

## Research Article

# Right Anterior Minithoracotomy Is an Alternative, Less Invasive Approach to Median Sternotomy during Aortic Valve Replacement for Patients with Low Left Ventricular Ejection Fraction

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The concept of minimally invasive cardiac surgery has been put forward for more than decades and continued to develop. Recently, minimally invasive aortic valve surgery is established as a safe and effective treatment for various aortic valvular heart diseases and ascending aorta disorders. This study is aimed at analyzing the safety and effectiveness of aortic valve replacement (AVR) through right anterior minithoracotomy for the treatment of patients with low left ventricular ejection fraction (LVEF). Retrospective analyses of 43 cases with low LVEF undergoing AVR through median sternotomy and 43 cases with low LVEF undergoing AVR through right anterior minithoracotomy were performed. Extracorporeal circulation time and aortic cross-clamping time were longer in patients undergoing AVR through right anterior minithoracotomy than those in patients undergoing AVR through median sternotomy ( $P < 0.05$ ). Patients undergoing AVR through right anterior minithoracotomy exhibited declines in the cardiac surgery intensive care unit (CSICU) stay, duration of mechanical ventilation, and the length of hospital stay than those undergoing AVR through median sternotomy ( $P < 0.05$ ). The volumes of 24 h chest drainage were reduced in patients undergoing AVR through right anterior minithoracotomy compared with those undergoing AVR through median sternotomy ( $P < 0.05$ ). The incidence rates of blood transfusion within 24 h and postoperative atrial fibrillation were lower in patients undergoing AVR through right anterior minithoracotomy than those in patients undergoing AVR through median sternotomy ( $P < 0.05$ ). As for cardiac function, patients with right anterior minithoracotomy had decreased left ventricular end diastolic diameter (LVEDD) but increased LVEF and left ventricular fractional shortening (LVFS) when compared to median sternotomy ( $P < 0.05$ ). With regard to inflammatory response, the serum levels of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in patients with right anterior minithoracotomy were much lower than those in median sternotomy ( $P < 0.05$ ). All these results indicate that right anterior minithoracotomy is an alternative, less invasive approach to median sternotomy during AVR for patients with low LVEF.

## 1. Introduction

Aortic valve disease, as the most common form of valvular heart disease, includes aortic stenosis and regurgitation [1–3]. Aortic stenosis refers to the abnormal structure of the aortic valve, which limits the blood flow to the body and ultimately overburdens left ventricular contraction function [4–6]. Aortic regurgitation represents a diastolic reversal of blood flow from the aorta to the left ventricle, which can be caused by the primary disease of aortic valve or the abnormal

tissue and structure around the aortic valve [7–9]. The incidence of aortic stenosis is age-dependent and thus is expected to increase due to demographic aging of the global population [10]. It is well recognized that severe aortic stenosis is followed by a poor prognosis if left untreated. The symptoms of aortic stenosis are associated with increased mortality [11]. Aortic valve replacement (AVR) through a median sternotomy incision has been the gold standard treatment as a safe, long-term, and effective treatment for aortic valve disease for decades since the 1950s [12–14]. In fact,

more and more surgeons aimed to reduce surgical infection and improve clinical and cosmetic results by changing the chest incision approach in the treatment of aortic valve disease [15]. Over the years, with the increasing application of minimally invasive and new techniques, aortic valve surgery has been significantly improved [16]. Minimally invasive aortic valve replacement (MIAVR) is defined as a smaller chest incision rather than median sternotomy, and the two main techniques of MIAVR are ministernotomy and right anterior minithoracotomy [17]. The main information available focused on the ministernotomy approaches; only a few studies evaluated the right anterior minithoracotomy approach for aortic valve disease, which revealed some advantages in terms of low incidence of atrial fibrillation and less blood transfusion and duration of mechanical ventilation [18–21]. Left ventricular ejection fraction (LVEF) refers to the ratio of stroke volume to end diastolic volume, which is an essential measurement of cardiac function [22, 23]. Reduced LVEF may be associated with worse patient outcomes, while the optimal threshold for “normal” LVEF is uncertain. Usually, LVEF more than 55% is regarded to be “normal” by guidelines [24]. According to the 2016 European Society of Cardiology Heart Failure guidelines, heart failure was newly defined with LVEF ranging from 40 to 49% [25–27]. This study retrospectively analyzed 43 cases with low LVEF undergoing AVR through median sternotomy and 43 cases with low LVEF undergoing AVR through right anterior minithoracotomy, in a bid to find an alternative, less invasive approach to median sternotomy during AVR for patients with low LVEF.

