not selected	–
Sodium	0.953 (0.921–0.986)	0.005	Not selected	–
Potassium	1.389 (1.167–1.654)	<0.001	Not selected	–
Bicarbonate	1.345 (1.122–1.613)	0.001	Not selected	–
Scoring systems				
SOFA scores	1.151 (1.110–1.194)	<0.001	Not selected	–
APS III scores	1.021 (1.016–1.026)	<0.001	1.010 (1.004–1.016)	0.001
SIRS scores	1.006 (0.901–1.122)	0.918	–	–
Vasoactive use	0.868 (0.696–1.083)	0.210	–	–
BAR				
Group 1: ≤ 6.45	Reference	–	Reference	–
Group 2: > 6.45, ≤ 10.23	2.617 (1.993–3.437)	<0.001	1.796 (1.349–2.392)	<0.001
Group 3: > 10.23	5.527 (4.303–7.098)	<0.001	2.895 (2.138–3.921)	<0.001
P for trend		<0.001		<0.001

BAR, blood urea nitrogen-to-albumin ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; SOFA, sequential organ failure assessment; APS III, Acute Physiology Score III; SIRS, systemic inflammatory response syndrome.

the risk of long-term mortality after CABG is of importance in the identification of patients at high-risk and timely therapeutic intervention.

Blood urea nitrogen is a blood parameter and its serum level is influenced by renal functions, neurohormonal, and sympathetic activity. BUN has long been recognized to function as an indicator of both cardiorenal dysfunction and neurohormonal activation (15) and a prognostic predictor of long-term mortality in acute and chronic heart failure (HF) (16, 17). Of note, the recent evidence suggested that serum elevation of BUN predicted a worse outcome in patients with acute MI, acute coronary syndrome, and following

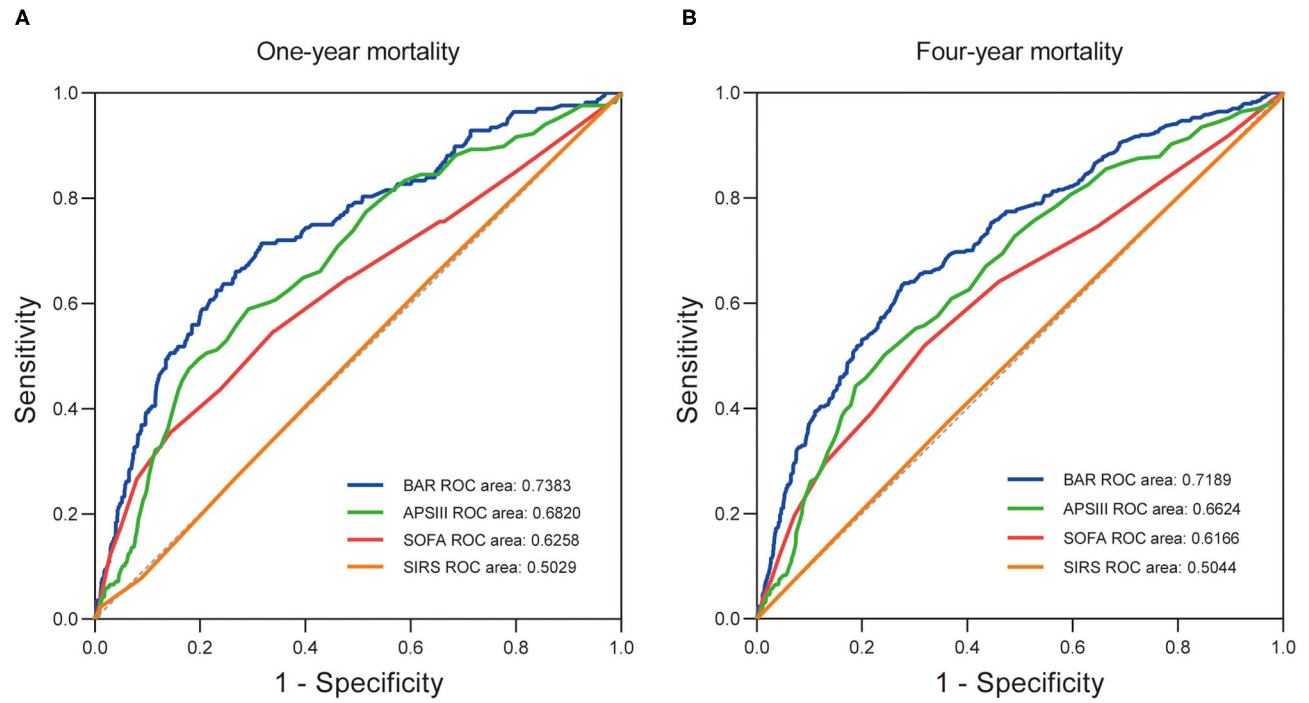

FIGURE 4 | The receiver operating characteristic curves of the predictive value of BAR, APS III, SOFA, and SIRS for 1- **(A)** and 4-year **(B)** all-cause mortality in patients after CABG. BAR, blood urea nitrogen-to-albumin ratio; APS III, acute physiology score III; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; CABG, coronary artery bypass grafting.

elective percutaneous coronary procedures (18–20). Recent work reported that BUN-to-left ventricular ejection fraction (LVEF) ratio independently predicted the incidence of long-term major adverse cardiac events (MACEs) including mortality and new-onset decompensated HF in patients undergoing CABG (21). Arnan and his colleagues identified that postoperative BUN was a marker of stroke risk following cardiac surgical procedures (21). Liu et al. observed that BUN could predict the in-hospital mortality of patients with acute aortic dissection (AAD) (7).

Low albumin levels have been considered as a marker of persistent arterial damage and progression of atherosclerosis and thrombosis (22). In the perioperative period, albumin loss, increased capillary permeability, intravenous infusion dilution, and liver dysfunction might be the primary causes of reduced albumin levels in patients (23). Thus, intravenous administration of human-derived albumin is uniformly used in intensive care units and during cardiac surgery (24, 25). Serum albumin maintains the intravascular volume by contributing to the integrity of the vascular wall as well as plasma oncotic pressure (26, 27). Albumin might exert additional benefits of anti-inflammatory and antioxidant effects (28, 29). However, potential adverse effects of albumin use include anaphylactic reactions, prion disease transmission, and acute kidney injury (AKI) (25, 30). A relevant review by Karas and et al. suggested that low-preoperative serum albumin level in patients undergoing cardiac surgery is associated with increased risk of postoperative mortality and morbidity, even in the long-term scenario (9). Beek and his team found that postoperative albumin levels independently correlated with postoperative myocardial damage (10). Engelman et al. reported that hypoalbuminemia independently predicted an increased rate of complications and mortality after cardiac surgery (31). Similarly, another study found that albumin was associated with mortality and morbidity in isolated CABG recipients (32). Kingeter and his colleagues demonstrated that administration of albumin solution was associated with significantly reduced in-hospital mortality and all-cause 30-day readmission rate compared with administration of crystalloids alone in adult on-pump cardiac surgery.

The BAR, a combination of these two parameters, has been reported as a promising indicator of various disease outcomes (33–35). In our study, we calculated the value of BAR based on the preoperative explored the relationship between BAR and the long-term outcomes of patients with CABG and our results aforementioned were consistent with the previous work. Identification of high-risk patients following CABG plays a major role in the prevention and treatment of CAD. Its benefits in clinical assessment might be guiding the prediction of long-term MACEs after CABG and closer follow-up and more active surgical reintervention. With the aid of risk stratification by BAR and also electrocardiogram, echocardiography, coronary angiography, early identification of patients at high risk and timely treatment might be achieved. Besides, the results of the diagnostic test suggested that BAR has a better predictive ability in long-term mortality after CABG. These results are awaiting further verification by the large-scale prospective studies in multiple ethnicities in the future.

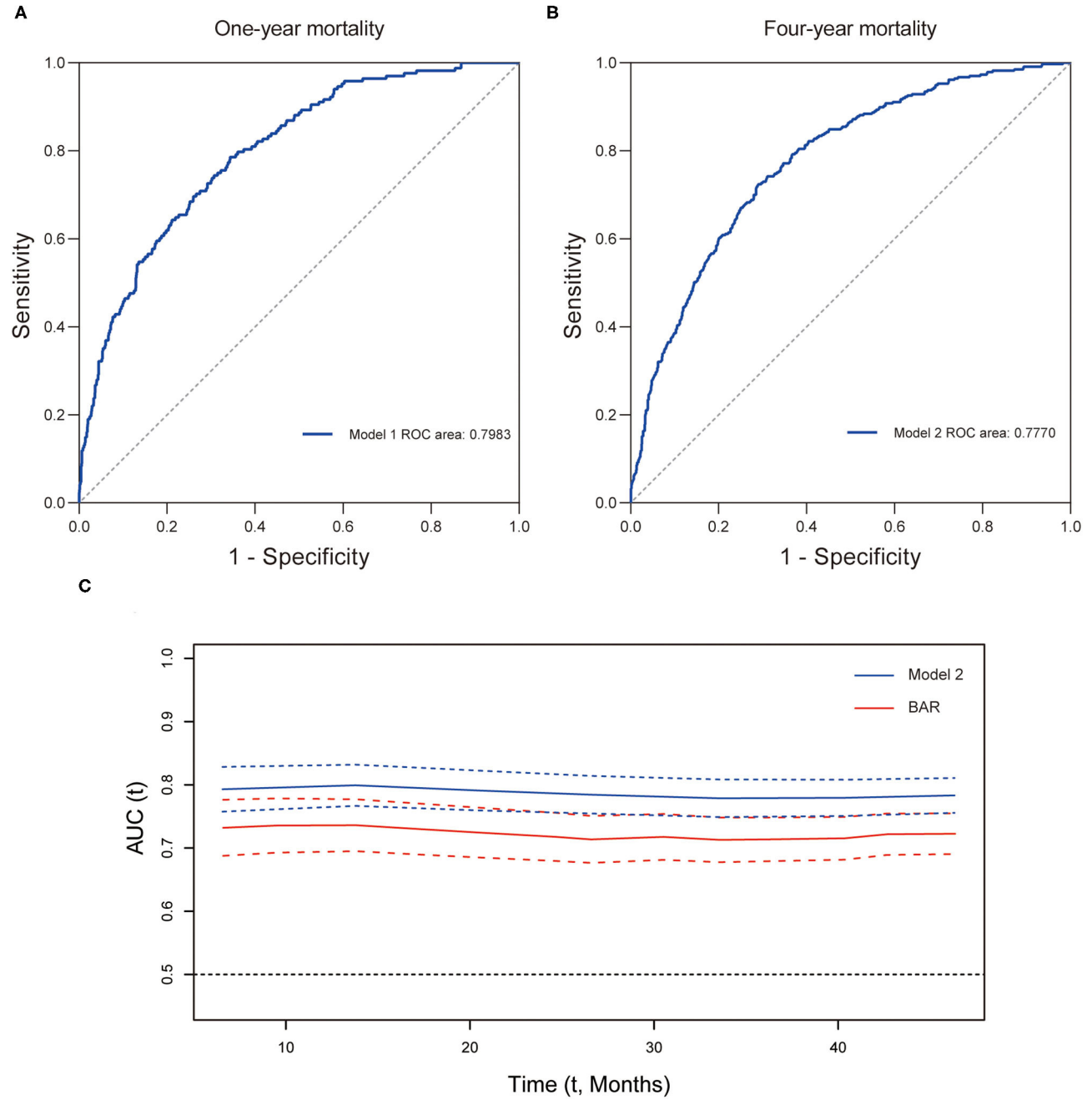

FIGURE 5 | The predictive value of prognostic models for long-term mortality in CABG patients. ROC curve for 1- **(A)** and 4-year **(B)** mortality. **(C)** Time-AUC curves of model 2 and BAR. CABG, coronary artery bypass grafting; ROC, receiver operating characteristic curve; AUC, area under the ROC curve; BAR, blood urea nitrogen-to-albumin ratio.

Limitations

There were several limitations that should be highlighted to interpret the results. First, this was a single-center retrospective study based on the MIMIC III public database, and potential selection bias was inevitable. Further studies with large, multicentered, prospective design was necessary to confirm our conclusions. Second, excluding patients with missing values of BUN and albumin might lead to sample selection bias. Third, due to the limited contents of MIMIC III database, some potential risk factors are missing, leading to a certain bias. Fourth, the linearity and proportional hazard assumption for predictor might not be satisfactory in real data, suggesting that the predictive value of BAR needs to be verified by further studies. In addition, machine learning algorithms, which have been widely utilized in the surgical literature, could help address this problem (36, 37). At last, only the results of BUN and albumin for the first time

TABLE 4 | Subgroup analysis of the relationship between BAR and 4-year mortality.

Characteristics	No. of patients	BAR levels (mg/g)			P for trend	P for interaction
		≤6.45 HR (95% CI)	>6.45, ≤ 10.23 HR (95%CI)	> 10.23 HR (95% CI)		
Age (years)						0.746
≤65	689	1 (ref)	1.682 (0.956–2.959)	2.095 (1.162–3.777)	0.013	
>65	773	1 (ref)	1.828 (1.306–2.560)	3.219 (2.243–4.618)	<0.001	
Gender						0.108
Female	442	1 (ref)	1.925 (1.215–3.051)	2.609 (1.545–4.406)	<0.001	
Male	1,020	1 (ref)	1.680 (1.163–2.425)	2.986 (2.045–4.359)	<0.001	
Hypertension						0.902
Yes	874	1 (ref)	1.556 (1.045–2.316)	2.575 (1.598–4.147)	<0.001	
No	588	1 (ref)	2.108 (1.380–3.220)	3.306 (2.178–5.018)	<0.001	
Chronic pulmonary disease						0.557
Yes	202	1 (ref)	1.341 (0.659–2.731)	1.954 (0.926–4.120)	0.078	
No	1,260	1 (ref)	1.902 (1.382–2.616)	3.231 (2.306–4.527)	<0.001	
Diabetes						0.111
Yes	599	1 (ref)	2.700 (1.625–4.487)	4.265 (2.570–7.075)	<0.001	
No	903	1 (ref)	1.457 (1.016–2.090)	2.334 (1.539–3.541)	<0.001	
Hyperlipidemia						0.052
Yes	714	1 (ref)	2.043 (1.285–3.247)	3.779 (2.264–6.307)	<0.001	
No	748	1 (ref)	1.620 (1.127–2.329)	2.680 (1.841–3.902)	<0.001	
Cerebrovascular disease						0.023
Yes	102	1 (ref)	1.099 (0.402–3.005)	1.248 (0.447–3.487)	0.673	
No	1,360	1 (ref)	1.889 (1.400–2.549)	3.171 (2.306–4.361)	<0.001	
Chronic kidney disease						0.351
Yes	95	1 (ref)	0.960 (0.266–3.460)	1.528 (0.437–5.347)	0.284	
No	1,367	1 (ref)	1.841 (1.367–2.479)	2.984 (2.154–4.132)	<0.001	
Atrial fibrillation						0.316
Yes	631	1 (ref)	1.762 (1.202–2.582)	3.013 (2.002–4.536)	<0.001	
No	831	1 (ref)	1.810 (1.171–2.796)	2.806 (1.785–4.410)	<0.001	
Vasoactive medication						0.862
Yes	587	1 (ref)	1.519 (0.930–2.483)	3.685 (2.160–6.286)	<0.001	
No	875	1 (ref)	1.913 (1.334–2.744)	2.728 (1.863–3.993)	<0.001	

BAR, blood urea nitrogen-to-albumin ratio; HR, hazard ratio.

after patient admission were included and their dynamic changes during hospital stay were ignored, which might not precisely reflect the predictive ability of BAR.

CONCLUSION

Blood urea nitrogen-to-albumin ratio is independently associated with long-term mortality in patients undergoing CABG. BAR might assist the identification of high-risk patients for closer follow-up and more active surgical reintervention. Future large-scale prospective studies are warranted to verify the results and clarify the underlying mechanisms.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.physionet.org/content/mimiciii/1.4/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Massachusetts Institute of Technology (Cambridge, MA) and the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DZ and XM performed the conception and design of this manuscript. YLiu and ZX provided useful suggestions in methodology. HS, SC, and SZ performed the data analysis. YLi, HZ, and CZ prepared the tables and figures. DZ and XM drafted and revised the

manuscript. All authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.801708/full#supplementary-material

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ORIGINAL RESEARCH
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Comparison of Single Axillary vs. Dual Arterial Cannulation for Acute Type a Aortic Dissection: A Propensity Score Matching Analysis

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Background: The optimal arterial cannulation site for acute aortic dissection repair is unclear, especially for complex arch surgery. Axillary artery cannulation is widely accepted but adding femoral artery cannulation to it was considered to potentially improve perfusion and early outcomes. To clarify this point, a comparison of perioperative outcomes for these two different cannulation strategies was conducted regarding the pathological features of dissection.

Methods: From January 2010 to December 2019, 927 consecutive patients underwent a total arch replacement combined with frozen elephant trunk for acute type A aortic dissection. The data, including detailed pathological features, were retrospectively collected and analyzed. Propensity score matching and multivariate logistic regression analysis were used for adjusting confounders that are potentially related to the outcome.

Results: A total of 523 patients (56.3%) accepted a dual arterial cannulation (DAC group), and 406 patients (43.7%) received a single axillary artery cannulation (SAC group). In total, 388 pairs of patients were well-matched. Whether before or after adjusting the preoperative characteristics by matching, there were no significant differences in operative mortality (6.7 vs. 5.4%, $P = 0.420$ before matching; 5.4 vs. 5.4%, $P = 1$ after matching), stroke (6.7 vs. 5.4%, $P = 0.420$ before matching; 6.4 vs. 5.2%, $P = 0.435$ after matching), spinal cord injury (5 vs. 5.7%, $P = 0.640$ before matching; 5.4 vs. 5.7%, $P = 1$. After matching), and acute renal failure requiring dialysis (13.8 vs. 9.6%, $P = 0.050$ before matching; 12.6 vs. 9.5%, $P = 0.174$) between the two groups. Dual arterial cannulation was not an independent protective factor of operative mortality (odds ratio [OR] 1.01, 95% confidence interval [CI] 0.55–1.86), stroke (OR 1.17, 95% CI 0.65–2.11), spinal cord injury (OR 1.17, 95% CI 0.65–2.11), and acute renal failure requiring continuous renal replacement therapy (CRRT) (OR 1.24, 95% CI 0.78–1.97) after adjusting for confounding factors by multivariable logistic regression analysis. In the subgroup analysis, no advantage of dual arterial cannulation was found for a particular population.

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Conclusions: Single axillary artery cannulation was competent in the complex arch repair for acute aortic dissection, presenting with a satisfactory result as dual arterial cannulation. Adding femoral artery cannulation was necessary when a sufficient flow volume could not be achieved by axillary artery cannulation or when a lower limb malperfusion existed.

Keywords: aortic dissection, total arch replacement, frozen elephant trunk, cannulation, propensity adjustment

INTRODUCTION

Nowadays on China, there is a tendency to perform a total arch replacement (TAR) with frozen elephant trunk (FET) as a standard approach for acute type A aortic dissection (ATAAD), involving arch or more distally. The TAR combined with FET is more invasive and complex so that more evidence is needed to prove the optimal management for each step of this procedure. Regarding the arterial cannulation site, although the latest expert consensus of AATS (1) recommended kinds of options, controversy always exists and high-level evidence is absent. In the past years, we had attempted to apply a dual arterial cannulation to reduce the malperfusion-related mortality and morbidities by extrapolation based on clinical experience. We sought to compare dual arterial cannulation and single axillary artery cannulation on early outcomes by rigorous statistical analysis.

MATERIALS AND METHODS

Study Cohort

The institutional database of aortic dissection was retrospectively reviewed. All consecutive patients who were surgically treated for ATAAD using TAR and FET from January 2010 to December 2019 were included. The patients, who were not appropriate for axillary cannulation (for example, the vessel was too thin or was dissected), accepted a single femoral cannulation and they were excluded from this study (flowchart of enrollment can be seen in **Supplementary Figure I**). The Ethics Committee of Fuwai Hospital (Beijing, China) approved this retrospective study, and the need for informed consent was waived. The data of demographics, clinical features, imaging materials, surgical characteristics, and postoperative outcomes were collected.

Institution-Specific Definition

To identify the special conditions and scenarios that would influence the progress and outcome of ATAAD, we defined some institution-specific terms to describe them. Hemodynamic instability was defined as persistent pre-anesthesia hypotension (systolic blood pressure <90 mmHg) that is preoperative for any reason. Innominate artery stenosis (IAS) was defined as severe stenosis of the true lumen caused by thrombus compression. Innominate artery, originating from the false lumen (IA-FL), as the name suggests, referred to the detachment or complete avulsion of its orifice. All the malperfusion mentioned in this study referred to the obviously disrupted blood flow of main branches of the aorta with radiographical evidence. Because superior mesenteric artery malperfusion had particular importance in ATAAD, it was identified and categorized into three types according to prior studies (2–4). Similarly, lower limb malperfusion was determined as mentioned above. Selective antegrade cerebral perfusion duration usually started from distal circulatory arrest initiation (at this moment three brachiocephalic arteries were clamped) until the anastomosis of the left common carotid artery was completed.

