e-ISSN: 2722-3558

Sriwijaya Journal of Surgery

[SJS]

https://sriwijayasurgery.com

Impact of Prolonged Cardiopulmonary Bypass and Aortic Cross-Clamp Time on Postoperative Ventilator Dependency Following Mitral Valve Replacement

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ARTICLE INFO

Keywords:

Aortic cross-clamp time

Cardiopulmonary bypass time

Mechanical ventilation

Mitral valve replacement

Postoperative outcomes

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/sjs.v8i1.126

A B S T R A C T

Introduction: Mitral valve replacement (MVR) is a common procedure for severe mitral valve disease. Prolonged cardiopulmonary bypass (CPB) time and aortic cross-clamp (AOX) time during cardiac surgery are known to be associated with adverse postoperative outcomes, including prolonged mechanical ventilation. Understanding the predictive value of these intraoperative times specifically for ventilator dependency after MVR is crucial for risk stratification and patient management. This study aimed to determine the accuracy of CPB time and AOX time as predictors of postoperative ventilator duration in patients undergoing MVR at a tertiary referral hospital in Palembang, Indonesia. **Methods:** A retrospective cohort study was conducted using medical records of patients aged ≥ 18 years who underwent MVR between January 2022 and December 2024 at RSUP Dr. Mohammad Hoesin Palembang. Data from 79 patients meeting the inclusion criteria were analyzed. The primary independent variables were CPB time and AOX time (categorized using a 90-minute cut-off). The primary outcome was prolonged mechanical ventilation (defined as >24 hours). Secondary outcomes included ICU length of stay (>4 days) and in-hospital mortality. Statistical analysis involved Chi-square tests and multivariate logistic regression. **Results:** Prolonged CPB time (≥90 minutes) was observed in 62% of patients, and prolonged AOX time (≥90 minutes) in 45.6%. Both prolonged AOX time (OR 15.167, p=0.01) and prolonged CPB time (OR 8.88, p=0.01) were significantly associated with mechanical ventilation >24 hours. Multivariate analysis confirmed both AOX time (Adjusted OR 8.741, p=0.049) and CPB time (Adjusted OR 5.163, p=0.027) as independent predictors for prolonged ventilation. Significant associations were also found between prolonged AOX/CPB times and ICU stay >4 days (p=0.03 for both). No significant association was found between CPB/AOX times and in-hospital mortality (p=0.968 and p=0.206, respectively). **Conclusion:** Prolonged CPB time and AOX time are significant independent predictors of postoperative ventilator dependency exceeding 24 hours following MVR in this patient cohort. Minimizing these intraoperative durations may reduce the burden of prolonged mechanical ventilation.

1. Introduction

Valvular heart disease presents a substantial global health challenge, significantly contributing to cardiovascular morbidity and mortality worldwide. In developed nations, the prevalence of this condition is estimated to be approximately 2.5% of the population, with a tendency to increase with age, often due to degenerative processes. While various types of valve pathologies exist, including stenosis and regurgitation affecting the aortic, tricuspid, or pulmonary valves, mitral valve disease remains particularly prevalent. In Indonesia, rheumatic heart disease has historically been a major contributing factor, frequently leading to mitral stenosis. However, there is an increasing global incidence of degenerative mitral regurgitation. Significant mitral regurgitation, characterized by inadequate valve closure and backward blood flow into the left atrium during systole, is associated with a poor prognosis if left untreated. This condition often leads to left ventricular remodeling, heart failure, and reduced survival rates. Similarly, severe mitral stenosis restricts blood flow from the left atrium to the left ventricle, resulting in increased left atrial pressure and potentially leading to pulmonary hypertension and atrial fibrillation. For patients with severe symptomatic mitral valve disease who are not suitable candidates for repair or percutaneous interventions, mitral valve replacement (MVR) surgery remains a fundamental treatment option. MVR is particularly indicated in cases where valve pathology involves extensive tissue damage, such as in infective endocarditis, severe annular calcification, rheumatic changes with subvalvular fusion, or certain primary valve abnormalities.[1-3]