## 2. Materials and Methods

**2.1. Subject Assignments.** A total of 86 patients diagnosed with aortic valve disease with low LVEF were retrospectively studied in our hospital from September 2019 to September 2020, among which 43 cases underwent AVR through median sternotomy and 43 cases underwent AVR through right anterior minithoracotomy. Patients undergoing AVR through median sternotomy consisted of 25 males and 18 females, aged ranging from 22 to 68 years and with an average age of  $47.17 \pm 12.27$  years. Patients undergoing AVR through right anterior minithoracotomy comprised of 26 males and 17 females, aged ranging from 22 to 76 years and with an average age of  $48.48 \pm 12.14$  years. More detailed baseline variables of included patients, such as smoking, alcohol consumption, body mass index, heart rate at admission, disease duration, NYHA classification, and type of aortic valve disease, complication with diabetes, and complication with hypertension between the two groups are listed in Table 1.

**2.2. Eligibility Criteria.** Patients who were included in this study should meet the following criteria: (a) the diagnosis of aortic valve diseases confirmed by clinical manifestations, physical examination, electrocardiogram, cardiac color Doppler ultrasound, and chest X-ray, (b) LVEF < 50%, (c) tolerance to surgery and no contraindication to surgery, (d) signed informed consent, and (e) requirement of coronary angiography for patients over 50 years old and with angina

pectoris symptoms before operation to exclude the influence of coronary heart disease. Patients were excluded for the following reasons: (a) serious mental diseases or cognitive impairment; (b) liver and kidney dysfunction, malignant tumors, malignant arrhythmia, and blood diseases; (c) other organic heart diseases; (d) sternum, spine malformation, and pericardial adhesions; (e) a history of cardiac surgery or thoracotomy; (f) pulmonary hypertension, severe atrioventricular block, acute infection, and requirement for emergency surgery; (g) poor pulmonary function; and (h) pregnancy and lactation.

**2.3. Surgery Protocols.** All patients underwent routine chest computed tomography (CT) scan to determine the location of the ascending aorta before operation. Minimally invasive AVR through right anterior minithoracotomy was performed if more than 50% of the ascending aorta was located on the right side of the sternum with the main pulmonary artery as transection, the distance between the ascending aorta and chest was less than 12 cm, there was no serious calcification in the aortic valve and aortic wall, and the aortic valve diameter was no less than 20 mm. In addition, severe obesity and thoracic deformity may lead to the difficulty of visual field exposure in minimally invasive surgery, and a cardiothoracic ratio < 0.7 should be considered.