Clinical Endpoints

Operative mortality, stroke, spinal cord injury, and acute renal failure requiring continuous renal replacement therapy (CRRT) were primary endpoints of interest. Operative mortality was defined as any death, regardless of cause, occurring within 30 days after surgery in or out of the hospital, and after 30 days during the same hospitalization subsequent to the operation. For stroke, spinal cord injury, and renal failure, only the new onsets were considered as complications. Spinal cord injury included permanent or transient paresis and paraplegia. All the outcomes were defined using the Society of Thoracic Surgeons definitions (see http://www.sts.org/sts-national-database/database-managers/adultcardiac-surgery-database/data-collection).

Operative Methods

All procedures were implemented by a median sternotomy and cardiopulmonary bypass (CPB). Eight surgeons finished these operations (QXY, GHW, YCT, SXG, WB, MQ, WYZ, and SY). Arterial cannulation was manipulated as follows: (1) right axillary artery: it was exposed by subclavian incision and a purse-string suture was made on it, then a cannula (Bio-Medicus, Medtronic, Minneapolis, MN, USA) with a tapered core was directly inserted through a small incision inside the purse-string; and (2) femoral artery: it was exposed by an incision parallel to the inguinal ligament and cannulated in the same manner as described above. We used axillary artery cannula according to body weight and axillary artery size, cannula size ranged from 17Fr- 21Fr, median size was 19 Fr. We usually selected the 19 Fr—21Fr cannula for the femoral artery.

After distal anastomosis of the arch was accomplished, the femoral artery cannula was removed and the perfusion conduit was shifted to 1 limb of the 4-branch prosthetic graft. In our institute, dual arterial cannulation (right axillary artery+ femoral artery) was individually selected, mainly according to the preference and judgment of the surgeon. In rare cases, we selected femoral artery cannulation as a supplement to

TABLE 1 | Baseline characteristics.

Variable	Unmatched			*P*	Missing	Matched			*P*
	Overall *n* = 929	DAC *n* = 523	SAC *n* = 406			Overall *n* = 776	DAC *n* = 388	SAC *n* = 388	
Age, year ($\overline{X} \pm$ SD)	46.8 ± 10.1	47.3 ± 10.2	46.2 ± 9.8	0.09	0 (0.0)	46.4 ± 10.0	46.4 ±10.1	46.3 ± 9.8	0.92
Male (*n*, %)	757 (81.5)	424 (81.1)	333 (82.0)	0.71	0 (0.0)	633 (81.6)	316 (81.4)	317 (81.7)	0.92
BMI, Kg/m^2 ($\overline{X} \pm$ SD)	26.4 ±4.1	26.6 ± 4.1	26.2 ± 4.0	0.17	2 (0.2)	26.2 ± 4.0	26.2 ± 3.9	26.2 ± 4.1	0.91
HT (*n*, %)	589 (63.4)	327 (62.5)	262 (64.5)	0.53	0 (0.0)	497 (64.0)	249 (64.2)	248 (63.9)	0.94
CAD (*n*, %)	58 (6.2)	37 (7.1)	21 (5.2)	0.23	0 (0.0)	43 (5.5)	22 (5.7)	21 (5.4)	0.88
AF (*n*, %)	8 (0.9)	3 (0.6)	5 (1.2)	0.31*	0 (0.0)	6 (0.8)	3 (0.8)	3 (0.8)	1.00
DM (*n*, %)	22 (2.4)	10 (1.9)	12 (3.0)	0.30	0 (0.0)	21 (2.7)	9 (2.3)	12 (3.1)	0.66
Marfan syndrome (*n*, %)	68 (7.3)	38 (7.3)	30 (7.4)	0.94	0 (0.0)	59 (7.6)	30 (7.7)	29 (7.5)	0.89
Previous stroke (*n*, %)	35 (3.8)	22 (4.2)	13 (3.2)	0.42	0 (0.0)	22 (2.8)	9 (2.3)	13 (3.4)	0.50
CRI (*n*, %)	7 (0.8)	3 (0.6)	4 (1.0)	0.71*	0 (0.0)	6 (0.8)	3 (0.8)	3 (0.8)	1.00
Scr, μmol/L ($\overline{X} \pm$ SD)	99.09 ± 40.80	102.09 ± 46.14	95.24 ± 32.35	0.008	2 (0.2)	98.80 ± 41.84	102.55 ± 49.27	95.04 ± 32.40	0.012
Previous heart surgery (*n*, %)				0.20	0 (0.0)				1.00
No	895 (96.3)	502 (96.0)	393 (96.8)			757 (97.6)	380 (97.9)	377 (97.2)	
TEVAR	12 (1.3)	9 (1.7)	3 (0.7)			0 (0.0)	0 (0.0)	0 (0.0)	
AVR	9 (1.0)	3 (0.6)	6 (1.5)			7 (0.9)	3 (0.8)	4 (1.0)	
Others	13 (1.4)	9 (1.7)	4 (1.0)			12 (1.5)	5 (1.3)	7 (1.8)	
EF, % ($\overline{X} \pm$ SD)	60.2 ± 4.3	60.1 ± 4.5	60.4 ± 4.0	0.18	4 (0.4)	60.4 ± 4.1	60.4 ± 4.2	60.4 ±4.0	0.90
AR>moderate (*n*, %)	110 (11.8)	70 (13.4)	40 (9.9)	0.09	1 (0.1)	74 (9.5)	34 (8.8)	40 (10.3)	0.46
Hemodynamic instability (*n*, %)	47 (5.1)	31 (6.0)	16 (4.1)	0.18	0 (0.0)	29 (3.7)	13 (3.4)	16 (4.2)	0.58
Tamponade	10 (1.1)	4 (0.8)	6 (1.5)	0.30		6 (0.8)	3 (0.7)	4 (1.0)	0.70
Entry tear (*n*, %)				0.009	0 (0.0)				0.68
aAO	608 (65.4)	363 (69.4)	245 (60.3)			483 (62.2)	243 (62.6)	240 (61.9)	
Arch	260 (28.0)	126 (24.1)	134 (33.0)			236 (30.4)	114 (29.4)	122 (31.4)	
DTA	61 (6.6)	34 (6.5)	27 (6.7)			57 (7.3)	31 (8.0)	26 (6.7)	
Extent (*n*, %)				0.14*	0 (0.0)				0.29
To arch	60 (6.5)	41 (7.8)	19 (4.7)			46 (5.9)	29 (7.5)	17 (4.4)	
To DTA	5 (0.5)	3 (0.6)	2 (0.5)			4 (0.5)	2 (0.5)	2 (0.5)	
To distal AA	864 (93.0)	479 (91.6)	385 (94.8)			726 (93.6)	357 (92.0)	369 (95.1)	
IA-FL (*n*, %)	22 (2.4)	13 (2.5)	9 (2.2)	0.79	0 (0.0)	19 (2.4)	10 (2.6)	9 (2.3)	1.00
IAS (*n*, %)	23 (2.5)	15 (2.9)	8 (2.0)	0.37	0 (0.0)	15 (1.9)	8 (2.1)	7 (1.8)	1.00
Coronary malperfusion (*n*, %)	26 (2.8)	19 (3.6)	7 (1.7)	0.07	0 (0.0)	13 (1.7)	6 (1.5)	7 (1.8)	1.00
Cerebral malperfusion (*n*, %)				0.004*	0 (0.0)				0.80
No	882 (94.9)	487 (93.1)	395 (97.3)			757 (97.6)	380 (97.9)	377 (97.2)	
Unilateral	45 (4.8)	35 (6.7)	10 (2.5)			17 (2.2)	7 (1.8)	10 (2.6)	
Bilateral	2 (0.2)	1 (0.2)	1 (0.2)			2 (0.3)	1 (0.3)	1 (0.3)	
SMA-malperfusion (*n*, %)				0.85*	0 (0.0)				0.97

(Continued)

TABLE 1 | Continued

Variable	Overall *n* = 929	Unmatched DAC *n* = 523	Unmatched SAC *n* = 406	*P*	Missing	Overall *n* = 776	Matched DAC *n* = 388	Matched SAC *n* = 388	*P*
No	777 (83.6)	434 (83.0)	343 (84.5)			659 (84.9)	331 (85.3)	328 (84.5)	
Dynamic	131 (14.1)	78 (14.9)	53 (13.1)			98 (12.6)	48 (12.4)	50 (12.9)	
Static	19 (2.0)	10 (1.9)	9 (2.2)			18 (2.3)	9 (2.3)	9 (2.3)	
Mix	2 (0.2)	1 (0.2)	1 (0.2)			1 (0.1)	0 (0.0)	1 (0.3)	
Renal malperfusion	62 (6.7)	32 (6.1)	30 (7.4)	0.44		59 (7.6)	32 (8.2)	27 (7.0)	0.50
Left lower limb malperfusion (*n*, %)				0.15*	0 (0.0)				0.99
No	876 (94.3)	498 (95.2)	378 (93.1)			730 (94.1)	366 (94.3)	364 (93.8)	
Dynamic	51 (5.5)	25 (4.8)	26 (6.4)			46 (5.9)	22 (5.7)	24 (6.2)	
Static	2 (0.2)	0 (0.0)	2 (0.5)			0	0 (0.0)	0 (0.0)	
Right lower limb malperfusion (*n*, %)				0.61	0 (0.0)				0.78
No	863 (92.9)	489 (93.5)	374 (92.1)			722 (93.0)	362 (93.3)	360 (92.8)	
Dynamic	41 (4.4)	20 (3.8)	21 (5.2)			38 (4.9)	19 (4.9)	19 (4.9)	
Static	25 (2.7)	14 (2.7)	11 (2.7)			16 (2.1)	7 (1.8)	9 (2.3)	

*DAC, dual arterial cannulation; SAC, axillary artery cannulation; BMI, body mass index; HT, hypertension; CAD, coronary artery disease; AF, atrial fibrillation; DM, diabetes mellitus; CRI, chronic renal insufficiency; Scr, serum creatinine; TEVAR, thoracic endovascular aortic repair; AVR, aortic valve replacement; AR, aortic regurgitation; aAO, ascending aorta; DTA, descending thoracic aorta; AA, abdominal aorta; IA-FL, innominate artery originating from false lumen; IAS, innominate artery stenosis; and SMA, superior mesenteric artery. *Fisher's exact test was used.*

axillary conduit owing to insufficient flow volume. Venous return was achieved *via* a two-staged cannula placed in the right atrium or cannulas in the vena cava as appropriate. Indication and technique of performing TAR combined with FET (CRONUS; MicroPort, Shanghai, China) in our institution were similar to those described by Sun et al. (5) (More detailed information about indication and technique was available in **Supplementary Material** Expanded Methods). Briefly, we used a 4-branch prosthetic graft to replace the arch and a stented graft that is deployed anterogradely into a descending aorta to isolate the false lumen. During FET deployment and distal arch anastomosis, hypothermia circulatory arrest (HCA) and unilateral selective cerebral perfusion were applied. The target nasopharyngeal temperature during HCA was 18–25°C in different periods.

Statistical Analysis

Data were presented as mean and standard deviation for a continuous data conforming to the normal distribution and as number (%) for categorical data. The mean of two continuous normally distributed variables was compared by independent samples student *t*-test. Comparison of categoric variables between groups was analyzed by the likelihood ratio of Chi-square test or Fisher's exact test. The continuous variable that did not conform to a normal distribution was demonstrated as the median and interquartile range (IQR) and were compared by Wilcoxon signed-rank test. The missing quantitative data were filled with mean and the qualitative data were filled with maximum frequency.

Propensity score matching was applied to achieve a balanced exposure between groups at baseline (i.e., minimal confounding). The probability of each patient having a dual arterial cannulation (i.e., the propensity score) was calculated using a logistic regression model. Covariates included age, gender, preoperative comorbidities, and pathologic features of dissection were adjusted (see **Supplementary Table I**). Patients were then matched one-to-one using the Nearest-neighbor matching and caliper width of 0.1 of the standard deviation of the logit of the propensity score. After propensity score matching, a comparison of continuous data conforming to normal distribution between groups was analyzed by paired *t*-test. Paired Chi-square test was used to compare multiple categorical variables between the two groups, statistics and the *P* value of the symmetric test were adopted. The McNemar test was used to compare binary variables between the two groups. To investigate the influence of cannulation strategy on primary outcomes and to avoid a large deviation result, three multivariate logistic regression models adjusting to different confounders were constructed. Confounders were determined according to our clinical experience and previous studies (6, 7). Stratified analysis was conducted to identify whether a dual arterial cannulation had an advantage over a single axillary artery cannulation for a particular population. Statistical significance was denoted by P values < 0.05. The statistical analyses were conducted by SAS (version 9.4, SAS Institute Inc., Cary, North Carolina, America).

TABLE 2 | Operative characteristics.

Variable	Unmatched			*P*	Matched			*P*
	Overall *n* = 929	DAC *n* = 523	SAC *n* = 406		Overall *n* = 776	DAC *n* = 388	SAC *n* = 388	
Aortic root surgery (*n,* %)				0.019				0.07
Supracoronary aortic replacement	667 (71.8)	377 (72.1)	290 (71.4)		564 (72.7)	290 (74.7)	274 (70.6)	
Bentall	241 (25.9)	136 (26.0)	105 (25.9)		193 (24.9)	90 (23.2)	103 (26.5)	
David	9 (1.0)	1 (0.2)	8 (2.0)		8 (1.0)	0 (0.0)	8 (2.1)	
AVR	12 (2.3)	9 (1.7)	3 (0.7)			8 (2.1)	3 (0.8)	
CABG (*n,* %)	113 (12.2)	66 (12.6)	47 (11.6)	0.63	83 (10.7)	38 (9.8)	45 (11.6)	0.41
Femoral artery bypass (*n,* %)	32 (3.4)	22 (4.2)	9 (2.2)	0.35	30 (3.9)	21 (5.4)	9 (2.3)	0.025
Carotid artery bypass (*n,* %)	15 (1.6)	10 (1.9)	5 (1.2)	0.42	13 (1.7)	8 (2.1)	5 (1.3)	0.40
CPB duration, min ($\overline{X} \pm$ SD)	195.1 ± 68.1	204.8 ± 62.7	182.7 ± 72.7	<0.001	192.6 ± 70.0	202.2 ± 64.6	183.0 ± 73.9	<0.001
X-clamp duration, min ($\overline{X} \pm$ SD)	108.3 ± 33.8	112.9 ± 31.9	102.4 ± 35.3	<0.001	106.6 ± 33.2	110.7 ± 30.3	102.4 ± 35.5	<0.001
HCA duration, min ($\overline{X} \pm$ SD)	18.7 ± 6.8	18.8 ± 8.0	18.6 ± 4.8	0.51	18.8 ± 6.6	19.13 ± 8.0	18.5 ± 4.7	0.29
SCP duration, min ($\overline{X} \pm$ SD)	27.1 ± 8.5	29.5 ± 8.7	23.9 ± 7.0	<0.001	26.8 ± 8.5	29.7 ± 8.9	23.9 ± 6.9	<0.001
Nasopharyngeal temperature, °C ($\overline{X} \pm$ SD)	22.0 ± 3.6	21.6 ± 3.8	22.4 ± 3.2	0.001	21.9 ± 3.5	21.5 ± 3.7	22.4 ± 3.2	<0.001
Rectal temperature, °C ($\overline{X} \pm$ SD)	24.9 ± 4.0	24.0 ± 3.9	26.2 ± 3.8	<0.001	25.0 ± 4.0	23.9 ± 3.8	26.1 ± 3.9	<0.001

DAC, dual arterial cannulation; SAC, axillary artery cannulation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; and SCP, selective cerebral perfusion.

TABLE 3 | Perioperative outcome characteristics.

Variable	Unmatched			*P*	Matched			*P*
	Overall *n* = 929	DAC *n* = 523	SAC *n* = 406		Overall *n* = 776	DAC *n* = 388	SAC *n* = 388	
MV duration, hour (median, IQR)	22.0 (14.0–56.0)	24.0 (14.0–64.0)	20.0 (14.0–45.0)	0.019*	22.0 (14.0–50.5)	24.0 (14.0–61.0)	20.0 (14.0–44.5)	0.038*
ICU stay, day (median, IQR)	3.0 (2.0–6.0)	4.0 (2.0–6.0)	3.0 (2.0–5.0)	<0.001*	3.0 (2.0–6.0)	4.0 (2.0–6.0)	3.0 (2.0–5.0)	0.002*
Operative mortality (*n,* %)	57 (6.1)	35 (6.7)	22 (5.4)	0.42	42 (5.4)	21 (5.4)	21 (5.4)	1.00
PMI (*n,* %)	4 (0.4)	3 (0.6)	1 (0.2)	0.64†	3 (0.4)	2 (0.5)	1 (0.3)	1.00
Stroke (*n,* %)	57 (6.1)	35 (6.7)	22 (5.4)	0.42	45 (5.8)	25 (6.4)	20 (5.2)	0.44
Spinal cord injury (*n,* %)	49 (5.3)	26 (5.0)	23 (5.7)	0.64	43 (5.5)	21 (5.4)	22 (5.7)	1.00
Reoperation for bleeding (*n,* %)	41 (4.4)	21 (4.0)	20 (4.9)	0.50	38 (4.9)	18 (4.6)	20 (5.2)	0.87
IABP (*n,* %)	3 (0.3)	1 (0.2)	2 (0.5)	0.58†	3 (0.4)	1 (0.3)	2 (0.5)	1.00
ECMO (*n,* %)	6 (0.6)	1 (0.2)	5 (1.2)	0.09†	6 (0.8)	1 (0.3)	5 (1.3)	0.22
CRRT (*n,* %)	111 (11.9)	72 (13.8)	39 (9.6)	0.05	86 (11.1)	49 (12.6)	37 (9.5)	0.17
Tracheotomy (*n,* %)	24 (2.6)	15 (2.9)	9 (2.2)	0.53	21 (2.7)	12 (3.1)	9 (2.3)	0.66
Intestinal ischemia (*n,* %)	12 (1.3)	8 (1.5)	4 (1.0)	0.46	9 (1.6)	5 (1.3)	4 (1.0)	1.00

*DAC, dual arterial cannulation; SAC, axillary artery cannulation; MV, mechanical ventilation; IQR, Interquartile Range; ICU, intensive care unit; PMI, perioperative myocardial infarction; IABP, intra-aortic balloon pump implantation; ECMO, extracorporeal membrane oxygenation; and CRRT, continuous renal replacement therapy. *Wilcoxon signed rank test was used. †Fisher's exact test was used.*

RESULTS

Baseline Characteristics

Between January 2010 and December 2019, a total of 1,119 patients suffering from ATAAD were admitted emergently for undergoing TAR and FET, whereas 185 met the criteria for exclusion (**Supplementary Figure I**). Of this total, 929 patients comprised the interest cohort.

The mean age of the patient was 46.8 ± 10.1years, with a male preponderance (81.5%). A total of 523 patients (56.3%) accepted dual arterial cannulation (DAC group), and 406 patients (43.7%) received single axillary artery cannulation (SAC group). The preoperative serum creatinine level was significantly higher in the DAC group. Entry tear locating in ascending aorta was more common in the DAC group (69.4 vs. 60.3%, $P = 0.009$), on the other hand, the patients in the SAC group were more likely to have entry tear in the arch (24.1 vs. 33.0%, $P = 0.009$). The proportion of unilateral cerebral malperfusion was significantly higher in the DAC group (6.7 vs. 2.5%, $P = 0.004$). Other preoperative features were similarly distributed between

the two groups. The baseline characteristics were shown in **Table 1**. For the whole cohort, 667 (71.8%) patients received a supracoronary aortic replacement. Bentall procedure, David procedure, and aortic valve replacement were carried out in 241 (25.9%), 9 (1.0%), and 12 (2.3%) patients, respectively. A total of 113 (12.2%) patients underwent a coronary artery bypass grafting for coronary artery disease or coronary artery involvement. Femoral and carotid artery bypass operations were implemented to rescue severely dissected vessels from occlusion caused by a thrombus compression. These bypass operations were performed in 32 (3.4%) and 15 (1.6%) patients. A similar proportion of concomitant procedures was found in the two groups. For patients undergoing dual arterial cannulation, CPB duration, X-clamp duration, and SCP, duration were all longer than those in the SAC group (204.8 ± 62.7 vs. 182.7 ± 72.6 min, 112.9 ± 31.9 vs. 102.4 ± 35.3 min, 29.5 ± 8.7 vs. 23.9 ± 7.0 min, $P < 0.001$). The nasopharyngeal temperature in the DAC group was significantly lower than in the SAC group (21.6 ± 3.8 vs. 22.4 ± 3.2°C, $P = 0.004$). Operative characteristics were demonstrated in **Table 2**. Altogether, 388 pairs of patients were matched using a propensity score matching. It was demonstrated that well-balanced absolute standardized differences between the two groups were achieved regarding the baseline characteristics (**Supplementary Table II**). After matching, there was no significant difference in terms of baseline characteristics between the 2 groups, although CPB duration, X-clamp duration, SCP duration, and nasopharyngeal temperature were still significantly different.