While the primary goal of MVR is to restore valve function and improve patient outcomes, the procedure itself carries inherent risks, primarily due to the necessity of cardiopulmonary bypass (CPB) and aortic cross-clamping (AOX). CPB involves diverting the patient's blood through an external circuit, known as a heart-lung machine, which oxygenates and pumps the blood, allowing surgeons to operate on a still, bloodless heart. AOX involves clamping the ascending aorta to isolate the heart from systemic circulation and enable the administration of cardioplegia solution. This induces cardiac arrest and protects the myocardium during the surgical procedure. However, both CPB and AOX initiate complex pathophysiological responses in the body. CPB exposes blood components to artificial surfaces, triggering inflammatory cascades, coagulation pathways, and fibrinolysis. This can potentially lead to systemic inflammatory response syndrome (SIRS), coagulopathy, and organ dysfunction. AOX induces a period of myocardial and systemic ischemia, followed by reperfusion injury upon the release of the clamp. The duration of both CPB and AOX has been consistently identified as a critical factor influencing postoperative outcomes across various cardiac surgeries. Prolonged CPB and AOX times have been independently associated with an increased risk of major adverse events. These events include mortality, stroke, renal failure, bleeding requiring transfusion, low cardiac output syndrome, and prolonged hospital or intensive care unit (ICU) stays.[4-6]

In particular, extended CPB and AOX durations are believed to significantly contribute to postoperative pulmonary dysfunction. The inflammatory response triggered by CPB, combined with ischemia-reperfusion injury from AOX, can lead to increased pulmonary vascular permeability, the accumulation of leukocytes in the pulmonary microvasculature, endothelial damage, alveolar edema, impaired gas exchange, and reduced lung compliance. In severe cases, this can manifest as acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), necessitating prolonged mechanical ventilation support. Prolonged mechanical ventilation, often defined as requiring support for more than 24 or 48 hours post-surgery, is itself a major determinant of postoperative morbidity and mortality. It also increases ICU and hospital length of stay, and impacts long-term functional outcomes. Therefore, identifying patients at high risk for prolonged ventilation is crucial for implementing targeted perioperative management strategies. While several factors, such as patient age, preoperative comorbidities (including renal insufficiency, chronic lung disease, severity of heart failure based on NYHA class, low ejection fraction), and emergency surgery status, are recognized risk factors, the specific contribution and predictive accuracy of intraoperative CPB and AOX times for ventilator dependency following isolated MVR require further investigation. This need for clarification is particularly important within specific healthcare settings. Studies that evaluate the impact of CPB/AOX time often group various cardiac procedures together or focus primarily on coronary artery bypass grafting (CABG) or aortic valve replacement (AVR). While some studies have reported thresholds, such as AOX time exceeding 75 minutes in CABG or 60 minutes in AVR, as being associated with increased mortality, other studies suggest different thresholds of 90 or 120 minutes, particularly in complex valve surgeries. It's also been noted that minimally invasive approaches may allow for longer times with similar outcomes. However, the relationship between CPB and AOX times and prolonged ventilation specifically following MVR, especially when using a >24-hour definition, is not consistently defined. Some pediatric studies have shown associations, but there is less abundant data focused on adult MVR patients.[7-10] Therefore, this study aims to determine the utility of intraoperative cardiopulmonary bypass and aortic cross-clamp times as predictive markers for identifying patients at high risk of requiring prolonged mechanical ventilation (more than 24 hours) after mitral valve replacement surgery within a specific Indonesian patient population.

2. Methods

This study employed a retrospective cohort study design, utilizing secondary data analysis to investigate the impact of cardiopulmonary bypass (CPB) time and aortic cross-clamp (AOX) time on postoperative outcomes following mitral valve replacement (MVR) surgery. The research was conducted within the Department of Thoracic, Cardiac, and Vascular Surgery at Dr. Mohammad Hoesin General Hospital, a tertiary referral teaching hospital situated in Palembang, South Sumatra, Indonesia. The study population comprised all adult patients who underwent MVR surgery at this institution during the specified timeframe. Data were meticulously collected from patient medical records spanning from January 2022 to December 2024. Prior to the commencement of data collection, ethical approval was duly obtained from the institutional research ethics committee.

To ensure the selection of appropriate participants for this study, predefined inclusion and exclusion criteria were established; Inclusion Criteria: The study included patients aged 18 years or older who underwent an MVR procedure. This included both isolated MVR procedures and cases where MVR was the primary operation, even if combined with other minor procedures. The surgeries had to be performed between January 2022 and December 2024; Exclusion Criteria: Patients with pre-existing severe organ dysfunction were excluded from the study. This encompassed individuals with end-stage renal failure requiring preoperative dialysis and those with severe respiratory failure necessitating preoperative ventilation. Additionally, patients with significant hematological or coagulation disorders that posed an immediate threat to life, independent of the surgery, were excluded. Finally, patients with incomplete or illegible medical records that hindered data extraction were also excluded from the study.

