

Article

Ventilation Dependency after Cardiac Operation for Infective Endocarditis: Risk Factors and Focus on Preoperative Aortic Regurgitation

Jun-jie Shi^{1,*}, Xiang-wei Li¹, Xiao-mao Long¹, Rui-hong Xu¹, Chang-chao Lu¹

¹Department of Cardiovascular Surgery, The People's Hospital of Guangxi Zhuang Autonomous Region, and Guangxi Academy of Medical Sciences, 530021 Nanning, Guangxi, China

*Correspondence: chengxing200316@163.com (Jun-jie Shi)

Submitted: 20 June 2024 Revised: 24 July 2024 Accepted: 31 July 2024 Published: 21 October 2024

Abstract

Introduction: The investigation was to elucidate predictors of ventilation dependency after cardiac operation for infective endocarditis. **Methods:** Patients with infective endocarditis undergoing cardiac operation were retrospectively investigated. Mechanical ventilation >72 hours was defined as ventilation dependency after cardiac operation. **Results:** 896 patients with infective endocarditis who underwent cardiac operation were assigned to group of mechanical ventilation ≤ 72 h ($n = 704$) and >72 h ($n = 192$). Multivariate analyses identified age, interval from symptoms to operation, vegetation size, aortic occlusion length, pump length, intensive care unit (ICU) retention length, serum creatinine before and 24 h after surgery, preoperative and postoperative left ventricular end diastolic dimension (LVEDD), preoperative aortic regurgitation and packed red blood cells to be associated with ventilation dependency after cardiac operation; ventilation dependency is significantly related to prolonged ICU stay (>3 d), 1- and 5-year mortality after cardiac operation. All-time mortality (45.3% versus 5.6%, $p < 0.001$) of mechanical ventilation >72 h group was higher than that of mechanical ventilation ≤ 72 h group. A significant positive correlation exists between preoperative aortic regurgitation and ventilation dependency after cardiac operation. A value of preoperative aortic regurgitation >5.25 cm² was 100% sensitive and 64.6% specific for the diagnosis of ventilation dependency after cardiac operation. **Conclusions:** We found modifiable risk factors of ventilation dependency after cardiac operation including interval from symptoms to operation, vegetation size, aortic occlusion length, pump length, ICU retention length, serum creatinine before and 24 h after operation, preoperative and postoperative LVEDD, preoperative aortic regurgitation and packed red blood cells and optimization of pre-, peri-, and postoperative factors that can reduce incidence of ventilation dependency, contributing to better short- and long-term outcomes.

Keywords

infective endocarditis; surgery; prolonged mechanical ventilation

Introduction

Infective endocarditis (IE) remains a complicated and life-threatening disease, with an in-hospital mortality of 15%–20% and 1-year mortality of about 40%, although its clinical, imaging, microbiological, and therapeutic profiles have made great progress. The treatment of IE patient needs a group of doctors with professional knowledge in all fields of the disease [1–4].

Ventilation dependency is a major complication after cardiac operation, previously associated with increased mortality, declined quality of life, and heavy economic cost [5–8]. Ventilation dependency is a recognized complication of cardiac operation, occurring in up to one-fifth of patients [9–11].

Ventilation dependency following heart operation, as a severe complication, requires the search for novel treatment strategies. Patients who undergo heart operation are usually capable of resuming spontaneous ventilation immediately after anesthesia recovery. However, according to the threshold used to delimit prolonged mechanical ventilation, about 2.6%–22.7% of patients require ventilation dependency. For these ventilation dependent patients, the in-hospital mortality rate may exceed 40% [12,13].

There is no unique definition for prolonged postoperative ventilation, and several studies have used different definitions. Consensus has defined 3 probable situations: weaning easy, weaning difficult, and long-term weaning. Easy Weaning easy is suitable for most patients, among whom only one successful attempt has been made to separate from mechanical ventilation; if separation attempt for the first time fails, it is defined as weaning difficult and requires more spontaneous breathing tests before extubation; long term weaning refers to the need for patients to undergo three or more spontaneous breathing tests or ventilation for



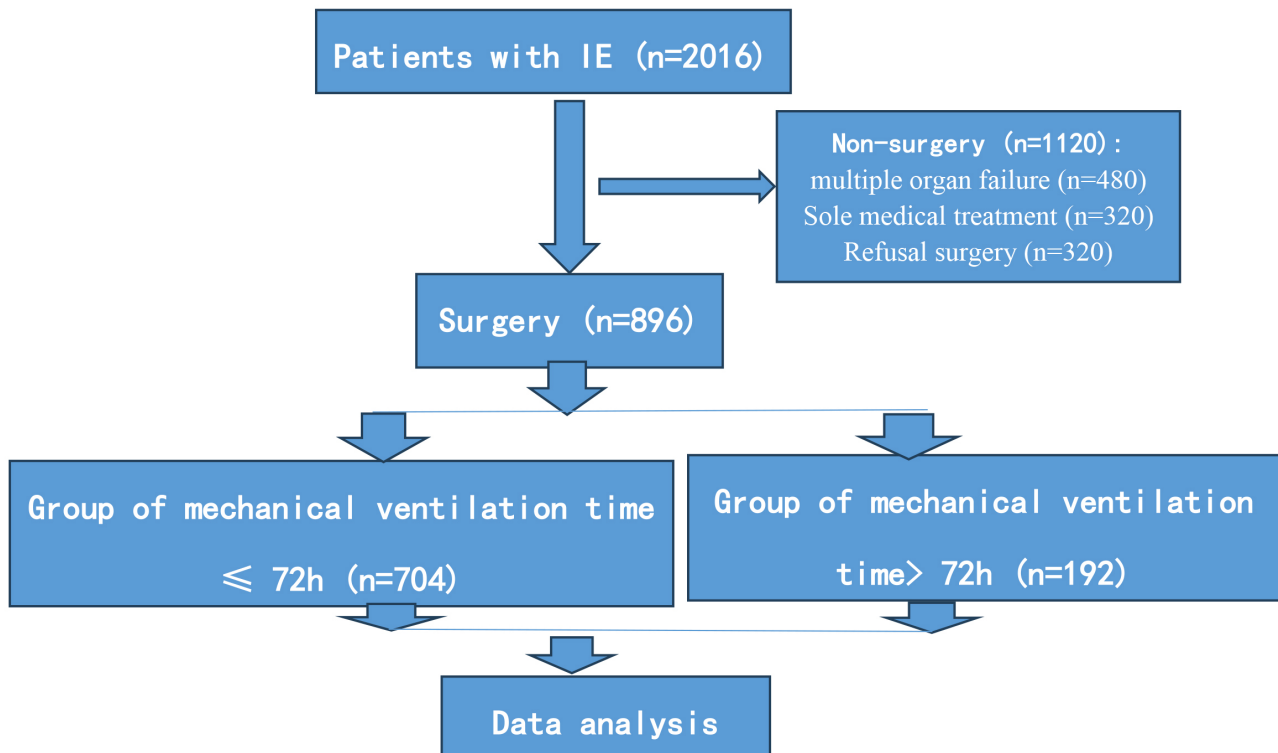


Fig. 1. Flow chart of patients. IE, infective endocarditis.

