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Long-term outcomes of repair in children with total anomalous pulmonary venous connection

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Original Article

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Abstract

Objectives: The clinical data of patients with total anomalous pulmonary venous connection who underwent repair in our centre in the past 13 years were reviewed. In this study, we systemically reviewed our experience in the optimal surgical strategy for patients with total anomalous pulmonary venous connection, aiming to provide evidence for clinical decision-making. *Methods:* From January 1, 2009, to December 31, 2021, 122 patients undergoing surgical treatment for total anomalous pulmonary venous connection in our hospital were enrolled. Among them, 18 patients with single ventricle repair were excluded from the study. Multivariate analysis was used to determine the risk factors for early and late death and the risk factors for pulmonary vein obstruction. *Results:* There were 64 males and 40 females. The median age at surgery was 107 days (range, 25 days–788 days), the median weight at surgery was 4.8 kg (range, 3 kg–22 kg), and the median follow-up was 59 months (range, 0–150 months). Seven patients died early after surgery and six died late after discharge. Multivariable analysis indicated that prolonged cardiopulmonary bypass time was the only independent risk factor for early postoperative mortality. Multivariate analysis did not identify risk factors for late death. Emergency surgery, preoperative moderate and severe pulmonary hypertension, and prolonged cardiopulmonary bypass time were independent risk factors for postoperative pulmonary vein obstruction. *Conclusion:* Early and long-term late outcomes of repair in patients with total anomalous pulmonary venous connection have been encouraging. Postoperative pulmonary vein obstruction remains a major problem for specialists worldwide. Pulmonary vein obstruction should be considered in children with preoperative emergency surgery, moderate to severe pulmonary hypertension and prolonged cardiopulmonary bypass time, and regular follow-up is necessary.

In recent years, with the popularisation of prenatal screening, the advancement of surgical techniques, the improvement of diagnostic accuracy, and the change in perioperative management methods, the perioperative mortality of total anomalous pulmonary venous connection has decreased significantly. Nevertheless, some factors such as surgical repair in the neonatal period, postoperative pulmonary vein obstruction, preoperative circulatory instability, mixed anatomical variation, functional single ventricle, and visceral heterotopia are still significant risk factors for poor postoperative survival.[1–3] Postoperative pulmonary vein obstruction is an ongoing surgical challenge, which is associated with increased late mortality. How to decrease the incidence of postoperative pulmonary vein obstruction has become a common concern of paediatric cardiac surgery experts around the world.

A retrospective study was conducted by using a single-centre cohort of patients to assess the impact of our current management strategy on total anomalous pulmonary venous connection repair outcomes and identify risk factors for early and late mortality and pulmonary vein obstruction in children with total anomalous pulmonary venous connection repair at our centre. It provides new ideas for the timely intervention of risk factors conducive to optimising our centre's total anomalous pulmonary venous connection disease management strategy and further improving the prognosis of such children.

Materials and methods

Patients

The Institutional Committee on Clinical Investigation of Beijing Children's Hospital affiliated with Capital Medical University approved this protocol with a waiver of informed consent. From January 1, 2009, to December 31, 2021, 122 patients undergoing surgical treatment for total anomalous pulmonary venous connection in our hospital were enrolled. Among them, 18 patients with single ventricle repair were excluded from the study. In total, 104 children who underwent total anomalous pulmonary venous connection correction were retrospectively

analysed. Echocardiography, CT, and related symptoms and signs were utilised to confirm the diagnosis. Children with total anomalous pulmonary venous connection who had repair were included in this study, but children with abnormalities including functional single ventricle and visceral heterotopia were excluded. The general information about the patients is shown in Table 1.

Data collection

Perioperative clinical data and postoperative follow-up data of all children were collected from the ward medical record system, outpatient medical record system, and telephone follow-up in our hospital. Patients underwent outpatient review at 1, 3, 6, and 12 months in the first postoperative year and annually thereafter. Echocardiography chest x-ray and electrocardiogram were routinely performed during follow-up.

Definition

Emergency surgery was defined as life-saving surgery requiring surgery within 24 hours of admission. Early mortality was defined as death that occurred during hospitalisation. Late mortality was defined as death that occurred after discharge from the hospital. Pulmonary hypertension was diagnosed by echocardiography as a measured peak tricuspid valve velocity greater than 3.4 m/s or pulmonary artery systolic pressure greater than 50 mmHg. Definition criteria for pulmonary vein obstruction: (1) the child had severe hypoxaemia or refractory hypotension at the time of consultation; (2) severe diffuse pulmonary congestion was seen in both lungs on chest x-ray; (3) The pulmonary vein velocity was more than 1.5 m/s by chest echocardiography; (If the child underwent multiple echocardiography examinations before surgery, the last pulmonary vein velocity value was taken. Postoperative pulmonary vein obstruction was the last pulmonary vein velocity value during the follow-up period). Pulmonary vein obstruction is considered to be present if any one of the above signs is present before or after surgery in children.[4] The endpoints were defined as early and late postoperative mortality and postoperative pulmonary vein obstruction.

Surgical technique

The procedure is as reported in our institution before.[5]

Statistical analysis

Median (min, max) was used to describe continuous variables, and the Wilcoxon-Mann-Whitney U-test was used to compare differences between groups. Descriptive statistics for categorical variables were reported as frequency/percentage and were compared using the Pearson chi-square or Fisher's exact test. Kaplan-Meier method was used for survival analysis, and Log-Rank test was used for comparison between groups. Binary logistic regression model was used to analyse the risk factors of early death after surgery. Receiver operating characteristic curve was used to find out the cut-off value of cardiopulmonary bypass time for early death and postoperative pulmonary vein obstruction. Multivariate analysis of pulmonary vein obstruction and late mortality was performed using the Cox proportional hazards model. SPSS 22.0 statistical software was used to analyse the data. $P \leq 0.05$ was considered statistically significant.

