



## ARTICLE

## Efficacy of Intravenous Treprostinil in High-Risk Single Ventricle Patients Undergoing Glenn Procedure

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### ABSTRACT

**Objective:** Pulmonary hypertension is a crucial factor affecting the recovery after Glenn procedure. This study explores the effects of intravenous treprostinil on hemodynamic status and hospital postoperative recovery under different administration strategies. **Methods:** We retrospectively included pediatric patients admitted to Fuwai Hospital from 2019 to 2022 who underwent the Glenn procedure and had intraoperative measurements of mean pulmonary artery pressure (mPAP) >15 mmHg postoperatively. Patients with non-anatomical single ventricle physiology undergoing the Glenn procedure and those requiring postoperative extracorporeal membrane oxygenation were excluded. Due to the standardized use of treprostinil in our center starting in 2021, patients from 2019–2020 were included in Group 1, and patients from 2021–2022 were included in Group 2. The changes in hemodynamic data before and after medication for both groups of patients, as well as the differences in postoperative recovery, were compared. **Results:** Twenty-eight patients were eventually enrolled in the study. Group 1 consisted of 14 cases, with a maintenance dose of  $11 \pm 2$  ng/(kg·min) 1 to 2 days postoperatively. Group 2 also consisted of 14 cases, with a maintenance dose of  $26 \pm 7$  ng/(kg·min) 1 day postoperatively. After a 24-h observation period, the mPAP decreased from  $17 \pm 3$  to  $13 \pm 3$  mmHg ( $p < 0.001$ ) in the first group and decreased from  $18 \pm 3$  to  $13 \pm 3$  mmHg ( $p < 0.001$ ) in the second group. The vasoactive-inotropic score in the first group decreased from 9 (6,17) to 6 (4,9) ( $p = 0.001$ ) and decreased from 12 (6,23) to 10 (3,15) ( $p = 0.002$ ) in the second group. Group 2 patients had a shorter postoperative hospital stay than Group 1, with durations of 18 (11,22) days and 29 (19,47) days, respectively ( $p = 0.021$ ). No severe adverse reactions occurred in all patients. **Conclusion:** Intravenous infusion of treprostinil in high-risk patients after the Glenn procedure can decrease pulmonary artery pressure, reduce vasoactive-inotropic score, and demonstrate satisfactory drug tolerance without severe adverse reactions. Standardized use of treprostinil facilitates postoperative recovery and shortens postoperative length of stay.

### KEYWORDS

Single ventricle; pulmonary hypertension; Glenn procedure; treprostinil



## Abbreviations

mPAP	Mean pulmonary artery pressure
VIS	Vasoactive-inotropic score

## 1 Introduction

The bidirectional superior cavopulmonary connection procedure, also known as the Glenn procedure, is typically the second-stage surgery for treating single ventricle patients [1]. The aim is to reduce ventricular preload and eventually prepare the patient for the third-stage Fontan procedure. Success of the surgery largely depends on the pulmonary artery pressure, in order to accommodate the non-pulsatile venous return. Increased mean pulmonary artery pressure (mPAP) has been clearly recognized as an independent high-risk factor, leading to increased postoperative complications and delayed recovery [2]. In contrast to the commonly used criterion of mPAP >20 mmHg [3], in single ventricle-related pulmonary hypertension (high-risk single ventricle), an mPAP >15 mmHg is the standard of diagnosis [4].

