Mid-term results and risk factors for functional single ventricles associated with total anomalous pulmonary venous connection

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Abstract

Backgroud: Surgical results of functional single ventricle (FSV) patients with totally anomalous pulmonary venous connection (TAPVC), have a poor outcome. We retrospectively analyzed our 10-year surgical clinical experience and risk factors of mortality of these patients. Methods: Between March 2008 and August 2018, 43 consecutive patients with FSV and TAPVC underwent initial surgical palliation and TAPVC repair or not. The median body weight and age were 12 (range 5-44) kg and 32 (range 2-256) months, respectively. Among these cases, there are 19 cases of supracardiac TAPVC, 22 of intracardiac type, and 2 of mixed type. 12 patients need to perform TAPVC repair during initial surgical palliation (supracardiac in 10 and mixed type in 2). Results: Overall survival at 1 and 5 years were 89.5% and 83.3%, respectively. In TAPVC repair group and non-TAPVC repair group, overall survival after the initial surgical palliation were 58.3 and 87.1% at 1 year, 40.0% and 87.1% at 3 years, respectively. Cox univariate analysis detected that preoperative pulmonary vein obstruction (PVO) (p=0.047) and concomitant TAPVC repair (p=0.007) were risk factors for mortality, and multivariable analysis indicated concomitant TAPVC repair as the only factor (p=0.033). Conclusions: The mid-term results of surgical results of FSV associated with TAPVC, especially for patients who need to concomitant TAPVC repair, remain poor. Preoperative PVO is identified as risk factor that increases mortality of these patients.

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KEYWORDS : Single ventricle, Total anomalous pulmonary venous connection, Pulmonary vein obstruction

1 | INTRODUCTION

Treatment of patients associated with FSV and TAPVC has a high mortality rate and poor prognosis[1-4]. Patients with FSV and TAPVC often have visceral heterotaxy syndrome[3,5,6], which may led to a worse clinical outcomes. In addition, Pulmonary atresia[2,7], pulmonary artery stenosis[3], preoperative PVO[1,7], right ventricular dominance[3,8], infracardiac or mixed TAPVC[7] , low weight and younger age[9]are considered risk factors that increase the mortality of these patients.

In fact, in 1999, J. William Gaynor and his colleagues[10] performed an autopsy on similar patients. Lung tissue was used for histopathological examination. It was found that pulmonary vein wall was very thick, and elastic tissue staining demonstrated elastic tissue in the pulmonary vein wall and arterialization of pulmonary veins. This pathological change of pulmonary veins may lead to increased pulmonary vascular resistance. This may explain why patients with FSV combined with TAPVC have a poor prognosis.

We retrospectively analyzed mid-term results and risk factors of petients with FSV and TAPVC in our center.

2 | METHODS

2.1 | Patient characteristics

The project was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. We screened and reviewed patients with a diagnosis of FSV and TAPVC were identified by echocardiography or CT scan from our central database. Patients with FSV and TAPVC without undergoing surgery were excluded.

In all 43 patients, initial surgical palliation procedures in our center included banding of the pulmonary trunk (PAB) in 4 patients, modified Blalock-Taussing shunt in 4 patients, BDG in 33, and Fontan procedure in 2. Other concomitant procedures included atrioventricular valvuloplasty in 4, PAB, that need to use to restrict excessive pulmonary blood flow during BDG, in 3. 12 patients need to perform TAPVC repair during BDG procedure. Subsequently, of these patients, BDG was performed in 2 patients, Fontan in 3.

2.2 Statistical analysis

Statistical analysis was performed by IBM SPSS Statistics 23.0. Frequencies and proportions were used to express categorical variables and continuous variables were mean ± standard deviation or medians and interquartile ranges (IQRs). Comparisons continuous data between two groups (TAPVC repair group and non-TAPVC repair group) are made by the Student unpaired t test or the Mann-Whitney U test, and comparisons categorical data by the χ^2 test. Survival probabilities were calculated using Kaplan-Meier curve.