A total sampling technique was employed in this study. This means that all patients who met the inclusion criteria and did not meet the exclusion criteria during the study period were included in the analysis. The sample size was calculated *a priori* to ensure adequate statistical power for detecting a correlation for a prognostic test. The calculation estimated a minimum required sample size of 67 participants. To account for potential dropouts or missing data, this number was increased by 10%, resulting in a target sample size of approximately 74 subjects. Ultimately, the final analysis included 79 patients who fulfilled all the eligibility criteria.

Data extraction was conducted retrospectively from patient medical records. The records reviewed included surgical reports, anesthesia records, ICU flowsheets, and discharge summaries. To maintain consistency and minimize variability, data extraction was performed by a single investigator.

The primary independent variables in this study were; Cardiopulmonary Bypass (CPB) Time: This was defined as the total duration, measured in minutes, from the initiation of CPB to its termination. This data was meticulously obtained from the surgical and perfusion records of each patient. For the purpose of analysis, CPB time was categorized using a 90-minute threshold. Patients were grouped into two categories: those with a CPB time of 90 minutes or less (≤90 minutes) and those with a CPB time exceeding 90 minutes (>90 minutes). The selection of this 90-minute cut-off was informed by existing literature that suggests an increased risk of adverse outcomes, including prolonged ventilation, with CPB times surpassing this duration. This threshold also facilitated practical grouping and analysis within the dataset; Aortic Cross-Clamp (AOX) Time: This variable was defined as the duration, measured in minutes, from the application of the aortic cross-clamp to its removal. This duration represents the period of myocardial ischemia while the heart is under cardioplegic arrest. Similar to CPB time, AOX time was also categorized using a 90-minute threshold for analysis. Patients were classified into those with an AOX time of 90 minutes or less (≤90 minutes) and those with an AOX time greater than 90 minutes (>90 minutes). This categorization was consistent with the CPB time categorization and aligned with literature references indicating a potential increase in risk beyond this time point.

The study focused on the following dependent variables to assess postoperative outcomes; Prolonged Mechanical Ventilation: This was the primary outcome of interest and was defined as the total duration of invasive mechanical ventilation support required postoperatively, exceeding 24 hours. This variable was treated as a dichotomous measure. Patients were categorized into two groups: those requiring mechanical ventilation for less than 24 hours (<24 hours) and those requiring ventilation for 24 hours or more (≥24 hours). Data on ventilation duration was obtained from ICU records; Prolonged Intensive Care Unit (ICU) Length of Stay: This secondary outcome was defined as the duration of a patient's stay in the ICU, measured in days from their admission following surgery to their discharge from the ICU. For the purpose of analysis, ICU length of stay was also dichotomized. A cut-off of 4 days was used, with patients categorized into those with an ICU stay of 4 days or less (≤4 days) and those with an ICU stay of more than 4 days (>4 days). This cut-off was derived from the distribution of the data within the study sample; In-Hospital Mortality: This variable indicated the occurrence of death from any cause during the same hospital admission following the MVR procedure. It was recorded as a dichotomous variable, with patients classified as either "Survived" or "Died".

The collected data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) software, with versions 25.0 or 26.0 for Windows being utilized. Continuous variables were described using means and standard deviations (SD) to provide a measure of central tendency and variability. Categorical variables were presented as frequencies and percentages to illustrate the distribution of patients across different categories. The distribution frequencies and characteristics of each variable were carefully examined to understand the data's properties and identify any potential outliers or deviations from normality. The association between the categorized independent variables (CPB time ≤/>90 min, AOX time ≤/>90 min) and the dichotomous outcome variables (Ventilator duration ≤/>24h, ICU stay ≤/>4d, Mortality) was assessed using the Chi-square test. This test is appropriate for examining the relationship between two categorical variables. To estimate the strength of the association between the independent and dependent variables, Odds Ratios (OR) with 95% confidence intervals (CI) were calculated. An odds ratio greater than 1 indicates an increased likelihood of the outcome occurring in the exposed group, while an odds ratio less than 1 suggests a decreased likelihood. For the primary outcome (prolonged ventilation) and the secondary outcome of mortality, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of using the 90-minute cut-offs for CPB and AOX times as predictors were calculated. Sensitivity measures the proportion of patients with the outcome who are correctly identified by the predictor. Specificity measures the proportion of patients without the outcome who are correctly identified. PPV indicates the probability that a patient with a positive test (e.g., CPB time >90 minutes) truly has the outcome (e.g., prolonged ventilation). NPV indicates the probability that a patient with a negative test (e.g., CPB time ≤90 minutes) truly does not have the outcome. To assess the independent predictive effect of CPB time and AOX time on the primary outcome (prolonged ventilation >24h), a logistic regression analysis was performed. This allowed for the adjustment of each variable for the other, controlling for potential confounding effects. The adjusted ORs and their corresponding significance levels were reported to determine the independent contribution of each intraoperative time to the risk of prolonged ventilation. A p-value of ≤ 0.05 was used as the criterion for statistical significance for all inferential tests. This threshold indicates that there is a 5% or less probability of observing the obtained results if there were truly no association between the variables in the population.