Table 1. Clinical baseline data of 104 patients

Patient characteristics	Number (%)/Median (Min, Max)
Gender (Male)	64 (61.5)
Birth weight (kg)	3.3 (2.35,4.6)
Surgical weight (kg)	4.8(3,22)
Surgical age(day)	107(25,788)
Prematurity	11(10.6)
Emergency operation	12(11.5)
Surgery period	
2009–2015	57(54.8)
2016–2021	47(45.2)
Anatomical type	
Supracardiac	49(47.1)
Cardiac	41(39.4)
Infracardiac	10(9.6)
Mixed	4(3.8)
Associated cardiac lesion	
PDA	104(100)
ASD/PFO	104(100)
Other cardiac lesion	24(23.1)
Concomitant extracardiac disease	3 (2.9)
Preoperative PVO	28 (26.9)
Preoperative moderate and severe PH	19 (18.5)
Preoperative moderate and severe TR	15 (14.4)
Cardiopulmonary bypass time (min)	95 (40,435)
Cross-clamp time (min)	55 (18,181)
CICU stay time (days)	5 (0,40)
Duration of ventilation (h)	24 (0,988)
Delayed chest closure	9 (8.7)
Early postoperative death	7 (6.7)
Late postoperative death	6 (5.8)
Postoperative PVO	12 (11.5)

PDA = patent ductus arteriosus; ASD = atrial septal defect; PFO = patent foramen ovale; PVO = pulmonary vein obstruction; PH = pulmonary hypertension; TR = pulmonary hypertension; CICU = cardiac intensive care unit.

Results

Baseline characteristics

Among the 104 children with total anomalous pulmonary venous connection, 64 (61.5%) were male, and 40 (38.7%) were female. The median birth weight was 3.3 (2.35,4.6) kg, and the median surgical weight was 4.8 (3,22) kg, the median surgical age was 107 (25,788) days, 11 cases (10.6%) were premature infants, and 12 cases (11.5%) underwent emergency surgery. All patients had atrial septal defect/patent foramen ovale and were combined with patent ductus arteriosus. Except atrial septal defect, patent foramen ovale, and patent ductus arteriosus, 24 cases (23.1%) were combined with other cardiac malformations. Combined with other extracardiac malformations in three cases. Darling anatomical type accounted for 49 cases (47.1%) of supracardiac type, 41 cases (39.4%) of

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Table 2. Univariable analysis of early mortality [Number (%)/Median (Min, Max)]

Variable	Total (n = 104)	Early mortality (n = 7)	Early survival (n = 97)	P-value
Gender (Male)	64 (61.5)	7 (100)	57 (58.8)	0.078
Birth weight (kg)	3.3 (2.35,4.6)	2.62 (2.5,3.75)	3.3 (2.35,4.6)	0.098
Surgical weight (kg)	4.8 (3,22)	3.6 (3.4,5)	5 (3,22)	0.004
Surgical age(day)	107 (25,788)	64 (44,214)	116 (25,788)	0.131
Prematurity	11 (10.6)	5 (71.4)	6 (6.2)	0.000
Emergency operation	12 (11.5)	6 (85.7)	6 (6.2)	0.000
Operation period				0.036
2009-2015	57 (54.8)	7 (100)	50 (51.5)	
2016-2021	47 (45.2)	0 (0)	47 (100)	
Anatomical type				0.049
Supracardiac	49 (47.1)	3 (42.9)	46 (47.4)	
Cardiac	41 (39.4)	1 (14.3)	40 (41.2)	
Infracardiac, Mixed	14 (13.5)	3 (42.9)	11 (11.3)	
Associated cardiac lesion	24 (23.1)	4 (57.1)	20 (20.6)	0.154
Preoperative PVO	28 (26.9)	6 (85.7)	22 (22.7)	0.001
Preoperative moderate and severe PH	19 (18.5)	7 (100)	12 (12.4)	0.000
Preoperative moderate and severe TR	15 (14.4)	4 (57.1)	11 (11.3)	0.006
Cardiopulmonary bypass time (min)	95 (40,435)	300 (100,435)	95 (40,250)	0.000
Cross-clamp time (min)	55 (18,181)	100 (65,181)	54 (18,133)	0.001
CICU stay time (day)	5 (0,40)	4 (0,12)	5 (2,40)	0.239
Duration of ventilation(h)	24 (0,988)	38 (0,79)	24 (0,988)	0.367
Delayed chest closure	9 (8.7)	0 (0)	9 (9.3)	1.000

Table 3. Risk factors for early mortality by multivariable analysis

Variable	B value	SE value	Wald value	P-value	OR value	95% confidence interval
Cardiopulmonary bypass time(h)	0.033	0.015	4.648	0.031	1.034	1.003–1.065
Constant	−11.165	4.886	5.222	0.022	0.000	–

intracardiac type, 10 cases (9.6%) of subcardiac type, and four cases (3.8%) of mixed type. Preoperative pulmonary vein obstruction accounted for 28 cases (26.9%), 19 (18.5%) had moderate and severe pulmonary hypertension and 15 (14.4%) had moderate and severe TR.