Risk factors for mortality in all cases (n = 43) were analyzed by Cox hazard models. Cox proportional hazard modeling and log-rank test were used for COX univariable analysis, and variables were entered into the COX multivariable analysis if p value < 0.1. All $p$value < 0.05 were considered significant.

3 | RESULTS

3.1 | Patient Characteristics

From March 2008 to August 2018, 97 patients were diagnosed as FSV with TAPVC at our center. Fifty-four patients who did not receive surgery for various reasons were excluded. Finally, forty-three patients were included in our retrospective study (Figure 1). The body weight and median age were 12 (range 5-44) kg and 32 (range 2-256) months, respectively. Among these cases, there are 19 cases of supracardiac TAPVC, 22 of intracardiac type, and 2 of mixed type. Right atrial isomerism was diagnosed in 34 patients (79%), and preoperative pulmonary vein obstruction, that was defined by transthoracic echocardiography as a flow rate more than 1.2 m/s, in 6 (13.9%).

According to whether TAPVC had been repaired, patients were divided into TAPVC repair group and non-TAPVC repair group (Table 1). Type of TAPVC ($p < 0.001$), preoperative pulmonary vein obstruction ($p = 0.001$), and totally mortality ($p = 0.002$) were significant difference between these two groups.

TABLE 1 . Patient Characteristics.

Variable	**TAPVC Repair (n=12)**	**non-TAPVC repair (n=31)**	P **value**
Sex			
Male	6(50)	15(48.4)	0.924
Female	6(50)	16(51.6)	
Weight (kg)	11.3(10-22)	12(8.8-18.5)	0.495
Age (month)	27(21.3-90)	36(12-68)	0.277
Ventricle morphology			
Single ventricle	4(33.3)	14(45.2)	0.438
Double ventricle	8(66.7)	17(54.8)	
Heart position			
Levocardia	6(50)	20(64.5)	0.328
Levoversion	3(25)	2(6.5)	
Dextrocardia	3(25)	7(22.5)	
Mirror dextrocentric	-	2(6.5)	
TAPVC type			
Infracardiac	-	21(67.7)	<0.001
Supercardiac	10(83.3)	10(32.3)	
Mixed	2(16.7)	-	
Right atrial isomerism	10(83.3)	24(77.4)	0.992
Endocardial cushion defect	7(58.3)	19(61.3)	0.859
Preoperative pulmonary vein obstruction	6(50)	-	0.001
Pulmonary valve			
Pulmonary atresia	2(16.7)	6(19.4)	0.846
Pulmonary stenosis	10(83.3)	22(71.0)	
Unobstructed	-	3(9.7)	
Abnormal systemic venous return	3(25)	7(22.5)	0.866

Bilateral superior vena cava	6(50)	15(48.4)	0.924
Aortic cross-clamp time (min)	58.8±32.6	84.0±45.9	0.254
Cardiopulmonary bypass time (min)	114.9±44.4	137.5±33.9	0.376
ICU detention time (d)	7.2±5.6	4.6±3.0	0.213
Ventilator use time (h)	92.1±95.7	40.5±47.7	0.153
Total mortality	58.3%	12.9%	0.002

Abbreviations: TAPVC, total anomalous pulmonary venous connection, ICU, intensive care unit.

Results of surgical treatment in patients with FSV and TAPVC in our study are summarized in Figure 1. In TAPVC repair group, all 12 patients underwent BDG procedure. There were 3 hospital death and 4 follow-up death. Four of them had preoperative PVO. In non-TAPVC repair group, 21 patients underwent BDG procedure. Other procedures were PAB in 4 patients, mBT shunt in 4 and Fontan in 2. Of these patients in non-TAPVC repair group, Fontan and BDG procedure were completed in 3 and 2 patients in the later stage of treatment, respectively. The follow-up period was 40 ± 29 months. There were 2 hospital death and 2 follow-up death in this group. Causes of death were pulmonary bleeding in 1, congestive heart failure in 4, pulmonary hypertension in 2, infection in 1, hypoxemia in 3.