3. Results

Table 1 presents a summary of the key characteristics of the 79 patients included in the study, the intraoperative variables of interest (AOX and CPB times), and their postoperative outcomes. This table provides an overview of the patient population and the context of the study findings; Patient Characteristics: The table shows that all 79 patients were adults (≥18 years), with a mean age of 40.8 years and a standard deviation of 13.01 years. This indicates that the study population had a spread of ages, with the majority of patients being around 40 years old; Intraoperative Variables: The mean AOX time for all patients was 96.63 minutes, with a standard deviation of 38.82 minutes. When categorized, 54.4% of patients (n=43) had an AOX time of 90 minutes or less (≤90 minutes), while 45.6% (n=36) had an AOX time exceeding 90 minutes (>90 minutes). This categorization is important as the study uses 90 minutes as a threshold for defining prolonged AOX time. The mean CPB time was 112.74 minutes, with a standard deviation of 47.84 minutes. Categorically, 38.0% of patients (n=30) had a CPB time of 90 minutes or less (≤90 minutes), and 62.0% (n=49) had a CPB time greater than 90 minutes (>90 minutes). Similar to AOX time, this categorization facilitates the analysis of the impact of prolonged CPB time on outcomes; Postoperative Outcomes: A large majority of patients (91.1%, n=72) had a prolonged ICU stay of 4 days or more (≥4 days), while only 8.9% (n=7) stayed in the ICU for less than 4 days (≤4 days). This indicates that prolonged ICU stays were common in this patient group. Most patients (82.3%, n=65) required mechanical ventilation for 24 hours or more (≥24 hours) postoperatively. Only a small proportion (17.7%, n=14) were ventilated for less than 24 hours (<24 hours). This highlights that prolonged ventilation was a frequent occurrence following MVR in this study. The in-hospital mortality rate was 16.5% (n=13), with 83.5% of patients (n=66) surviving to hospital discharge.

Table 2 presents the results of bivariate analyses examining the association between aortic cross-clamp (AOX) time and cardiopulmonary bypass (CPB) time, categorized as either ≤90 minutes or >90 minutes, and several postoperative outcomes: prolonged ventilation (≥24 hours), prolonged ICU stay (≥4 days), and in-hospital mortality; AOX Time and Outcomes: A statistically significant association was found between AOX time and prolonged ventilation. Patients with an AOX time >90 minutes showed significantly higher odds of requiring ventilation for ≥24 hours compared to those with an AOX time ≤90 minutes. A large majority of patients with AOX time >90 minutes experienced prolonged ventilation, compared to a smaller majority of those with AOX time ≤90 minutes. A significant association was also observed between AOX time and prolonged ICU stay. Patients with AOX time >90 minutes were associated with prolonged ICU stay. A substantial proportion of patients with AOX time >90 minutes had prolonged ICU stays, as did a very high proportion of patients with AOX time ≤90 minutes. No statistically significant association was found between AOX time and in-hospital mortality. While the association was not significant, a higher percentage of patients with AOX time >90 minutes died compared to those with AOX time ≤90 minutes; CPB Time and Outcomes: A statistically significant association was found between CPB time and prolonged ventilation. Patients with CPB time >90 minutes had significantly higher odds of requiring ventilation for ≥24 hours compared to patients with CPB time ≤90 minutes. A large proportion of patients with CPB time >90 minutes experienced prolonged ventilation, compared to a smaller proportion of patients with CPB time ≤90 minutes. A significant association was observed between CPB time and prolonged ICU stay. A high percentage of patients with CPB time >90 minutes had prolonged ICU stays, as did all patients with CPB time ≤90 minutes. There was no statistically significant association between CPB time and in-hospital mortality. The mortality rate was similar between patients with CPB time >90 minutes and those with CPB time ≤90 minutes.