Perioperative Outcomes

In the whole cohort, 57 patients (6.1%) died, and the main presumed causes of death were heart-related circulatory failure, acidosis induced by visceral malperfusion, and stroke. Stroke and spinal cord injury occurred in 57 (6.1%) and 49 (5.3%) patients, respectively. In total, 111 (11.9%) patients had acute renal failure and required CRRT. Operative mortality was similar between the 2 groups (6.7 vs. 5.4%, $P = 0.42$ before matching; 5.4 vs. 5.4%, $P = 1$ after matching). Unadjusted and adjusted risks of stroke were similar across the initial cannulation sites (6.7 vs. 5.4%, $P = 0.42$ before matching; 6.4 vs. 5.2%, $P = 0.44$ after matching). Spinal cord injury was also distributed similarly in the two groups (5 vs. 5.7%, $P = 0.64$ before matching; 5.4 vs. 5.7%, $P = 1$ after matching). A trend that CRRT was more frequent in the DAC group was observed (13.8 vs. 9.6%, $P = 0.05$), but the trend disappeared after matching (12.6 vs. 9.5%, $P = 0.17$). The incidences of other complications were similar between the 2 groups whether before or after matching. The perioperative outcomes were listed in **Table 3**.

Multivariate Logistic Regression Analysis and Stratification Analysis

Dual arterial cannulation was not an independent protective factor of operative mortality (odds ratio [OR] 1.01, 95% confidence interval [CI] 0.55–1.86), stroke (OR 1.17, 95% CI 0.65–2.11), spinal cord injury (OR 1.17, 95% CI 0.65–2.11), and acute renal failure requiring CRRT (OR 1.24, 95% CI 0.78–1.97) after adjusting for confounding factors by multivariable logistic regression analysis (see detailed results of three models in **Table 4**). After stratification according to BMI, dual arterial cannulation was associated with a significantly higher risk of CRRT in patients with a body mass index (BMI) of ≤ 26 (OR, 1.98; 95% CI 1.06–3.7). In other subgroups of entry tear location, innominate artery originating from false lumen, superior mesenteric artery malperfusion, and innominate artery stenosis, and dual arterial cannulation had no significant advantage over a single axillary artery cannulation on the primary outcomes. The incidence of stroke, spinal cord injury, and CRRT in the subgroup of IAS was low or even 0, making stratification results meaningless so that subgroup analysis of IAS was conducted only for operative mortality. The results of subgroup analysis were demonstrated in **Figures 1–4**.

TABLE 4 | Multivariable analyses of operative mortality, stroke, spinal cord injury, and acute renal failure requiring CRRT for dual arterial cannulation vs. single axillary artery cannulation.

	Odds ratio (95% CI)	*P* value	Reference
Operative mortality			Axillary cannulation
Model 1	1.06 (0.58, 1.92)	0.85	
Model 2	1.04 (0.57, 1.9)	0.89	
Model 3	1.01 (0.55, 1.86)	0.98	
Stroke			Axillary cannulation
Model 1	1.11 (0.62, 1.96)	0.73	
Model 2	1.12 (0.63, 1.99)	0.70	
Model 3	1.17 (0.65, 2.11)	0.60	
Spinal cord injury			Axillary cannulation
Model 1	0.83 (0.45, 1.5)	0.53	
Model 2	0.85 (0.46, 1.54)	0.59	
Model 3	1.17 (0.65, 2.11)	0.60	
ARF-CRRT			Axillary cannulation
Model 1	1.17 (0.75, 1.81)	0.49	
Model 2	1.18 (0.76, 1.84)	0.46	
Model 3	1.24 (0.78, 1.97)	0.36	

OR, odds ratio; CI, confident interval. Model 1: adjusted for age/CAD/previous stroke/coronary malperfusion/cerebral malperfusion/superior mesenteric artery malperfusion/hemodynamic instability/CPB duration/preoperative serum creatinine. Model 2: adjusted for age/BMI /CAD/EF/previous stroke/chronic renal insufficiency/ aortic regurgitation>moderate/coronary malperfusion/ cerebral malperfusion/superior mesenteric artery malperfusion/hemodynamic instability/CPB duration/preoperative serum creatinine. Model 3: adjusted for age/BMI /CAD/EF/previous stroke/chronic renal insufficiency/ aortic regurgitation>moderate/coronary malperfusion/ cerebral malperfusion/superior mesenteric artery malperfusion/hemodynamic instability/CPB duration/preoperative serum creatinine/left lower limb malperfusion/right lower limb malperfusion.

DISCUSSION

The present study is important because it compares two cannulation strategies in the context of varying complexity of acute type A aortic dissection. The main findings of our study can be summarized as follows:

1) Regarding pathological features of dissection, single axillary cannulation was comparable with dual arterial cannulation for complex arch repair in the acute type A aortic dissection.

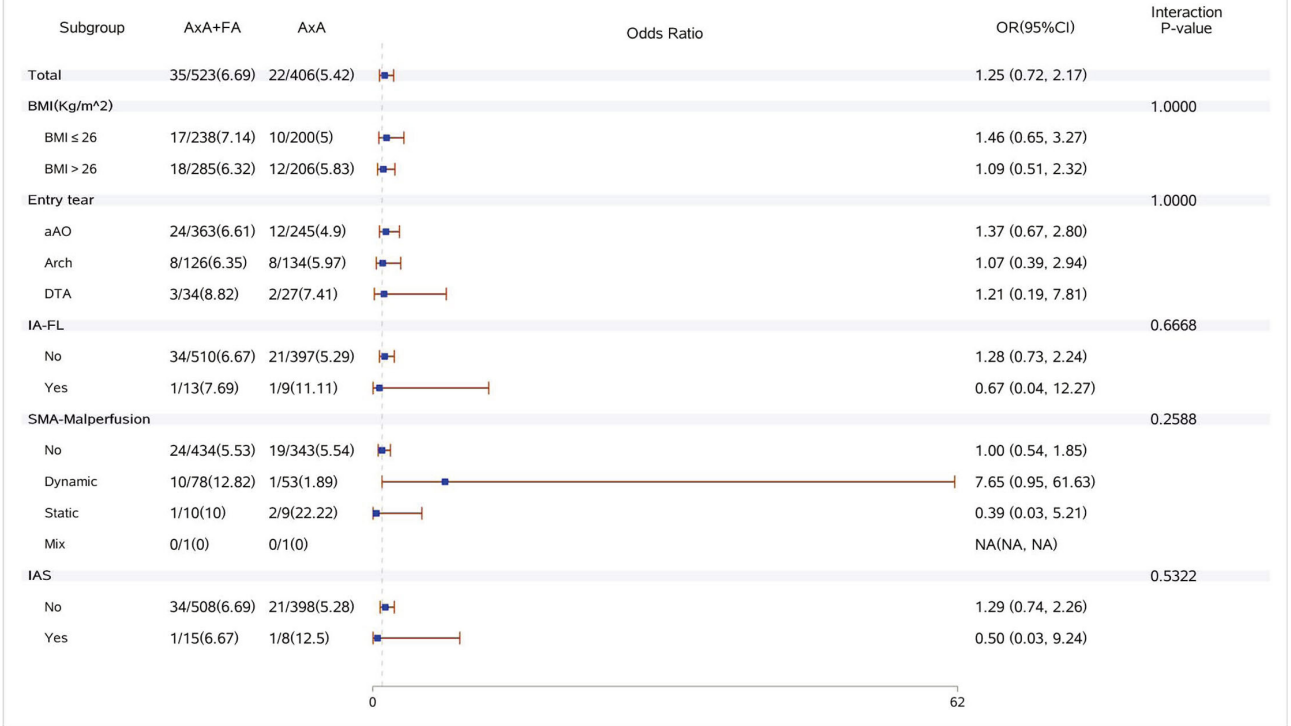

FIGURE 1 | Forest plot of dual arterial cannulation vs. axillary artery cannulation regarding operative mortality by subgroups. AXA+FA, axillary artery cannulation+femoral artery cannulation; AXA, axillary artery cannulation; IA-FL, innominate artery originating from false lumen; SMA, superior mesenteric artery; and IAS, innominate artery stenosis.

2) Based on antegrade perfusion, adding femoral artery cannulation did not result in an elevated rate of stroke caused by a retrograde blood flow.

Total arch replacement (TAR) combined with FET could provide a stable distal anastomosis and ideal remodeling of the downstream aorta, therefore, it was appropriate for patients with extensive dissection, presenting with satisfactory early and long-term results (5, 6, 8). Overall, compared with recent studies (6, 7), we had a lower operative mortality and a comparable incidence of main complications in the present study. The SCP time of the single axillary group was 5 min faster than that of the dual arterial group, in fact, the dual cannulation group mainly consisted of the patients who received operation in the earlier stage, and the single axillary cannulation group mainly consisted of the patients in the later stage. We became more skillful and the SCP time was shorter in the later stage. A higher incidence of spinal cord injury was found in our study. The FET products we used had only two length specifications: 100 mm and 120 mm. In most cases, we preferred a 120 mm FET in order to achieve a better remodeling of the distal aorta. The FET depth, which varied with body height, ranged from T5-T8 vertebral body. It was well-discussed that an intercostal artery originating from false lumen is a risk factor of spinal cord injury besides application of FET. So, we speculated that longer FETs for patients who were at risk of SCI were responsible for the high incidence of SCI in our cohort.

Restoring organ perfusion was critical in the early stage of CPB because pulsatile blood flow attenuated and even disappeared. The arterial cannulation site was an important issue of the whole procedure. Many types of research (9–12) were conducted to discover the optimal cannulation strategy, drawing an identical or conflicting conclusion. Axillary artery cannulation providing antegrade perfusion was advocated by more surgeons. The advantages and limitations of axillary artery cannulation vs. femoral artery cannulation were well-discussed in previous studies (13, 14). Some investigators attempted to apply a dual arterial cannulation to overcome their respective drawbacks (15, 16). It was considered reasonable that morphologic variability of dissection might interplay with cannulation and affect outcomes (17). That is why the cannulation site would possibly make a difference in clinical outcomes, although it worked for a short period of time (usually less than 1 h) from the establishment of CPB to the initiation of hypothermic circulatory arrest. But, this point was seldom taken into full consideration when the cannulation strategy was investigated in previous studies. In our study, we adjusted the preoperative comorbidities and special pathological features of aortic dissection by propensity-score matching. Judging from the statistical results, single axillary artery cannulation was competent in a complex aortic dissection regarding primary outcomes. According to the analysis of some investigators (18–20), persistent false lumen perfusion and true lumen collapse after initiation of CPB might lead to an

FIGURE 2 | Forest plot of dual arterial cannulation vs. axillary artery cannulation regarding stroke by subgroups. AXA+FA, axillary artery cannulation+femoral artery cannulation; AXA, axillary artery cannulation; IA-FL, innominate artery originating from false lumen; and SMA, superior mesenteric artery.

exacerbation of pre-existing malperfusion or a newly emerging malperfusion. Theoretically, a persistent false lumen perfusion occurred more frequently in patients using a retrograde blood flow through femoral artery cannulation (18, 19); and if entry tear is located farther distally (in or beyond the transverse arch) or an innominate artery is originated from false lumen, the same phenomenon might occur when axillary artery cannulation was applied. As Orihashi et al. (18) reported, false lumen perfusion was detected in 8.5% of cases while axillary artery cannulation was used. Lin and coworkers (15) reported that dual arterial cannulation had significant advantages on hospital mortality, stroke, and malperfusion-related complications over a single arterial cannulation. In their single arterial cannulation group, femoral artery cannulation was predominant so that the gap in results might be exaggerated. In our cohort, either operative mortality or incidence of main complications was similar between the two groups. When the innominate artery was involved, axillary artery cannulation was also safe, this finding was similar to previous studies (21, 22). Regarding malperfusion-related complications, such as acute renal failure and intestinal ischemia, there was still no significant difference. The statistical results of the three models were consistent no matter how many variables were adjusted. In stratification analysis, for patients with innominate artery originating from the false lumen and distal entry tear, the single axillary artery cannulation group did not have disadvantages on primary outcomes. On the other hand, there were still some studies showing comparable results of single femoral artery cannulation without a raised risk of malperfusion-related complications (13, 14). According to these findings, it can be hypothesized that a persistent false lumen perfusion might be a random effect and is not as common as Orihashi et.al reported (18). As Rosinski proposed (9): "outcomes are largely determined according to patient presentation rather than cannulation site". To prevent over-interpretation of the results, a detailed monitoring and fluid dynamics analysis were needed to explain the mechanism.

Indeed, whether using additional cannulation should base on intraoperative findings. Firstly, if high-flow resistance occurred when a single axillary artery was used, an extra femoral artery cannulation was necessary (9, 23). In fact, we seldom encountered insufficient flow volume *via* single axillary artery cannulation because patients in our cohort had a relatively small body mass index. Even single axillary artery cannulation was competent in 8 patients with innominate artery stenosis. Secondly, if malperfusion was detected after initiation of CPB, shifting or adding cannulation should be considered (17–19). Peripheral arterial blood pressure and near-infrared spectroscopy were available in most institutes. Transesophageal echocardiography and orbital Doppler could be used to detect intraoperative superior mesenteric artery and cerebral malperfusion (18). Even though it is not easy to implement multiple monitoring methods

FIGURE 3 | Forest plot of dual arterial cannulation vs. axillary artery cannulation regarding spinal cord injury by subgroups. AXA+FA, axillary artery cannulation+femoral artery cannulation; AXA, axillary artery cannulation; IA-FL, innominate artery originating from false lumen; and SMA, superior mesenteric artery.

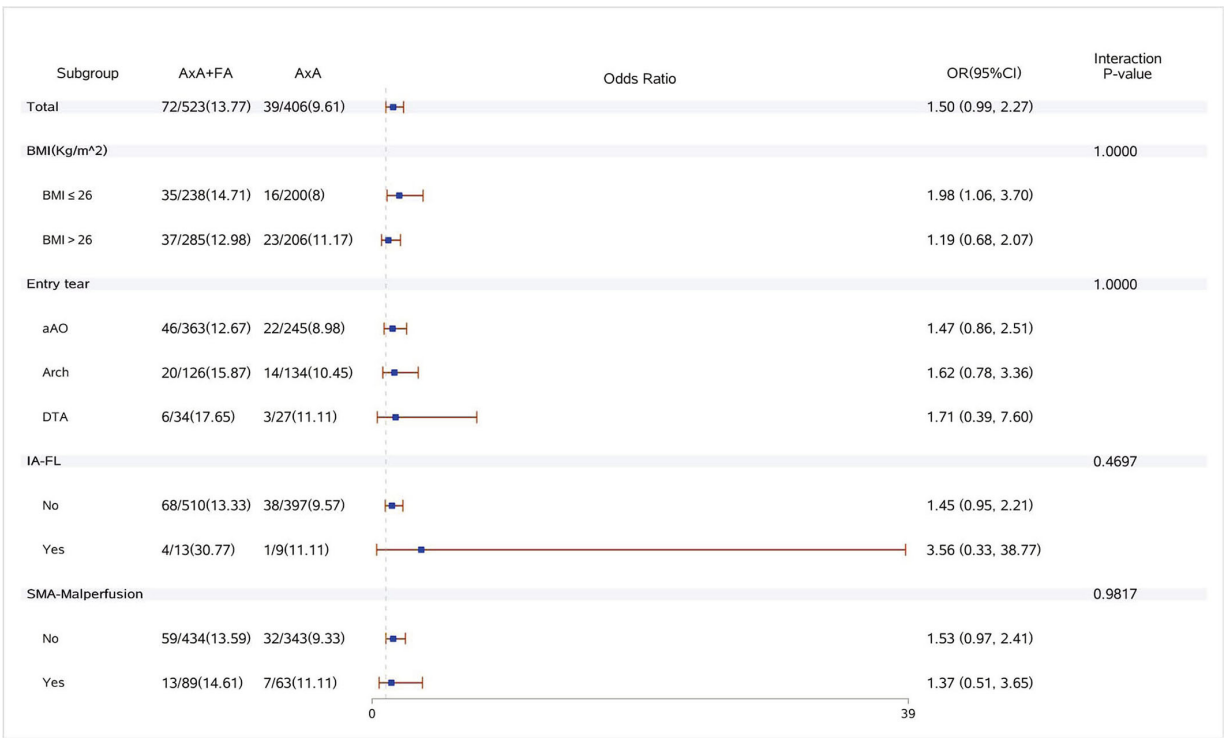

FIGURE 4 | Forest plot of dual arterial cannulation vs. axillary artery cannulation regarding acute renal failure requiring dialysis by subgroups. AXA+FA, axillary artery cannulation+femoral artery cannulation; AXA, axillary artery cannulation; IA-FL, innominate artery originating from false lumen; and SMA, superior mesenteric artery.

simultaneously, we still believe that an accurate monitoring can avoid strategic blindness.

This study has some important limitations. Firstly, it is a retrospective study and selection bias might exist although a propensity-score matching partially made up for the deficiency. Secondly, we did not use a direct intraoperative surveillance to evaluate malperfusion during CPB. Third, cases with adverse events were very few in subgroups and statistical analysis was of limited significance.

CONCLUSION

Single axillary artery cannulation was competent in most cases, presenting with a satisfactory result as dual arterial cannulation. Adding femoral artery cannulation was necessary when the sufficient flow volume could not be achieved by axillary artery cannulation or lower limb malperfusion existed. Under antegrade blood flow, femoral artery cannulation would not increase the stroke risk.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because institutional policy restriction. Requests to access the datasets should be directed to Yi Chang, chantlinguish@163.com.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

YC was responsible for the conceptualization, data curation, statistical analysis, and writing—original draft. HL was responsible for the statistical analysis. XQ was responsible for the conceptualization, methodology, investigation, and funding acquisition. HG, CY, XS, BW, QM, YW, and YS were responsible for the investigation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.809493/full#supplementary-material

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Concomitant Atrial Fibrillation Procedures During Cardiac Surgery in a UK Center: Reflection of Worldwide Practice?

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Background: Guidelines recommend concomitant atrial fibrillation (AF) ablation during cardiac surgery to restore normal sinus rhythm (NSR). The study determines, to what extent patients with AF undergoing cardiac surgery at our institution received a concomitant AF procedure, what these procedures entailed, and short-term outcomes.

Methods: A retrospective study of 2,984 patients undergoing cardiac surgery over 18 months. Patients who were in preoperative AF were identified and those who underwent a concomitant AF procedure (Group 1) were compared with those who did not (Group 2).

Results: Three hundred and thirteen (10.5%) patients had pre-operative AF; paroxysmal (19.5%), persistent (11.8%), longstanding (63%), unknown (5.8%). 116/313 (37.1%) patients had a concomitant AF procedure: 7.7% patients had a concomitant AF ablation and 29.4% had only a Left Atrial Appendage Occlusion (LAAO). Fewer patients with paroxysmal and persistent AF underwent concomitant AF procedures compared with the ones who had no AF procedures (6.7 vs. 12.8% and 17.6 vs. 31%, respectively). Greater in-hospital survival (99.1 vs. 93.9%, $p = 0.025$) and survival at a mean follow up of 6 weeks (97.4 vs. 89.3%, $p = 0.09$) was probably determined by patient's preoperative comorbidities. There were no differences in readmission rates, permanent pacemaker insertion, cerebral events or NSR at discharge or follow-up, between groups.

Conclusions: In our center, concomitant AF ablation is performed only in 7.7% of cases, 29.4% had only an LAAO performed at the time of surgery. There was no difference in restoring NSR, cerebral events, or readmission rates compared with patients who had nothing done for their preoperative AF.

Keywords: atrial fibrillation, concomitant ablation, cardiac surgery, Cox-Maze, left atrial appendage occlusion

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INTRODUCTION

Atrial fibrillation (AF) is a common supraventricular arrhythmia, with increased prevalence with increasing age. The incidence of AF is greater in patients who have significant coronary artery disease or valvular heart pathology (1). AF is associated with a five-fold risk of stroke, a three-fold incidence of congestive heart failure, higher hospitalization and mortality (2). It significantly impairs patients' quality of life and reduces long-term survival. Management strategies include rate and rhythm control, anticoagulation following risk assessment for stroke and bleeding, and AF ablation.

AF ablation can be performed as a stand-alone surgical procedure, on a beating heart, via thoracotomy or sub-xiphoid approach or using cardio-pulmonary bypass, through mini or full midline sternotomy or concomitantly with other cardiac surgery, with good results reported (2). Concomitant AF ablation can vary from pulmonary vein isolation to a bi-atrial ablation or a full Cox-Maze procedure. The Cox-Maze (CM) procedure is considered the gold standard surgical AF ablation technique. Clinical results have shown that the CM IV achieves equivalent success rate of the original CM procedure while significantly reducing operative time and lowering complication rates (3).

Left atrial appendage occlusion (LAAO) in patients with AF, although not an ablation procedure has been shown to reduce perioperative stroke and the long-term risks of thromboembolic complications (4). The most recent 2017 guidelines from the Society of Thoracic Surgeons (STS) recommend concomitant AF ablation for patients undergoing all types of cardiac procedures but particularly during mitral valve (MV) surgery, with good results in restoring normal sinus rhythm (NSR) (5).

There is increasing evidence demonstrating reduced stroke rates (6), fewer bleeding incidents (7), fewer readmissions for AF or heart failure (8, 9), but also improved long term survival and quality of life (10, 11), for patients who have a concomitant AF ablation procedure. The best outcomes following concomitant AF ablation during cardiac surgery depend on good patient selection. Higher chances in restoring NSR after concomitant AF ablation, are seen in patients with preoperative AF duration <1 year (paroxysmal or persistent) (12). Other studies show that the echocardiographic dimensions of the left atrium (LA) are also important to determine the chances of restoring normal sinus rhythm, with best results achieved if LA dimensions are <55 mm (13). Other factors such as diabetes, hypertension, or smoking are associated with worse results after AF ablation (13, 14).