Surgery protocols for patients undergoing AVR through right anterior minithoracotomy were as follows: after general anesthesia and tracheal cannula, the patients were maintained in the supine position, with the right chest back raised, followed by a scan of ultrasound probe through the esophagus and equipment with defibrillation electrodes on the body surface with the sternum and rib marked. After a transverse incision (6–8 cm) in the third intercostal space at the right sternum, the right internal mammary artery can be ligated and separated for exposure requirement, and the pericardium was cut and suspended for about 3 cm in front of the phrenic nerve to locate the aorta with increasing exposure by cutting the 3<sup>rd</sup> or 4<sup>th</sup> costal cartilage at the right edge of the sternum. The patients were injected with heparin into the vein, with separation of the femoral artery and vein, and the femoral artery was inserted with blood-supply catheter and the femoral vein was inserted with drainage catheter aimed at building an extracorporeal circulation system. The ascending aorta was occluded with blocking forceps, and the aorta was obliquely cut on the aortic valve annulus to infuse cardioplegia through the left and right coronary arteries, respectively. The diseased aortic valve should be cut off when detected, the artificial valve should be replaced according to the size of the diseased valve, and the aortic incision was sutured if there was no abnormality. The left ventricular gas should be exhausted, and the blocking forceps at the ascending aorta was removed to observe the heartbeat, making use of a defibrillator to return the normal heartbeat if necessary. The extracorporeal circulation instruments were withdrawn when everything runs normal, and temporary pacing leads were sutured into the epicardium in case of arrhythmia, and a catheter was placed into the right ribs as a drainage tube to exhaust gas or collect effusion from the chest; the chest tissue was sutured after lung tissue restored its function.

TABLE 1: Baseline variables of included patients.

Variable	Median sternotomy	Right anterior minithoracotomy	<i>P</i>
Age (years, mean $\pm$ SD)	47.17 $\pm$ 12.27	48.48 $\pm$ 12.14	0.62
Gender/male (%)	25 (58.1%)	26 (60.5%)	0.83
Smoking (%)	16 (37.2%)	17 (39.5%)	0.83
Alcohol consumption (%)	9 (20.9%)	11 (25.6%)	0.61
Body mass index (kg/m <sup>2</sup> , mean $\pm$ SD)	24.57 $\pm$ 4.12	24.81 $\pm$ 4.07	0.79
Heart rate at admission (time (min), mean $\pm$ SD)	87.76 $\pm$ 18.49	88.26 $\pm$ 18.78	0.90
Disease duration (years, mean $\pm$ SD)	8.11 $\pm$ 1.71	8.02 $\pm$ 1.65	0.80
NYHA classification (%)			0.93
Class I	4 (9.3%)	5 (11.6%)	
Class II	16 (37.2%)	14 (32.6%)	
Class III	15 (34.9%)	17 (39.5%)	
Class IV	8 (18.6%)	7 (16.3%)	
Type of aortic valve disease (%)			0.91
Aortic stenosis	8 (18.6%)	7 (16.3%)	
Aortic insufficiency	21 (48.8%)	23 (53.5%)	
Both	14 (32.6%)	13 (30.2%)	
Diabetes (%)	9 (20.9%)	8 (18.6%)	0.79
Hypertension (%)	10 (23.3%)	9 (20.9%)	0.79

There were 43 cases undergoing AVR through median sternotomy and 43 cases undergoing AVR through right anterior minithoracotomy.

Surgery protocols for patients undergoing AVR through median sternotomy were as follows: after general anesthesia and tracheal cannula, the patients were maintained in the supine position, with the sternum split completely under the extracorporeal circulation system. Next, the patients underwent left ventricular venting, aorta occlusion, aortotomy, and perfusion of cardioprotective solution through left and right coronary arteries. The remaining operation procedures were similar as right anterior minithoracotomy.

After treatment, all patients were moved to the cardiac surgical intensive care unit (CSICU) equipped with a ventilator until they were conscious and breathed spontaneously with stable vital signs. Protamine and heparin were given routinely to improve myocardial edema and to stabilize circulation, and warfarin anticoagulation was performed in case of chest drainage less than 100 ml in 6 hours after operation. The patients were transferred to the general ward for further treatment, and electrocardiogram, echocardiography, and anteroposterior and lateral chest X-ray were reviewed before discharge.