>7 days after the spontaneous breathing test for the first time [14–16]. In our study, ventilation dependency is defined as 72 hours or more of postoperative tracheal intubation, starting from the completion of the indicator procedure.

There is limited predictive data on ventilation dependency after cardiac operation for infective endocarditis [17–19]. We hypothesized that identifying modifiable risk factors for ventilation dependency after cardiac operation and optimizing preoperative, intraoperative, and postoperative factors that can reduce mechanical ventilation will help achieve better short-term and long-term outcomes.

Methods

Design

Patients with infective endocarditis undergoing cardiac operation at our medical center from January 2006 to November 2022 were retrospectively investigated. Their medical records were reviewed.

Diagnosis

Based on the modified Duke criteria, all patients were diagnosed [20]. We reviewed the data of operation and pathology to affirm the preoperative diagnosis.

Eligibility Criteria

Patients with infective endocarditis undergoing cardiac operation were enrolled in the study. Patients without cardiac operation were excluded (Fig. 1).

Operative Technique

Based on the guidelines of American Association for Thoracic Surgery (AATS) for the management of IE, cardiac operation for IE was indicated. We thoroughly debrided all infected tissues and foreign objects and performed extensive flushing after surgery [4]. Operations included sole mitral valve surgery, sole aortic valve replacement, double valve operation, sole tricuspid valve surgery, and Bentall + mitral valve replacement.

Management in Intensive Care Unit (ICU)

At the end of the surgery, the patient was directly admitted to the cardiothoracic ICU. All patients were continuously controlled for hemodynamic status using arterial catheters. The patient is ventilated through volume assisted control mode, with a tidal volume of 8–10 mL/kg body weight. We adjusted the inhalation oxygen (FiO₂) fraction and respiratory rate based on routine blood gas analysis to maintain arterial oxygen partial pressure (PaO₂) between 80 and 100 mmHg, and arterial carbon partial pressure of 35–40 mmHg. Sedation was completed by use of sufentanil.

Table 1. Operations, in-hospital deaths and complications (n = 896).

Variable	Value
Operations	
Sole AVR, %	19.6% (176/896)
Sole MVR, %	41.1% (368/896)
Double valve operation, %	28.6% (256/896)
Bentall + MVR, %	1.8% (16/896)
Sole tricuspid annuloplasty, %	8.9% (80/896)
Extracorporeal Membrane Oxygenation, n	0.3% (3/896)
Causes of in-hospital deaths	
Paravalvular leakage + Cardiogenic shock + septicemia + AKI + hepatic failure, %	3.6% (32/896)
Cerebral hemorrhage, %	1.8% (16/896)
Complications	
AKI, %	28.7% (257/896)
Mechanical ventilation time >72 h, %	21.4% (192/896)
Liver failure, %	4.4% (39/896)
Respiratory failure, %	15.1% (135/896)
Ventricular fibrillation, %	3.7% (33/896)

AKI, acute kidney injury; AVR, aortic valve replacement; MVR, mitral valve replacement.

tanil and midazolam postoperatively. The decision to extubate the patient is made independently by consulting an anesthesiologist, usually after a spontaneous breathing test. Patients must maintain neural alertness and orientation before extubation, be able to move limbs equally, breathe autonomously, and obey commands [9,10].

Variables Investigated

Variables investigated comprised age, gender, body weight, interval from symptoms to operation, New York Heart Association (NYHA) class, aortic regurgitation, mitral regurgitation, tricuspid regurgitation, left ventricular end diastolic dimension (LVEDD), left ventricular ejection fractions (LVEF), serum creatinine, mechanical ventilation length, ICU retention length, hospital stay, postoperative chest drainage, red blood cells (RBC), fresh-frozen plasma, fluid balance, acute kidney injury, multiorgan failure, hepatic failure, respiratory failure, ventricular fibrillation, extracorporeal membrane oxygenation (ECMO), and mortality.

Mechanical ventilation >72 hours was defined as ventilation dependency after cardiac operation [9,10].

Interval from symptoms to operation refers to length between symptoms onset and operation date.

In-hospital mortality refers to any death that occurs within 30 days of the cardiac operation or in the same hospital in which the surgery was performed.

Aortic regurgitation is quantified by an area (cm²) of aortic regurgitation, not regurgitant volume.

Follow-up

All patients discharged were followed up to date of death or the end date of the study. Echocardiogram, electrocardiogram, and X-ray chest film were accessed for all patients, once every 3 to 12 months at the outpatient department. In the final follow-up, the patients were seen at the outpatient department or contacted by phone or WeChat.

Statistical Analysis

Continuous data was presented as means $\pm$ standard error (SE). Kolmogorov-Smirnov test was conducted to investigate the normality of all variables. We used the chi-square test, the Wilcoxon rank-sum test or the Kruskal-Wallis test to investigate relationships between the variables. We also used contingency table methods and logistic regression analysis to assess the relationships of perioperative predictors. Survival curves were investigated with Kaplan-Meier method and log-rank test. Hazard ratios for mortality since operation were calculated by Cox proportional hazards regression model. Association among two variables was tested by the Spearman's correlation coefficient. The receiver operating characteristic (ROC) curve with the respective area under the curves (AUC) was plotted to investigate the diagnostic value of the risk factors. The optimal cutoff was assessed by using Youden's index in ROC analysis. $p < 0.05$ was statistically significant. Statistical calculations were completed using IBM SPSS version 24.0 software (IBM SPSS Inc., Armonk, NY, USA).

Table 2. Preoperative data, operative and follow-up outcomes.