Despite strong evidence for concomitant AF ablation, surgeons are still reluctant to offer this treatment during cardiac surgery for a variety of reasons including increased operative time, the need to open the left or right atria and concerns regarding intraoperative complications. However, patients may be missing a unique opportunity to have their AF treated at the time of their cardiac surgery.

The aim of this study is to determine to what extent patients with AF undergoing cardiac surgery at our institution received a concomitant AF procedure, what these procedures entailed, and whether these procedures are adequate in restoring NSR and maintaining it at short term follow up. Through this study we aim to raise awareness about the potential advantage of concomitant AF ablation during cardiac surgery. Finally, we aim to provide some recommendations to improve the management of patients with atrial fibrillation undergoing cardiac surgery.

METHODS

A retrospective study of all patients who underwent cardiac surgery at our institution between June 2017 and January 2019. Our hospital is a large tertiary cardiac center undertaking around 2,500 cardiac cases per annum. Study cohort were patients presenting with preoperative AF. The types of AF were stratified further and defined as following: (i) Paroxysmal AF- recurrent AF ($\geq$2 episodes) that terminates spontaneously within 7 days or episodes of AF $\leq$48 h duration, ended with electrical or pharmacologic conversion; (ii) Persistent AF- continuous AF, sustained beyond 7 days or episodes of AF in which the decision of electrical or pharmacological cardioversion is made after $\geq$48 h, but prior to 7 days; (iii) Longstanding persistent AF- continuous AF of >12 months (15).

Patients with preoperative AF were divided into two groups: Group 1 patients underwent a concomitant AF procedure at the time of cardiac surgery and Group 2 patients did not. The two groups were compared with respect to patient characteristics and comorbidity, postoperative complications, hospital stay, and early outcomes (in-hospital and at routine follow-up at 6–8 weeks following discharge from hospital).

Definitions: severe renal impairment: patient on dialysis or creatinine clearance <30 mls/min; extracardiac arteriopathy: claudication, carotid occlusion or >50% stenosis, amputation for arterial disease or previous or planned intervention on the abdominal aorta, limb arteries, or carotids; chronic pulmonary disease: long term use of bronchodilators or steroids for lung disease; pulmonary hypertension: systolic pressure >55 mg Hg.

The following procedures were considered as AF ablation procedures: Cox-Maze procedure, pulmonary vein (PV) isolation (radiofrequency or cryoablation) and left atrium (LA) ablation (radiofrequency or cryoablation). We included left atrial appendage occlusion (LAAO) as an AF procedure and not an ablation.

We recorded patient's rhythm before the surgical procedure, postoperatively, at discharge from hospital and in the out-patient clinic, 6–8 weeks from discharge. The ECG was the main tool used to record the rhythm. Only a few patients had a 24 h ECG at follow up review. The duration of preoperative AF was documented from patient's medical records.

Continuous variables were expressed as mean $\pm$ 1 standard deviation. Differences between the two Groups were analyzed with Chi-squared test and *T*-test for Independent Means. A $p < 0.05$ was considered significant.

RESULTS

A total of 2,984 patients underwent a cardiac surgical procedure over this 18 month period at our institution. Three hundred and thirteen (10.4%) had preoperative AF: 61 (19.5%) paroxysmal, 37 (11.8%) persistent, 45 (14.4%) longstanding, 152 (48.5%) permanent, and 18 (5.8%) could not be classified. **Table 1** shows the characteristics of Group 1 and Group 2 patients with preoperative AF. Overall the characteristics of the two groups of patients were similar, except for two of them: the presence of infective endocarditis (0.9 vs. 6.1%, $p = 0.025$) and previous cardiac surgery (1.7 vs. 14.2%, $p = 0.001$), both significantly higher in Group 2 patients.

Table 2 shows the type of AF in both Group 1 and Group 2 patients. The majority 77 (66.4%) of patients in Group 1 (who had a concomitant AF procedure performed) mainly presented with

TABLE 1 | Patients characteristics.

	Group 1: AF procedure $n = 116$	Group 2: No AF procedure $n = 197$	*P*-value
Male gender	70 (60.3%)	123 (62.4%)	0.713
Age at operation (years)	71 ± 9.67	70 ± 10.39	0.984
Severe renal impairment	27(23.3%)	59 (29.9%)	0.206
Active IE	**1 (0.9%)**	**12 (6.1%)**	**0.025**
Extracardiac arteriopathy	3 (2.6%)	11 (5.6%)	0.215
Chronic pulmonary disease	17 (14.6%)	26 (13.2%)	0.717
MI within 30 days	5 (4.3%)	8 (4.1%)	0.914
Previous TIA or CVA	18 (15.5%)	20 (10.1%)	0.160
IDDM	2 (1.7%)	8 (4.1%)	0.256
HTN	90 (77.6%)	158 (80.2%)	0.581
Smoking history	6 (5.2%)	13 (6.6%)	0.609
Pulmonary HTN	23 (19.8%)	54 (27.4%)	0.132
Poor LV function preop (LVEF<30%)	6 (5.2%)	19 (9.6%)	0.158
NYHA III/IV preop	19 (16.4%)	23 (11.7%)	0.238
Preop PPM	6 (5.2%)	14 (7.1%)	0.499
Previous cardiac surgery	**2 (1.7%)**	**28 (14.2%)**	**<0.001**

IE, infective endocarditis; MI, myocardial infarction; IDDM, insulin-dependent diabetes mellitus; HTN, hypertension; TIA, transient ischemic attack; CVA, cerebrovascular accident; LV, left ventricle; NYHA, New York Heart Association classification; PPM, permanent pacemaker. Bold value indicate that the difference between the values was statistically significant.

TABLE 2 | Type of AF in group 1 and group 2 patients.

AF type	Group 1: AF procedure $n = 116$	Group 2: No AF procedure $n = 197$	*P*-value
Paroxysmal 61 (19.5%)	21 (18.1%)	40 (20.3%)	0.634
Persistent 37 (11.8%)	15 (12.9%)	22 (11.2%)	0.640
Longstanding 197 (62.9%)	77 (66.4%)	120 (60.9%)	0.333
Unknown 18 (5.8%)	3 (2.6%)	15 (7.6%)	—

AF, atrial fibrillation.

longstanding AF. Only 27 (31%) of patients who presented with AF duration <1 year before cardiac surgery (paroxysmal and persistent) had a concomitant AF procedure (ablation procedure or just a LAAO).

Table 3 illustrates the types of cardiac procedures which the patients included in Group 1 underwent. The cardiac procedures performed for patients included both in Group 1 and Group 2 were similar. Most commonly performed procedures were: isolated valve replacement/repair (aortic/mitral), double or triple valve replacement, coronary artery bypass graft surgery (CABG), major aortic surgery (aortic root replacement, ascending aorta, or hemiarch replacement) and combined procedures. Of those patients undergoing a concomitant atrial fibrillation procedure, 92 (79%) underwent isolated left atrial appendage occlusion. Two (1.7%) further patients had isolated pulmonary vein isolation. Twenty two (19%) patients who had left atrial appendage occlusion combined with an ablation procedure as follows: Cox-Maze 5 (4.3%), LA ablation 10 (8.6%) and PV Isolation 7 (6%). **Table 4** shows the exact AF procedures undertaken in relation to the type of AF: paroxysmal, persistent, and longstanding. **Figure 1** shows the type of concomitant AF procedures undertaken at the time of the respective cardiac procedure performed.

Patients in Group 1 and Group 2 were classified into three categories based on preoperative cardiac echocardiography dimensions of the left atrium [dilated (LA < 55 mm), significantly dilated (LA > 55 mm) and severely dilated (≥65 mm)] and the preoperative duration of AF as illustrated in **Table 5**. Of 79 patients with longstanding AF and severely dilated LA, 37 (46.8%) patients had a concomitant AF procedure and 42 (53.2%) did not ($p = 0.987$).

Postoperative complications in both patient groups are shown in **Table 6**. Group 1 patients had a significantly lower return to theater compared with Group 2 patients (2.6 vs. 9.1%, $p = 0.026$), a shorter hospital stay (11.9 ± 6 vs. 16.6 ± 19, $p = 0.013$) and better in-hospital survival (99.1 vs. 93.9%, $p = 0.025$). The majority of patients were discharged on antiarrhythmic medication (amiodarone, beta-blockers, or calcium channels blockers), except for a few cases where patients were bradycardiac and could not be discharged on any antiarrhythmic medications. Group 1 patients were more likely to be discharged on antiarrhythmic drugs compared with Group 2 patients, 85.3 vs. 73.1%, $p = 0.012$), respectively.

In Group 1, patients who had an AF procedure done, 114/116 pts (98.3%) had a LAAO.

In 79/114 pts (69.3%) with LAAO the rhythm identified at discharge was AF. The rhythm identified for the other 2 pts with isolated PVI at discharge was AF, as well. Overall, in Group 1 the rate of postoperative AF at discharge was 69.8%. Looking at Group 2, 110/197 pts (55.8%) were discharged in AF. Postoperative AF was significantly higher at discharge for Group 1 compared with Group 2 (69.8 vs. 55.8%, $p = 0.01$).

In addition to antiarrhythmic therapy, patients were discharged on oral anticoagulant therapy [warfarin or direct oral anticoagulants (DOACs)]. The majority [74 (68%)] of patients without a mechanical valve replacement and in AF at discharge were discharged on DOACs. Patients undergoing an AF procedure (even just an LAAO procedure) were more likely to be discharged on anticoagulation therapy compared with those who did not (93.9 vs. 82.2%, $p = 0.033$).

277/313 patients (88.5%) had a mean follow up of 6.09 ± 1.57 weeks, excluding the 22 patients who died and another 14 patients who were lost to follow up. Patients in Group 1 with a concomitant AF procedure had better survival compared with patients in Group 2, although this did not reach significance (97.4 vs. 89.3%, $p = 0.09$). There were no differences between the two Groups in the incidence of normal sinus rhythm (58.7 vs. 56.9%, $p = 0.759$) or hospital readmissions for AF or anticoagulation issues (7.7 vs. 6%, $p = 0.569$), at follow up.

At follow up, 47/114 pts (41.2%) with LAAO were identified as being in AF, and overall 41.4% pts were in AF in Group 1. In Group 2, 73/197 pts (37.1%) were identified as being in AF. There is a small difference between the 2 groups with

TABLE 3 | Cardiac procedures performed in n=116 patients undergoing concomitant AF procedure.

Isolated procedures				Mixed procedures						
CABG	**Valve repair/replacement**			**Double/triple valve procedures**			**Other procedures**			
***n* = 12**	***n* = 46**			***n* = 31**			***n* = 27**			
	Mitral *n* = 34	Aortic *n* = 11	Tricuspid *n* = 1	AVR+ MVR/+ TV repair *n* = 10	MVR +TV repair *n* = 14	MV repair +TV repair/+ AVR *n* = 7	VR/ repair + CABG *n* = 16	VR+ SM *n* = 5	AAR/hemiarch+ VR/CABG *n* = 4	AM + CABG *n* = 2

AAR, ascending aorta replacement; AM, atrial myxoma; CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement; MV, mitral valve; SM, septal myectomy; TV, tricuspid valve; VR, valve replacement.

TABLE 4 | Concomitant AF procedure performed in different types of AF.

AF type	Concomitant AF procedure *n* = 116				
	Cox-Maze + LAAO ***n* = 5**	**LAa + LAAO** ***n* = 10**	**PVI + LAAO** ***n* = 7**	**PVI** ***n* = 2**	**LAAO** ***n* = 92**
Paroxysmal	2 (1.7%)	3 (2.6%)	2 (1.7%)	1 (0.9%)	13 (11.2%)
Persistent	2 (1.7%)	1 (0.9%)	0	0	12 (10.3%)
Longstanding	1 (0.9%)	5 (4.3%)	5 (4.3%)	1 (0.9%)	65 (56%)
Unknown	0	1 (0.9%)	0	0	2 (1.7%)

AF, atrial fibrillation; LAa, left atrial ablation; LAAO, left atrial appendage occlusion; PVI, pulmonary vein isolation.

more pts with postoperative AF at follow up in Group 1 (41.4 vs. 37.1%, $p = 0.44$).

DISCUSSION

Concomitant AF ablation during cardiac surgery is strongly supported by the most recent 2017 guidelines from the STS. Studies confirm that restoring NSR through concomitant AF ablation reduces the risk of stroke (5), bleeding (6), rate of readmissions for AF (7), risk of heart failure in addition to improving long term survival of patients and their quality of life (8–11). We have shown that adherence to these guidelines remains low, even in a high volume cardiac surgery center. In our study, out of 313 patients who presented with preoperative AF, and undergoing cardiac surgery, 37% had an AF procedure performed, of whom only 7.7% had an AF ablation. The majority of patients having a concomitant AF procedure only had a LAA clip, despite evidence showing that when a more complex ablation procedure was performed, there was a higher chance of restoring NSR and improved outcomes.

Despite evidence-backed guidelines regarding the safety and efficacy of concomitant AF ablation, this was not routinely performed in our cohort of patients. One frequent explanation provided for this is that in the presence of comorbidities, the risk to the patient is increased. In our study, both Groups (patients who had a concomitant AF ablation and those who did not) were similar regarding patient characteristics and co-morbidity, except the presence of preoperative infective endocarditis and previous cardiac surgery, which are both indeed associated with increased procedure risks. Hypertension, diabetes, and smoking are major independent predictors for AF ablation failure (1), however this did not appear to play a role in selection of our patients (**Table 1**).

Patients undergoing all types of cardiac surgery will benefit from a concomitant AF ablation, but those undergoing procedures on the mitral valve are most likely to benefit and given that the left atrium is opened, no extra incisions are required (5). In our study, 34 patients with preoperative AF and undergoing an isolated MV procedure had a concomitant AF procedure however only three had a full Cox-Maze procedure. Further investigation would be required to understand why this group of patients does not gain the benefit of an ablation.

Concomitant AF ablation is effective restoring sinus rhythm in patients undergoing aortic valve replacement (AVR) or coronary artery bypass surgery (CABG), only one patient had a concomitant Cox-Maze procedure performed in this cohort of our study (16). This may be explained by reluctance to open the heart purely to perform an ablation.

Preoperative AF duration and left atrial dimensions predict the time until AF recurrences after concomitant left atrial ablation (17). The authors report that the sinus rhythm conversion rate was superior when preoperative AF duration was 2 years or less. Forlani et al. report that preoperative AF <1 year (paroxysmal/ persistent) is more likely to convert back to sinus rhythm after AF ablation (11). In our study, of the 98 patients most likely to benefit from a concomitant AF procedure (with paroxysmal / persistent AF), only one third had a concomitant AF procedure performed, and paradoxically, more than half of the patients with longstanding AF (patients who are least likely to benefit) had a concomitant AF procedure. The nature of an individual's AF history together with education of the cardiologist and surgeon is critical to perioperative decision making.

Preoperative LA dimensions predict AF recurrence after an ablation procedure (18). LA dimensions <55 mm predict a higher rate of success in restoring NSR after a concomitant AF

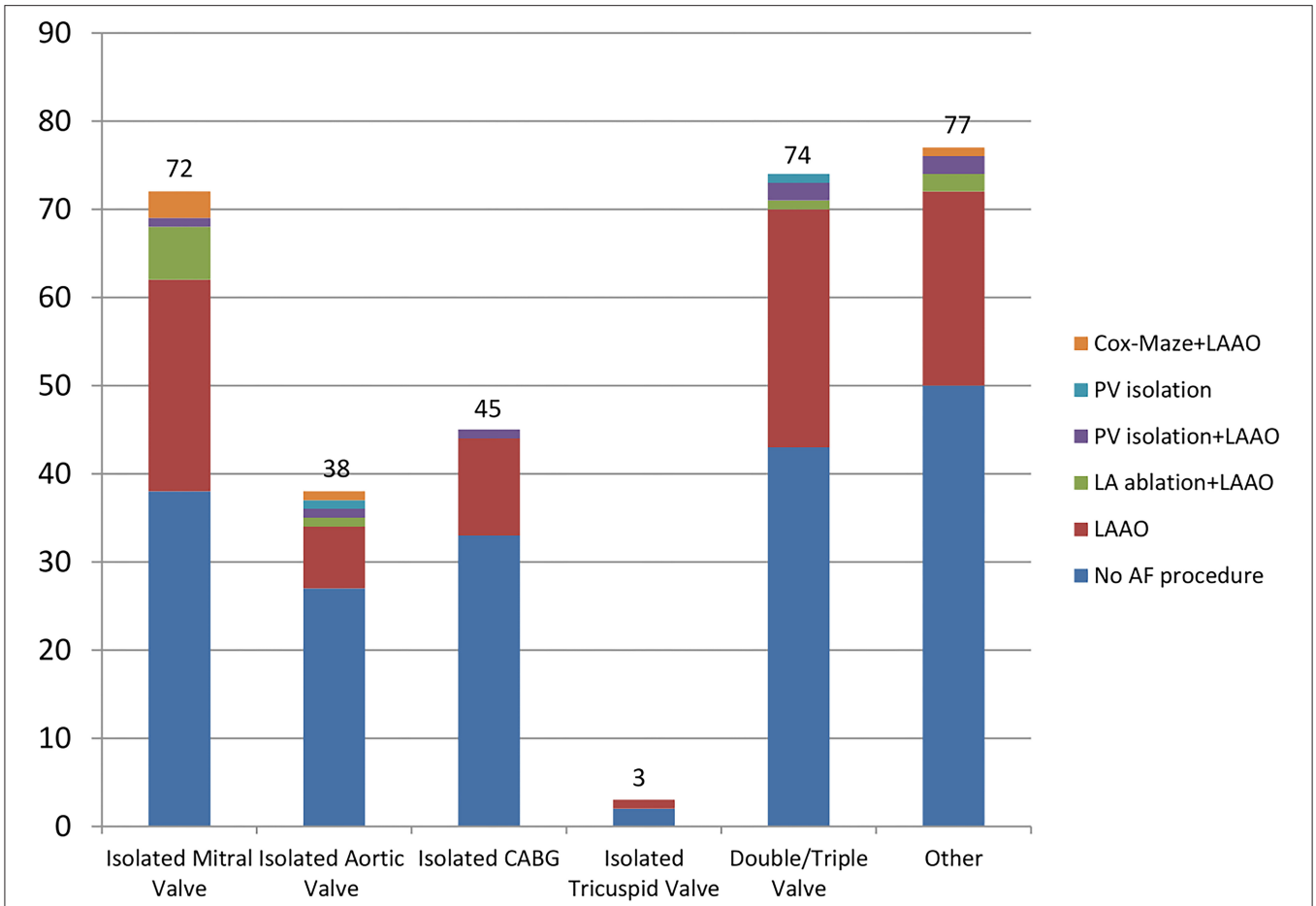

FIGURE 1 | Cardiac procedures and concomitant AF procedures performed. AF, atrial fibrillation; PV, pulmonary vein; LAAO, left atrial appendage occlusion; LA, left atrium; CABG, coronary artery bypass graft; "Other" procedures category includes: Valve replacement + CABG, Valve replacement + septal myectomy, Ascending aorta/hemiarch replacement + CABG/valve replacement, myxoma + CABG.

TABLE 5 | LA dimensions and type of AF in group1 vs. group 2 patients.

AF type	Preoperative LA dimensions								
	Dilated (<55 mm)			Significantly dilated (>55 mm)			Severely dilated (≥65mm)		
	Group 1 *n* (%)	Group 2 *n* (%)	*P*=	Group 1 *n* (%)	Group 2 *n* (%)	*P*=	Group 1 *n* (%)	Group 2 *n* (%)	*P*=
Paroxysmal	9 (2.9)	25 (8)	0.442	2 (0.6)	3 (1)	0.701	6 (1.9)	6 (1.9)	0.813
Persistent	5 (1.6)	6 (1.9)	0.300	3 (1)	7 (2.2)	0.845	7 (2.2)	6 (1.9)	0.586
Longstanding	22 (7)	44 (14)	0.651	7 (2.2)	16 (5.2)	0.745	**37 (4.2)**	**42 (1.6)**	**0.987**
Unknown	1 (0.3)	5 (1.6)	0.418	1 (0.3)	1 (0.3)	0.586	1 (0.3)	4 (1.3)	0.219

LA, left atrium; AF, atrial fibrillation. Bold value indicate that the difference between the values was statistically significant.

ablation. In our patients with preoperative AF duration <1 year and LA dimensions <55 mm only a third had a concomitant AF procedure. Thus, almost 70% of the patients with the greatest chance of maintaining NSR after concomitant AF procedure did not have specific treatment for their AF. Pecha et al. (18) showed that the duration of AF and a preoperative smaller left atrial diameter are statistically significant predictors of long term ablation success. The authors investigated whether performing a concomitant AF ablation on patients with an enlarged LA >55 mm is successful and showed freedom from AF in 64.4% of patients at 1-year follow-up. However, they concluded that these patients need more interventions (medical or electrical cardioversion) and additional catheter-based ablation to achieve satisfactory results.

TABLE 6 | In-hospital outcomes.