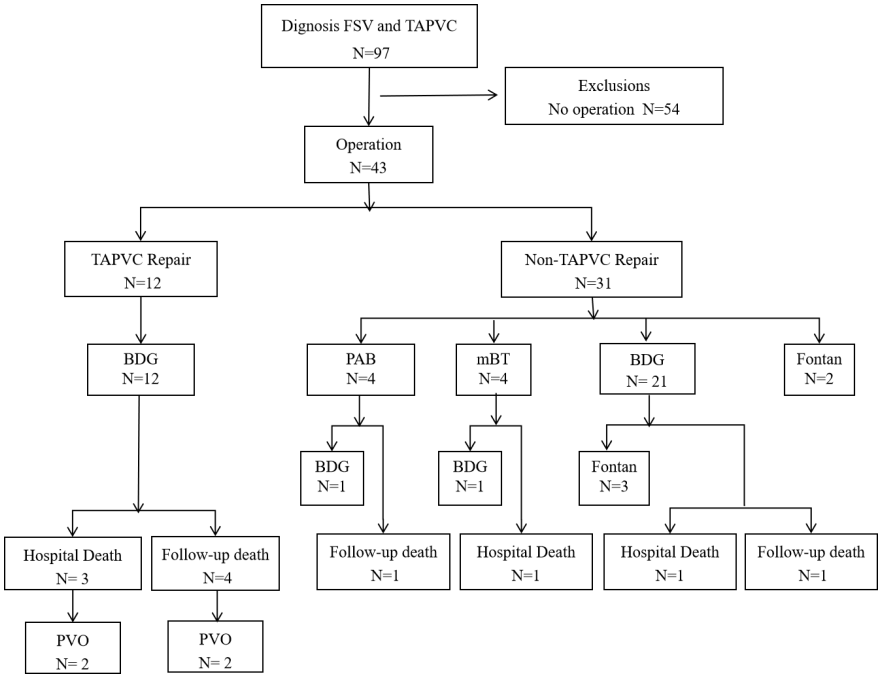

FIGURE 1 Diagram of surgical treatment in FSV patients with TAPVC in our study. TAPVC, total anomalous pulmonary venous connection, FSV, functional single ventricle, BDG, bi-directional Glenn, PAB, pulmonary artery banding, mBT, modified Blalock-Taussig shunt, PVO, pulmonary vein obstruction.

3.2 | Risk Analysis for Death

Univariate analysis indentified preoperative pulmonary vein obstruction ($p = 0.047$, HR:3.489, 95% CI:1.016-11.979) and concomitant TAPVC repair ($p = 0.007$, HR:5.412 , 95% CI:1.578-18.566) as significant risk

factors for mortality. Right atrial isomerism, TAPVC type, and pulmonary valve were not correlated with death. Multivariate analysis identified only concomitant TAPVC repair ($p = 0.033$, HR:4.671, 95% CI:1.132-19.273) as significant risk factor for mortality (Table 2).

TABLE 2. Risk factor for Death.