Variable	Group of mechanical ventilation ≤ 72 h (n = 704)	Group of mechanical ventilation > 72 h (n = 192)	p value
Preoperative			
Male, n (%)	416 (59.1%)	134 (69.8%)	< 0.001
Age, years	37.09 ± 0.54	43.42 ± 0.91	< 0.001
Weights, kg	55.92 ± 0.48	53.88 ± 0.52	0.034
Interval from symptoms to operation, months	2.26 ± 0.85	3.82 ± 0.24	< 0.001
Vegetation size, mm	9.31 ± 0.24	13.42 ± 0.49	< 0.001
LVEDD preoperative, mm	59.30 ± 0.31	67.42 ± 0.74	< 0.001
LVEF preoperative, %	62.84 ± 0.27	58.75 ± 0.64	< 0.001
Preoperative aortic regurgitation, cm^2	3.53 ± 0.18	12.78 ± 0.57	< 0.001
Preoperative mitral regurgitation, cm^2	7.66 ± 0.25	5.83 ± 0.33	< 0.001
Preoperative tricuspid regurgitation, cm^2	4.57 ± 0.19	5.03 ± 0.19	0.227
Serum creatinine before operation, $\mu\text{mol/L}$	74.93 ± 0.87	104.08 ± 3.74	< 0.001
Operative			
Operative death, n	1 (0.2%)	47 (13.4%)	< 0.001
Aortic occlusion length, minutes	81.09 ± 1.26	105.92 ± 2.60	< 0.001
CPB length, minutes	133.00 ± 1.76	168.17 ± 2.96	< 0.001
ICU retention length, days	3.66 ± 0.07	8.75 ± 0.22	< 0.001
Hospital stay postoperative, days	18.75 ± 0.29	19.67 ± 0.58	0.147
Serum creatinine 24 h after operation, $\mu\text{mol/L}$	81.59 ± 1.39	113.50 ± 3.92	< 0.001
Serum creatinine 48 h after operation, $\mu\text{mol/L}$	86.59 ± 1.93	168.58 ± 6.23	< 0.001
Fluid balance on operation day, mL	-686.59 ± 28.13	-341.67 ± 60.93	< 0.001
Fluid balance on 1st day postoperative, mL	-585.23 ± 25.38	-729.17 ± 140.81	0.102
Fluid balance on 2nd day postoperative, mL	-552.27 ± 24.26	-525.00 ± 70.10	0.645
Postoperative LVEDD, mm	46.70 ± 0.26	52.42 ± 0.42	< 0.001
Postoperative LVEF, %	59.90 ± 0.27	55.42 ± 0.34	< 0.001
Thoracic drainage, mL	610.00 ± 15.66	680.00 ± 23.57	0.031
Plasma	550.23 ± 17.55	882.50 ± 26.82	< 0.001
Packed red blood cells	2.02 ± 0.75	5.25 ± 0.36	< 0.001
Follow-up			
	Group of mechanical ventilation ≤ 72 h (n = 677)	Group of mechanical ventilation > 72 h (n = 137)	p value
Length of follow-up, months	74.71 ± 2.00	42.48 ± 4.11	< 0.001
All-time mortality, n	38 (5.6%)	62 (45.3%)	< 0.001

LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fractions; CPB, cardiopulmonary bypass; ICU, intensive care unit.

Results

896 patients with infective endocarditis who underwent cardiac operation during the research period were divided into group of mechanical ventilation ≤ 72 h (n = 704) and > 72 h (n = 192). There were 48 in-hospital deaths (5.4%). Incidence of ventilation dependency after cardiac operation was 21.4% (192/896) (Table 1, Fig. 1).

Preoperative Data

Age (43.42 ± 0.91 versus 37.09 ± 0.54 years), interval from symptoms to operation (3.82 ± 0.24 versus 2.26 ± 0.85 months), vegetation size (13.42 ± 0.49 versus 9.31 ± 0.24 mm), preoperative LVEDD (67.42 ± 0.74 versus

59.30 ± 0.31 mm), preoperative aortic regurgitation (12.78 ± 0.57 versus 3.53 ± 0.18 cm^2), serum creatinine before operation (104.08 ± 3.74 versus 74.93 ± 0.87 $\mu\text{mol/L}$) in mechanical ventilation > 72 h group were significantly greater than those in mechanical ventilation ≤ 72 h group, all $p < 0.001$ (Table 2).

Operative Outcomes

In-hospital death (13.4% versus 0.2%, $p < 0.001$), aortic occlusion length (105.92 ± 2.60 versus 81.09 ± 1.26 minutes, $p < 0.001$), cardiopulmonary bypass (CPB) length (168.17 ± 2.96 versus 133.0 ± 1.76 minutes, $p < 0.001$), ICU retention length (8.75 ± 0.22 versus 3.66 ± 0.07 days, $p < 0.001$), serum creatinine 24 h after operation (113.50 ± 3.92 versus 81.59 ± 1.39 $\mu\text{mol/L}$, $p < 0.001$), serum cre-

Table 3. Risk factors of ventilation dependency after cardiac operation for infective endocarditis.

Model	OR	95% CI	<i>p</i> value
Univariable analysis			
Age	1.032	1.020–1.044	<0.001
Interval from symptoms to operation	1.217	1.149–1.288	<0.001
Vegetation size	1.134	1.017–1.161	<0.001
Neurological complications before operation	1.137	1.012–3.026	0.001
Aortic occlusion length	1.112	1.016–1.266	<0.001
CPB length	1.113	1.010–1.816	<0.001
Double valve operation	3.446	2.591–4.585	<0.001
ICU retention time	2.256	2.013–2.529	<0.001
Serum creatinine before operation	1.025	1.019–1.031	<0.001
Serum creatinine 24 h after operation	1.016	1.012–1.020	<0.001
Serum creatinine 48 h after operation	1.127	1.014–1.723	<0.001
Preoperative LVEDD	1.104	1.083–1.125	<0.001
Postoperative LVEDD	1.136	1.106–1.167	<0.001
Packed red blood cells	1.379	1.293–1.470	<0.001
Preoperative aortic regurgitation	1.243	1.203–1.285	<0.001
Multivariable analysis			
Age	1.035	1.024–1.047	<0.001
Interval from symptoms to operation	1.203	1.134–1.276	<0.001
Vegetation size	1.148	1.119–1.178	<0.001
Aortic occlusion length	1.236	1.126–2.158	<0.001
CPB length	1.313	1.186–3.816	<0.001
Double valve operation	2.860	2.103–3.890	<0.001
ICU retention length	2.244	1.984–2.538	<0.001
Serum creatinine before operation	1.318	1.013–2.624	<0.001
Serum creatinine 24 h after operation	1.718	1.126–3.215	<0.001
Preoperative LVEDD	1.853	1.098–2.698	<0.001
Postoperative LVEDD	1.674	1.041–3.108	<0.001
Preoperative aortic regurgitation	1.358	1.293–1.427	<0.001
Packed red blood cells	1.659	1.477–1.862	<0.001

OR, odds ratio; CI, confidence interval.

atinine 48 h after surgery (168.58 ± 6.23 versus 86.59 ± 1.93 $\mu\text{mol/L}$, $p < 0.001$), postoperative LVEDD (52.42 ± 0.42 versus 46.70 ± 0.26 mm, $p = 0.002$), thoracic drainage (680.0 ± 23.57 versus 610.0 ± 15.66 mL, $p = 0.031$), fresh-frozen plasma (882.50 ± 26.82 versus 550.23 ± 17.55 mL, $p < 0.001$), packed red blood cells (5.25 ± 0.36 versus 2.02 ± 0.75 units, $p < 0.001$) in mechanical ventilation >72 h group were significantly greater than those in mechanical ventilation ≤ 72 h group (Table 2).

Fluid balance on operation day (-341.67 ± 60.93 versus -686.59 ± 28.13 mL, $p < 0.001$) in mechanical ventilation >72 h group were significantly less negative than that in mechanical ventilation ≤ 72 h group (Table 2).