	Group 1: concomitant AF procedure $n = 116$	Group 2: no AF procedure $n = 197$	$P =$
Return to theater	**3 (2.6%)**	**18 (9.1%)**	**0.026**
Mean ITU LOS (nights)	4.7 ± 6	6.5 ± 11	0.120
Post-op cerebral events	3 (2.6%)	12 (6.1%)	0.161
Post-op PPM insertion	16 (13.8%)	29 (14.7%)	0.821
Mean hospital LOS (days)	**11.9 ± 6**	**16.6 ± 19**	**0.013**
NSR at discharge	35 (30.2%)	61 (31%)	0.883
In-hospital survival	**115 (99.1%)**	**185 (93.9%)**	**0.025**

Continuous variables are listed as mean ± standard deviation; AF, atrial fibrillation; n, number; P, p-value; ITU, intensive therapy unit; LOS, length of stay; post-op, postoperative; PPM, permanent pacemaker; NSR, normal sinus rhythm. Bold value indicate that the difference between the values was statistically significant.

In our study, both Group 1 and Group 2 patients had similar rates of sinus rhythm at discharge and at short-term follow-up. More patients who had an AF procedure (98.3% had a LAAO) performed for their preoperative AF (Group 1) compared with those who had noting done, presented postoperative AF at discharge, as was highlighted by Yao et al. (19). Similar incidences of postoperative cerebral events, PPM insertion, and readmissions for AF or anticoagulation issues were also observed in both Groups. These findings may be explained by inconsistent patient selection and incomplete AF ablation (a full Cox-Maze was performed in only 4.3% of cases and majority of patients didn't have an AF ablation performed, but only a clip on their LAA), but does not address the effectiveness of the AF ablation procedures.

Patients who had an AF procedure performed were less likely to return to theater, had a shorter hospital stay, and improved survival. These findings can be explained by the patient's selection and inclusion in our cohort group. The patients included in Group 1, who had an AF procedure performed, were identified as lower risk for surgery compared with Group 2, which may explain the shorter hospital stay and improved survival, related to their comorbidities and not to have or not an AF procedure performed.

There are multiple ways to encourage surgeons to perform concomitant AF ablation in addition to education of the benefits as per international guidelines. This study, for example, was performed in a public health system where concomitant ablation attracts no additional reimbursement. Adherence to guidelines can be encouraged with increased reimbursement for additional procedures of proven benefit, such as AF ablation and application of a LAAO device, or withholding of reimbursement from those who do not follow guidelines or at least recommendations by a multi-disciplinary heart team.

STUDY LIMITATIONS

During data collection, we encountered limited information in some patients' records regarding the duration of the preoperative AF and were, thus, unable to classify the type of AF. There was an absence of standardized echocardiography reporting with respect to LA dimensions, as our patient population came from many different referring centers, making the pre-operative assessment of LA size and the preoperative selection of patients for AF ablation, variable. In addition, our patient follow up has been incomplete, with only a small number of patients having a 24 h tape ECG to determine rhythm, some just a 12 lead ECG in out-patient clinic and some only a clinical determination of the heart rhythm and review by a trainee surgeon.

Our small cohort size does not allow for adjusted comparisons such as with propensity matching which requires large samples, with substantial overlap between treatment and control groups.

CONCLUSIONS

Despite strong recommendations for, concomitant AF ablation is still not undertaken in most patients with preoperative AF undergoing cardiac surgery (in our center, AF ablation is performed in 7.7% of cases). The patients from both groups had similar rates of sinus rhythm at discharge and at short-term follow-up, but also similar incidences of postoperative cerebral events and readmissions for AF, which may be explained by inconsistent patient selection and incomplete AF ablation.

RECOMMENDATIONS

As a consequence of these findings, we have made and implemented the following recommendations: establishing a dedicated multidisciplinary team meeting attended by cardiac electrophysiologists, general cardiologists and cardiac surgeons; identified a group of surgeons dedicated to and experienced in the surgical management of AF to champion this treatment; establishment of an AF register to improve the accuracy of patient data collection; standardized the reporting of cardiac investigations and the post-operative follow-up of patients undergoing AF procedures; employment of a specialist AF nurse.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Barts Health Clinical Effectiveness Unit Audit ID 10421 11/07/2019. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

A-AM, MY, and WA have contributed in different but equal ways to this work. All authors contributed to the article and approved the submitted version.

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1-Year Outcomes of a Multicenter Randomized Controlled Trial of the Ankura II Thoracic Endoprosthesis for the Endovascular Treatment of Stanford Type B Aortic Dissections

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Background: The Ankura II Thoracic Stent Graft System (Lifetech, Shenzhen, China) is an evolution of the Ankura stent graft. This study reports one-year outcomes of the Ankura II Thoracic Stent Graft System for endovascular treatment of Stanford type B aortic dissections.

Methods: The Ankura II Thoracic Aortic Endovascular Trial was a randomized, single-blinded, clinical trial conducted at 12 Chinese institutes. The enrolled patients diagnosed with Stanford type B aortic dissections (TBADs) were randomly assigned to the Ankura group or Ankura II group. Standard follow-up examinations were performed at 1, 6, and 12 months. Safety and efficacy data were analyzed.

Results: 132 patients with TBADs were enrolled. The outcomes for the primary safety end points revealed that the Ankura II stent graft was statistically non-inferior compared to the Ankura stent graft. The 1-month device-related major adverse events (1.6 vs. 0%; $p = 0.48$), 1-month all-cause mortality (1.7 vs. 4.5%; $p = 0.621$), 12-month survival rate (95.2 ± 2.7% vs. 94.1 ± 2.9%; $p = 0.769$), and major adverse event (MAE) rate (5.1 vs. 4.7% at 1 month; $p = 0.73$ and 5.8 vs. 8.9% at 12 months; $p = 0.718$) of Ankura II group

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are all comparable to Ankura group. The two groups showed similar primary effectiveness and true lumen expansion effect, and false lumen remodeling was improved in Ankura II group (−100.0 vs. −48.5%; $p = 0.08$).

Conclusions: The one-year outcomes from this prospective, randomized, multicenter study demonstrate that Ankura II stent graft shows comparable results to Ankura for treating TBADs, resulting in low mortality rates, MAEs and reintervention rates.

Clinical Trial Registration: ChiCTR-TRC-12002844.

Keywords: Ankura II, RCT, thoracic endovascular aortic repair, type B aortic dissection, stent – evolution

INTRODUCTION

The thoracic endovascular aortic repair (TEVAR) has been well-studied and demonstrated it can improve the early treatment outcomes of thoracic lesions compared to conventional best medical therapy (BMT) and open surgery (1, 2). The several pioneering thoracic stent graft clinical trials established TEVAR combined with BMT as a safe and effective strategy for treating Stanford type B aortic dissection (TBADs), especially for high risk and complicated patients (3–5). Recently, TEVAR was extended to manage stable uncomplicated type B dissection due to the potential role of remodeling dissected aorta and preventing late expansion and malperfusion (6, 7). The booming of TEVAR really changes the treatment therapy of thoracic lesions.

However, the current commercialized stent graft design still faces some anatomic challenge, since the diameter of thoracic aorta is decreasing from proximal end to distal end (8). The size mismatch between the distal end of the stent graft and the remarkably small diameter of a compressed distal true lumen (TL) may contribute to the distal endoleak or stent graft-induced new entry (SINE) (9, 10). Moreover, the relative short stent can cause incomplete false lumen (FL) thrombosis of the aorta, thus affecting vessel remodeling (11). Recent studies have shown that the degree of FL thrombosis and aortic remodeling are associated with better long-term outcomes of TEVAR (12, 13).

Given the challenge as we mentioned above, the Ankura II Thoracic Stent Graft System (Lifetech, Shenzhen, China), an evolution of the Ankura stent graft, is designed. Compared to first generation product, The Ankura II stent graft is available in straight or tapered configurations. And the new shape provides flexibility and conformability in the stent graft, exerting radial force to enhance seal and fixation. The old system has already showed early evidence of a safe, effective, and durable endoprosthesis for the treatment of descending aortic aneurysms (14). Yet no study has been done for the Ankura II system. Since the new system has many theoretical advantages and available to more patients, we conduct this non-inferiority study. Our goal is to present characteristics and early outcomes of this novel endovascular stent graft, Ankura II Thoracic Stent Graft System, for the treatment of TBADs. Our early data from multicenter in China reveals the safety and efficacy of the Ankura II stent graft in the treatment of TBADs and better aortic remodeling compared to Ankura stent graft.

MATERIALS AND METHODS

Enrollment

The Ankura II Thoracic Aortic Endovascular Trial was a prospective, randomized, multicenter study designed to evaluate the safety and efficacy of the Ankura II Graft System for the treatment of thoracic lesion (Clinical trial registration number: ChiCTR-TRC-12002844). The study was approved by the Institutional Review Board of each participating institution. All participates were well-informed the potential benefit and risk and signed the consent. The trial enrolled 134 patients (two patients withdrew consent before surgery) with TBADs and 10 patients with aortic aneurysm from 12 institutions in China between November 2012 and December 2016. Since the sample size of aneurysmal patients was too small, only patients with TBADs were analyzed in this article to ensure homogeneous results. Data from aneurysmal patients can be provided to readers with reasonable require. The block randomization method was adopted, with a block size of four. The random envelopes were used. Patients were randomly assigned to the Ankura II group or Ankura group in a 1:1 ratio. The anatomic and medical inclusion and exclusion criteria were described in **Table 1**. All the anatomic enrollment criteria were assessed by independent clinical research associates and attending physicians together.

TABLE 1 | Anatomic and medical inclusion and exclusion criteria.

Inclusion criteria
Age ≥18-years-old;
Diagnosed with Stanford type B aortic dissection, landing zone ≥20 mm distance to the left subclavian artery (or the landing zone ≥20 mm distance to the left common cervical artery and the left vertebral artery is non-superior);
Patent femoral and iliac arteries or can tolerate a vascular conduit allowing endovascular access to dissection area via a delivery system;
• Life expectancy ≥1 year.
Exclusion criteria
Pregnant or breastfeeding women;
Medical history of aortic surgery (open or endovascular);
History of cardiac or cerebral infarction within 3 months;
Diagnosed with connective tissue disease or active systemic infection;
Severe coagulation dysfunction;
Potential genetic deficiencies and congenital diseases;
Trauma patients or patients using illicit drugs.

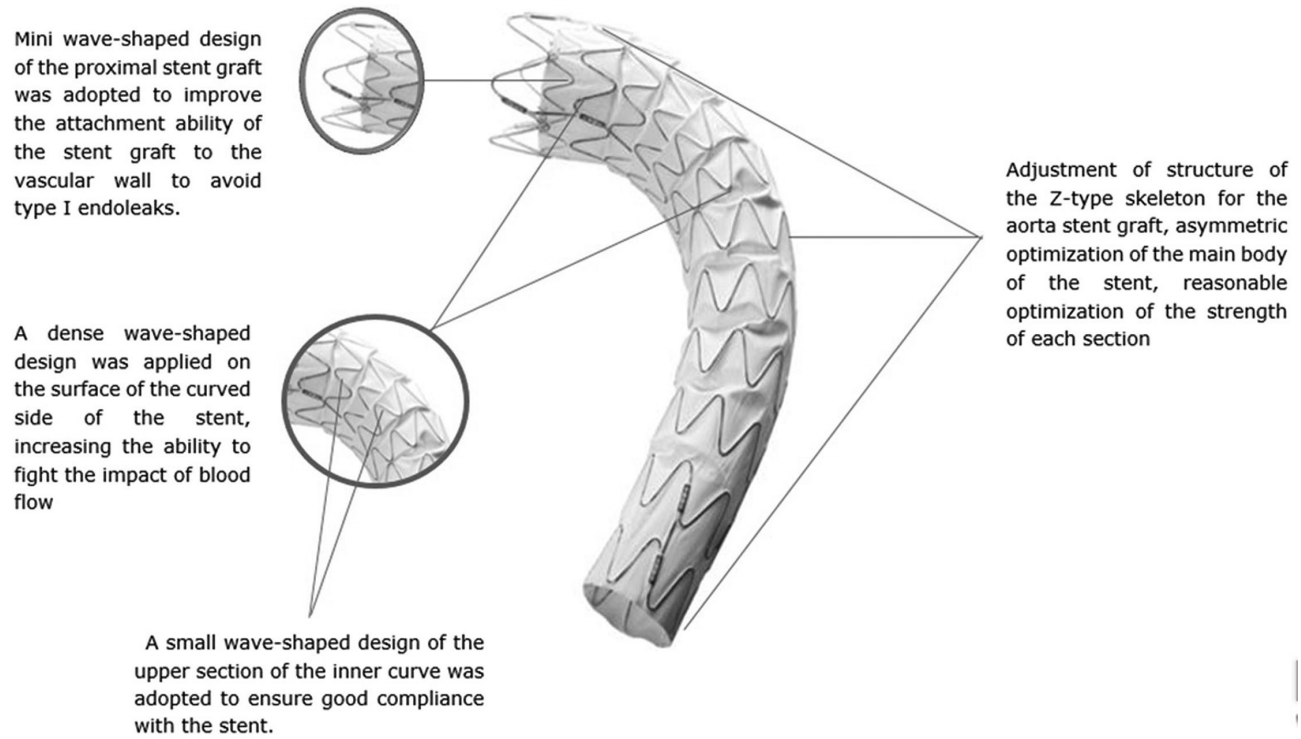

FIGURE 1 | Overall observation of the Ankura II stent graft.

Device Description

The Ankura II Thoracic Stent Graft System is a modular device comprising of a self-expanding metal stent dual-layer hot oxygen fusion polytetrafluoroethylene membrane with a bare proximal stent and covered distal stent. Based on the original Ankura stent graft, Ankura II includes some new improvements as shown in **Figure 1**. No suture was found on the main body to avoid pinhole leakage, thus providing better biocompatibility and durability. The sinusoidal shape and placement of the self-expanding nitinol springs also provide flexibility and conformability in the stent graft, exerting radial force to enhance seal and fixation. The Ankura II stent graft is available in straight or tapered configurations (6-mm, 8-mm or 10-mm taper) and is offered in diameters ranging from 24 to 42 mm and covered lengths ranging from 60 to 200 mm. The detailed deployment process is described in the **Supplementary data**. The consistency of treatment was tested after the deployment process.

End Points and Definitions

The primary safety end point was device-related major adverse events (MAEs) rate at 1 month, which includes stent could not open successfully; stent thrombosis, migration, collapse, and fracture, accidental blockage of other branches of blood vessels, and stent-related endoleaks.

The secondary safety end points were all-cause mortality rates and MAEs rates at 1, 6, and 12 months after surgery. The definitions of MAEs were as follows: cardiovascular events [heart failure, myocardial infarction, cardiac tamponade, retrograde type A aortic dissection (RTAD), rupture of dissection and ischemia of left subclavian artery (LSA)], neurological events (stroke, paraplegia, and coma), acute kidney failure, respiratory failure needs non-invasive or invasive respiratory support, and death. The primary effectiveness end points were clinically successful treatments, which were defined as the absence of any type I or type III endoleaks. The FL thrombosis rates and diameter and area changes in the FL and TL were also compared at 1, 6, and 12 months after surgery.

Endoleaks were defined according to the well-established type I to IV nomenclature (15). Migration was defined as >10 mm proximal or distal movement of the stent graft relative to fixed anatomic landmarks.

Data Management and Statistical Analysis

The standard follow-up protocol for the study included physical examination and computed tomography angiography (CTA) at 1, 6, and 12 months after surgery. We reported our data based on either intention-to-treat analysis (ITT) or per-protocol (PP) analysis. Due to the missing data, we cannot perform full set ITT analysis. For those who had missing category data, we consider the data from previous time follow-up as this time follow-up.

All data analysis and reports of aortic dissection followed the Society for Vascular Surgery and Society of Thoracic Surgeons' reporting standards (3). All imaging studies were performed at the participating sites and reviewed by the core laboratory, which was in second Xiangya hospital, Changsha, Hunan, China. To assess the change and remodeling of the aortic lumen

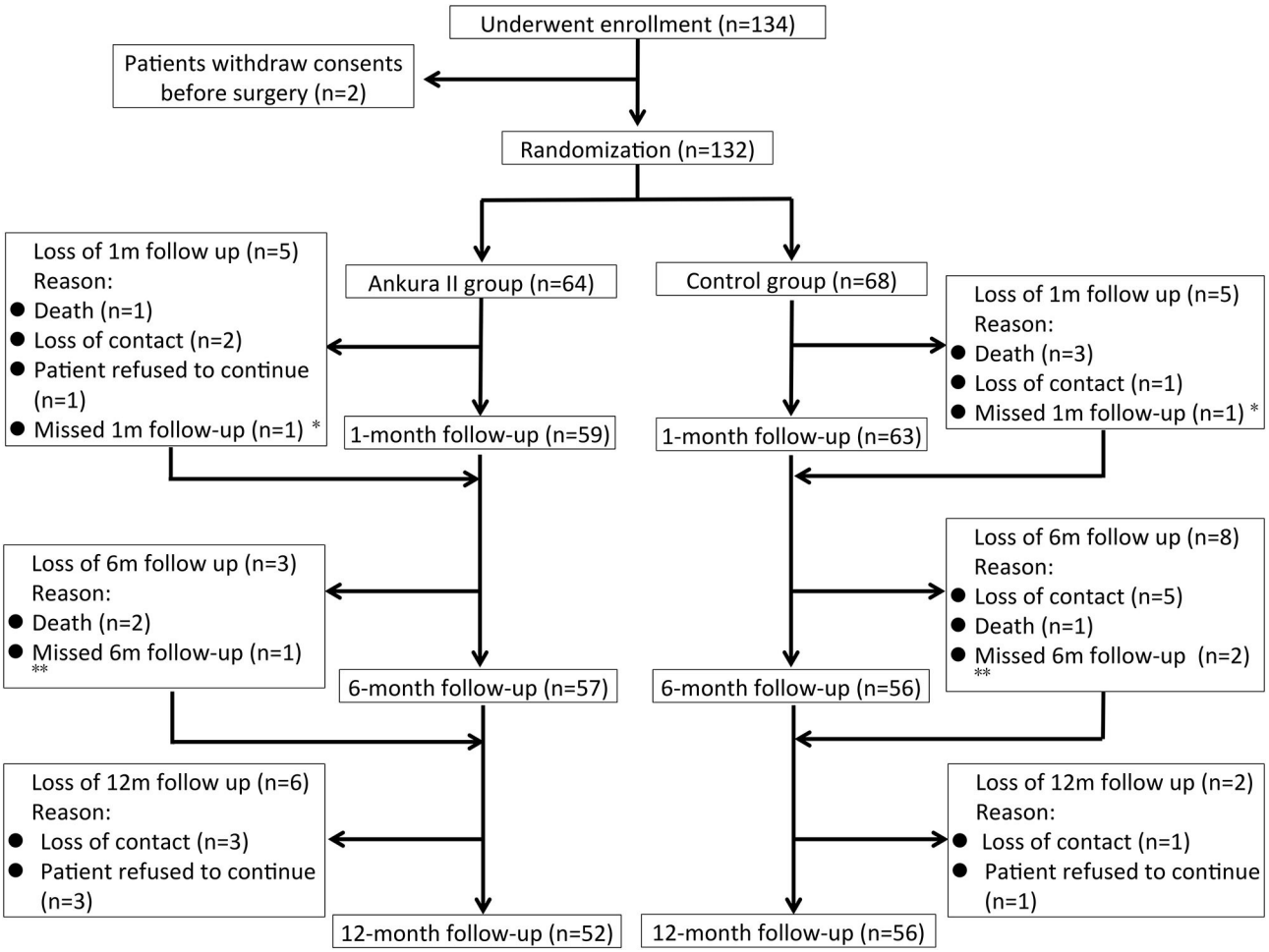

FIGURE 2 | Illustration of the study cohort and the follow-up process. *Ankura II group Patient No. 11 and Ankura group Patient No. 129 missed the 1-month follow-up but finished the 6- and 12-month follow-ups. **Ankura II group Patient No. 117 and Ankura group Patient No. 50 and No. 120 missed the 6-month follow-up but finished the 12-month follow-up.

during follow-up, three different representative aortic planes were selected. Plane 1 was the aorta plane with the maximal diameter. Plane 2 was the aorta plane where the TL was most constricted by the FL. Plane 3 was the aorta plane of the distal end of the stent.

All deaths and MAEs were reported by the participating site and adjudicated by the clinical events committee to determine whether they were secondary to failure of the device, related to the procedure, or both.

The normally distributed continuous variables were expressed as mean ± standard deviation and other continuous variables were presented as median (interquartile range). Categorical variables were expressed as proportions (percentage). The two-sided Student's *t*-test and Mann-Whitney *U* test are used to compare continuous variables. And Chi-square test or Fisher's exact probabilities were used to compare category variables. The cumulative survival estimates were generated by using the Kaplan-Meier non-parametric method and compared using the log-rank test. The primary safety end point, the device-related MAEs rates at 1 month, was submitted to a non-inferiority comparison with a null hypothesis that $Rate_{AnkuraII}$-$Rate_{Ankura} \leq$-.1. (The rate refers the risk of the MAEs)

The sample size calculation was based on power analysis. According to a previous report, the incidence of device-related MAEs was.05 in the control group at the 1-month follow-up (16–18). Based on statistical requirements (unilateral $\alpha = 0.05$, $\beta = 0.20$, non-inferiority margin $\delta = 0.1$), 118 cases were required after calculation. Considering that the 1-month follow-up rate should not be lower than 90%, the total sample size required was 130 cases. In the trial, 132 dissecting patients were enrolled to ensure statistical power.

RESULTS

Follow-Up Process and Results

134 patients with TBADs were enrolled in the study, two of which withdrew consent before surgery. The study cohort and follow-up process are described in **Figure 2**. A total of 108 (81.8%) patients

TABLE 2 | Demographics of the enrolled subjects.