Patients with elevated pulmonary artery pressures may benefit from targeted pulmonary hypertension medications following Glenn procedure to reduce pulmonary circulation resistance, potentially improving hemodynamic status and surgical outcomes. Currently used targeted medications include endothelin receptor antagonists, phosphodiesterase –5 inhibitors or guanylate cyclase agonists, prostacycline and its analogues [5]. Agarwal et al. retrospectively reviewed 16 pediatric patients who underwent the Glenn procedure at a single center and studied the therapeutic effects of inhaled nitric oxide using a self-controlled method [6]. Eleven patients showed response to inhaled nitric oxide treatment, with effects including decreased Glenn pressure (from 22.4 to 17.1 mmHg,  $p < 0.001$ ), improved PaO<sub>2</sub>/FiO<sub>2</sub> (from 49 to 74.3,  $p = 0.001$ ) and oxygenation index (from 17 to 12,  $p = 0.005$ ), reduced inotrope score (from 14.9 to 11.4,  $p < 0.001$ ), and decreased volume requirements (from 11.4 to 2.3 mL/kg,  $p < 0.001$ ). However, five patients showed no response to inhaled nitric oxide treatment, all of whom had anatomical lesions. Hirono et al. [7] conducted a study on the clinical and hemodynamic improvements of single ventricle physiology patients with bosentan, including eight patients (five undergoing the Glenn procedure) who ultimately successfully underwent Fontan surgery after bosentan treatment. Mori et al. [8] conducted a multicenter retrospective study involving 42 single ventricle physiology patients with pulmonary vascular resistance index >2.5 wood units × m<sup>2</sup>, including 11 post-Glenn procedure patients. After receiving sildenafil treatment, the pulmonary vascular resistance index decreased from  $3.2 \pm 0.5$  wood units × m<sup>2</sup> to  $1.6 \pm 0.6$  wood units × m<sup>2</sup> ( $p < 0.001$ ) in these 11 patients without adverse effects. Jeremiasen et al. [9] retrospectively analyzed pulmonary hypertension-related data from British children between 2004 and 2017, including 36 single ventricle physiology patients receiving pulmonary hypertension-targeted therapy, with eight of them having undergone the Glenn procedure. The drugs used included sildenafil and/or bosentan, with 56% of patients receiving combination therapy. Among 17 patients with hemodynamic parameters, mPAP decreased from 19 to 14 mmHg ( $p < 0.01$ ). In 16 patients treated with single or initial combination therapy, oxygen saturation increased from 80% to 85% ( $p < 0.01$ ). Oxygen saturation did not improve in patients treated with sequential combination therapy. Among the eight post-Glenn procedure patients, two eventually underwent Fontan surgery.

However, these studies still have limitations. Inhalation of nitric oxide depends on the respiratory support system, which cannot be continued after extubation. The studies on oral sildenafil and bosentan mainly involve outpatient follow-up after discharge, the absorption of drugs after the operation may be insufficient due to impaired gastrointestinal function, resulting in unstable efficacy in this period. If drugs administered via intravenous/subcutaneous administration could be found as bridge therapy for inhaled and oral targeted medications, it theoretically could lead to a smoother postoperative recovery by stabilizing pulmonary artery pressure.

Treprostinil is the preferred and required medication for severe pulmonary arterial hypertension patients [10]. Although there is some evidence suggesting the efficacy of treprostinil in treating pulmonary arterial hypertension related to congenital heart disease [11], for the specific disease of a single ventricle, there is very limited research evidence. Chen et al. [12] found a linear relationship between the blood concentration of Treprostinil and its dose. In this self-controlled study involved 8 pediatric functional single ventricle pulmonary arterial hypertension, the mPAP, pulmonary-to-systemic arterial pressure ratio, and the ratio between arterial oxygen partial pressure and inhaled oxygen concentration were used to evaluate the efficacy of treatment.

Sullivan et al. [13] conducted a cohort study that included 17 high-risk single-ventricle patients who received long-term treprostinil to facilitate surgical opportunities. Regarding surgical opportunities, 3 out of 6 patients (50%) after Glenn's surgery were given the opportunity for Fontan surgery. However, current studies still have certain limitations: 1) The sample size of studies on treprostinil after Glenn surgery is small, and there is a lack of clinical studies specifically targeting Glenn patients; 2) For early postoperative patients, there is a lack of research on the standard use of treprostinil administration; 3) There is a lack of studies on the recovery after Glenn surgery.

In summary, the purpose of this study is to investigate, through a retrospective cohort study, whether standardizing the administration timing and maintenance dosage of treprostinil can improve the hemodynamics and postoperative recovery of high-risk single-ventricle heart patients following Glenn surgery.

## 2 Materials and Methods

### 2.1 Patient Inclusion and Grouping

This study analyzed pediatric patients who received the Glenn procedure at Fuwai Hospital between 2019 and 2022 retrospectively. Inclusion criteria included: 1) The mPAP >15 mmHg in the operating room after surgery completion (by direct needle manometry); 2) Postoperative intravenous infusion of treprostinil in the ICU. Exclusion criteria included: 1) Patients with non-anatomic single ventricle or single ventricle physiology undergoing Glenn procedure; 2) Postoperative use of extracorporeal membrane oxygenation assistance. Due to the standardized use of treprostinil in our center starting in 2021, patients from 2019–2020 were included in Group 1, and patients from 2021–2022 were included in Group 2.