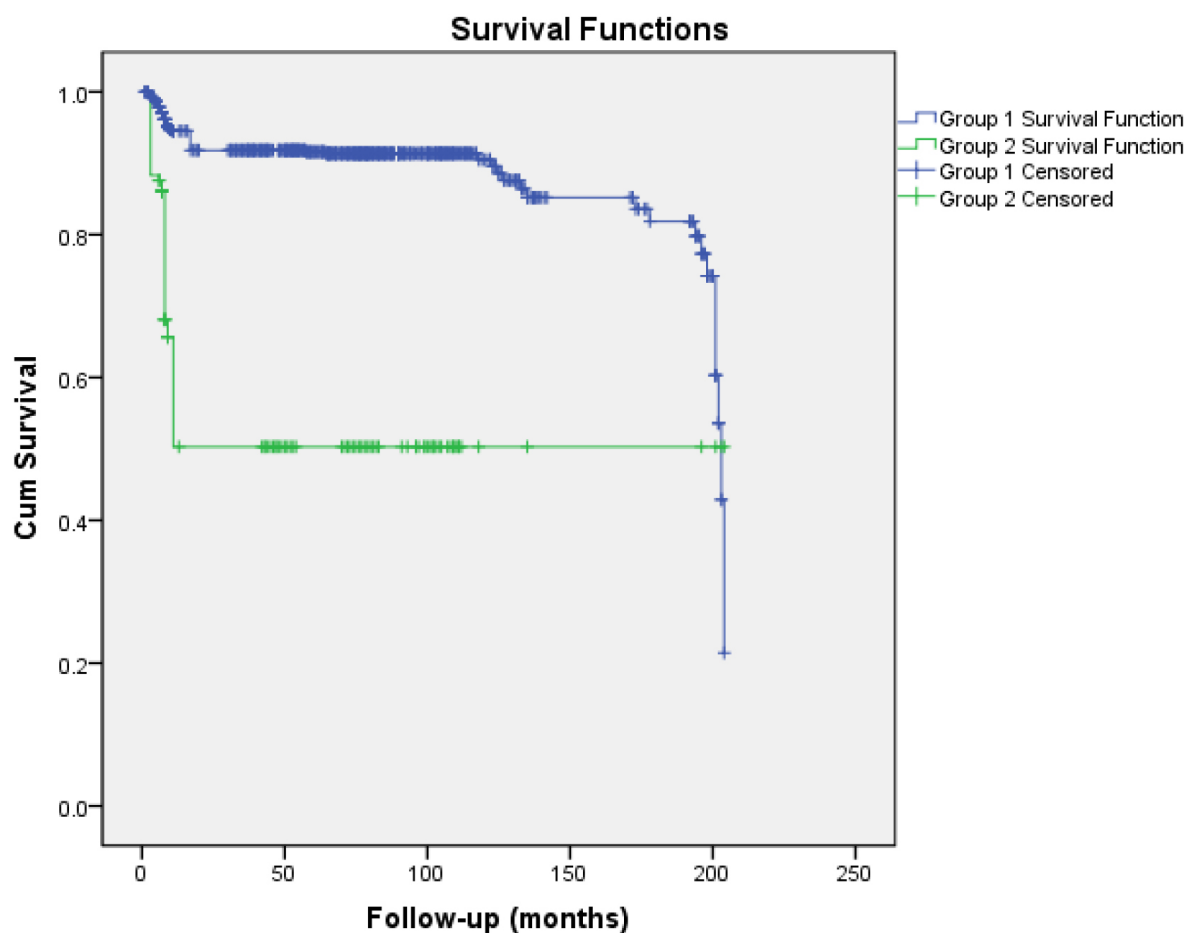
Postoperative LVEF (55.42 ± 0.34 versus $59.90 \pm 0.27\%$, $p < 0.001$) in mechanical ventilation >72 h group was significantly less than that in mechanical ventilation ≤ 72 h group (Table 2).

Reasons for in-hospital mortality mainly included septic shock followed by multiorgan failure and cerebral hemorrhage. Acute kidney injury (272/896, 30.4%) and long-

term mechanical ventilation >72 h (192/896, 21.4%) were the early complications postoperative (Table 1).

Risk Factors of Ventilation Dependency after Cardiac Operation

Multivariable analyses identified age (odds ratio (OR): 1.035, 95% confidence interval (CI): 1.024–1.047), interval from symptoms to operation (OR: 1.203, 95% CI: 1.134–1.276), vegetation size (OR: 1.148, 95% CI: 1.119–1.178), aortic occlusion length (OR: 1.236, 95% CI: 1.126–2.158), CPB length (OR: 1.313, 95% CI: 1.186–3.816), double valve operation (OR: 2.860, 95% CI: 2.103–3.890), ICU retention length (OR: 2.244, 95% CI: 1.984–2.538), serum creatinine before operation (OR: 1.318, 95% CI: 1.013–2.624), serum creatinine 24 h after operation (OR: 1.718, 95% CI: 1.126–3.215), preoperative LVEDD (OR: 1.853, 95% CI: 1.098–2.698), postoperative LVEDD (OR: 1.674, 95% CI: 1.041–3.108), preoperative aortic regurgitation (OR: 1.358, 95% CI: 1.293–1.427) and packed red blood cells (OR: 1.659, 95% CI: 1.477–1.862) to be asso-



Patients at risk

Months	50	100	150	200	250
Group of mechanical ventilation ≤ 72 h	467	189	56	19	0
Group of mechanical ventilation > 72 h	47	21	11	3	0

Fig. 2. Kaplan-Meier curve for survival. Blue line, group of mechanical ventilation ≤ 72 h (Group 1); Green line, group of mechanical ventilation > 72 h (Group 2).

ciated with ventilation dependency after cardiac operation, all $p < 0.001$ (Table 3).

Analysis of the Significance of Ventilation Dependency after Cardiac Operation

Multivariable analysis found ventilation dependency significantly associated with prolonged ICU stay (> 3 d) (OR: 1.857, 95% CI: 1.148–3.167), 1-year mortality (OR:

5.032, 95% CI: 2.199–9.897), and 5-year mortality after cardiac operation (OR: 6.611, 95% CI: 2.837–12.731), all $p < 0.001$, respectively (Table 4).

Follow-up Outcomes

Follow-up of 814 patients were accomplished (96.0%, 814/848). 87 deaths (87/814, 10.7%) occurred within 12 months due to IE recurrence and cerebral hemorrhage. The

Table 4. Analysis of the implication of ventilation dependency in infective endocarditis (n = 896).