Variable	Univariate Models Hazard Ratio (95% CI)	Univariate Models p Valve	Multivariate Models Hazard Ratio (95% CI)	Multivariate Models p Valve
Sex				
Male	Reference			
Female	0.848(0.258-2.782)	0.780		
Weight(kg)				
5-10	Reference			
10-20	1.252(0.554-2.827)	0.589		
>20	0.859(0.366-2.013)	0.724		
Age(month)				
1-12m	Reference			
12-36m	1.577(0.353-7.055)	0.551		
36-60m	0.569(0.059-5.472)	0.625		
>60m	0.845(0.170-4.192)	0.837		
Ventricle morphology				
Single ventricle	Reference			
Double ventricle	1.386(0.749-2.562)	0.298		
TAPVC type				
Cardiac	Reference			
Supercardiac	1.411(0.570-3.491)	0.457		
Mixed	0.464(0.166-1.296)	0.143		
Right atrial isomerism	1.141(0.530-2.455)	0.737		
Endocardial cushion defect	1.409(0.778-2.552)	0.258		
Preoperative pulmonary vein obstruction	3.489(1.016-11.979)	0.047	1.378(0.333-5.702)	0.658
Pulmonary valve				
Pulmonary atresia	Reference			
Pulmonary stenosis	1.333(0.476-3.737)	0.584		
Unobstructed	0.651(0.264-1.609)	0.353		
Abnormal systemic venous return	1.123(0.522-2.419)	0.766		
Bilateral superior vena cava	0.715(0.387-1.323)	0.286		
Concomitant TAPVC repair	5.412 (1.578-18.566)	0.007	4.671(1.132-19.273)	0.033
Atrioventricular valvuloplasty	1.098(0.392-3.075)	0.858		

Abbreviations: CI: confidence interval.

3.3 | Survival

Overall survival at 1 and 5 years were 89.5% (95% CI: 74.2% to 95.8%) and 83.3% (95% CI: 66% to 91.9%) , respectively (Figure 2). Cumulative survival rate of patients in TAPVC repair group was inferior to that in non-TAPVC repair group ($p = 0.002$, HR:0.430). One year survival is 58.3% (95% CI: 27% to 80%) in TAPVC repair group and 87.1% (95% CI: 68.7% to 94.6%) in non-TAPVC repair group. Three years survival is 40% (95% CI: 13% to 65%) in TAPVC repair group and 87.1% (95% CI: 68.7% to 94.6%) in non-TAPVC repair group (Figure 3). Cumulative survival rate of patients with preoperative PVO was lower than that of patients without preoperative PVO ($p = 0.03$, HR:0.535) (Figure 4).

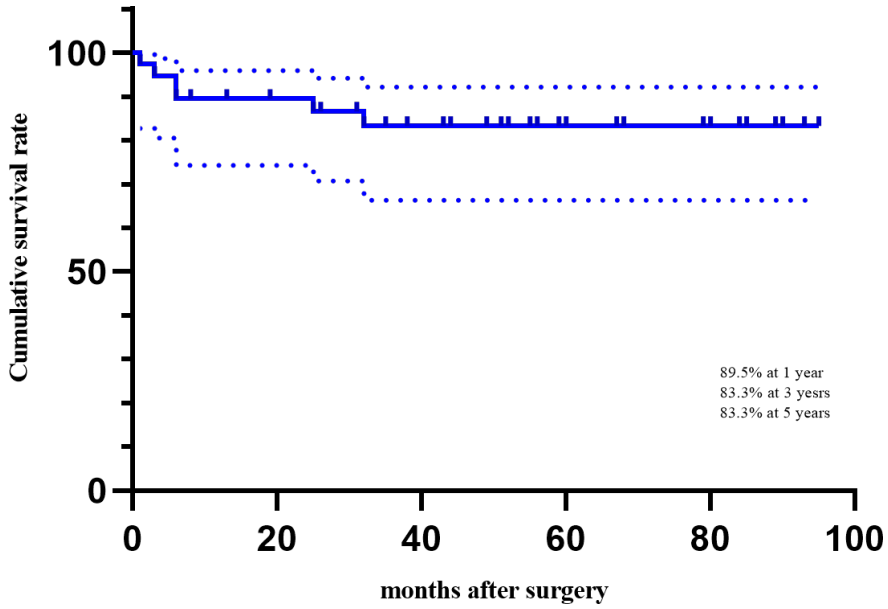

FIGURE 2. Overall survival rate for FSV patients with TAPVC.