Among a total of 184 patients after the Glenn procedure, 33 patients met the inclusion criteria. Among the 33 patients, 4 patients were excluded for non-anatomic single ventricle or single ventricle physiology, and 1 patient was excluded for receiving ECMO assistance, resulting in the final inclusion of 28 patients. Among them, there were 14 patients in the first Group who received maintaining treprostinil 1–2 days postoperatively ranging from 10–15 ng/(kg·min) with an average dose of  $11 \pm 2$  ng/(kg·min). 14 patients were included in Group 2 who received maintaining treprostinil therapy within 1 day postoperatively ranged 20–40 ng/(kg·min) with an average dose of  $26 \pm 7$  ng/(kg·min).

### 2.2 All Targeted Drug Administration Strategies

There were no patients being treated for pulmonary hypertension preoperatively. For patients after the Glenn procedure, blood pressure stability was initially maintained. Inhaled nitric oxide at 20 ppm was administered via the ventilator, gradually reducing the concentration before extubation, along with sildenafil at 0.5 mg/kg per dose, a maximum of 20 mg per dose, three times daily. After hemodynamic stability was achieved, an intravenous infusion of treprostinil was prescribed. Because of the limited clinical experience, the initial infusion rate was 4 ng/(kg·min), with increments of 2–4 ng/(kg·min) every 2 h until clinical improvement was achieved (atrial pressure, volume requirement, and tachycardia improvement), and the current dose was maintained for ongoing treatment. Standardized treprostinil

treatment began in 2021, with an initial treatment dose of 5 ng/(kg·min), increasing by 5 ng/(kg·min) every 30 min until the maximum tolerated dose (indicated by blood pressure instability) was reached for maintenance treatment. Once gastrointestinal function recovered, oral medications were added, including bosentan at 2 mg/kg (up to 125 mg/kg) twice daily, as sequential combined treatment with sildenafil. After starting oral targeted drugs, we gradually reduced and discontinued the intravenous infusion of treprostinil, without transitioning to subcutaneous administration.

### **2.3 Data Collection**

Record preoperative, intraoperative, and postoperative parameter data for both groups of patients. Preoperative data includes age, weight, heterotaxy syndrome, and mPAP measured by right heart catheterization in the catheterization laboratory before surgery. Intraoperative data includes concurrent surgeries such as atrioventricular valve plasty/correction of pulmonary vein stenosis, cardiopulmonary bypass duration, aortic cross-clamp duration, and mPAP measured in the operating room after surgery. Postoperative data includes treprostinil maintenance dose, hemodynamic parameters before and after the maintenance dose at 6, 12, 18, and 24 h, including mPAP, atrial pressure, and the vasoactivity-inotropic score calculated as dopamine dose ( $\mu\text{g}/\text{kg}/\text{min}$ ) + dobutamine dose ( $\mu\text{g}/\text{kg}/\text{min}$ ) + milrinone dose ( $\mu\text{g}/\text{kg}/\text{min}$ )  $\times$  10 + epinephrine dose ( $\mu\text{g}/\text{kg}/\text{min}$ )  $\times$  100 + vasopressin dose (U/kg/min)  $\times$  10000. Postoperative recovery parameters include mechanical ventilation duration, length of ICU stay and postoperative hospital stay, tachycardia, chest tube drainage, duration of chest tube placement, thromboembolic events, renal replacement therapy, reintubation, tracheostomy, in-hospital mortality, and adverse reactions to treprostinil treatment.

### **2.4 Statistical Analysis**

Statistical analyses were conducted utilizing IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was employed to evaluate the normality of continuous variables. Continuous variables that followed a normal distribution were reported as mean  $\pm$  standard deviation, while those not normally distributed were presented as median (interquartile range). Categorical variables were described using frequency (percentage). The study employs a one-way repeated measures analysis of variance to compare alterations in hemodynamic parameters before and after the administration of treprostinil, as well as between different groups. The assumption of sphericity is evaluated using Mauchly's test of sphericity, with the Greenhouse-Geisser correction applied if necessary. Depending on the normality of the data distribution, comparisons of continuous variables between groups are conducted using either independent samples *t*-tests or Wilcoxon rank-sum tests. Categorical variables are analyzed using Fisher's exact test where applicable. Missing values are estimated through the expectation-maximization algorithm. A *p*-value of 0.05 or less is regarded as the threshold for statistical significance.