Model	OR	95% CI	p value
Univariable analysis, prolonged ICU stay (>3 d) after heart operation (n = 480)			
prolonged mechanical ventilation	1.523	1.048–2.215	<0.001
Multivariable analysis, prolonged ICU stay (>3 d) after heart operation (n = 480)			
prolonged mechanical ventilation	1.857	1.148–3.167	<0.001
Univariable analysis, 1-year mortality after heart operation (n = 87)			
prolonged mechanical ventilation	6.319	2.816–18.15	<0.001
Multivariable analysis, 1-year mortality after heart operation (n = 87)			
prolonged mechanical ventilation	5.032	2.199–9.897	<0.001
Univariable analysis, 5-year mortality after heart operation (n = 100)			
prolonged mechanical ventilation	8.627	3.220–16.490	<0.001
Multivariable analysis, 5-year mortality after heart operation (n = 100)			
prolonged mechanical ventilation	6.611	2.837–12.731	<0.001

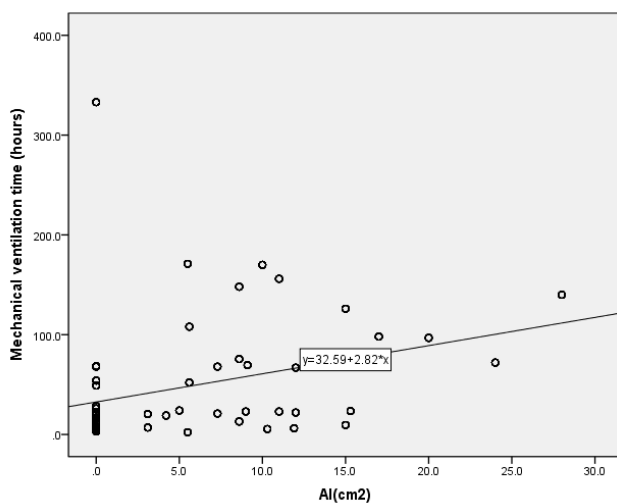


Fig. 3. Association between preoperative aortic regurgitation and ventilation dependency after cardiac operation. Spearman correlations analysis showed a significant positive correlation between preoperative aortic regurgitation and ventilation dependency after cardiac operation ($r = 0.558$, $p < 0.001$).

final follow-up showed that 681 survivors were in NYHA class I (681/707, 96.3%) and 26 in class II (26/707, 3.7%). The presence of ventilation dependency after cardiac operation for IE significantly raised all-time mortality. It is also an important risk factor for long-term survival (Fig. 2).

Length of follow-up (42.48 ± 4.11 versus 74.71 ± 2.0 months) in mechanical ventilation >72 h group was significantly less than that in mechanical ventilation ≤ 72 h group. All-time mortality (45.3% versus 5.6%, $p < 0.001$) in mechanical ventilation >72 h group was significantly higher than that in mechanical ventilation ≤ 72 h group, $p < 0.001$ (Table 2).

Spearman correlations analysis demonstrated a significant positive correlation between preoperative aortic regurgitation and ventilation dependency after cardiac operation ($r = 0.558$, $p < 0.001$) (Fig. 3). The value of preoperative

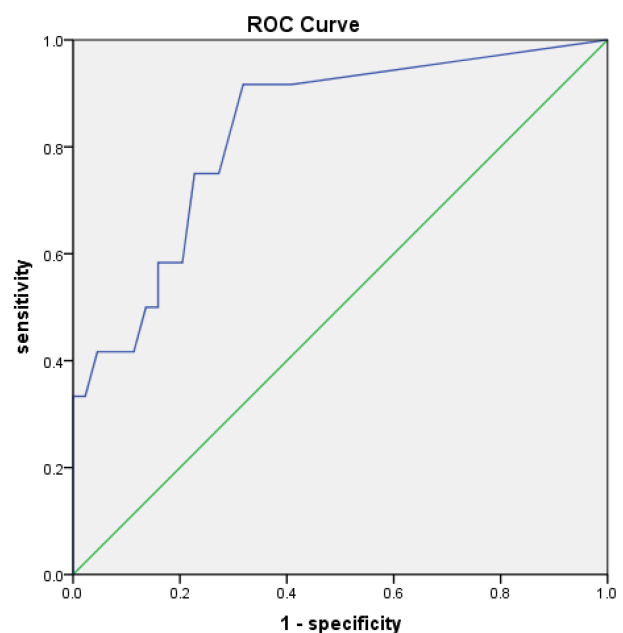


Fig. 4. The receiver operating characteristic (ROC) curve of diagnostic accuracy with preoperative aortic regurgitation for predicting ventilation dependency after cardiac operation. The value of preoperative aortic valve regurgitation >5.25 cm² has 100% sensitivity and 64.6% specificity for diagnosing ventilation dependency after infective endocarditis (IE) cardiac surgery, with an area under the curves (AUC) of 0.846 (95% CI: 0.815–0.878; $p < 0.001$). Youden index was 0.646.

aortic valve regurgitation >5.25 cm² has 100% sensitivity and 64.6% specificity for diagnosing ventilation dependency after IE cardiac surgery, with an AUC of 0.846 (95% confidence interval: 0.815–0.878; $p < 0.001$). Youden index was 0.646 (Fig. 4). Table 5 showed the comparison of groups of preoperative aortic regurgitation $<$ and ≥ 5.25 cm².

Table 5. Comparison of groups of preoperative aortic regurgitation < and $\geq 5.25 \text{ cm}^2$.

Variable	Group of preoperative aortic regurgitation <5.25 cm ² (n = 496)	Group of preoperative aortic regurgitation $\geq 5.25 \text{ cm}^2$ (n = 400)	p value
Male, n (%)	272 (54.8%)	320 (80.0%)	<0.001
Age, years	35.58 $\pm$ 0.69	42.0 $\pm$ 0.59	<0.001
Weights, kg	54.87 $\pm$ 0.61	56.24 $\pm$ 0.46	0.086
Interval from symptoms to operation, months	2.14 $\pm$ 0.07	3.17 $\pm$ 0.17	<0.001
Vegetation size, mm	8.77 $\pm$ 0.28	11.96 $\pm$ 0.34	<0.001
Preoperative LVEDD, mm	56.70 $\pm$ 0.31	66.32 $\pm$ 0.46	<0.001
Preoperative LVEF, %	64.03 $\pm$ 0.25	59.44 $\pm$ 0.46	<0.001
Preoperative mitral regurgitation, cm ²	9.07 $\pm$ 0.29	5.02 $\pm$ 0.26	<0.001
Preoperative tricuspid regurgitation, cm ²	5.17 $\pm$ 0.26	4.04 $\pm$ 0.15	<0.001
Serum creatinine before operation, $\mu\text{mol/L}$	75.13 $\pm$ 1.67	88.68 $\pm$ 1.35	<0.001
Aortic occlusion length, minutes	77.10 $\pm$ 1.54	97.96 $\pm$ 1.66	<0.001
CPB length, minutes	126.77 $\pm$ 2.11	157.60 $\pm$ 2.63	<0.001
ICU retention length, days	3.61 $\pm$ 0.11	6.16 $\pm$ 0.15	<0.001
Hospital stay postoperative, days	17.68 $\pm$ 0.28	20.52 $\pm$ 0.45	<0.001
Serum creatinine 24 h after operation, $\mu\text{mol/L}$	76.26 $\pm$ 1.71	103.52 $\pm$ 2.24	<0.001
Serum creatinine 48 h after operation, $\mu\text{mol/L}$	87.48 $\pm$ 2.91	124.84 $\pm$ 3.43	<0.001
Fluid balance on operation day, mL	-571.29 $\pm$ 31.20	-664.0 $\pm$ 43.71	0.077
Fluid balance on 1st day postoperative, mL	-603.23 $\pm$ 35.12	-632.0 $\pm$ 68.36	0.693
Fluid balance on 2nd day postoperative, mL	-577.29 $\pm$ 26.55	-508.0 $\pm$ 43.18	0.155
Postoperative LVEDD, mm	45.63 $\pm$ 0.25	50.72 $\pm$ 0.38	<0.001
Postoperative LVEF, %	60.93 $\pm$ 0.25	56.51 $\pm$ 0.38	<0.001
Thoracic drainage, mL	513.55 $\pm$ 18.81	763.20 $\pm$ 16.19	<0.001
Plasma	440.97 $\pm$ 21.04	845.20 $\pm$ 17.80	<0.001
Packed red blood cells	2.32 $\pm$ 0.16	3.20 $\pm$ 0.14	<0.001