Early mortality

Early death occurred in seven patients (6.7%) after the initial surgery. Among them, two patients died of cardiopulmonary bypass failure, and their parents gave up extracorporeal membrane oxygenation, three patients died of low cardiac discharge syndrome caused by postoperative left ventricular insufficiency, and one patient died of pulmonary hypertension crisis. The remaining one patient died of multiple organ dysfunction. Prematurity ($p = 0.000$), low surgical weight ($p = 0.004$), emergency surgery ($p = 0.000$), preoperative pulmonary vein obstruction ($p = 0.001$), subcardiac and mixed anatomic variation ($p = 0.049$), preoperative moderate and severe pulmonary hypertension ($p = 0.000$), preoperative moderate and severe tricuspid regurgitation ($p = 0.006$), prolonged cardiopulmonary bypass time ($p = 0.000$), prolonged cross-clamp time ($p = 0.001$), and the operation period from 2009 to 2015 ($p = 0.036$) were identified as risk factors for early mortality by univariable analysis (Table 2). Logistic regression model multivariate analysis showed that prolonged cardiopulmonary bypass time ($p = 0.031$) was the only independent risk factor for early death in patients with total anomalous pulmonary venous connection repair (Table 3). According to the receiver operating characteristic curve analysis, the cut-off value of cardiopulmonary bypass time between the two groups of children who died early after total anomalous pulmonary venous connection repair and children who survived early after surgery repair in our hospital was 148 min [AUC = 0.916, 95% CI 0.811–1.000], the sensitivity was 86%, and the specificity was 90% (Fig. 1a,b).

Late mortality

Ninety-seven patients were discharged successfully. Fortunately, none of them were lost to follow-up with a follow-up rate of 100%. After discharge, six patients (6.2%) died late, two patients died of pneumonia, two patients died of

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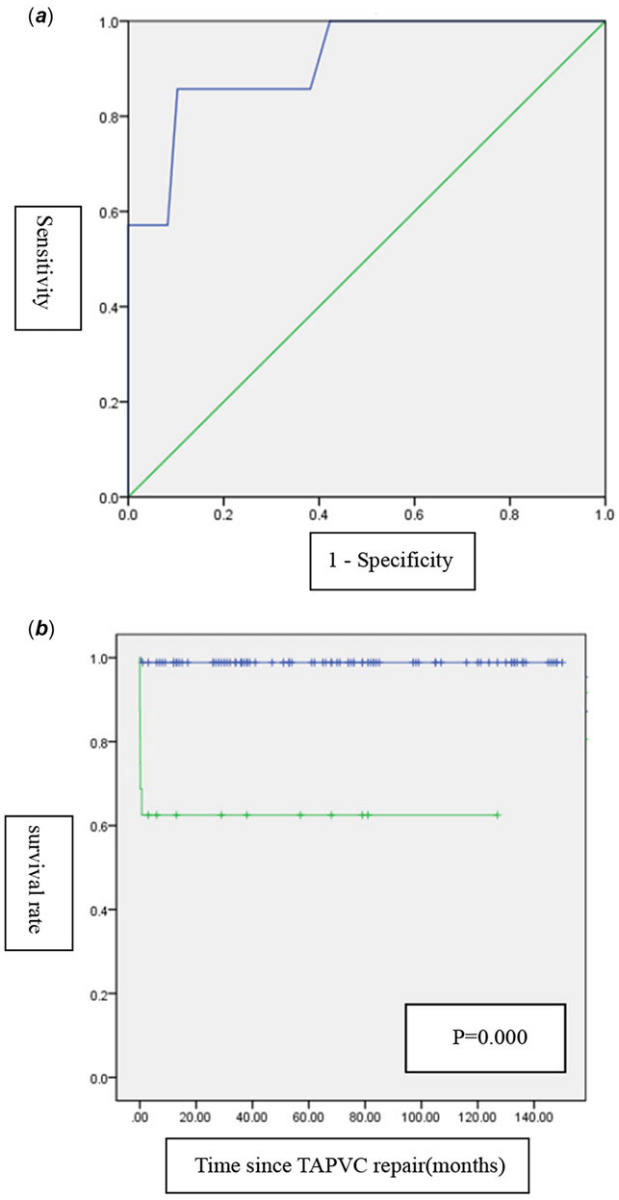

Figure 1. (***a***) Receiver operating characteristic curve analysis (AUC = 0.916, p = 0.000) (***b***) Comparison of early postoperative survival rate between the cardiopulmonary bypass (CPB) duration ≥ 148 min group and the CPB duration < 148 min group total anomalous pulmonary venous connection children(Blue line: CPB duration < 148 min; green line: CPB duration ≥ 148 min).

respiratory failure, one patient died of left heart failure, and one patient died of sudden death. Prematurity (p = 0.000), low surgical weight (p = 0.000), low birth weight (p = 0.000), emergency surgery (p = 0.000), preoperative pulmonary vein obstruction (p = 0.000), preoperative moderate and severe pulmonary hypertension (p = 0.000), preoperative moderate and severe TR (p = 0.000), prolonged cardiopulmonary bypass time (p = 0.000), prolonged cross-clamp time (p = 0.000), and prolonged cardiac ICU stay time (p = 0.000), prolonged duration of ventilator-assisted ventilation (p = 0.001), and postoperative pulmonary vein obstruction (p = 0.000) are risk factors for late mortality in patients with total anomalous pulmonary venous connection repair (Table 4). Multivariate analysis did not find statistically significant variables.

Overall survival

Seven (6.7%) patients died before discharge, and six (5.8%) patients died after discharge. The specific prognosis and outcome of the 104 children with total anomalous pulmonary venous connection after surgery are presented in Figure 3. The overall survival rates at 6 months, 1 year, 5 years, and 10 years after primary surgical repair were 89.4, 87.5, 87.5, and 87.5%, respectively (Fig. 2a). The 6 months, 1 year, 5 years, and 10 years cumulative survival rates of the 2009–2015 group were 82.5, 80.7, 80.7, and 80.7%, respectively, and the 2016–2021 group's 6 months, 1 year, and 5 years cumulative survival rates were 97.9, 95.7, and 95.7%, respectively (Log-Rank p = 0.02) (Fig. 2b).