**2.4. Efficacy Criteria and Endpoints.** The efficacy was determined according to the following criteria: the aortic valve returning to normal and the cardiac function recovering to above grade II were regarded as excellent, the aortic valve restoring partially and cardiac function returning to grade I were regarded as good, and no any positive changes on the aortic valve and the cardiac function were regarded as poor. Total cure rate = (excellent + good)/total patients. Before operation and 1 month after operation, the LVEF, left ventricular end diastolic dimension (LVEDD), and left ventricular fractional shortening (LVFS) were detected, respectively, 3 times by multifunctional color echocardiog-

raphy (Philips, Netherlands). Fasting venous blood (at least fasting 8 hours) (5 ml) was collected before and 3 h after operation. The serum samples were detected by an enzyme-linked immunosorbent assay (ELISA) kit (RapidBio, USA), in order to determine the levels of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

**2.5. Statistical Analysis.** All data were processed by SPSS 25.0 software and were consistent with the normal distribution. The measurement data were described as mean  $\pm$  standard deviation and analyzed by the *t*-test. The counting data were defined as a ratio or percentage and analyzed by the chi-squared test. A level of *P* < 0.05 was considered statistically significant.

### 3. Result

**3.1. Efficacy Comparison between AVR through Right Anterior Minithoracotomy and Median Sternotomy.** The total curative rate was 88.37% for patients with low LVEF undergoing AVR through right anterior minithoracotomy, including 16 cases (37.21%) defined as excellent, 22 cases (51.16%) defined as good, and 5 cases (11.63%) defined as poor. The total curative rate of patients undergoing AVR through median sternotomy was 86.05%, involving 14 cases (32.56%) defined as excellent, 23 cases (53.49%) defined as good, and 6 cases (13.95%) defined as poor. There was no significant difference in the total curative rate between the two groups ( $\chi^2 = 1.167$ , *P* = 0.093, Figure 1).

**3.2. AVR through Right Anterior Minithoracotomy Improved Intraoperative Indicators.** There was no significant difference in surgery time between patients with low

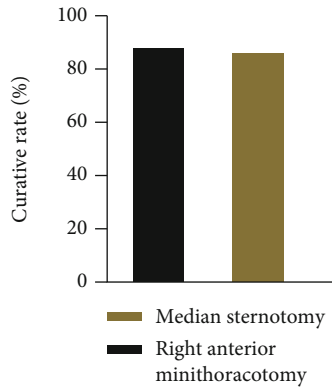


FIGURE 1: The total curative rate between patients with low LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy.

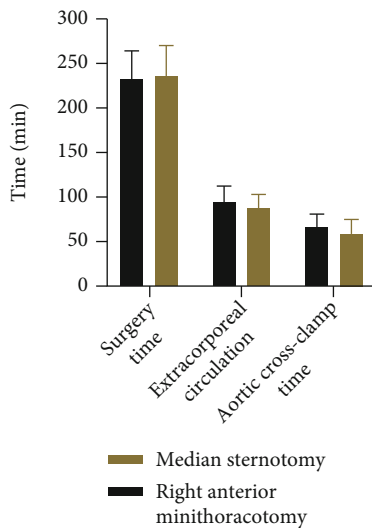


FIGURE 2: The time of surgery, extracorporeal circulation, and aortic cross-clamping between patients with low LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy.

LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy ( $233.45 \pm 30.94$  min vs.  $236.77 \pm 33.96$  min,  $P > 0.05$ ). The durations of extracorporeal circulation ( $95.78 \pm 16.23$  min vs.  $87.67 \pm 15.93$  min) and aortic cross-clamping ( $66.79 \pm 15.92$  min vs.  $58.98 \pm 15.61$  min) in patients undergoing AVR through right anterior minithoracotomy were longer than those in patients undergoing AVR through median sternotomy, respectively ( $P < 0.05$ , Figure 2).