Discussion

Despite the prevention and active treatment, the incidence rate of infective endocarditis is still stable and the prognosis is poor (the 1-year mortality rate is 30%). Surgical treatment of endocarditis is still challenging and associated with significant incidence rate and mortality [21,22].

Mechanical ventilation length and ICU stay may be beyond 2 to 3 weeks, which can have significant economic impacts and effects on quality of life. The effective cost per survivor for patients receiving mechanical ventilation length >4 days is 18 times higher than that of weaned patients [23,24]. New intervention measures or strategies of treatment are needed to better the prognosis of patients with infective endocarditis.

Our goal is to identify patients with infective endocarditis who require mechanical ventilation for >72 hours following surgery. We are trying to confirm those who have a high likelihood of successful weaning to avoid unnecessary interventions such as early tracheotomy.

Risk factors for ventilation dependency after heart operation have been clarified, such as female sex, age, body mass index, smoking, hypertension, chronic renal disease, chronic obstructive pulmonary disease, cardiac function class, endocarditis surgery, preoperative pulmonary oedema, combined coronary artery bypass graft + valvular

surgery, ventilation before surgery, re-do operation, urgent-emergent operation, mitral valve operation, aortic operation, cardio-pulmonary bypass duration >90 min, serum creatinine, peripheral vascular disease, bleeding, inotrope dependency, cardiogenic shock, low cardiac output, decreased cardiac index, complications after open heart surgery, LVEF <30%, recent myocardial infarction, blood products transfusion, presence of atrial arrhythmias [7,14–16,18,19]. Double valve replacement and aortic root replacement surgery generally have more severe conditions and more complex surgeries, longer extracorporeal circulation time and aortic occlusion time, and longer mechanical ventilation time. Compared to sole valve operation group, mechanical ventilation length increased in double valve operation group (68.64 $\pm$ 4.09 versus 36.72 $\pm$ 2.01 hours, $p < 0.001$). Multivariable analyses identified double valve operation (OR: 2.860, 95% CI: 2.103–3.890, $p < 0.001$) to be associated with ventilation dependency after cardiac operation (Table 3).

Gender, history of chronic obstructive pulmonary disease, chronic kidney disease and endocarditis, type of surgery, operation length, aortic occlusion length, transfusion during operation, bleeding and dependency of inotrope had significant differences in patients with and without prolonged ventilation after open heart surgery [18].

The data of epidemiological studies show that gender is a significant factor of the incidence of active aortic infective endocarditis, and the rate of affected men is higher. The incidence rate as a ratio of men to women, ranging from 2:1 to 9:1, has been reported. Healthy natural valves are typically protected from bacterial invasion by intact endothelium; the endothelium of patients with endocarditis is no longer a fused monolayer, with bacteria attached to the surface leading to formation of a biofilm [18]. The bacterial biofilm has inherent resistance to antimicrobial agents due to its encapsulation effect. The cyst includes bacteria producing extracellular polymers and proteolytic enzymes that destroy near tissues and enhance infection. Estrogen has protective effects on endothelial cells, explaining the difference of incidence rate of endocarditis in men and women. It has been reported the antioxidant effect of estrogen on bovine aortic endothelial cells. Because of decrease in junction proteins between endothelial cells, deficiency of estrogen and migration of microphageal are more apparent [18].

Rheumatic heart disease has been near eradicated in the United States, while the incidence of infective endocarditis continues to rise. Medical related procedures have become an important cause of IE because of more and more chronic disease patients receiving intensive and invasive treatment, hemodialysis being the main risk factor. The incidence rate of IE in chronic dialysis patients is 18 times higher than that in the general population. In a series of 20-year surgical experiences of end-stage renal disease patients undergoing dialysis treatment, patients undergoing chronic hemodialysis have a higher incidence of postoperative mechanical ventilation, pneumonia, sepsis, cardiac arrest, and gastrointestinal events. End-stage renal disease is related to increased mortality rates at 30 days, 5 years, and 10 years after surgery [19].

In our study, multivariate analyses identified age, interval from symptoms to operation, vegetation size, aortic occlusion length, pump length, ICU retention length, serum creatinine before and 24 h after operation, preoperative and postoperative LVEDD, preoperative aortic regurgitation and packed red blood cells to be associated with ventilation dependency after cardiac operation. Ventilation dependency is significantly related to prolonged ICU stay (>3 d), 1- and 5-year mortality after cardiac operation. All-time mortality in mechanical ventilation >72 h group was significantly higher than that in mechanical ventilation ≤ 72 h group. A positive correlation exists between preoperative aortic regurgitation and ventilation dependency after cardiac operation ($r = 0.558$, $p < 0.001$).

A value of preoperative aortic regurgitation >5.25 cm² has 100% sensitivity and 64.6% specificity for the diagnosis of ventilation dependency after cardiac operation.

21.4% (192/896) of patients with infective endocarditis require mechanical ventilation for >72 hours, which is higher than the proportion reported in other series, ranging from 3.2% to 9.1% [3,25,26]. The mortality rate of

critically ill patients in these groups is significantly higher than that of patients who rapidly stop mechanical ventilation. In our research, in-hospital mortality rate in mechanical ventilation >72 hours group was significantly higher than that in mechanical ventilation ≤ 72 hours group, and ventilation dependency was significantly correlated with long-term mortality. Another study showed that vegetation size was significantly correlated with destructive annulus, preoperative neurological complications, acute kidney injury, prolonged ventilation duration, prolonged ICU stay, in-hospital and 1-year mortality [27].