Postoperative pulmonary vein obstruction

Two patients died during the operation, and among the remaining 102 children, 12 patients (11.8%) developed pulmonary vein obstruction after the operation, and 90 patients (88.2%) had no postoperative pulmonary vein obstruction during the follow-up. There were nine patients (1.3%) with postoperative pulmonary vein obstruction in the 2009–2015 group and three patients (75%) with postoperative pulmonary vein obstruction in the 2016–2021 group. Early postoperative mortality in five cases (41.7%) combined with postoperative pulmonary vein obstruction and postoperative pulmonary vein obstruction was found on the 1st, 3rd, 4th, 6th, and 15th days after the operation, respectively. There were five patients (41.7%) with late mortality and postoperative pulmonary vein obstruction, of which two patients developed pulmonary vein obstruction 2 months after the operation, two patients developed pulmonary vein obstruction 5 months after the operation, and one patient developed pulmonary vein obstruction 6 months after the operation. In addition, two patients developed pulmonary vein obstruction at 1 year and 5 years after the operation, respectively, and the children were still alive at the end of follow-up. Univariable analysis indicated that risk factors for postoperative pulmonary vein obstruction included younger surgical age (p = 0.009), prematurity (p = 0.000), low surgical weight (p = 0.006), lower birth weight (p = 0.024), emergency surgery (p = 0.000), preoperative pulmonary vein obstruction (p = 0.000), subcardiac and mixed anatomic variation (p = 0.004), preoperative moderate and severe pulmonary hypertension (p = 0.000), preoperative moderate and severe TR (p = 0.000), prolonged cardiopulmonary bypass time (p = 0.000), and prolonged cross-clamp time (p = 0.000) are risk factors for postoperative pulmonary vein obstruction in patients with total anomalous pulmonary venous connection repair (Table 5). Cox proportional hazards model multivariate analysis indicated that emergency surgery (p = 0.22), preoperative moderate and severe pulmonary hypertension (p = 0.001), and prolonged cardiopulmonary bypass time (p = 0.017) were independent risk factors for postoperative pulmonary vein obstruction in children with total anomalous pulmonary venous connection (p = 0.22) (Table 6, Fig. 4a–c). The survival rate of patients with supracardiac and cardiac types who were free from postoperative pulmonary vein obstruction was higher than those with infracardiac and mixed types (Log-Rank p = 0.011) (Fig. 4d). Kaplan-Meier survival analysis indicated that the survival rate of term infants free from postoperative pulmonary vein obstruction was higher than that of preterm infants (Log-Rank p = 0.000) (Fig. 4e). There was no significant difference in the survival rate of children in the 2009–2015 group and those in the 2016–2021 group free from postoperative pulmonary vein obstruction (Log-Rank p = 0.167) (Fig. 4f). Children with preoperative pulmonary vein obstruction

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Table 4. Univariable analysis of late mortality [Number (%)/Median (Min, Max)]

Variable	Total (n = 97)	Late postoperative mortality (n = 6)	Late postoperative survival (n = 91)	P-value
Gender (Male)	57 (58.8)	3 (50)	54(59.3)	0.982
Birth weight (kg)	3.4 (2.35,4.6)	2.86 (2.5,3.3)	3.5 (2.35,4.6)	0.000
Surgical weight (kg)	5.5 (3,22)	3 (3.3,4.5)	5.5 (3,22)	0.000
Surgical age(day)	154 (25,788)	35 (25,94)	155 (31,788)	0.000
Prematurity	6(6.2)	4(66.7)	2(2.2)	0.000
Emergency surgery	6(6.2)	4(66.7)	2(2.2)	0.000
Surgery period				0.617
2009-2015	50(51.5)	2(33.3)	48(52.7)	
2016-2021	47(48.5)	4(66.7)	43(47.3)	
Anatomical type				0.110
Supracardiac	46(47.4)	3 (50)	43 (47.3)	
Cardiac	40 (41.2)	1 (16.7)	39 (42.9)	
Infracardiac	8 (8.2)	2 (33.3)	6 (6.6)	
Mixed	3 (3.1)	0 (0)	3 (3.3)	
Associated cardiac lesion	20 (20.6)	2 (33.3)	18 (19.8)	0.784
Preoperative PVO	22 (22.6)	6 (100)	16 (17.6)	0.000
Preoperative moderate and severe PH	12 (12.4)	6 (100)	6 (6.6)	0.000
Preoperative moderate and severe TR	11 (11.3)	6 (100)	5 (5.5)	0.000
Cardiopulmonary bypass time (min)	101 (40,250)	130(96,193)	100(40,250)	0.000
Cross-clamp time (min)	62(18,133)	70(45,101)	60(18,133)	0.000
CICU stay time (day)	7(2,40)	18(9,40)	6(2,564)	0.001
Duration of ventilation(h)	24(2,988)	430(73,988)	24(2,564)	0.001
Delayed chest closure	9(9.3)	0(0)	9(9.9)	1.000
Postoperative PVO	7 (7.2)	5 (83.3)	2 (2.2)	0.000

were more likely to develop pulmonary vein obstruction after the operation than those without preoperative pulmonary vein obstruction (Log-Rank p = 0.000) (Fig. 4g).

Discussion

Total anomalous pulmonary venous connection is the direct and indirect connection of the left and right pulmonary veins to the right atrium, allowing pulmonary venous blood to return to the right atrium, and mixed with the superior and inferior vena cava blood in the right atrium to enter the left atrium through the atrial septal defect. The incidence accounts for 1–5 per cent of CHD.[6] In recent years, with the development of surgical diagnosis, treatment technology, and perioperative management of total anomalous pulmonary venous connection, the postoperative mortality rate has been significantly reduced to less than 10%, but the incidence of early postoperative mortality in such patients is still high.[7]