	Ankura II %(n/N)	Ankura %(n/N)	*P*-value
Age (year)	56.4 ± 10.5	55.8 ± 11.7	0.85
Height (cm)	167.0 ± 8.2	166.9 ± 7.4	0.79
Weight (kg)	68.7 ± 12.3	66.8 ± 11.4	0.22
Male	81.3% (52/64)	83.8% (57/68)	0.70
Smoking	42.2% (27/64)	44.1% (30/68)	0.82
Cardiovascular history	65.6% (42/64)	64.7% (44/68)	0.91
Hypertension	64.1% (41/64)	61.8% (42/68)	0.78
Coronary artery disease	1.6% (1/64)	2.9% (2/68)	0.96
PCI	1.6% (1/64)	1.5% (1/68)	0.50
Medical treatment	65.6% (42/64)	64.7% (44/68)	0.91
Cerebral infarction History	3.1% (2/64)	1.5% (1/68)	0.96
Diabetes	6.3% (4/64)	4.4% (3/68)	0.93
COPD	1.6% (1/64)	0% (0/68)	0.48
Chronic renal failure	0% (0/64)	0% (0/68)	
Back pain	67.2% (43/64)	73.5% (50/68)	0.70
Chest pain	15.6% (10/64)	8.8% (6/68)	0.23
Abdominal pain	28.1% (18/64)	22.1% (15/68)	0.69
Asymptomatic	7.8% (5/64)	8.8% (6/68)	0.83
High-rsik TBADs			
Aorta diameter >40 or false lumen diameter >22 mm	79.7% (51/64)	66.2% (45/68)	0.08
Refractory pain	76.6% (49/64)	70.6% (48/68)	0.44
Complicated TBADs			
Ischemia of branch arteries	9.4% (6/64)	11.8% (8/68)	0.66
HR with medicine (bpm)	74.2 ± 10.5	74.5 ± 11.5	0.88
BP with medicine (mmHg)	127.0 ± 19.2/78.2 ± 12.0	126.4 ± 16.1/74.5 ± 9.4	0.85/0.050

Bpm, beats per minute; BP, blood pressure, systolic/diastolic; COPD, Chronic obstructive pulmonary disease; HR, heart rate; PCI, Percutaneous coronary intervention; TBAD, Stanford type B aortic dissection.

completed the 12-month follow-up, 7 patients (5.2%) died during the follow-up, and 17 (12.9%) patients were lost to follow-up. Of the patients who were lost to follow-up, 12 were unfortunately lost to contact, and five patients refused to continue in the study. Overall, 132 patients were included in ITT analysis and 108 patients were included in PP analysis.

Demographics of the Enrolled Subjects

The demographics and risk factors showed no significant differences between the Ankura II and Ankura group (**Table 2**). Based on the definition of high-risk and complicated TBADs from Society for Vascular Surgery in 2020, we clarified the type of TBADs in both group by the data we had. The high risk of TABDs is defined as having an aorta diameter >40 mm or false lumen diameter >22 mm. The complicated TABDs is defined as existing ischemia of branch arteries. 66.2% of patients in Ankura group are high risk patients and 79.7% of patients in Ankura II group are high risk patients ($p = 0.120$). 11.8% of patients in Ankura group are complicated patients and 9.4% of patients in Ankura II group are complicated TABDs patients ($p = 0.656$). Besides, the rates of persistence of pain despite adequate blood pressure control and pain medications was 77.4% in Ankura group vs. 83.1% in Ankura II group ($p = 0.499$).

Baseline Anatomical Features of Aortic Lesions

Comparable baseline anatomical features, including important anatomical factors such as ischemia of branch arteries, primary entry tear site, landing zone situation, and TL and FL diameter, were found between the Ankura II and Ankura group, Detailed information is listed in the **Supplementary data** and **Supplementary Table 1**.

Surgical Procedures

The detailed results of the surgical procedures, including the deployment of stents, anesthesia methods, total surgery time, time for stent deployment, contrast agent volume and digital subtraction angiography (DSA) time, are described and compared (**Supplementary data** and **Supplementary Table 2**). No significant difference was found between the two groups.

Device-Related Major Adverse Events, Mortality, and MAEs

Migration, collapse, fracture, or thrombosis of the stent was not found in either group during the 12-month follow-up, only one stent-related endoleaks (Type IV) occurred in the Ankura II group (**Table 3**). The incidence of 1-month device-related MAEs was 1.6% in the Ankura II group and 0% in the Ankura group.

TABLE 3 | Device-related major adverse events, mortality, and major adverse events.

	1 month (ITT analysis)			12 months (PP analysis)		
	Ankura II (n/N)	**Ankura (n/N)**	***P*-value**	**Ankura II (n/N)**	**Ankura (n/N)**	***P*-value**
Device-related MAEs	1.6% (1/64)	0% (0/68)	0.48	-	-	-
Stent migration	0% (0/64)	0% (0/68)	-	0% (0/52)	0% (0/56)	-
Stent collapse	0% (0/64)	0% (0/68)	-	0% (0/52)	0% (0/56)	-
Stent fracture	0% (0/64)	0% (0/68)	-	0% (0/52)	0% (0/56)	-
Stent thrombosis	0% (0/64)	0% (0/68)	-	0% (0/52)	0% (0/56)	-
Stent-related endoleaks (IV)	1.6% (1/64)	0% (0/68)	.48	1.9% (1/52)	0% (0/56)	0.48
Device-related re-intervention	0% (0/64)	0% (0/68)	-	0% (0/52)	0% (0/56)	-
1-month all-cause mortality	1.6% (1/64)	4.4% (3/68)	0.66	-	-	-
12-month survival	-	-	-	95.2 ± 2.7%	94.1 ± 2.9%	0.77[a]
Major adverse events	5.1% (3/64)	4.7% (3/68)	.73	5.8% (3/52)	8.9% (5/56)	0.72
Cardiovascular events						
Heart failure	1.6% (1/64)	0% (0/68)	0.48	1.9% (1/52)	0% (0/56)	0.48
Cardiac tamponade	0% (0/64)	1.5% (1/68)	>0.99	0% (0/52)	1.8% (1/56)	>0.99
RTAD	0% (0/64)	1.5% (1/68)	>0.99	0% (0/52)	1.8% (1/56)	>0.99
Rupture of dissection	0% (0/64)	1.5% (1/68)	>0.99	0% (0/52)	1.8% (1/56)	>0.99
Ischemia of LSA	0% (0/64)	1.5% (1/68)	>0.99	0% (0/52)	1.8% (1/56)	>0.99
Neurological events						
Stroke	1.6% (1/64)	0% (0/68)	0.48	1.9% (1/52)	3.6% (2/56)	>0.99
Paraplegia	1.6% (1/64)	0% (0/68)	0.48	1.9% (1/52)	0% (0/56)	0.48
Coma	1.6% (1/64)	0% (0/68)	0.48	1.9% (1/52)	0% (0/56)	0.48
Acute kidney injury	0% (0/64)	0% (0/68)	-	0% (0/52)	0% (0/56)	-
Respiratory failure	1.6% (1/64)	0% (0/68)	0.48	1.9% (1/52)	0% (0/56)	0.48
Endoleaks						
Endoleaks I	3.1% (2/64)	0% (0/68)	0.23	1.9% (1/52)	1.8% (1/56)	>0.99
Endoleaks II	1.6% (1/64)	0% (0/68)	0.48	0% (0/52)	0% (0/56)	-
Endoleaks III	0% (0/64)	0% (0/68)	-	0% (0/52)	0% (0/56)	-
Re-intervention rates	1.6% (1/64)	0% (0/68)	0.48	7.7% (4/52)	7.1% (4/56)	>0.99

LSA, left subclavian artery; MAE, major adverse events; RTAD, retrograde type A aortic dissection. [a]Log-rank test; ITT analysis, intention to treat analysis; PP analysis, per-protocol analysis.

And the lower limit of the unilateral 95% CI between the Ankura II and Ankura group was -.055. According to the non-inferiority standard of -.1, the Ankura II stent system was non-inferior to the Ankura stent. No reintervention was required for device related MAEs in either group during the follow-up.

The 1-month all-cause mortality rate for the Ankura II group was 1.6% (1/64), that for the Ankura group was 4.4% (3/68). Considering the loss of follow-up, the 12-month cumulative survival (Ankura II 95.2 ± 2.7% vs. Ankura 94.1 ± 2.9%; $p = 0.769$) was compared instead of the mortality rate. No significant difference was found between the two groups (**Table 3**). The Kaplan-Meier survival analysis with the exact time of death for Ankura II and Ankura patients is presented in **Figure 3**.

One patient in the Ankura II group exhibited paraplegia immediately after surgery and stroke after 5 days. Considering the poor prognosis, his family discontinued all treatment, and the patient unfortunately died. And there were three patients in the Ankura group who died within 1 month. One patient died 1 day after surgery with acute shock possibly due to rupture. Another patient died of acute pericardial tamponade, and RTAD 2 days after surgery. The third patient suddenly died at home 17 days after surgery with unknown cause.

Within 12-month follow-up, there were another two deaths in the Ankura II group. One patient died of multiple organ failure 50 days after surgery, and another died suddenly at home 168 days after surgery with unknown cause. In the Ankura group, one patient suddenly died at home of an unknown cause 65 days after surgery.

The distribution of MAEs at 1 month (ITT analysis, Ankura II: 4.7% (3/64): Ankura: 4.4% (3/68), $p = 0.73$) and 12 months (PP analysis, Ankura II: 5.8% (3/52): Ankura: 8.9% (5/56), $p = 0.718$) is shown in **Table 3**. In the Ankura II group, the cardiovascular events included a 1.6% (1/64) heart failure rate with respiratory failure within 1 month. In the Ankura group, the cardiovascular events included the rupture of dissection (1.5%), ischemia of the LSA (1.5%) and RTAD with cardiac tamponade (1.5%) occurring within 1 month. Neurologic events in the Ankura II group included paraplegia complicated with a later stroke (1.5%) and transient coma (1.5%) within 1 month. In the Ankura group, two stroke events occurred within the 12-month follow-up.

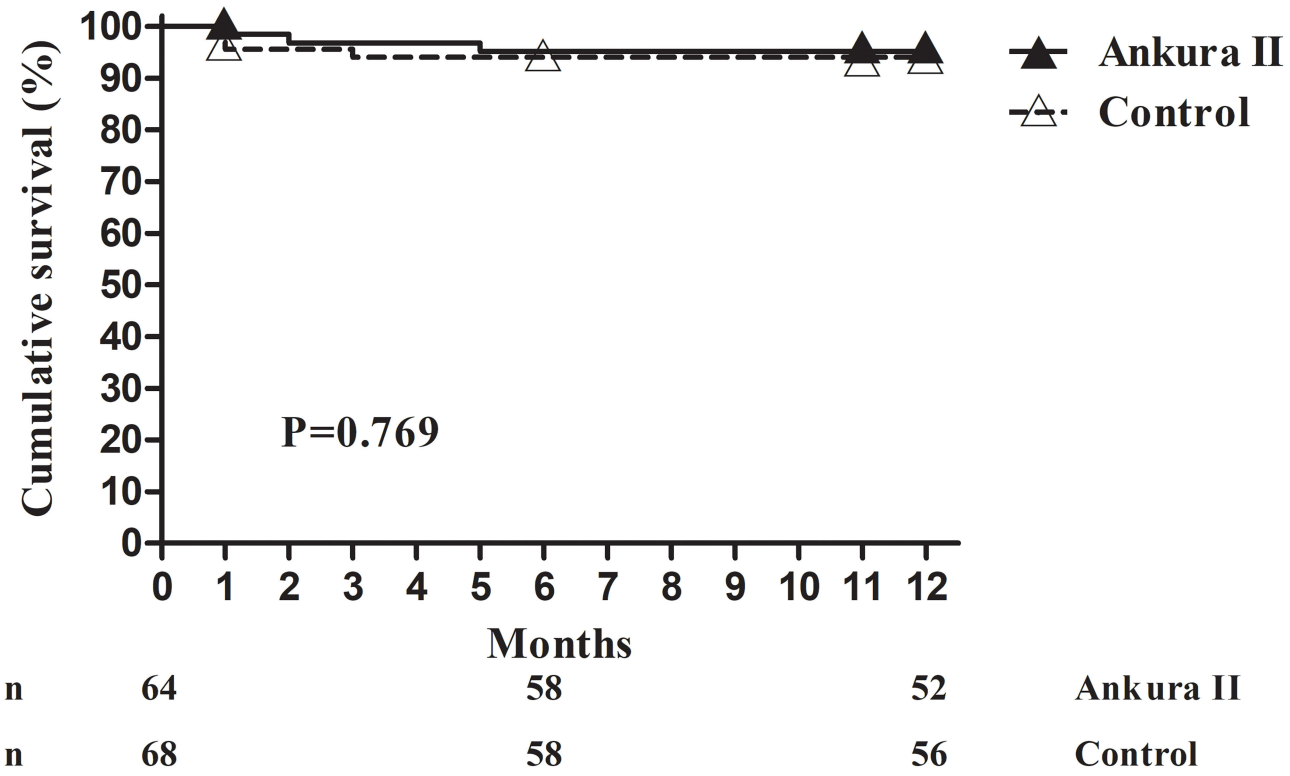

FIGURE 3 | Kaplan-Meier survival analysis. The available number of patients between the Ankura II and Ankura groups was 64 and 68 at 0 months, 58 and 58 at 6 months, and 52 and 56 at 12 months, respectively.

The endoleaks rate was low for both groups. At 1 month, the type I endoleaks rate was 3.1% (2/64) in the Ankura II group and 0% in the Ankura group ($p = 0.232$). At 12 months, the type I endoleaks rate was 1.9% (1/52) in the Ankura II group and 1.8% (1/56) in the Ankura group ($p = 1.000$), medical treatment was continued. Additionally, one type II endoleaks occurred in the Ankura II group within 1 month but disappeared during the 12-month follow-up. No type III endoleaks occurred.

The reintervention rates for 1 month (1.6% vs. 0%: p=.48) and 12 months (7.7 vs. 7.1%: $p = 1.000$) between the Ankura II and Ankura groups are also shown in **Table 3** and no dissection or aneurysm vascular-related intervention occurred in either group. Detailed reintervention events included one lumbar disc herniation, one renal cancer, one multiple organ failure and one adrenal adenoma in the Ankura II group and two strokes, one kidney stone and one lung cancer in the Ankura group.

Stent Effectiveness and Remodeling of TL and FL in TBADs Patients

The 12-month follow-up was completed for 52 patients in Ankura II and 56 patients in Ankura group (**Table 4**). To evaluate the effectiveness of stents and compare the ability of stents to expand the TL and facilitate FL thrombosis in AD patients (51/52 and 55/56 patients in the Ankura II and Ankura group, respectively), the FL thrombosis rate was compared. Three different aorta planes were chosen, and the diameter and area of the TL and FL were measured before surgery and at the follow-up in dissection patients.

The two groups showed comparable clinical success rates-Ankura II: 51/52 (98.1%) vs. Ankura: 54/56 (96.4%), $p = 1.000$. The complete thrombosis rate was significantly increased at 12 months compared with that at the 1-month follow-up in both groups. However, no significant difference in the thrombosis rate was found between the two groups.

The percentage change in the diameter and area 12 months after surgery was calculated before statistical analysis. In Plane 1 and Plane 2, the TL was expanded, and the FL diameter was decreased but without significant difference (**Table 4**). In Plane 3, Ankura II stents showed a possible advantage in facilitating thrombosis of the FL, with a decrease trend in diameter of −100.0% (−100.0 to −100.0%) (vs.−100.0% (−100.0% to −16.4%) for the Ankura; $p = 0.18$) and a decrease trend in area of −100.0% (−100.0% to −67.5%) (vs. −48.5% (−100.0% to −3.6%) for the Ankura; $p = 0.08$). The 12-month follow-up results demonstrated that the Ankura II and Ankura groups both performed well in expanding the TL and aortic remodeling was improved in patients treated with Ankura II.

DISCUSSION

In the present trial, the Ankura II Thoracic Stent Graft System was safe and effective in treating TBADs. In terms of primary

TABLE 4 | Effectiveness of Ankura II, remodeling of the aorta and percentage change in the TL and FL diameter and area in TBADs (PP analysis).

	Ankura II (%)	Ankura (%)	*P*-value
Clinical successful treatment	51/52 (98.1%)	54/56 (96.4%)	>0.99
FL thrombosis rate			
Partially, 1 month	27 (45.8%)	27 (43.5%)	0.81
Completely, 1 month	32 (54.2%)	35 (56.5%)	
Partially, 12 months	20 (39.2%)	15 (26.8%)	0.15
Completely, 12 months	31 (60.8%)	41 (73.2%)	
12-month follow-up			
Plane 1			
Diameter of TL	36.4 (8.1–102.5)	48.2 (23.4–111.0)	0.18
Diameter of FL	−100.0 (−100.0 to −100.0)	−100.0 (−100.0 to −99.8)	0.76
Area of TL	153.7 ± 69.9	36.4 (8.1–102.5)	0.23
Area of FL	−100.0 (−100.0 to −100.0)	−100.0 (−100.0 to −100.0)	0.17
Plane 2			
Diameter of TL	90.39 (8.6–332.3)	89.9 (25.1–225.1)	0.90
Diameter of FL	−100.0 (−100.0 to −95.8)	−100.0 (−100.0–95.34)	0.72
Area of TL	267.9 ± 79.1	170.2 ± 30.8	0.99
Area of FL	−100.0 (−100.0 to −93.5)	−100.0 (−100.0 to −93.5)	0.99
Plane 3			
Diameter of TL	56.8 (11.4–118.3)	32.9 (1.4–121.0)	00.35
Diameter of FL	−100.0 (−100.0 to −100.0)	−100.0 (−100.0 to −16.4)	**0.18**
Area of TL	128.7 ± 33.9	146.2 ± 49.8	0.82
Area of FL	−100.0 (−100.0 to −67.5)	−48.5 (−100.0 to −3.6)	**0.08**

FL, false lumen; TL, true lumen. "-" stands for decrease in the diameter and area. PP analysis, per-protocol analysis. Plane 1 was the aorta plane with the maximal diameter. Plane 2 was the aorta plane where the TL was most constricted by the FL. Plane 3 was the aorta plane of the distal end of the stent.

outcomes, no migration, collapse, fracture, or thrombosis of the stent occurred. Comparisons of the 1-month and 12-month MAEs showed no significant difference between Ankura and Ankura II. And comparison of 1-month and 12-month secondary outcomes further demonstrated that Ankura II had possible advantages in promoting FL thrombosis. Both groups had a low 1-month all-cause mortality rate (Ankura II 1.7 vs. Ankura 4.5%) and a high 12-month survival rate (Ankura II 94.2 ± 2.8 vs. Ankura 92.9 ± 3.1%) compared to other studies (7). Lower mortality rates are believed to result from multiple factors, including improvement in the stent design, good preoperative preparation and blood pressure control, and restricted inclusion criteria that excluded complicated cases.

Despite the benefits of TEVAR over conventional open repair, its adverse effects, reintervention rates and endoleaks events still raise concerns, particularly in situations with an unfavorable anatomy (9, 19). Notably results published by other centers suggest that the diameter mismatch between the stent and aortic lesions may be related to the occurrence of RTAD (10). In our trial, because of a smaller distal end diameter design compared to Ankura (27.7 ± 3.3 mm for Ankura II vs. 29.6 ± 3.1 mm for the Ankura; $p < 0.001$), the distal end of the stent in the Ankura II group complied better with the anatomy of the aorta. And follow-up results coincidentally showed that one RTAD and another dissection rupture occurred in the Ankura group. Furthermore, published results reveal that the rate of secondary intervention after elective TEVAR ranges from 0 to 32.3%, 1 month to 5 years, respectively (12, 20–22). Most were performed because of endoleaks or device-related complications. In our study, the reintervention rates for Ankura II group at 1 month is 1.7 and 7.7% after 12 months follow up.

Given the fact both endoleaks and reintervention rate are low in our study, we think it is most likely because of the improvements in the device design, thus resulting a better adherence between the graft and aorta, which also reminds surgeon to pay more attention to stent graft instructions when planning TEVAR to get a better adherence. But our follow up time is only 1 year, our data is far from sufficient to make any conclusions. the long-term reintervention rates and endoleaks are still required in following up and future studies are still warranted to prove the above conclusion.

Another interesting finding of current study is we found Ankura II stents could facilitate FL thrombosis better compared to the first-generation stent near the stent distal end area. As is all known, remodeling of the aorta after stent deployment, particularly FL thrombosis, is critical for stent stability and long-term outcomes (11). More importantly, the diameter of FL is negatively correlated with survival in patients undergoing endovascular therapy for chronic TBADs (12). Our trial showed the complete FL thrombosis rates at 12 months are 60.8 and 73.2% in the Ankura II and Ankura groups, respectively. Moreover, both groups had successful and satisfactory TL expansion rates and FL reducing rates. Ankura II stents also showed a possible advantage in facilitating FL thrombosis near the stent distal end area, with a decrease in the diameter (85.7 ± 4.4 vs. 66.9 ± 7.8%; $p = 0.048$) and a decrease in area (77.4 ±

7.9% (vs. 49.6 ± 10.1%). We speculate it is because of the tapered design of Ankura II and leading to better adhesion between the stent and aorta. And the availability of longer-length devices may also contribute to these more favorable outcomes (174.1 ± 19.2 mm for Ankura II vs. 165.6 ± 14.0 mm for the Ankura, $p = 0.003$). However, close postoperative surveillance by imaging with CTA or magnetic resonance angiography (MRA) remains extremely important for long-term results.