**3.3. AVR through Right Anterior Minithoracotomy Reduced Hospital Stay and Incidence of Postoperative Atrial Fibrillation.** For patients undergoing AVR through right anterior minithoracotomy, the length of CSICU stay, the duration of mechanical ventilation, the length of hospital stay, and the volume of chest drainage within 24 h were  $1.78 \pm 0.28$  d,  $15.44 \pm 5.74$  h,  $8.68 \pm 2.74$  d, and  $159.85 \pm 25.99$  ml, respectively. For patients undergoing AVR through

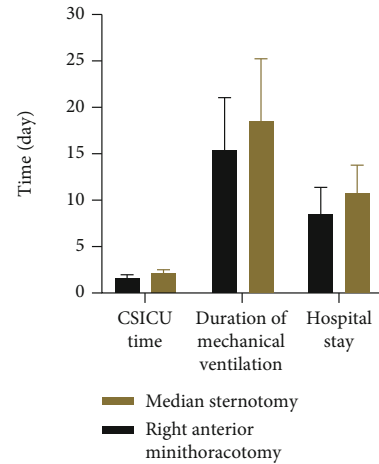


FIGURE 3: The CSICU stay, hospital stay, and duration of mechanical ventilation between patients with low LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy.

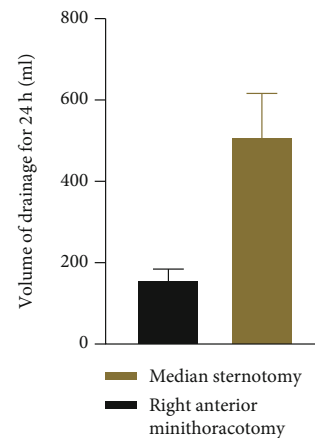


FIGURE 4: The volume of chest drainage within 24 hours between patients with low LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy.

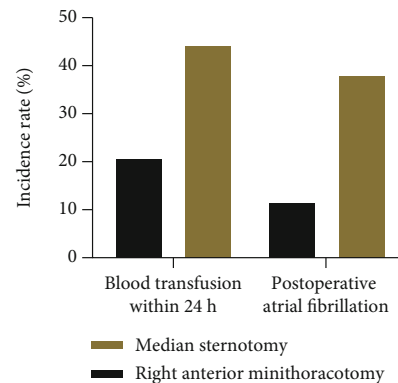


FIGURE 5: The incidence rates of blood transfusion within 24 h and postoperative atrial fibrillation between patients with low LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy.

TABLE 2: Cardiac function between patients with low LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy.

Group	Case	Time	LVEDD (mm)	LVFS (%)	LVEF (%)
Median sternotomy	43	Before operation	65.66 ± 10.12	26.86 ± 4.23	29.64 ± 5.52
		After operation	53.79 ± 9.63	30.37 ± 4.48	51.37 ± 6.12
Right anterior minithoracotomy	43	Before operation	64.56 ± 8.29	26.92 ± 4.76	29.15 ± 5.04
		After operation	49.02 ± 7.61	37.89 ± 6.68	59.81 ± 7.32
<i>t/P</i> (median sternotomy)			5.632/0.013	6.146/0.001	7.042/0.001
<i>t/P</i> (right anterior minithoracotomy)			14.510/0.001	7.510/0.001	8.050/0.001
<i>t/P</i> (group comparison after treatment)			7.154/0.001	4.972/0.017	6.134/0.001

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic dimension; LVFS: left ventricular fractional shortening.

TABLE 3: The levels of inflammatory factors in patients with low LVEF undergoing AVR through right anterior minithoracotomy and patients undergoing AVR through median sternotomy.

Group	Case	Time	IL-6 (pg/ml)	IL-8 (pg/ml)	TNF- $\alpha$ (pg/ml)
Median sternotomy	43	Before operation	99.61 ± 11.35	0.38 ± 0.12	11.84 ± 10.33
		After operation	145.62 ± 29.52	0.80 ± 0.17	25.34 ± 15.94
Right anterior minithoracotomy	43	Before operation	99.38.56 ± 12.05	0.37 ± 0.13	11.82 ± 10.26
		After operation	131.41 ± 27.53	0.67 ± 0.12	21.31 ± 12.18
<i>t/P</i> (median sternotomy)			21.473/0.001	5.384/0.001	10.476/0.001
<i>t/P</i> (right anterior minithoracotomy)			35.296/0.001	4.215/0.017	6.942/0.001
<i>t/P</i> (group comparison after treatment)			14.152/0.001	3.981/0.033	5.172/0.011