In this group of 104 patients, seven patients died before discharge, and the early mortality rate was 6.7%, which was slightly higher than the 3.4% reported by Mao Jun et al.[4] from Beijing Anzhen Hospital. Considering that the surgical age and surgical weight of the children in this group were lower than the latter, the development of organ systems was relatively immature, and the ability to resist surgical attack was poor. The results of this group are consistent with the level reported by Guangdong Provincial People's Hospital. Yangyan Ou et al.[8] retrospectively analysed the prognosis of 328 cases of total anomalous pulmonary venous connection patients who underwent a surgical correction in Guangdong Provincial People's Hospital from January 2006 to December 2013. A total of 23 (7%.) children died during hospitalisation. In Australia, Matthew S. Yong et al.[9] retrospectively reported the long-term prognosis of 214 neonates and infants with simple total anomalous pulmonary venous connection from the Royal Children's Hospital in Melbourne with surgical repair. Early infant mortality was 2.5% and early neonatal mortality was 11% throughout the study period. Takeaki Harada et al.[10] reviewed the prognosis of 256 patients who underwent total anomalous pulmonary venous connection surgical repair at the Children's Hospital of Fukuoka, Japan, from 1981 to 2016: seven (2.7%) early deaths occurred. The research team of the Pediatric Cardiovascular Department of Sejong General Hospital in Bucheon City, South Korea reported the results of surgical treatment of 53 total anomalous pulmonary venous connection patients in their institution from January 2000 to December 2008: the study included 36 biventricular patients and 17 single ventricle patients with a total of eight (15%) early deaths, which is much higher than the 6.7% in this group of patients[11]. Possibly compared with this group of cases, the former study had a single ventricle rate as high as 32% and a lower surgical age and surgical weight. Seale et al.[12] retrospectively analysed the data of 406 children with total

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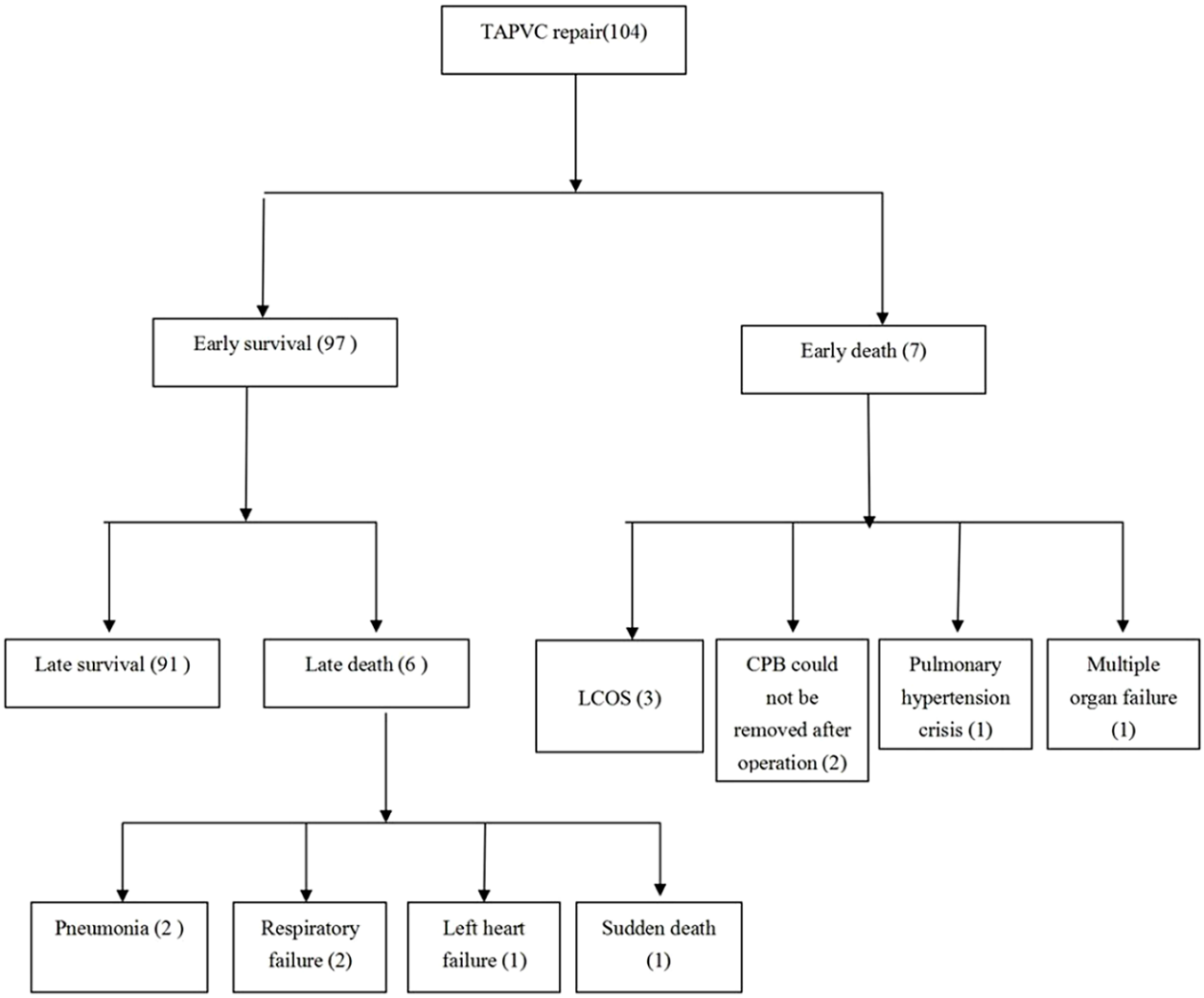

Figure 2. (***a***) Overall survival rate (***b***) Comparison of overall rate survival between 2009–2015 and 2016–2021(Blue line:2016–2021; green line:2009–2015).

anomalous pulmonary venous connection from 19 centres of the British Congenital Heart Association from 1998 to 2004 and found that the early mortality rate was 14.3%. Researchers from Guangdong Provincial People's Hospital and Shanghai Children's Medical Center reported the multicentric results of 768 children with total anomalous pulmonary venous connection surgical correction from 2005 to 2014, and 38 (5%) died early, which is consistent with 6.7% in our institution[13].