Emboli from vegetations can result in stroke and fungal aneurysms. The guidelines of American Association for Thoracic Surgery (AATS) suggest urgent or even emergency surgery in patients with left-sided infective endocarditis with mobile vegetations size >10 mm and clinical evidence of embolism despite appropriate antibiotic treatment. It has been confirmed that mobile vegetations size >10 mm on the anterior leaflet of the mitral valve is associated with a higher risk of embolism. Surgery is required when the mobile vegetations size >10 mm without embolization. Early surgery can prevent stroke suffered from left-sided infective endocarditis. The European guidelines for the prevention, diagnosis, and treatment of infective endocarditis also provide guidance on this matter. At present, early surgery has become the preferred treatment for infective endocarditis. According to the American Association for Thoracic Surgery (AATS) guidelines, once surgical indications are determined, patients should undergo surgery within a few days. For patients with large mobile vegetations at risk of embolism, early surgery (emergency or within 48 hours) is reasonable [1,4,28,29].

Preoperative serum creatinine reflects renal function before surgery, and preoperative LVEDD and preoperative aortic regurgitation are important parameters of the heart. Due to the progressive nature of infective endocarditis, early surgical intervention is recommended to avoid preoperative renal dysfunction, severe aortic regurgitation, and excessive LVEDD.

We also found that the interval from symptoms to operation is a risk factor for ventilation dependency. In our study, 2016 patients were diagnosed with infective endocarditis during the study period, and 896 patients underwent cardiac operation (44.4%, 896/2016). The time point distinction of group with ventilation dependency and group without ventilation dependency was approximate 4 versus 2 months.

Due to the lack of a good primary, secondary, and tertiary prevention network, these patients seek medical attention later in the hospital, usually diagnosed later and referred to our tertiary referral hospital. Therefore, early diagnosis and treatment of infective endocarditis are very important. The rapid and accurate diagnosis of cases of infective endocarditis is still a challenge. A conceptual framework consisting of required baseline information and re-

quirements for implementing primary, secondary, and tertiary preventive measures is considered the optimal model for IE control [30].

Our study identified packed red blood cells transfusion to be associated with ventilation dependency after cardiac operation. Due to various morphological and functional changes that occur during blood storage, such as reduced deformability, inflammation, consumption of 2,3-diphosphoglycerol, release of free hemoglobin, and decreased bioavailability of nitric oxide, red blood cell infusion cannot restore sufficient microcirculation oxygenation [31].

We also found a significant positive correlation between preoperative aortic regurgitation and ventilation dependency after cardiac operation. The cut-off value of preoperative aortic regurgitation is 5.25 cm², which has 100% sensitivity and 64.6% specificity for the diagnosis of ventilation dependency. Endocarditis is the most common cause of acute aortic valve regurgitation. In a native valve, endocarditis can lead to leaflet perforation, leaflet prolapse due to annular destruction, or failure of coaptation because of vegetation. Acute native valve aortic regurgitation is a rapidly fatal condition resulting from the sudden loss of valve competency [32]. The large volume of retrograde diastolic flow into a left ventricle without compensatory dilation results in an abrupt decrease in cardiac output and increase in left ventricular end-diastolic pressure. This in turn leads to elevated capillary wedge and pulmonary artery pressures, resulting in symptoms of acute congestive heart failure and persistent pulmonary edema [33]. In natural valves, endocarditis can lead to leaflet perforation, leaflet prolapse caused by annulus destruction, or failure of coaptation caused by vegetation. Acute autologous valve aortic regurgitation is a rapidly fatal disease caused by sudden loss of valve function. A large amount of retrograde diastolic blood flow enters the left ventricle without compensatory dilation, resulting in a sudden decrease in cardiac output and an increase in left ventricular end diastolic pressure. This in turn results in an increase in capillary wedge and pulmonary artery pressure, leading to symptoms of acute heart failure and persistent pulmonary edema. Myocardium damage and pulmonary edema resulted from preoperative aortic regurgitation in infective endocarditis will take more time for the heart and lung to recover [33]. However, the present study primarily offers descriptive insights and does not support mechanistic conclusions.

Strength and Limitations

The present research clarified risk factors and impacts of ventilation dependency after cardiac operation for infective endocarditis on short- and long-term outcomes. The limitations of this study include its retrospective design. Due to the retrospective nature of the study and our hospital's role as a tertiary referral center, there may

be selection bias. Preoperative respiratory assessments—including acute lung edema, results of lung imaging, arterial blood gas analysis, SpO₂ levels, or level of oxygen supplementation—are notably absent from the present study. Surgical procedure was improved during these fifteen years and the influence of surgical procedure should be considered. In recent years, we have realized that the destructive aortic annulus is related to early aortic valve leakage, in-hospital and 1-year mortality. The main causes of in-hospital mortality are early valve leakage and sepsis. Early perivalvular leakage mainly occurs in patients with aortic annulus destruction. Compared with aortic valve replacement, aortic root replacement achieves more comprehensive clearance of infected tissue and reconstruction of cardiac morphology, thus reducing the rates of reinfection and graft deterioration. Compared with aortic valve replacement, aortic root replacement has favorable postoperative characteristics. Aortic root replacement surgery can be suggested as the best practice choice for treating aortic valve endocarditis with peri annular abscess and destructive aortic annulus. The inclusion of cases over a long period of time may adversely affect the accuracy of the results. Careful studies, including prospective cohort studies, are required, and programs aimed at reducing in-hospital morbidity rate and mortality due to ventilation dependency after cardiac operation are desired.

Conclusions

We found modifiable risk factors of ventilation dependency after cardiac operation including interval from symptoms to operation, vegetation size, aortic occlusion length, pump length, ICU retention length, serum creatinine before and 24 h after operation, preoperative and postoperative LVEDD, preoperative aortic regurgitation and packed red blood cells and optimization of pre-, peri-, and postoperative factors that can reduce incidence of ventilation dependency, contributing to better short- and long-term outcomes.

Abbreviations

AKI, acute kidney injury; AKIN, acute kidney injury network; BMI, body mass index = weight/(height²), (kg/m²); CPB, cardiopulmonary bypass; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; MOF, multiple organ failure; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fractions; IE, infective endocarditis; ICU, intensive care unit.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