IL-6: interleukin-6; IL-8: interleukin-8; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ .

median sternotomy, the length of CSICU stay, the duration of mechanical ventilation, the length of hospital stay, and the volume of chest drainage within 24 h were  $2.14 \pm 0.57$  d,  $18.53 \pm 6.72$  h,  $10.78 \pm 2.95$  d, and  $508.97 \pm 102.37$  ml, respectively. As shown in Figure 3, patients undergoing AVR through right anterior minithoracotomy exhibited declines in the CSICU stay, duration of mechanical ventilation, and the length of hospital stay than those undergoing AVR through median sternotomy ( $P < 0.05$ ). The volumes of 24 h chest drainage were reduced in patients through right anterior minithoracotomy compared with those through median sternotomy ( $P < 0.05$ , Figure 4). Among patients undergoing AVR through right anterior minithoracotomy, 9 cases (20.93%) required blood transfusion within 24 h, 1 died (2.33%) within 30 d after treatment, 6 cases (13.95%) had ventricular arrhythmia, 2 cases (4.65%) had low cardiac output syndrome, 2 cases (4.65%) had infection, 2 cases (4.65%) had renal failure, 1 case had pleural effusion (2.33%), 2 cases had pneumothorax (4.65%), and 4 cases (9.30%) had atrial fibrillation. Among patients undergoing AVR through median sternotomy, 19 cases (44.19%) required for blood transfusion within 24 h, 2 deaths (4.65%) within 30 d after surgery, 7 cases (16.29%) with ventricular arrhythmia, 3 cases (6.98%) with low cardiac output syndrome, 2 cases (4.65%) with infection, 3 cases (6.98%) with renal failure, 1 case with pleural effusion (2.33%), 3 cases with pneumothorax (6.98%), and 13 cases (30.23%) with atrial fibrillation were observed. The incidence rates of blood transfusion within 24 h and postoperative atrial fibrillation were

lower in patients undergoing AVR through right anterior minithoracotomy than those in patients undergoing AVR through median sternotomy ( $P < 0.05$ , Figure 5). In terms of death within 30 d after surgery, incidence rates of ventricular arrhythmia, low cardiac output syndrome, infection, renal failure, pleural effusion, and pneumothorax, no remarkable difference was found between these two groups of patients ( $P > 0.05$ ).

**3.4. AVR through Right Anterior Minithoracotomy Improved Cardiac Function.** After AVR through right anterior minithoracotomy or median sternotomy, patients with low LVEF showed declined LVEDD concomitant with elevated LVFS and LVEF ( $P < 0.05$ ). Lower LVEDD with higher LVFS and LVEF was revealed in patients undergoing AVR through right anterior minithoracotomy than those through median sternotomy ( $P < 0.05$ , Table 2).

**3.5. AVR through Right Anterior Minithoracotomy Attenuated Inflammatory Response.** To compare the effects of AVR through right anterior minithoracotomy and median sternotomy on inflammatory response of patients with low LVEF, the serum levels of IL-6, IL-8, and TNF- $\alpha$  were determined by ELISA methods before and after surgery. No matter AVR through right anterior minithoracotomy or median sternotomy could reduce the serum levels of IL-6, IL-8, and TNF- $\alpha$  in patients with low LVEF. As listed in Table 3, the serum levels of IL-6, IL-8, and TNF- $\alpha$  were lower in patients

undergoing AVR through right anterior minithoracotomy than those through median sternotomy ( $P < 0.05$ ).