To date, reports of risk factors for early mortality in children with total anomalous pulmonary venous connection repair vary from institution to institution. Jianfeng Hou et al.[14] showed that age ≤ 1 year was a risk factor for perioperative death of total anomalous pulmonary venous connection, and elective surgery was a protective factor for perioperative death of total anomalous pulmonary venous connection. Pengfei Yu et al.[15] found that the complexity of malformation in children with total anomalous pulmonary venous connection, low surgical weight, prolonged cardiopulmonary bypass time, and cross-clamp time were risk factors affecting the prognosis of surgery. Erchao Ji et al.[16] believed that preoperative acidosis, prolonged cardiopulmonary bypass time, and increased postoperative CVP were independent risk factors for postoperative mortality. Takeaki Harada et al.[10] reported that the preoperative predictors of operative mortality were younger age and total anomalous pulmonary venous connection repair age < 1998, low weight, and emergency cases. The results of the team from the German Heart Center Munich showed that in patients with isolated total anomalous pulmonary venous connection, preoperative pulmonary vein obstruction and deep hypothermic circulatory arrest were risk factors for death, and functional single ventricle was the only significant risk factor for death in multivariate analysis[17]. Results jointly reported by Shanghai Children's Medical Center and the Cardiovascular Research Institute of Guangdong Provincial People's Hospital showed younger surgical age, mixed and infracardiac total anomalous pulmonary venous connection, preoperative pulmonary vein obstruction, longer cardiopulmonary bypass time, and longer ventilation time is associated with mortality.[13]

The perioperative period is a particularly important time because anaesthesia, surgical stress, and the immunostimulatory effects of the cardiopulmonary bypass circuit combine to create a systemic inflammatory response. During cardiopulmonary bypass, ischaemia-reperfusion injury, activation of complement systems, disorders of blood dilution and coagulation, hypothermia, surgical blow, and other factors lead to the release of a large number of

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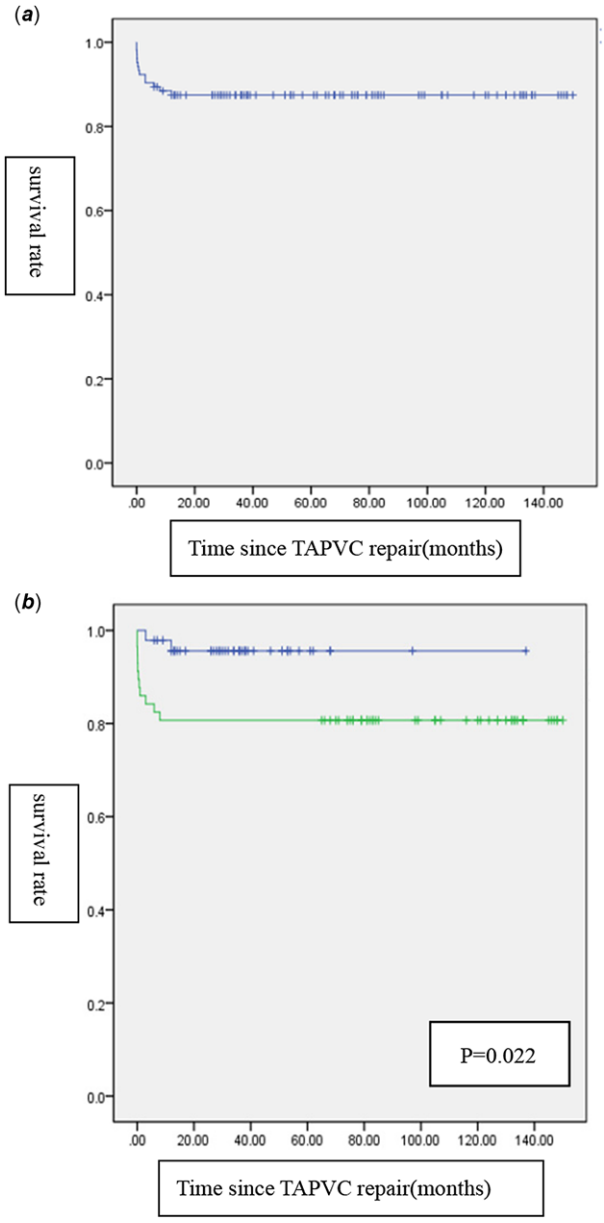

Figure 3. Postoperative prognosis and outcome of 104 children with total anomalous pulmonary venous connection repair.

inflammatory mediators from tissue cells and trigger a cascade of inflammatory responses. Prolonged cardiopulmonary bypass time can lead to damage to multiple systems and organs such as respiratory, urinary, circulatory, nerve, endocrine, blood, etc., and adversely affect the early prognosis of children with total anomalous pulmonary venous connection. It is interesting to note that all the early deaths occurred in the period 2009–2015, which is about 5 years, considering that there may be a learning curve with the surgeons in our institution for this type of surgery.

In terms of overall survival rate, the 6 months, 1 year, and 5 years overall survival rates of children who underwent surgery in 2016–2021 were significantly improved compared with those who underwent surgery in 2009–2015. Karamlou et al.[18] summarised the mortality rate of 377 total anomalous pulmonary venous connection patients in the single centre of Hospital for Sick Children in Toronto from 1946 to 2005, which decreased from nearly 50% before the 1970s to less than 5% in the last year. It was consistent with the single-centre research results of our institution. The improvement in survival rate is mainly related to the popularisation of prenatal screening, the progress of diagnosis treatment methods, the improvement of surgical techniques, and the improvement of perioperative management level.