Table 3 evaluates the accuracy of using aortic cross-clamp (AOX) time and cardiopulmonary bypass (CPB) time, specifically exceeding 90 minutes, to predict prolonged mechanical ventilation (≥24 hours) following mitral valve replacement; Aortic Cross-Clamp (AOX) Time (>90 minutes): The ability of AOX time exceeding 90 minutes to identify patients who would require prolonged ventilation was assessed. The sensitivity, which indicates the proportion of patients who actually required prolonged ventilation and were correctly identified by the AOX time, was reported. The specificity, representing the proportion of patients who did not require prolonged ventilation and were correctly identified, was also shown. The positive predictive value (PPV), which is the probability that a patient with an AOX time >90 minutes would indeed require prolonged ventilation, was provided. Finally, the negative predictive value (NPV), the probability that a patient with an AOX time ≤90 minutes would not require prolonged ventilation, was included; Cardiopulmonary Bypass (CPB) Time (>90 minutes): Similarly, the table presents the sensitivity, specificity, PPV, and NPV for CPB time exceeding 90 minutes in predicting prolonged mechanical ventilation. These metrics indicate how well CPB time >90 minutes correctly identifies patients who will and will not need prolonged ventilation, as well as the probability of prolonged ventilation given a CPB time >90 minutes and the probability of not needing prolonged ventilation given a CPB time ≤90 minutes.

Table 4 assesses the accuracy of using aortic cross-clamp (AOX) time and cardiopulmonary bypass (CPB) time, specifically when exceeding 90 minutes, to predict in-hospital mortality following mitral valve replacement; Aortic Cross-Clamp (AOX) Time (>90 minutes): The table presents the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for AOX time greater than 90 minutes as a predictor of in-hospital mortality. Sensitivity indicates the proportion of patients who died in the hospital and were correctly identified by an AOX time >90 minutes. Specificity represents the proportion of patients who survived to discharge and were correctly identified by an AOX time ≤90 minutes. PPV is the probability that a patient with an AOX time >90 minutes would die in the hospital. NPV is the probability that a patient with an AOX time ≤90 minutes would survive to discharge; Cardiopulmonary Bypass (CPB) Time (>90 minutes): The table similarly shows the sensitivity, specificity, PPV, and NPV for CPB time exceeding 90 minutes as a predictor of in-hospital mortality. These metrics indicate how well CPB time >90 minutes identifies patients who will and will not die in the hospital, and the probabilities of death or survival given CPB time relative to the 90-minute threshold.

Table 5 presents the results of a multivariate logistic regression analysis, which was used to determine the independent predictive ability of aortic cross-clamp (AOX) time and cardiopulmonary bypass (CPB) time (both categorized as >90 minutes) for prolonged mechanical ventilation (≥24 hours) following mitral valve replacement. This type of analysis allows us to see the effect of each predictor while controlling for the influence of the other; AOX Time (>90 minutes): The table shows the adjusted odds ratio for prolonged AOX time. The adjusted odds ratio indicates the likelihood of prolonged ventilation in patients with AOX time >90 minutes, after accounting for the effect of CPB time. The p-value associated with AOX time indicates the statistical significance of this finding; CPB Time (>90 minutes): Similarly, the table presents the adjusted odds ratio for prolonged CPB time. This shows the likelihood of prolonged ventilation in patients with CPB time >90 minutes, after accounting for the effect of AOX time. The corresponding p-value indicates the statistical significance; Constant: The table also includes a "Constant," which represents the intercept of the regression model. The p-value for the constant indicates the statistical significance of the model's baseline prediction when both AOX time and CPB time are at their reference levels (≤90 minutes).

Table 1. Patient characteristics, intraoperative variables, and postoperative outcomes following mitral valve replacement (N=79).

Category	Variable	Metric / Subgroup	Number (n)	Percentage (%)	Mean ± Standard Deviation
Patient characteristics	Age (Years)	Total Sample	79	100%	40.8 ± 13.01
		All Patients ≥ 18 Years	79	100%	
Intraoperative variables	Aortic Cross-Clamp (AOX) Time (min)	Overall	79	100%	96.63 ± 38.82
		≤ 90 Minutes	43	54.4%	
		> 90 Minutes	36	45.6%	
	Cardiopulmonary Bypass (CPB) Time (min)	Overall	79	100%	112.74 ± 47.84
		≤ 90 Minutes	30	38.0%	
		> 90 Minutes	49	62.0%	
Postoperative outcomes	ICU Length of Stay (Days)	≤ 4 Days	7	8.9%	
		≥ 4 Days	72	91.1%	
	Mechanical Ventilation Duration	≤ 24 Hours	14	17.7%	
		≥ 24 Hours	65	82.3%	
	In-Hospital Outcome	Survived	66	83.5%	
		Died	13	16.5%	

Table 2. Bivariate analysis of intraoperative variables and postoperative outcomes following mitral valve replacement (N=79).