### **2.5 Ethical Approval**

This study has been reviewed and approved by the Ethics Committee of Fuwai Hospital, with the number: 2022-1859. Due to its retrospective nature, informed consent was waived. Throughout the research process, the ethical principles outlined in the Declaration of Helsinki in 1964 were followed. This retrospective analysis is based on anonymized data collected for routine clinical care and administrative purposes. Therefore, the need for informed consent was waived.

## **3 Results**

The demographic and surgical characteristics of the two groups of patients are shown in [Table 1](#). The median age of all patients was 5.3 years, median weight was 15.3 kg, 14% had associated heterotaxy syndrome, and median cardiopulmonary bypass and aortic cross-clamp times were 159 and 83 min,

respectively. Seventy-five percent of patients underwent concurrent additional cardiac surgeries, and both preoperative and intraoperative mPAP were  $17 \pm 3$  mmHg. There was no statistical difference between the two groups in demographic and surgical characteristics, as detailed in Table 1. The main congenital heart defects in both groups are shown in Table 2.

**Table 1:** Demographic and surgical characteristics

Variable	Overall (n = 28)	Group 1 (n = 14)	Group 2 (n = 14)	p-value
Age (years)	5.3 (0.9,8)	6.7 (2.2,10.5)	4.0 (0.7,8)	0.205
Weight (kg)	15.3 (7.9,21.3)	18.1 (9.8,36.6)	8.6 (7.6,19.5)	0.073
Heterotaxy syndrome (case, %)	4 (14)	3 (21)	1 (7)	0.589
Preoperative mPAP (mmHg)	$17 \pm 3$	$17 \pm 3$	$18 \pm 4$	0.813
Cardiopulmonary bypass (min)	159 (86,189)	165 (75,189)	142 (98,203)	0.554
Aortic cross-clamp (min)	83 (66,113)	101 (63,123)	80 (71,92)	0.503
Other surgeries (case, %)	21 (75)	10 (71)	11 (79)	1.0
Intraoperative mPAP (mmHg)	$17 \pm 3$	$17 \pm 3$	$18 \pm 3$	0.292

Note: mPAP: mean pulmonary arterial pressure.

**Table 2:** Main congenital heart defects

Group	Patient	Main congenital heart defects
1	1	Ebstein’s anomaly of the tricuspid valve atrioventricular valve regurgitation
	2	Pulmonary atresia with intact ventricular septum
	3	Single ventricle atrioventricular valve regurgitation
	4	Single ventricle atrioventricular valve regurgitation
	5	Single ventricle atrioventricular valve regurgitation
	6	Single ventricle atrioventricular valve regurgitation
	7	Single ventricle atrioventricular valve regurgitation
	8	Tricuspid atresia
	9	Unbalanced double outlet right ventricle
	10	Unbalanced atrioventricular septal defects atrioventricular valve regurgitation
	11	Heterotaxy syndrome
	12	Tricuspid atresia
	13	Heterotaxy syndrome
	14	Tricuspid atresia
2	15	Unbalanced atrioventricular septal defects total anomalous pulmonary venous connection
	16	Tricuspid atresia subvalvular aortic stenosis
	17	Pulmonary atresia with intact ventricular septum
	18	Ebstein’s anomaly of the tricuspid valve atrioventricular valve regurgitation
	19	Single ventricle atrioventricular valve regurgitation

(Continued)

Group	Patient	Main congenital heart defects
	20	Tricuspid atresia
	21	Single ventricle
	22	Single ventricle atrioventricular valve regurgitation
	23	Single ventricle atrioventricular valve regurgitation
	24	Ebstein's anomaly of the tricuspid valve atrioventricular valve regurgitation
	25	Single ventricle
	26	Hypoplastic left heart syndrome restrictive atrial septal defect
	27	Heterotaxy syndrome
	28	Unbalanced atrioventricular septal defects

In terms of hemodynamic changes after the administration of treprostinil, as shown in [Table 3](#), the decrease in mPAP was statistically significant in both groups, but there was no statistical difference between the two groups. There were no statistically significant differences in changes in atrial pressure among patients overall, in Group 1, in Group 2, or between groups. The decrease in vasoactive-inotropic score was statistically significant in both groups, but there was no statistical difference between the two groups.