A common complication of total anomalous pulmonary venous connection is residual pulmonary vein obstruction, and the incidence of postoperative pulmonary vein obstruction is 5–15%[7]. This complication consists of fibrotic constriction of the opening of each pulmonary vein by the anastomosis and or an unexplained intimal proliferative process that often involves the entire length of the pulmonary vein. It has been reported in the literature that postoperative pulmonary vein obstruction is a significant risk factor for poor prognosis in children.[19] Our study showed that emergency surgery, preoperative moderate and severe pulmonary hypertension, and prolonged cardiopulmonary bypass time were independent risk factors for postoperative pulmonary vein obstruction. Preoperative moderate and severe pulmonary hypertension suggests that preoperative pulmonary vascular bed may have undergone functional and anatomical changes in children with total anomalous pulmonary venous connection repair, and there may be diffuse stenosis of veins in the pulmonary parenchyma, while surgical correction of total anomalous pulmonary venous connection only occurs at the level of distal veins outside the pulmonary parenchyma. However, the diffuse stenosis of the proximal veins outside the pulmonary parenchyma and the veins inside the pulmonary parenchyma cannot be intervened, so these children still have pulmonary vein obstruction after surgery. This study concluded that prolonged cardiopulmonary bypass time is an independent risk factor for postoperative pulmonary vein obstruction, which is similar to the report of Anzhen Hospital. There was a trend for a higher proportion of postoperative pulmonary vein obstruction in 2009–2015 than in 2016–2021 (9/55 versus 3/47 $p = 0.119$), although no statistical significance was found. Considering that there may be a period of a learning curve for this type of surgery, the inexperienced intraoperative technique may be the cause of postoperative pulmonary vein obstruction. In this study, we also concluded that emergency surgery was an independent risk factor for postoperative pulmonary vein obstruction. Most of the children undergoing emergency surgery had unstable circulation before surgery and insufficient preoperative preparation. The proportion of postoperative pulmonary vein obstruction was significantly higher than that of children with non-emergency surgery. Considering that most patients undergoing emergency surgery have preoperative pulmonary vein obstruction and poor preoperative conditions, it may explain why emergency surgery is a risk factor. The survival rate of patients who were free from postoperative pulmonary vein obstruction in this group was 11.8%, which was lower than the 18.6% recently reported by the Anzhen Hospital team. This may be related to the higher proportion of patients with preoperative pulmonary vein obstruction (13.7% versus 39%) and the lower definition of pulmonary vein obstruction (1.5 m/s versus 1.2 m/s). Qin Wu et al.[20] recently reported the pulmonary vein obstruction single-centre experience of 174 children with total anomalous pulmonary venous connection in Qingdao Women and Children's Hospital from October 2013 to October 2019. The survival rate of freedom from pulmonary vein obstruction after surgery in this group was 15.3%, and 22 cases occurred within 6 months after surgery. In order to improve the prognosis of patients, we believe that

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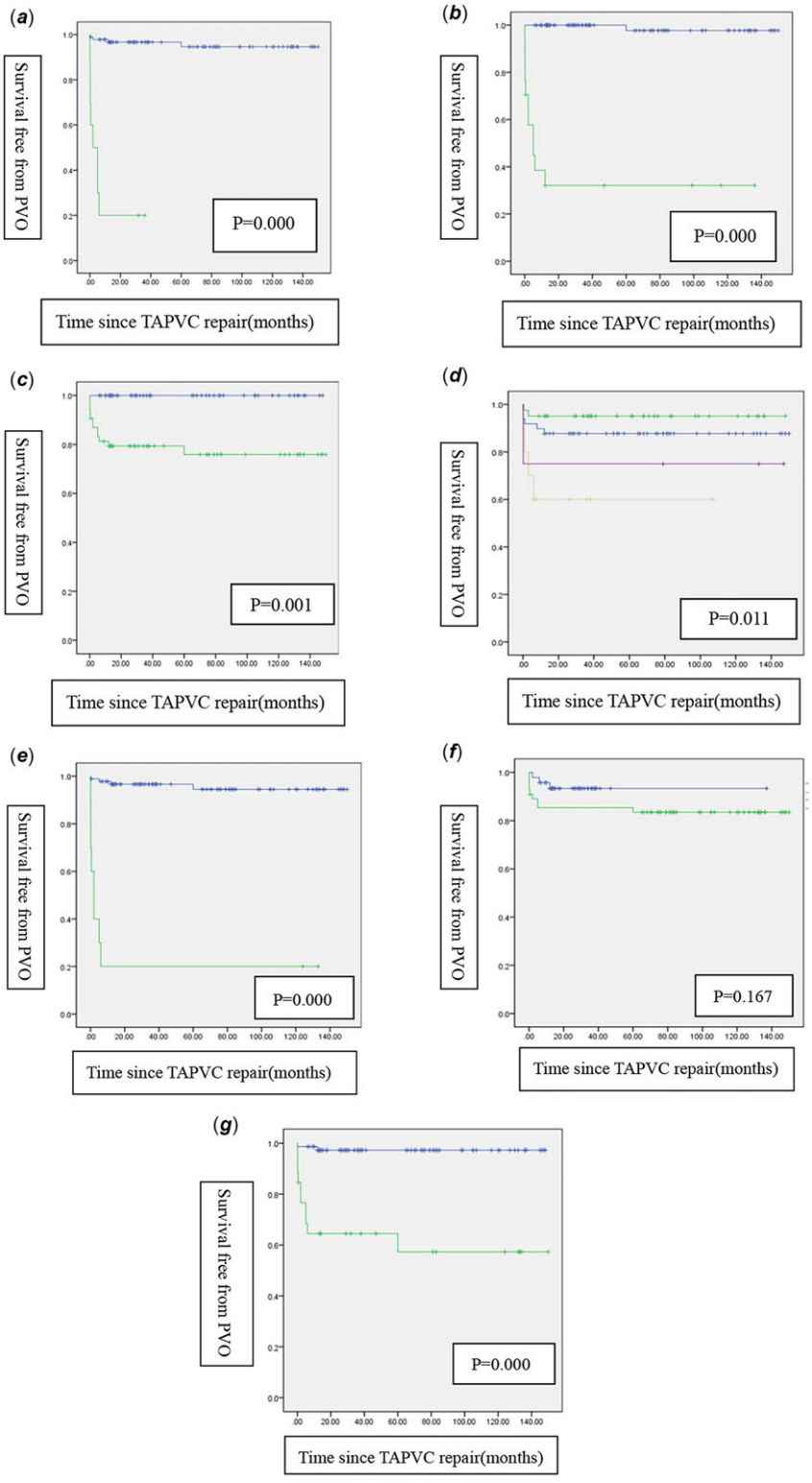