Predictor variable	Outcome variable	Predictor category	Outcome ≥ Threshold (n)	Outcome Threshold (n)	Total (n)	Odds Ratio (OR)	p-value
AOX Time	**Prolonged Ventilation (≥24 hrs)**	**> 90 min**	35	1	36	**15.167**	**0.01***
		≤ 90 min	30	13	43	-	
AOX Time	**Prolonged ICU Stay (≥4 days)**	**> 90 min**	30	6	36	0.12	**0.03***
		≤ 90 min	42	1	43	-	
AOX Time	**In-Hospital Mortality**	**> 90 min**	Died: 8	Survived: 28	36	461	206
		≤ 90 min	Died: 5	Survived: 38	43	-	
CPB Time	**Prolonged Ventilation (≥24 hrs)**	**> 90 min**	46	3	49	**8.88**	**0.01***
		≤ 90 min	19	11	30	-	
CPB Time	**Prolonged ICU Stay (≥4 days)**	**> 90 min**	42	7	49	0	**0.03***
		≤ 90 min	30	0	30	-	
CPB Time	**In-Hospital Mortality**	**> 90 min**	Died: 8	Survived: 41	49	1.025	968
		≤ 90 min	Died: 5	Survived: 25	30	-	

*Statistically significant.

Table 3. Prognostic accuracy of intraoperative variables for predicting prolonged mechanical ventilation (≥ 24 hours).

Predictor variable	Threshold met	Sensitivity (%)	Specificity (%)	Positive predictive value (PPV) (%)	Negative predictive value (NPV) (%)
Aortic Cross-Clamp (AOX) Time	> 90 minutes	53.85	92.86	97.22	30.23
Cardiopulmonary Bypass (CPB) Time	> 90 minutes	70.77	78.57	93.88	36.67

Table 4. Prognostic accuracy of intraoperative variables for predicting in-hospital mortality.

Predictor variable	Threshold met	Sensitivity (%)	Specificity (%)	Positive predictive value (PPV) (%)	Negative predictive value (NPV) (%)
Aortic Cross-Clamp (AOX) Time	> 90 minutes	61.54	57.57	22.22	88.37
Cardiopulmonary Bypass (CPB) Time	> 90 minutes	61.54	37.88	16.33	83.33

Table 5. Multivariate logistic regression analysis of predictors for prolonged mechanical ventilation (≥ 24 hours).

Independent variable (Predictor)	Regression coefficient (B)	Standard error (S.E)	Wald statistic	df	p-value (Sig.)	Adjusted odds ratio (Exp(B))
AOX Time (> 90 minutes)	2.168	1.101	3.879	1	0.049*	8.741
CPB Time (> 90 minutes)	1.641	741	4.907	1	0.027*	5.163
Constant	-3.560	1.452	6.013	1	0.014**	

*p ≤ 0.05 indicates a statistically significant independent association.