**Table 3: Hemodynamic changes**

	Baseline	6-h	12-h	18-h	24-h	<i>p</i> -value
mPAP (mmHg)						
Overall	17 ± 3	14 ± 3	13 ± 3	13 ± 3	13 ± 3	<0.001
Group 1	17 ± 3	13 ± 3	13 ± 3	13 ± 3	13 ± 3	<0.001
Group 2	18 ± 3	14 ± 3	14 ± 3	13 ± 2	13 ± 3	<0.001
Atrial pressure (mmHg)						
Overall	7 ± 3	7 ± 3	7 ± 2	7 ± 2	7 ± 2	0.764
Group 1	7 ± 3	7 ± 4	7 ± 3	7 ± 3	7 ± 3	0.822
Group 2	8 ± 2	8 ± 3	7 ± 2	7 ± 2	7 ± 2	0.252
VIS						
Overall	10 (6,18)	9 (4,14)	9 (4,14)	9 (4,14)	7 (4,13)	<0.001
Group 1	9 (6,17)	8 (4,11)	8 (4,11)	7 (4,9)	6 (4,9)	0.001
Group 2	12 (6,23)	11 (3,19)	10 (3,17)	10 (3,15)	10 (3,15)	0.002

Note: mPAP: mean pulmonary arterial pressure; VIS: vasoactive-inotropic score.

When comparing the postoperative recovery, the postoperative length of stay was 18 (11,22) days vs. 29 (19,47) days, shorter in Group 2 patients ( $p = 0.021$ ). There were no severe side effects that occurred in the two groups. The details of postoperative recovery are shown in [Table 4](#).



**Table 4:** Postoperative recovery

	Overall (n = 28)	Group 1 (n = 14)	Group 2 (n = 14)	<i>p</i> -value
Mechanical ventilation duration (hours)	47 (23,122)	59 (22,139)	28 (23,123)	0.713
ICU length of stay (days)	9 (4,18)	11 (4,21)	7 (4,13)	0.381
Postoperative length of stay (days)	21 (15,33)	29 (19,47)	18 (11,22)	0.021
Duration of chest tube placement (days)	7 (6,15)	7 (6,18)	7 (6,12)	0.762
Chest tube drainage volume (mL/kg)	31 (12,88)	32 (10,71)	29 (11,101)	0.662
Thromboembolic events (cases, %)	3 (11)	2 (14)	1 (7)	1.0
Tachycardia (cases, %)	12 (43)	6 (43)	6 (43)	1.0
Renal replacement therapy (cases, %)	2 (7)	1 (7)	1 (7)	1.0
Tracheal re-intubations (cases, %)	4 (14)	3 (21)	1 (7)	0.589
Tracheostomy (cases, %)	0 (0)	0 (0)	0 (0)	NA
Mortality (cases, %)	3 (11)	1 (7)	2 (14)	1.0
Side effects (cases, %)	0 (0)	0 (0)	0 (0)	NA

#### 4 Discussion

This study is the first investigation only focused on the effects of intravenous administration of treprostinil in high-risk Glenn procedures, with an emphasis on observing the impact of different administration strategies on hemodynamic status and postoperative recovery during hospitalization. Due to our center's management strategy of early extubation in the ICU following the Glenn procedure and the inability to accurately calculate relevant indicators post-tracheal extubation, the effects of treprostinil on the oxygenation index were not studied.

The patients enrolled in this study were significantly older than the best-recommended age for Glenn's operation, which was mainly due to the national conditions of our country. China, a large developing country, exhibits notable variations in its medical conditions across diverse regions. Many patients from poor areas do not receive timely treatment, resulting in delayed visits, increased pulmonary artery pressure, and increased incidence of cardiac malformations requiring surgical treatment. Since some patients undergoing Glenn procedure simultaneously require other cardiac surgeries to correct cardiac malformations, preoperative mPAP may overestimate pulmonary vasculature disease [14], hence an intraoperative mPAP >15 mmHg (after correcting the anatomical malformations) was used as the diagnostic criteria for the high-risk patient.