#### 4. Discussion

Aortic valve stenosis and aortic valve regurgitation are the main clinical manifestations of aortic valve diseases, which are very common in valvular heart diseases [28, 29]. Aortic stenosis is the most common valvular heart disease that is associated with aging in developed countries [30–32]. The European system for cardiac operative risk evaluation (EuroSCORE) reports that preoperative low LVEF is a risk factor for heart surgery. According to previous results, patients with aortic valve disease and low LVEF had a poor prognosis after conservative drug therapy, and the 3-year mortality rate is still relatively high [33]. For decades, conventional AVR has been considered the first recommendation for the treatment of aortic valve diseases, especially for severe or symptomatic aortic stenosis [34, 35]. The first AVR was reported in 1962 by Harken et al. [36]. AVR for patients with low LVEF is still challenging, and the prognosis is still controversial. With the development of surgical techniques, a new approach MIAVR was first proposed by Cosgrove and Sabik in 1996. It was reported as an effective treatment with lower costs and less surgical trauma [37, 38]. Several studies have shown that MIAVR achieved much better outcomes compared with conventional AVR [39, 40].

In this study, we analyzed the safety and effectiveness of AVR through right anterior minithoracotomy for treating patients with LVEF. We found that extracorporeal circulation time and aortic cross-clamping time were longer in patients undergoing AVR through right anterior minithoracotomy than those in patients undergoing AVR through median sternotomy. The difference may be explained by limited exposure to the operation field and requirement for high-quality surgical skills. However, the surgery time for patients undergoing AVR through right anterior minithoracotomy or median sternotomy was similar, which may be explained by reduced time of chest closure and blood stopping. These findings were similar to other studies. For instance, Ariyaratnam et al. demonstrated that MIAVR has similar hospital outcomes compared to conventional AVR, and it is quicker and does not confer any significant increase in complications or length of hospital stay [41]. Although there was a slight difference in surgery time between the two groups in our analysis, it is determined by a variety of factors, such as severity of condition on patients, the skill of surgeons, and accident occurrence during operation. According to the data in this study, patients undergoing AVR through right anterior minithoracotomy exhibited declines in the CSICU stay, duration of mechanical ventilation, and the length of hospital stay than those undergoing AVR through median sternotomy. The volumes of 24 h chest drainage were reduced in patients undergoing AVR through right anterior minithoracotomy compared with those undergoing AVR through median sternotomy. The incidence rates of blood transfusion within 24 h and postoperative atrial fibrillation were lower in patients undergoing AVR through right anterior minithoracotomy than those in patients under-

going AVR through median sternotomy. There were more other studies indicating some advantages on the above aspects [17, 21, 42, 43]. Some researches indirectly demonstrated that MIAVR restored the myocardium function of the left ventricles to a certain degree [44–46]. Lower LVEDD with higher LVFS and LVEF was revealed in patients undergoing AVR through right anterior minithoracotomy than those through median sternotomy. The pathobiology of degenerative aortic valve stenosis is complex and involves immunological and inflammatory responses, including oxidized lipids, various cytokines, and biomineralization [47]. In addition, inflammation has received much attention in shaping the biomarker network of aortic valve stenosis [48]. We also found that the serum levels of IL-6, IL-8, and TNF- $\alpha$  were lower in patients undergoing AVR through right anterior minithoracotomy than those through median sternotomy, which suggested that MIAVR made less injury and reduced inflammatory response in patients.

In summary, our study indicates that right anterior minithoracotomy is an alternative, less invasive approach to median sternotomy during AVR for patients with low LVEF, since patients undergoing AVR through right anterior minithoracotomy showed reduced hospital stay and lower incidence of postoperative atrial fibrillation, with decreased pain, limited skin incision, and maintained cardiac function. Considering that this investigation is a retrospective study, further studies including patients with data about sudden cardiac death after a one-year follow-up are required to evaluate the long-term efficacy and safety of AVR through right anterior minithoracotomy for treating patients with low LVEF. Nevertheless, power analysis to ensure sample size was warranted in further prospective studies.

#### Data Availability

The data used to support the findings of this study are included within the article.

#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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