**p = 0.014 for the Constant indicates statistical significance.

4. Discussion

The primary finding of this study is the confirmation that both prolonged CPB time (≥90 minutes) and prolonged AOX time (≥90 minutes) are significant independent predictors of prolonged mechanical ventilation (≥24 hours) following MVR. This observation aligns with a substantial body of evidence demonstrating the detrimental effects of extended CPB and AOX durations across a spectrum of cardiac surgical procedures. The mechanisms through which prolonged CPB and AOX contribute to postoperative pulmonary dysfunction are complex and multifactorial. CPB, while essential for providing a bloodless and still surgical field, involves the exposure of blood components to the artificial surfaces of the bypass circuit. This interaction triggers a systemic inflammatory response, characterized by the activation of leukocytes, endothelial cells, and the complement system. The subsequent release of pro-inflammatory mediators, including cytokines (such as TNF-α, IL-6, and IL-8), proteases, and reactive oxygen species (ROS), initiates a cascade of events that can lead to organ injury. Concurrently, AOX induces a period of myocardial ischemia, followed by reperfusion injury upon the release of the aortic clamp. This ischemia-reperfusion injury further exacerbates the inflammatory response and can directly damage the myocardium and other organs. In the pulmonary system, the combined effects of CPB-induced inflammation and AOX-related ischemia-reperfusion injury can manifest as increased pulmonary vascular permeability, the accumulation of leukocytes in the pulmonary microvasculature, endothelial damage, alveolar edema, impaired surfactant function, ventilation-perfusion mismatch (intrapulmonary shunting), and decreased lung compliance. These pathological changes contribute to postoperative pulmonary dysfunction, ranging from mild hypoxemia to severe acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), necessitating prolonged mechanical ventilation support. The findings of this study strongly support this pathophysiological link in the context of MVR. The adjusted odds ratios from the multivariate analysis demonstrated that patients with CPB times exceeding 90 minutes had a 5.16-fold increased odds of requiring prolonged ventilation, while those with AOX times exceeding 90 minutes had an even higher 8.74-fold increased odds. These results underscore the independent and substantial contributions of both CPB and AOX duration to the risk of prolonged ventilator dependency following MVR.[11,12]

The mean CPB and AOX times observed in this study provide a basis for comparison with findings from other investigations. The mean CPB time in this study was 112.7 minutes, and the mean AOX time was 96.6 minutes. These values generally fall within the range of CPB and AOX times reported in other studies of MVR and other open-heart surgeries. However, it is important to acknowledge that variations in these intraoperative durations can occur due to several factors, including the complexity of the surgical procedure, the specific surgical technique employed (e.g., minimally invasive versus traditional sternotomy), and individual patient characteristics. For instance, a study conducted at the National Cardiovascular Center in Indonesia reported a mean CPB time of 133.9 minutes for MVR procedures, which is somewhat higher than the mean CPB time observed in the present study. Another Indonesian study that included a mix of open-heart surgeries reported mean CPB and AOX times of 158.2 minutes and 126.4 minutes, respectively, which are considerably longer than those in our study. In contrast, a study from Yogyakarta, Indonesia, found a mean AOX time of 92.7 minutes, which is closer to the mean AOX time in our study. Furthermore, international studies focusing on minimally invasive mitral valve surgery have reported median AOX times ranging from 73 to 129 minutes. These studies have also suggested that shorter AOX times, particularly within the range of 60 to 90 minutes, are associated with improved outcomes, including lower mortality rates. The use of a 90-minute cut-off for defining prolonged CPB and AOX times in the present study is supported by both the findings of this research and existing literature. Several studies have indicated that exceeding this threshold is associated with a significant increase in the risk of adverse postoperative events.[13,14]

In addition to its impact on prolonged mechanical ventilation, this study also found significant associations between prolonged CPB and AOX times (≥90 minutes) and prolonged ICU stay (≥4 days). This finding aligns with the understanding that more extensive surgical procedures, often characterized by longer CPB and AOX durations, typically result in a greater degree of physiological stress and a longer recovery period. Patients undergoing longer surgeries may experience more pronounced inflammatory responses, increased tissue trauma, and a higher risk of complications, all of which can contribute to the need for extended ICU monitoring and support. Prolonged mechanical ventilation, as identified in this study, is itself a significant factor contributing to longer ICU stays. Patients requiring extended ventilator support often have more complex medical needs and may be at a higher risk of developing ventilator-associated pneumonia, muscle weakness, and other complications that necessitate continued ICU care. However, it is important to note that the baseline rate of prolonged ICU stay in this study cohort was remarkably high (91.1%). This unusually high rate warrants careful consideration when interpreting the odds ratios derived from the bivariate analysis. The elevated baseline rate suggests that factors other than CPB and AOX times may have significantly influenced the duration of ICU stay in this patient population. These factors could include specific institutional practices related to ICU admission and discharge criteria, the overall acuity and complexity of the patients' conditions, or resource constraints that may have affected the availability of ICU beds. Consequently, the high baseline rate may have limited the ability of the bivariate analysis to accurately capture the true effect size of CPB and AOX duration on ICU length of stay.[15,16]