JJS designed the research study. XWL, XML, RHX, and CCL performed the research. CCL analyzed the data. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The protocol of study for involving humans was based on Helsinki Statement and national guidelines and was approved by the Medical Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region (number: PHGX0186), and the approval to waive the need for patient consent for data of publication in the research was given.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, *et al.* Challenges in Infective Endocarditis. *Journal of the American College of Cardiology*. 2017; 69: 325–344.
- [2] Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, *et al.* 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021; 143: e72–e227.
- [3] Chu VH, Park LP, Athan E, Delahaye F, Freiburger T, Lamas C, *et al.* Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. *Circulation*. 2015; 131: 131–140.
- [4] Pettersson GB, Hussain ST. Current AATS guidelines on surgical treatment of infective endocarditis. *Annals of Cardiothoracic Surgery*. 2019; 8: 630–644.
- [5] Engoren M, Buderer NF, Zacharias A. Long-term survival and health status after prolonged mechanical ventilation after cardiac surgery. *Critical Care Medicine*. 2000; 28: 2742–2749.
- [6] Zante B, Kubik M, Reichenspurner H. Predictors of prolonged mechanical ventilation after cardiac surgery. *The Thoracic and Cardiovascular Surgeon*. 2010; 58: 45.
- [7] Totonchi Z, Baazm F, Chitsazan M, Seifi S, Chitsazan M. Predictors of prolonged mechanical ventilation after open heart surgery. *Journal of Cardiovascular and Thoracic Research*. 2014; 6: 211–216.
- [8] Fernandez-Zamora MD, Gordillo-Brenes A, Banderas-Bravo E, Arboleda-Sánchez JA, Hinojosa-Pérez R, Aguilar-Alonso E, *et al.* Prolonged Mechanical Ventilation as a Predictor of Mortality After Cardiac Surgery. *Respiratory Care*. 2018; 63: 550–557.
- [9] Trouillet JL, Combes A, Vaissier E, Luyt CE, Ouattara A, Pavie A, *et al.* Prolonged mechanical ventilation after cardiac surgery: outcome and predictors. *The Journal of Thoracic and Cardiovascular Surgery*. 2009; 138: 948–953.
- [10] Murthy SC, Arroliga AC, Walts PA, Feng J, Yared JP, Lytle BW, *et al.* Ventilatory dependency after cardiovascular surgery. *The Journal of Thoracic and Cardiovascular Surgery*. 2007; 134: 484–490.
- [11] Suarez-Pierre A, Fraser CD, Zhou X, Crawford TC, Lui C, Metkus TS, *et al.* Predictors of operative mortality among cardiac surgery patients with prolonged ventilation. *Journal of Cardiac Surgery*. 2019; 34: 759–766.
- [12] Pappalardo F, Franco A, Landoni G, Cardano P, Zangrillo A, Alfieri O. Long-term outcome and quality of life of patients requiring prolonged mechanical ventilation after cardiac surgery. *European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery*. 2004; 25: 548–552.
- [13] Canver CC, Chanda J. Intraoperative and postoperative risk factors for respiratory failure after coronary bypass. *The Annals of Thoracic Surgery*. 2003; 75: 853–853–857; discussion 857–858.
- [14] Nicolotti D, Grossi S, Nicolini F, Galligani A, Rossi S. Difficult Respiratory Weaning after Cardiac Surgery: A Narrative Review. *Journal of Clinical Medicine*. 2023; 12: 497.
- [15] Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, *et al.* Weaning from mechanical ventilation. *The European Respiratory Journal*. 2007; 29: 1033–1056.
- [16] Thille AW, Gacouin A, Coudroy R, Ehrmann S, Quenot JP, Nay MA, *et al.* Spontaneous-Breathing Trials with Pressure-Support Ventilation or a T-Piece. *The New England Journal of Medicine*. 2022; 387: 1843–1854.
- [17] Huang JB, Wen ZK, Lu CC, Yang JR, Li JJ. Risk factors of prolonged intensive care unit stay following cardiac surgery for infective endocarditis. *Medicine*. 2023; 102: e35128.
- [18] Dohmen PM, Binner C, Mende M, Daviewala P, Etz CD, Borger MA, *et al.* Gender-Based Long-Term Surgical Outcome in Patients with Active Infective Aortic Valve Endocarditis. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*. 2016; 22: 2520–2527.
- [19] Guo M, St Pierre E, Clemence J, Jr, Wu X, Tang P, Romano M, *et al.* Impact of Chronic Renal Failure on Surgical Outcomes in Patients With Infective Endocarditis. *The Annals of Thoracic Surgery*. 2021; 111: 828–835.
- [20] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr, Ryan T, *et al.* Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clinical Infectious Diseases: an Official*

cial Publication of the Infectious Diseases Society of America. 2000; 30: 633–638.

- [21] Lalani T, Cabell CH, Benjamin DK, Lasca O, Naber C, Fowler VG, Jr, *et al.* Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. *Circulation*. 2010; 121: 1005–1013.
- [22] Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, *et al.* Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. *European Heart Journal*. 2019; 40: 3222–3232.
- [23] Walts PA, Murthy SC, Arroliga AC, Yared JP, Rajeswaran J, Rice TW, *et al.* Tracheostomy after cardiovascular surgery: an assessment of long-term outcome. *The Journal of Thoracic and Cardiovascular Surgery*. 2006; 131: 830–837.
- [24] Suematsu Y, Sato H, Ohtsuka T, Kotsuka Y, Araki S, Takamoto S. Predictive risk factors for delayed extubation in patients undergoing coronary artery bypass grafting. *Heart and Vessels*. 2000; 15: 214–220.
- [25] Nozawa E, Azeka E, Ignêz Z M, Feltrim Z, Auler Júnior JOC. Factors associated with failure of weaning from long-term mechanical ventilation after cardiac surgery. *International Heart Journal*. 2005; 46: 819–831.
- [26] Huang JB, Lu CC, Wen ZK, Yang JR, Li JJ, Lu CC. Impact of Vegetation Length on Clinical Complications During Surgical Intervention and Long-Term Survival in Infective Endocarditis. *The American Journal of Cardiology*. 2023; 201: 335–340.
- [27] Arregle F, Martel H, Philip M, Gouriet F, Casalta JP, Ribéri A, *et al.* Infective endocarditis with neurological complications: Delaying cardiac surgery is associated with worse outcome. *Archives of Cardiovascular Diseases*. 2021; 114: 527–536.
- [28] Huang JB, Lu CC, Wen ZK, Yang JR, Li JJ. Surgical treatment of left-sided infective endocarditis with symptomatic neurological complications before surgery in China. *Frontiers in Cardiovascular Medicine*. 2023; 10: 1217148.
- [29] Head SJ, Mokhles MM, Osnabrugge RLJ, Bogers AJJC, Kapteijn AP. Surgery in current therapy for infective endocarditis. *Vascular Health and Risk Management*. 2011; 7: 255–263.
- [30] Mutagaywa RK, Vroon JC, Fundikira L, Wind AM, Kunambi P, Manyahi J, *et al.* Infective endocarditis in developing countries: An update. *Frontiers in Cardiovascular Medicine*. 2022; 9: 1007118.
- [31] Chen Y, Cai X, Cao Z, Lin J, Huang W, Zhuang Y, *et al.* Prediction of red blood cell transfusion after orthopedic surgery using an interpretable machine learning framework. *Frontiers in Surgery*. 2023; 10: 1047558.
- [32] Akinseye OA, Pathak A, Ibebuogu UN. Aortic Valve Regurgitation: A Comprehensive Review. *Current Problems in Cardiology*. 2018; 43: 315–334.
- [33] Hamirani YS, Dietl CA, Voyles W, Peralta M, Begay D, Raizada V. Acute aortic regurgitation. *Circulation*. 2012; 126: 1121–1126.