Several unavoidable limitations exist in this study. First, as a non-inferiority study, the non-inferiority margin (0.1) is a little wider compared to the incidence of MAEs (0.05), which makes the results underpower. Second, the follow up rate of current study is low (82.8% at 1 month) and thus have many missing data, making either ITT analysis or PP analysis have the type II or type I bias. And our total follow up time is limited (1 year), which is insufficient to make statistical conclusion. Finally, we haven't distinguished the complicated and uncomplicated TBAD during the patients recruiting process. Given the fact the complicated and uncomplicated TBAD behave differently in terms of MAE (23, 24), this is one major weakness of our study.

Overall, the 1-year outcomes from our prospective, randomized, multicenter study demonstrate that Ankura II shows comparable results to Ankura for treating TBADs and yields low mortality rates, MAEs and reintervention rates. Additionally, Ankura II shows a possible advantage in FL thrombosis. More data are warranted to evaluate the long-term effects of Ankura II and its performance in complicated cases.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of each participating institution. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CS and HH designed the study. HH, WF, WG, ML, EX, SG, XC, ZX, SY, JH, XD, ZW, WL, QZ, and FG collected the clinical data. HH, QL, LW, ML, XL, and JW analyzed and interpreted the data. HH and CS wrote the draft. CS, HH, WF, WG, ML, EX, SG, XC, ZX, SY, JH, XD, ZW, WL, QZ, QL, LW, ML, XL, JW, and FG edited the final version. CS guided all the process. 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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Appropriate Timing of Coronary Artery Bypass Graft Surgery for Acute Myocardial Infarction Patients: A Meta-Analysis

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Background: Currently, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are commonly used in the treatment of coronary atherosclerotic heart disease. But the optimal timing for CABG after acute myocardial infarction (AMI) is still controversial. The purpose of this article was to evaluate the optimal timing for CABG in AMI.

Methods: We searched the PubMed, Embase, and Cochrane library databases for documents that met the requirements. The primary outcome was in-hospital mortality. The secondary outcomes were perioperative myocardial infarction (MI) incidence and cerebrovascular accident incidence.

Results: The search strategy produced 1,742 studies, of which 19 studies (including data from 113,984 participants) were included in our analysis. In total, 14 studies compared CABG within 24 h with CABG late 24 h after AMI and five studies compared CABG within 48 h with CABG late 48 h after AMI. The OR of in-hospital mortality between early 24 h CABG and late 24 h CABG group was 2.65 (95%CI: 1.96 to 3.58; $P < 0.00001$). In the undefined ST segment elevation myocardial infarction (STEMI)/non-ST segment elevation myocardial infarction (NSTEMI) subgroup, the mortality in the early 24 h CABG group (OR: 3.88; 95%CI: 2.69 to 5.60; $P < 0.00001$) was significantly higher than the late 24 h CABG group. Similarly, in the STEMI subgroup, the mortality in the early 24 h CABG group (OR: 2.62; 95% CI: 1.58 to 4.35; $P = 0.0002$) was significantly higher than that in the late 24 h CABG group. However, the mortality of the early 24 h CABG group (OR: 1.24; 95%CI: 0.83 to 1.85; $P = 0.29$) was not significantly different from that of the late 24 h CABG group in the NSTEMI group. The OR of in-hospital mortality between early 48 h CABG and late 48 h CABG group was 1.91 (95%CI: 1.11 to 3.29; $P = 0.02$). In the undefined STEMI/NSTEMI subgroup, the mortality in the early 48 h CABG group (OR: 2.84; 95%CI: 1.31 to 6.14; $P < 0.00001$) was higher than the late 48 h CABG group. The OR of perioperative MI and cerebrovascular accident between early CABG and late CABG group were 1.38 (95%CI: 0.41 to 4.72; $P = 0.60$) and 1.31 (95%CI: 0.72 to 2.39; $P = 0.38$), respectively.

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Conclusion: The risk of early CABG could be higher in STEMI patients, and CABG should be delayed until 24 h later as far as possible. However, the timing of CABG does not affect mortality in NSTEMI patients. There was no statistical difference in perioperative MI and cerebrovascular accidents between early and late CABG.

Keywords: myocardial infarction, coronary artery bypass graft, early surgery, late surgery, meta-analysis

INTRODUCTION

Coronary heart disease (CHD), which is the main cause of death in middle-aged and elderly people, can lead to angina pectoris, myocardial infarction, and ischemic heart failure. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) can reconstruct adequate blood supply in myocardial blood supply areas caused by severe coronary artery stenosis (1). Although PCI has become the main intervention method for acute myocardial infarction (AMI), CABG is still a safe and feasible choice for patients with acute coronary syndrome (ACS). Moreover, it is an appropriate treatment for PCI failure, severe multivessel disease, or diabetes mellitus (2). CABG can obtain complete revascularization earlier and minimize cardiac ischemia.

However, the optimal timing for CABG is still controversial. Most of the literature does not define early CABG clearly, and the statistics were based more on the CABG time limit of 24 or 48 h. Some previous studies have shown that the mortality was higher in the early CABG (within 1 day, 2 days, or 1 week) group. Delayed CABG surgery was recommended in patients with AMI to reduce mortality. However, other research studies (3–9) showed that the timing of CABG did not affect the mortality of patients with ST segment elevation myocardial infarction (STEMI) or non-ST segment elevation myocardial infarction (NSTEMI). Therefore, the purpose of this study was to compare the mortality of early CABG (within 24 or 48 h after AMI) with that of late CABG for the optimal timing of CABG in patients with AMI, so as to better practice in the clinical work.

METHODS

Publication Search

Two trained researchers independently searched articles in PubMed, Embase, and Cochrane library databases for suitable studies. The search form is [Myocardial Infarction (MeSH Terms)] OR [Infarction, Infarction (title/Abstract)] OR [Infarctions, Myocardial (title/Abstract)] OR [Myocardial infants (title/Abstract)] OR [Cardiovascular Stroke (title/Abstract)] OR [Cardiovascular Strokes (title/Abstract)] [Stroke, Cardiovascular (title/Abstract)] OR [Strokes, Cardiovascular (title/OR)] OR (Myocardial Infarctt) [Cardiovascular Stroke (title/Abstract)] OR [Cardiovascular Stroke (title/Abstract)] [Cardiovascular (title/Abstract)] [Myocardial (title/Abstract)] OR [Infarcts, Infarcts (title/Abstract)] OR [Myocardial infants (title/Abstract)] OR [Heart targets (title/Abstract)] OR [Heart targets (title/Abstract)] AND [coronary artery bypass (MeSH Terms)] AND [coronary artery bypass (MeSH Terms)] OR (Artery Bypass, (title/Abstract)] OR [Artery Bypasses, (title/Abstract)] [Coronary artists (title/Abstract)] OR [Coronary Artery classes (title/Abstract)] OR [Coronary Artery Bypass surfaces (title/Abstract)] OR [Bypass, Coronary Artery (title/Abstract)] OR [Aortocoronary Bypass (title/Abstract)] OR [Aortocoronary Bypasses (title/Abstract)] OR [Bypass, Aortocoronary (title/Abstract)] OR [Bypasses, Aortocoronary (title/Abstract)] OR [Aortocoronary Bypass (title/Abstract)] OR [Aortocoronary Bypasses (title/Aortocoronary)] OR [Aortocoronary Bypasses (title/title)] OR [Aortocoronary Bypasses (title/title)] Coronary Artery Bypass [Coronary surfaces (title/Abstract)] OR [Bypass, Coronary Art (title/Abstract)] OR [Aortocoronary Bypass (title/Abstract)] [Coronary artifact (title/Abstract)] OR [Coronary Artery Bypass grafting (title/Abstract)] OR [CABG (title/Abstract)] AND [time (Title/Abstract)] OR [early surgery (title/Abstract)] OR [late surgery (Title/Abstract)]. The purpose of this search strategy is to include the effects of early 24 or 48 h CABG and late 24 or 48 h CABG on in-hospital mortality in AMI. In addition, we also manually searched and supplemented the relevant literature.

Study Selection and Data Extraction

The references were examined independently by two researchers, and the criteria were as follows: (1) population: patients undergoing CABG; (2) intervention: CABG in the early stage of AMI (<24 and <48 h); (3) comparative intervention: late CABG (>24 and >48 h); (4) results: the primary outcome included in-hospital mortality and the secondary outcome involved perioperative MI and cerebrovascular accident; and (5) study design: clinical-controlled trial. The exclusion criteria were as follows: (1) PCI for patients; (2) overlapping population; and (3) pediatric studies. The two researchers conducted an independent evaluation of the selected study and finally reached a consensus with a third researcher to resolve the final differences.

Two authors independently extracted data from the research and analyzed it. The included research should meet the criteria. The primary outcome was in-hospital mortality. The secondary outcomes were perioperative MI incidence and cerebrovascular accident incidence.

Statistical Analysis

We evaluated the difference in in-hospital mortality between the early CABG group and the late CABG group. The types of myocardial infarction were divided into STEMI and NSTEMI and analyzed by subgroup analysis. The confidence intervals of odds ratio (OR) and 95%CI are used as summary statistics. Statistical heterogeneity is summarized by I^2 statistics. The fixed-effect model or the random-effect model was selected according

TABLE 1 | Characteristics of the included studies.

References	Country	Patient number (n)	Type of MI	Time to CABG (day)	Age(years)	Gender (female), %	Patient number (n)	In hospital death (n)	In hospital mortality (%)	NOS
Braxton et al. (13)	United States	116	STEMI/NSTEMI	<2	NG	55 (4)	7	3	42.9	6
				3–5		23 (3)	13	1	7.7	
				6–42		27 (26)	96	5	5.2	
Creswell et al. (12)	United States	2296	STEMI/NSTEMI	<0.25	62.3 ± 12.0	NG	11	1	9.1	6 6
				0.25–2	65.0 ± 11.3		132	11	8.3	
				2–14 14–42	63.9 ± 10.7		869	45	5.2	
				>42	65.1 ± 10.5		261	17	6.5	
					63.6 ± 10.0		1023	30	2.9	
Kaul et al. (3)	United States	642	STEMI/NSTEMI	<0.25	NG	NG	46	9	19.56	
				0.25–1			121	5	4.13	
				1–3			140	6	4.28	
				3–7			135	5 8	3.7	
				7–14			129	5	6.2	
				14–28			71		7	
Lee et al. (4)	United States	316	STEMI/NSTEMI	<1	NG	NG	37	8	26.0	7
				1–7			125	4	3.2	
				8–21			154	4	2.6	
Bana et al. (14)	India	123	STEMI/NSTEMI	<2	NG	NG	10	2	20	6
				3–14			36	1	2.8	
				15–30			77	1	1.3	
Lee et al. (15)	United States	44365	STEMI/NSTEMI	<0.25	NG	NG	885	104	11.8	7
				0.25–1			556	53	9.5	
				>1			42924	1207	2.8	
Lee et al. (16)	United States	32099	STEMI	<0.25	NG	27.8 (157)	564	80	14.2	8
				0.25–1		23.4 (78)	333	46	13.8	
				1–3		25.9 (45)	946	75	7.9	
				4–7		26.1 (788)	3021	115	3.8	
				8–14		26.6 (1095)	4118	119	2.9	
				>15		24.2 (5594)	23117	624	2.7	
Voisine et al. (10)	Spain	7219	STEMI/NSTEMI	<0.25	NG	NG	26	5	19.2	8
				0.25–1			51	5	9.8	
				1–7			313	27	8.6	
				8–30			917	29	3.2	
				>30			5912	144	2.4	
Thielmann et al. (11)	Germany	138	STEMI	<0.25	NG	NG	37	4	10.8	8
				0.25–1			21	5	23.8	
				1–3			15	1	6.7	
				4–7			24	1	4.2	
				8–14			41	1	2.4	
Weiss et al. (17)	United States	9476	STEMI/NSTEMI	<2	66.6	NG	4676	262	5.6	8
				>2	68.6		4800	182	3.8	
Parikh et al. (5)	United States	2647	NSTEMI	<2	63.0	24.5 (202)	825	30	3.6	8
				>2	65.0	31.7 (578)	1822	69	3.8	
Filizcan et al. (18)	Turkey	85	STEMI	<0.25	NG	NG	33	2	6.1	7
				0.25–1			24	12	50.0	
				15–30			28	2	7.1	
Assmann et al. (19)	Germany	1168	STEMI/NSTEMI	<0.25	66.3 ± 13.4	27 (4)	14	2	14.8	8
				0.25–1	66.5 ± 12.5	28 (14)	51	5	10.2	
				2–3	68.4 ± 13.6	23.2 (22)	96	8	8.8	
				4–10	66.5 ± 13.2	24.8 (29)	116	5	4.2	
				11–20	66.2 ± 12.8	271 (99)	366 525	8	2.3	
				21–30	67.4 ± 13.2	26.9 (141)		10	2.0	
Davierwala et al. (6)	Germany	758	NSTEMI	<1	68.0 ± 10.0	23.3 (31)	133	8	6.0	8
				1–3	70.0 ± 10.0	26.6 (51)	192	9	4.7	
				3–21	70.0 ± 10.0	23.8 (103)	433	22	5.1	
Khan et al. (7)	United States	184	STEMI	<1	63.0 ± 12.0	25 (26)	105	19	18.1	8
				>1	66.1 ± 11.0	33 (26)	79	9	11.4	

(Continued)

TABLE 1 | (Continued)

References	Country	Patient number (n)	Type of MI	Time to CABG (day)	Age(years)	Gender (female), %	Patient number (n)	In hospital death (n)	In hospital mortality (%)	NOS
Nichols et al. (20)	United States	3060	STEMI/NSTEMI	<1	NG	23.2 (23)	99	5	5.0	8
				1–2		27.6 (102)	369	7	2.0	
				3–7		24 (472)	1966	33	2.0	
				8–21		26.7 (167)	626	14	2.0	
Liakopoulos et al. (8)	Germany	1836	STEMI/NSTEMI	<1	NG	NG	369	47	12.7	7
				1–3			434	32	7.4	
				>3			468	36	7.7	
Lemaire et al. (21)	United States	5963	STEMI	<1	62.8 ± 11.6	24 (408)	1697	139	8.0	8
				2–3	63.2 ± 11.0	23.3 (501)	2154	75	4.0	
				4–7	63.2 ± 10.8	22.3 (471)	2112	61	3.0	
Bianco et al. (9)	United States	2058	STEMI/NSTEMI	<1	66.0	26.39 (76)	288	12	4.1	8
				>1	66.0	29.31 (519)	1770	81	4.6	

CABG, coronary artery bypass graft; MI, myocardial infarction; NG, not given; NOS, Newcastle–Ottawa Scale; OR, odds ratio; STEMI, ST segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction.

to heterogeneity. The overall effect was determined by the *Z*-test, Review Manager, version5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Characteristics

The search strategy produced 1,742 studies, of which 19 (data from 113,984 participants) were included in our analysis (**Table 1**). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart provided detailed descriptions of publication screening and reasons for exclusion are shown in **Figure 1**. There were 6 prospective studies (3–5, 8, 10, 11) and 13 retrospective studies (6, 7, 9, 12–21). A total of 7 studies (7–9, 11, 16, 18, 21) were evaluated in the STEMI population, 4 studies (5, 6, 8, 9) were evaluated in the NSTEMI population, and 10 studies (3, 4, 10, 12–15, 17, 19, 20) were evaluated in undefined STEMI/NSTEMI population. Two studies (8, 9) analyzed the data from patients of both STEMI and NSTEMI groups at the same time. We evaluated the quality of each literature according to Newcastle–Ottawa Scale (NOS). The funnel plot was symmetrical, which suggested no significant publication bias (**Figure 2**).

Primary Outcome

Early 24 h vs. Late 24 h Coronary Artery Bypass Grafting

We used in-hospital mortality as the primary outcome. A total of 14 studies were included, including 99,326 patients. Overall, in the early 24 h CABG group, in-hospital mortality was 4.0–24.6% and the average in-hospital mortality rate was 10.5% (575/5490). In the late 24 h CABG group, the in-hospital mortality was 1.8–11.4% and the average in-hospital mortality was 3.0% (2788/93836). The OR of in-hospital mortality between early 24 h CABG and late 24 h CABG group was 2.65 (95%CI: 1.96 to 3.58; $Z = 6.35$; $I^2 = 81\%$; $P < 0.00001$).

In addition, we divided the entire population into STEMI subgroup, NSTEMI subgroup, and undefined STEMI/NSTEMI subgroup. Subgroup analyses showed that in SETMI and undefined STEMI/NSTEMI subgroups, the mortalities in the early 24 h CABG group were significantly higher than those in the late 24 h CABG group (**Figure 3**). However, the heterogeneity of the STEMI group is very high. In the STEMI group, after excluding a study (16), we found that heterogeneity decreased significantly, and the conclusion was still consistent. However, in the NSTEMI subgroup, there was no significant difference in the mortality between the early 24 h CABG group and the late 24 h CABG group (OR: 1.24; 95%CI: 0.83 to 1.85; $I^2 = 0\%$; $Z = 1.06$; $P = 0.29$). The early 24 h CABG was associated with increased mortality except for the NSTEMI population.

Early 48 h vs. Late 48 h Coronary Artery Bypass Grafting

A total of 5 studies were included, including 14,658 patients. In the early 48 h CABG group, the in-hospital mortality was from 3.6 to 42.9%, and the average in-hospital mortality was 5.5% (309/5661). In the late 48 h CABG group, the in-hospital mortality was from 1.8 to 5.5%, and the average in-hospital mortality was 3.9% (351/8997). The OR of in-hospital mortality between the early 48 h CABG and the late 48 h CABG group was 1.91 (95%CI: 1.11 to 3.29; $Z = 2.34$; $I^2 = 74\%$; $P = 0.02$). In the undefined STEMI/NSTEMI subgroup, the mortality in the early 48 h CABG group (OR: 2.84; 95%CI: 1.31 to 6.14; $Z = 2.64$; $I^2 = 72\%$; $P < 0.00001$) was higher than that in the late 48 h CABG group. In the NSTEMI subgroup, only one study was included, and heterogeneity could not be calculated, with no difference in mortality between the early 48 h CABG and the late 48 h CABG group (OR: 0.96; 95%CI: 0.62 to 1.48; $Z = 0.19$; $P = 0.85$) (**Figure 4**).

Secondary Outcomes

Perioperative MI and cerebrovascular accident were selected as secondary outcomes. The OR of perioperative MI incidence between early 24 or 48 h CABG and late 24 or 48 h CABG group was 1.38 (95%CI: 0.41 to 4.72; $Z = 0.52$; $I^2 = 81\%$; $P = 0.60$). In the NSTEMI subgroup, there was no significant difference in the perioperative MI between the early 24 or 48 h CABG group

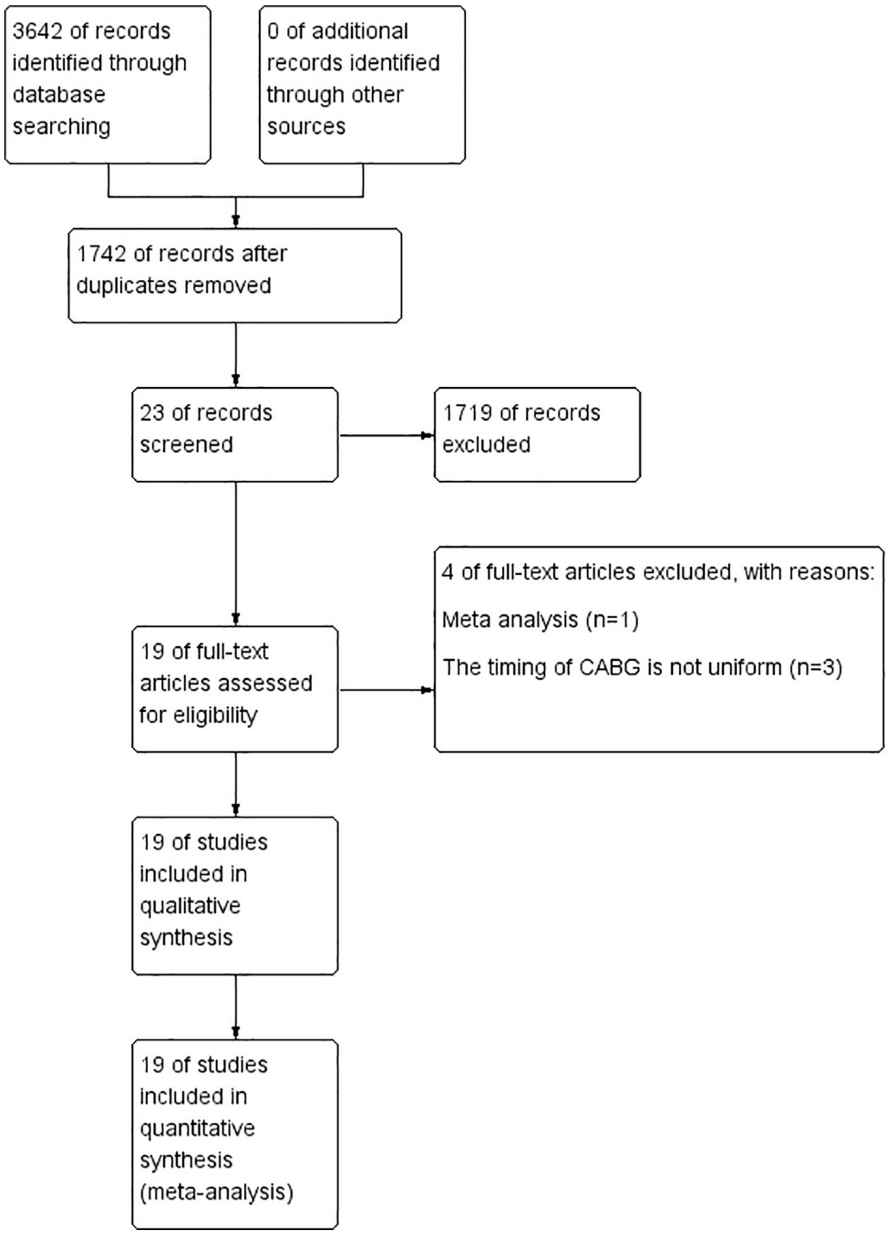

FIGURE 1 | Study selection flow diagram.