Our center began using treprostinil to treat high-risk patients after Glenn's surgery in 2019. Initially, due to a lack of experience and concerns about early postoperative blood flow insufficiency [15], the dosage of treprostinil was titrated cautiously, the maintenance dose was chosen based on the effectiveness of the drug, after which the dose was not further increased. Based on experience, our center implemented a standardized strategy in 2021, with earlier administration times and higher maintenance doses. Therefore, the purpose is to compare the effects of these two different strategies in improving hemodynamics and postoperative recovery.

About the improvement in hemodynamics, through an observation period of 24 h, we found out that treprostinil can decrease pulmonary arterial pressure in patients after the Glenn procedure, suggesting that targeted drug therapy for pulmonary arterial hypertension also takes its effects in single ventricle patients. Although treprostinil theoretically reduces systemic vascular resistance, in this study, the vasoactive-inotropic score after treprostinil administration continued to decrease, suggesting a significant improvement in ventricular function under the maintaining dose used in this study. In the assessment of

improvement in atrial pressure, it was found that there was no significant change in atrial pressure. Considering the findings of this study that treprostinil can improve ventricular function, it is speculated that the insignificant change in atrial pressure in patients may be attributed to its reduction of pulmonary vascular resistance, increase in the proportion of systemic-to-pulmonary circulation blood flow and ventricular volume load, which can offset its improvement in ventricular function by reducing systemic vascular resistance.

In discussing postoperative recovery, compared with Group 1, the postoperative hospital stay was significantly reduced in Group 2. In terms of cause analysis, although there was no statistical difference between the two groups in reducing pulmonary artery pressure, the pharmacological effects of treprostinil also included reducing systemic ventricular afterload and inhibiting smooth muscle cell proliferation [16]. It is speculated that the high dose of treprostinil exerted its comprehensive pharmacological effects, thereby improving the prognosis of the patients.

In addition to treprostinil, all patients enrolled in this study also received other targeted drugs, such as inhaled nitric oxide and oral bosentan/sildenafil, which also played an important role in improving postoperative recovery in high-risk patients. The purpose of treprostinil in our study was to bridge the window period when inhaled nitric oxide cannot be continued after tracheal extubation and oral drugs cannot be effective before gastrointestinal function recovery after the Glenn procedure. There was no difference in the administration schedules of inhaled nitric oxide and oral drugs between the two groups. In this condition, it was considered the difference in the treprostinil administration regimen contributed to the improvement in recovery in the standardized treatment group of patients.

In this study, three patients experienced postoperative death within 30 days after surgery, resulting in an overall mortality rate of approximately 11%. This relatively high mortality rate was considered to be related to the inclusion of high-risk patients in this study. It also suggested that for such high-risk patients, careful assessment of surgical indications was necessary. For patients at high risk, mechanical support could be considered if conditions permit [17], otherwise, palliative treatment might be considered.

This study also had certain limitations. 1) The sample size of the study is small, which may lead to the lack of statistical differences in some clinically significant results, and it is necessary to increase the sample size or conduct multicenter studies in the future to address the research deficiencies. 2) Since this study is a retrospective analysis, its evidence level is still inadequate, and future higher-level clinical studies are needed. 3) Long-term follow-up of these patients is needed in the future to study final outcomes such as the proportion of patients who completed total cavo-pulmonary connection surgery and overall mortality rate.

## 5 Conclusion

Intravenous infusion of treprostinil in high-risk patients after the Glenn procedure can decrease pulmonary artery pressure, reduce vasoactive-inotropic score, and demonstrate satisfactory drug tolerance without severe adverse reactions. Standardized use of treprostinil facilitates postoperative recovery and shortens postoperative length of stay.

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Wang, Xingwei Chen; draft manuscript preparation: Zhongyuan Lu, Wenlong Wang. All authors reviewed the results and approved the final version of the manuscript.

**Availability of Data and Materials:** The data underlying this article will be shared upon reasonable request with the corresponding author.

**Ethics Approval:** This study has been reviewed and approved by the Ethics Committee of Fuwai Hospital, with ID: 2022-1859. Due to its retrospective nature, informed consent was waived. The ethical principles outlined in the 1964 Helsinki Declaration were adhered to throughout the study.

**Conflicts of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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