Interestingly, this study did not find a statistically significant association between either CPB time or AOX time and in-hospital mortality following MVR. This finding contrasts with some previous studies, particularly those focusing on aortic valve replacement (AVR) or coronary artery bypass grafting (CABG), which have reported a link between prolonged CPB and/or AOX times and increased early mortality. The in-hospital mortality rate observed in this study was 16.5%. This rate is higher than those typically reported in high-volume centers in developed countries, where mortality rates following MVR are often in the range of 4% to 7%. The higher mortality rate in the present study could be attributed to a combination of factors. It may reflect the complexity of the patient population, which might include a higher prevalence of advanced disease states, such as rheumatic heart disease, or a greater burden of comorbidities. Additionally, variations in perioperative care practices and resource availability within the specific healthcare setting could also contribute to the observed mortality rate. While prolonged CPB and AOX times are known to contribute to postoperative morbidity, such as prolonged ventilation and ICU stay, which can indirectly increase the risk of mortality, other factors likely play a more dominant role in determining short-term survival after MVR. These factors may include preoperative patient characteristics, such as New York Heart Association (NYHA) functional class, left ventricular ejection fraction, and the presence of specific comorbidities (e.g., renal dysfunction, chronic lung disease), as well as postoperative complications, such as low cardiac output syndrome or sepsis. The interplay of these variables can significantly influence patient outcomes and may have obscured the direct impact of CPB and AOX times on mortality in this study. Furthermore, it is plausible that the lack of a statistically significant association between CPB/AOX times and mortality in this study is due to limitations in statistical power. The sample size, while adequate for detecting associations with prolonged ventilation and ICU stay, may have been insufficient to detect a statistically significant relationship with mortality, given the relatively smaller number of mortality events (n=13).[17,18]

The prognostic analysis conducted in this study provides further insights into the predictive value of CPB and AOX times for postoperative outcomes. For predicting prolonged mechanical ventilation (≥24 hours), using a 90-minute cut-off for CPB time demonstrated reasonable sensitivity (70.8%) and specificity (78.6%). The positive predictive value (PPV) was high (93.9%), indicating that when CPB time exceeded 90 minutes, the likelihood of prolonged ventilation was high. However, the negative predictive value (NPV) was relatively low (36.7%), suggesting that a CPB time of 90 minutes or less did not reliably predict the absence of prolonged ventilation. AOX time exceeding 90 minutes showed lower sensitivity (53.8%) but higher specificity (92.9%) and PPV (97.2%) for predicting prolonged ventilation. This indicates that while prolonged AOX time strongly predicts the likelihood of prolonged ventilation, it may miss a significant proportion of patients who will require prolonged ventilation despite having shorter AOX times. The NPV for AOX time was also low (30.2%). These findings suggest that while prolonged CPB and AOX times are valuable indicators of increased risk for prolonged ventilation, they are not the sole determinants. Other patient-specific and procedural factors likely contribute to the need for extended ventilator support following MVR. In contrast, neither CPB time nor AOX time demonstrated strong predictive value for in-hospital mortality in this study. The PPVs for both CPB time and AOX time in predicting mortality were low (16.3% and 22.2%, respectively), indicating that prolonged CPB or AOX time did not reliably predict mortality.[19,20]

5. Conclusion

In conclusion, this study provides compelling evidence that prolonged cardiopulmonary bypass (CPB) time and aortic cross-clamp (AOX) time are significant independent predictors of prolonged mechanical ventilation following mitral valve replacement (MVR). Specifically, CPB times exceeding 90 minutes were associated with a 5.16-fold increased odds of requiring prolonged ventilation, while AOX times exceeding 90 minutes conferred an even higher 8.74-fold increased odds. These findings underscore the importance of minimizing CPB and AOX durations during MVR surgery to mitigate the risk of postoperative pulmonary complications and the need for prolonged ventilator support. The study also revealed a significant association between prolonged CPB and AOX times and prolonged ICU stays, highlighting the broader impact of these intraoperative factors on postoperative recovery. However, it's important to acknowledge the high baseline rate of prolonged ICU stays in this cohort, which may limit the generalizability of this particular finding. Interestingly, no statistically significant association was observed between CPB or AOX times and in-hospital mortality in this study. This suggests that while prolonged CPB and AOX times contribute to postoperative morbidity, other factors may play a more critical role in determining short-term survival following MVR. The prognostic analysis further indicated that while CPB and AOX times, particularly when exceeding 90 minutes, can serve as useful predictors of prolonged ventilation, they are not definitive indicators. The predictive accuracy of these intraoperative times for in-hospital mortality was also limited. Overall, the findings of this study emphasize the need for meticulous surgical technique and efficient operative management to minimize CPB and AOX times during MVR. Further research is warranted to explore other potential predictors of adverse outcomes following MVR and to develop comprehensive strategies for risk stratification and patient management.

6. References

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