Figure 4. (***a***) Comparison of the survival rate of postoperative freedom from pulmonary vein obstruction (PVO) between the emergency surgery group and the non-emergency surgery group (Blue line: non-emergency surgery; green line: emergency surgery). (***b***) Comparison of the survival rate of postoperative freedom from PVO between the group with preoperative moderate and severe pulmonary hypertension (PH) and the group without preoperative moderate and severe PH (Blue line: without preoperative moderate and severe PH; green line: preoperative moderate and severe PH). (***c***) Kaplan-Meier curves show the differences in postoperative PVO-free survival rate in the cardiopulmonary bypass (CPB) duration ≥ 95 min group venous the CPB duration < 95 min group(Blue line: CPB duration < 95 min; green line: CPB duration ≥ 95 min). (***d***) Kaplan-Meier curves show the differences in postoperative PVO-free survival rate by subtypes (Blue line: supracardiac; green line: cardiac; purple line: mixed; grey line: infracardiac). (***e***) Kaplan-Meier curves show the differences in postoperative PVO-free survival rate without prematurity venous prematurity (Blue line: without prematurity; green line: prematurity). (***f***) Comparison of postoperative PVO-free survival rate in different surgical periods (Blue line:2016-2021; green line:2009-2015). (***g***) Kaplan-Meier curves show the differences in postoperative PVO-free survival rate without preoperative PVO venous preoperative PVO (Blue line: without preoperative PVO = green line: preoperative PVO).

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Table 5. Univariable analysis of postoperative pulmonary vein obstruction (PVO) [Number (%)/Median (Min, Max)]

Variable	Total (n = 102)	With PVO after surgery (n = 12)	Without PVO after surgery (n = 90)	P-value
Gender (Male)	62(60.8)	9(75)	53(58.9)	0.448
Birth weight (kg)	3.3 (2.35,4.6)	2.9 (2.5,3.9)	3.35(2.35,4.6)	0.024
Surgical weight (kg)	4 (3.3,8.5)	4 (3.3,8.5)	5 (3,22)	0.006
Surgical age(day)	109 (22,788)	56 (25,214)	120 (31,788)	0.009
Prematurity	10 (9.8)	8 (66.7)	2 (1.1)	0.000
Emergency surgery	10(9.8)	8(66.7)	2(2.2)	0.000
Surgery period				0.119
2009–2015	55(53.9)	9 (75)	46(51.1)	
2016–2021	47(46.1)	3(25)	44(48.9)	
Anatomical type				0.004
Supracardiac	48(47.1)	5(41.7)	43(47.8)	
Cardiac	41(40.2)	2(16.7)	39(43.3)	
Infracardiac, Mixed	13(12.7)	5(41.7)	8(8.9)	
Associated cardiac lesion	23(22.5)	3(25)	30(33.3)	0.802
Preoperative PVO	14(13.7)	10(83)	4(4.4)	0.000
Preoperative moderate and severe PH	17(16.7)	11(97.1)	6(6.7)	0.000
Preoperative moderate and severe TR	14(13.7)	7(58.3)	7(7.8)	0.000
Cardiopulmonary bypass time (min)	95(40,394)	150(96,394)	90(40,250)	0.000
Cross-clamp time (min)	54(18,133)	87.5(45,120)	52.5(18,133)	0.000
CICU stay time (day)	5(1,40)	10(1,40)	5(2,36)	0.060
Duration of ventilation(h)	24.5(2,988)	58.5(5,988)	24(2,564)	0.059

Table 6. Multivariate analysis of Cox proportional hazards model for postoperative pulmonary vein obstruction

Variable	B value	SE value	Wald value	P-value	HR value	95% confidence interval
Emergency surgery	1.918	0.836	5.271	0.022	6.809	1.324–35.019
Preoperative moderate and severe pulmonary hypertension	3.639	1.132	10.331	0.001	38.038	4.136–349.803
Cardiopulmonary bypass time(h)	0.009	0.004	5.742	0.017	1.009	1,002–1.017

perioperative management is essential, and the use of preoperative catheterisation may improve the preoperative conditions of patients, which is beneficial to improve the long-term prognosis of patients.

Limitations

There are several limitations to this study. First of all, it was a retrospective study. The data of the subjects were collected by consulting the case data and telephone follow-up, and some of the data were quite old. Secondly, the number of research objects in this group is smaller than in other published literature samples.

Conclusion

In conclusion, with advances in surgical technique and perioperative management over the past twelve years, the outcomes of children treated with total anomalous pulmonary venous connection repair at our centre have generally improved. However, surgical repair remains challenging, and early mortality remains high in children with prolonged cardiopulmonary bypass time. It is worth noting that cardiopulmonary bypass time has a high predictive value for early postoperative mortality in children with total anomalous pulmonary venous connection. Postoperative pulmonary vein obstruction often occurs in children who underwent emergency surgery before surgery, combined with moderate and severe pulmonary hypertension and prolonged cardiopulmonary bypass time.

Data availability statement. The data that support the findings of this study are available from the first author upon reasonable request.

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Author contributions. Zhangwei Wang: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualisation; Writing—original draft. Kai Ma: Writing—review & editing. Shoujun Li: Writing—review & editing.

Competing interests. None.

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Ethics statement. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The consideration was retrospective and informed consent was waived.

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