(OR:0.73; 95%CI: 0.37 to 1.44; $Z = 0.91$; $I^2 = 0\%$; $P = 0.36$) and the late 24 or 48 h CABG group. In the undefined STEMI/NSTEMI subgroup, heterogeneity could not be calculated because only one article was included. The OR of cerebrovascular accident incidence between early 24 or 48 h CABG and late 24 or 48 h CABG group was 1.31 (95%CI: 0.72 to 2.39; $Z = 0.87$; $I^2 = 47\%$; $P = 0.38$). In the undefined STEMI/NSTEMI subgroup, the OR was 2.32 (95%CI: 1.31 to 4.11; $Z = 2.88$; $I^2 = 0\%$; $P = 0.04$). In the STEMI subgroup, the OR was 1.45 (95%CI: 0.44 to 4.76; $Z = 0.62$; $I^2 = 0\%$; $P = 0.54$). In the NSTEMI subgroup, the OR was 0.49 (95%CI: 0.11 to 2.21; $Z = 0.93$; $I^2 = 67\%$; $P = 0.35$) (**Figures 5**, **6**).

DISCUSSION

The optimal CABG time of patients with AMI is still a matter of debate. The results of a previous meta-analysis (22) showed that early CABG (within 24 or 48 h)after AMI increased patient mortality. However, only insufficient data for NSTEMI patients was available. Moreover, some of the recent studies we included contradicted the previous conclusion. In this article, patients with different types of myocardial infarction were divided into early 24 or 48 h CABG group and late 24 or 48 h CABG group. In conclusion, in the STEMI group, early CABG was associated with higher mortality, while in the

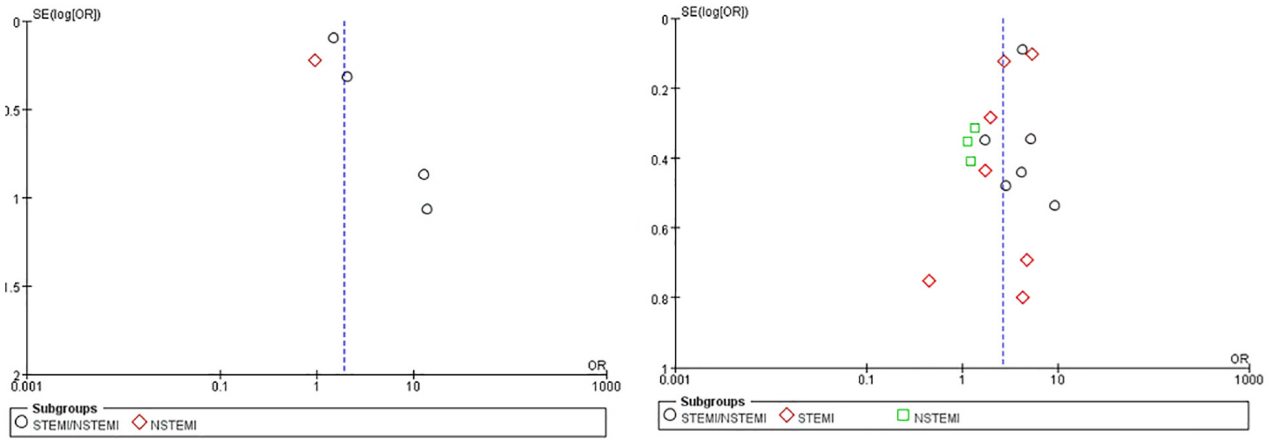

FIGURE 2 | The funnel plot for included studies. The funnel plot was symmetrical which meant no significant publication bias. The former compared early 48 h CABG with late 48 h CABG, the latter compared early 24 h CABG with late 24 h CABG.

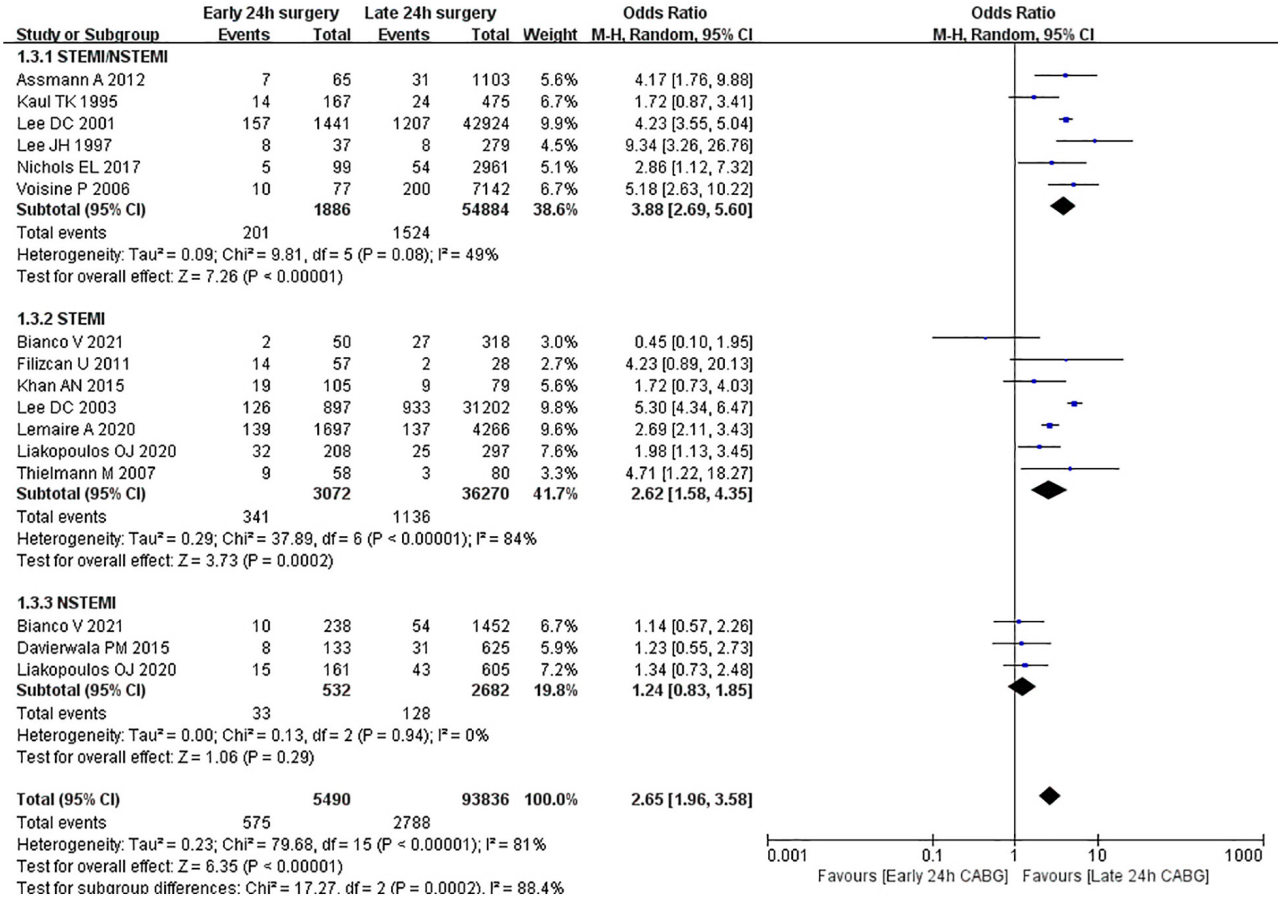

FIGURE 3 | In-hospital mortality in early 24 h CABG groups vs. late 24 h CABG groups.

NSTEMI group, the timing of CABG surgery did not affect the mortality of patients.

Some professionals recommended avoiding emergency CABG surgery for patients with STEMI because of the higher incidence of complications and mortality. Studies have shown that early coronary artery revascularization may increase the risk of death. If there was no absolute indication for emergency surgical intervention, such as structural complications and persistent

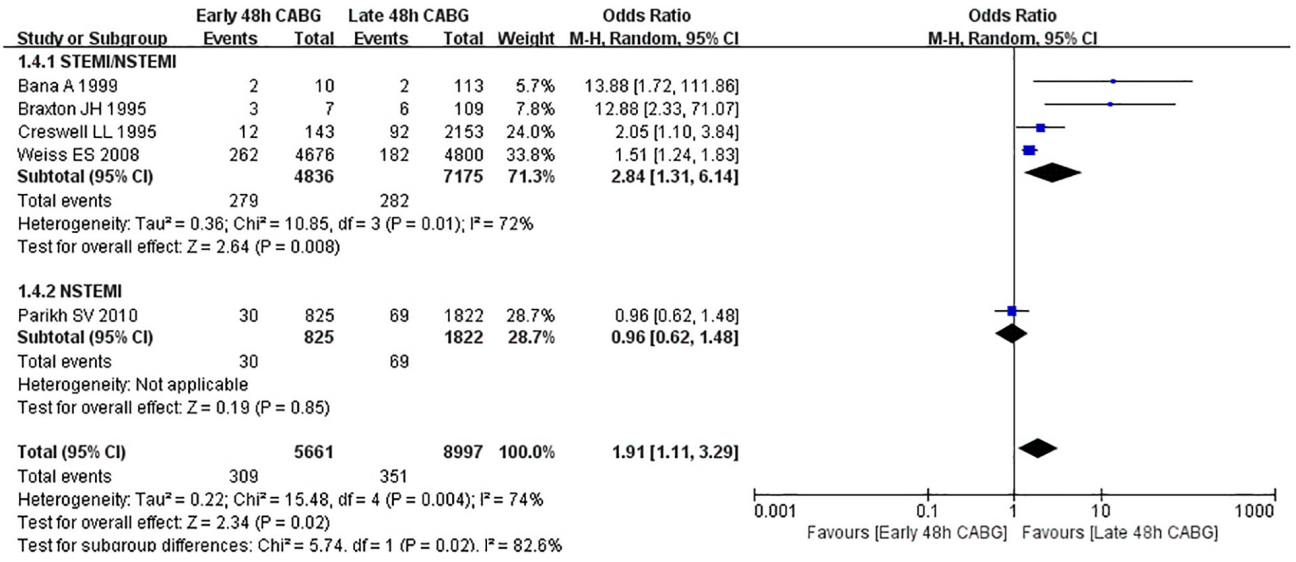

FIGURE 4 | In-hospital mortality in early 48 h CABG groups vs. late 48 h CABG groups.

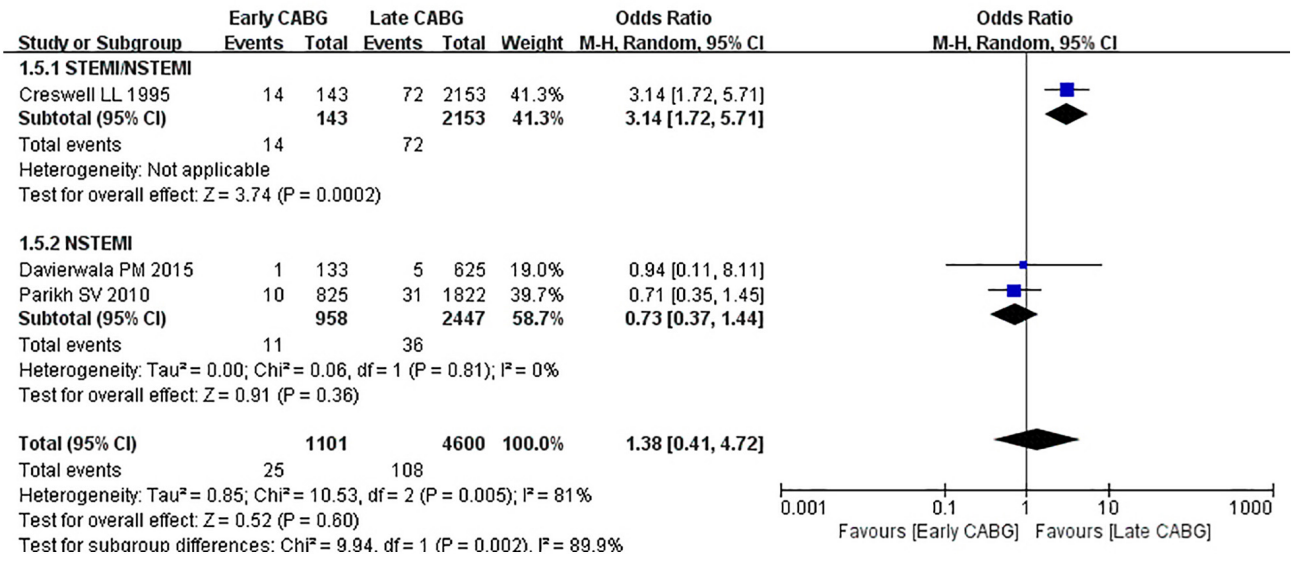

FIGURE 5 | Perioperative myocardial infarction in early CABG groups vs. late CABG groups.

ischemia, delayed surgery should be considered (8, 11, 16, 21). Additionally, other studies have identified early or emergency CABG as predictors of higher mortality (15, 17). On the contrary, studies (7, 9, 18) also showed that the timing of CABG surgery did not affect the mortality of patients with STEMI. It is worth noting that Bianco V et al. (9) conducted a large single-center retrospective study, which adjusted the baseline characteristics of patients in the early CABG group and the late CABG group by tendency score. Previous studies failed to identify the timing of CABG as an independent predictor of mortality (3, 23, 24).

There were several possibilities contributing to these contradictory conclusions: first, serum C-reactive protein (CRP), a marker of an acute inflammatory response, has been reported to rise sharply after transmural AMI, and it plateaued on day 3 after infarction. Furthermore, this peak level was a strong indicator of outcome after a first transmural myocardial infarction (25, 26). At the elevated stage of CRP, early surgical revascularization after AMI might further enhance this systemic inflammatory response and affect the prognosis because CABG was known to cause an increase in serum CRP level with or without cardiopulmonary bypass (27). Second, each surgeon and hospital may use different protocols and standards related to surgical techniques, cardiopulmonary bypass, and cardiac cardioplegia. Third, patients who need early CABG have

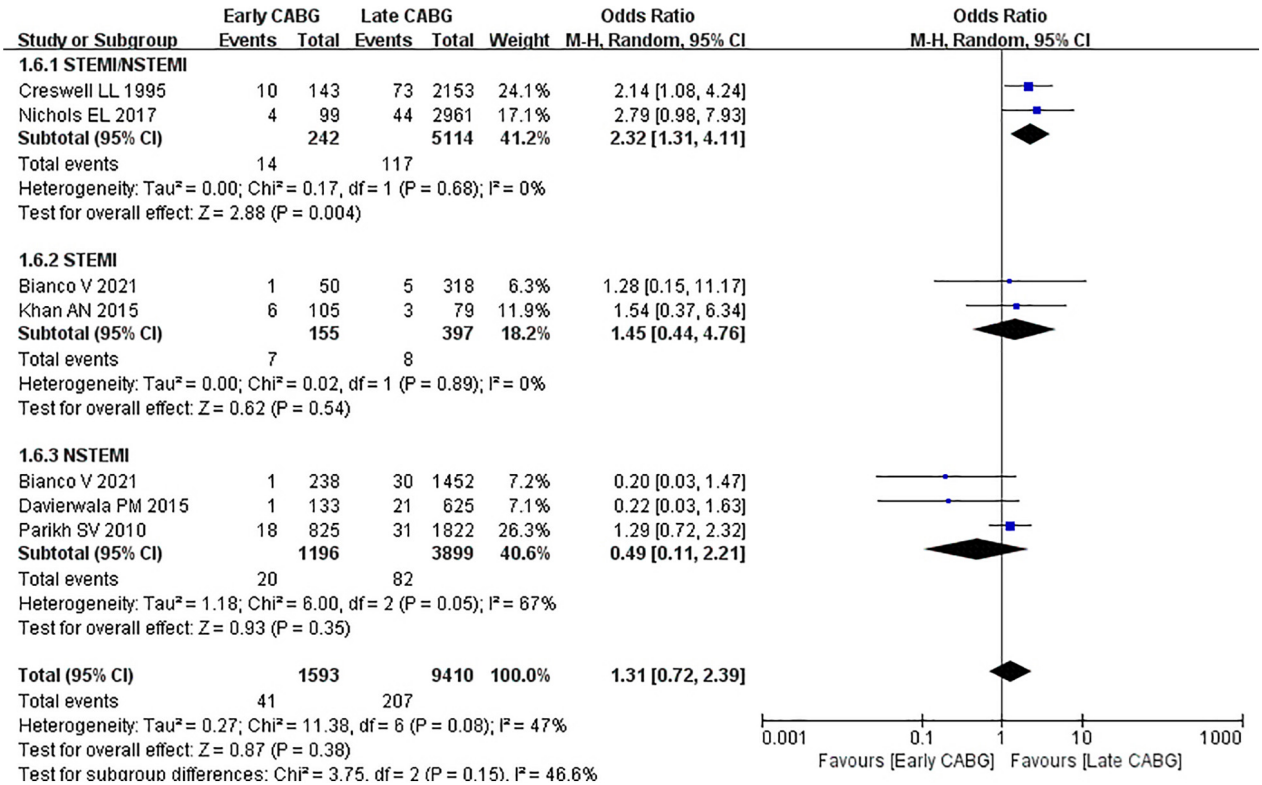

FIGURE 6 | Cerebrovascular accident in early CABG groups vs. late CABG groups.

significantly more complications, and surgeons have to perform immediately. Meanwhile, some patients in critical condition who could not afford early CABG were able to choose assisted circulation, such as cardiopulmonary bypass (CPB), to maintain hemodynamics, and then followed the treatment of CABG to obtain personalized and patient-friendly treatment strategies. On the other hand, some critical patients who were eligible for early CABG but did not undergo surgery for other reasons should be compared to other patients in the early CABG group, which was more meaningful. Although, some studies have shown that early CABG increased mortality in patients with STEMI, the optimal timing of CABG after AMI has not been determined. It is necessary to carry out appropriate effective RCT to determine whether early CABG actually increases patient mortality.

The incidence of NSTEMI has increased significantly compared to STEMI (28). Due to the progress of myocardial protection and mechanical support technology and the improvement of anesthesia and perioperative management in patients undergoing cardiac surgery, surgical intervention played an important role in the treatment of all these clinical conditions. CABG was used as a treatment choice for patients with NSTEMI. For NSTEMI patients, some researchers believed that the timing of CABG surgery after AMI did not affect the mortality of patients. Although the results of the study showed that there was no significant difference between early and late CABG, delayed surgical intervention in NSTEMI patients may lead to increased use of hospital resources, with little benefit to the patients (5). NSTEMI was characterized by non-transmural necrosis. Early blood supply reconstruction can prevent progression into transmural necrosis, limiting ventricular remodeling and maintaining left ventricular function.

In summary, the current literature comparing the timing of CABG following MI is at moderate to serious risk of bias due to patient selection and confounding (29). We also need further RCT to provide best practices for the best timing of CABG after AMI, especially for patients with STEMI, and we need to further study whether early CABG actually has a worse impact on patients in the future.

Study Limitations

First, the included literature studies were retrospective, lacking relevant RCTs. A large number of multicenter RCTs were needed to prove whether early CABG actually increased the mortality of patients with AMI. Second, the undefined NSTEMI/STEMI subgroup had a large heterogeneity, which required further differentiation of patients with myocardial infarction type. Third, this meta-analysis set up two time-points, 24 and 48 h. Due to the lack of relevant original data, we could not objectively compare and judge which time point was better. Finally, there were pieces of literature containing secondary outcomes, and

there was insufficient data to compare the secondary outcomes of early CABG and late CABG.

CONCLUSION

In conclusion, patients with STEMI who underwent early CABG after AMI showed increased mortality. However, the timing of CABG did not affect mortality in NSTEMI patients. Meanwhile, there was no statistical difference in perioperative MI and cerebrovascular accident between early and late CABG. It was worth noting that the OR of mortality was progressively seen to be decreasing with the timing of CABG (2.65 at 24 h, 1.91 at 48 h). Actually, it is necessary to carry out appropriate effective RCTs to evaluate the results.

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.

AUTHOR CONTRIBUTIONS

QL and CQ were responsible for retrieving literature, extracting, and analyzing the data. WM was responsible for the supervision and guidance. All authors made important contributions to the manuscript.

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