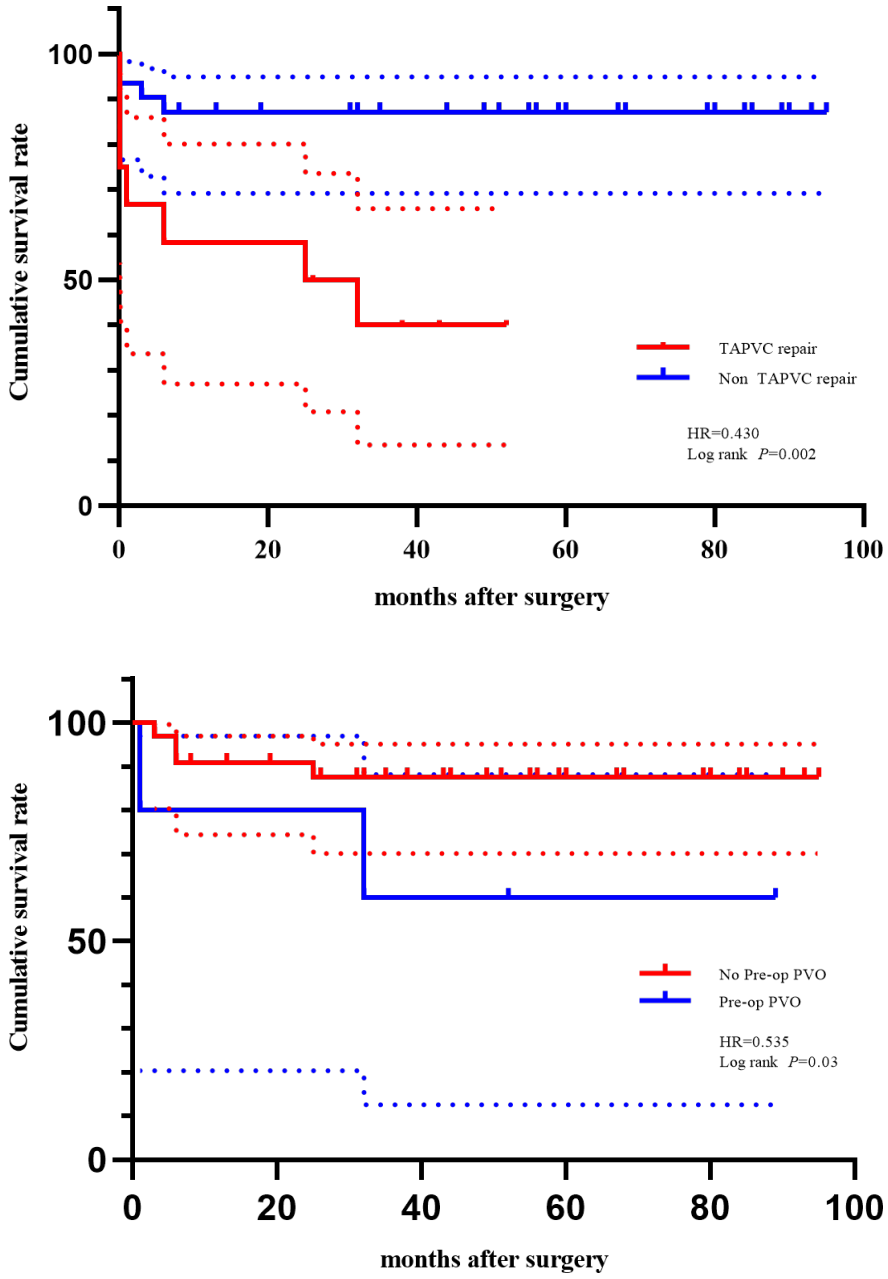

FIGURE 3. Survival rate for TAPVC repair and non-TAPVC repair.

FIGURE 4. Survival rate for pre-op PVO and no pre-op PVO. PVO, pulmonary venous obstruction.

4 | DISCUSSION

The purpose of the surgical treatment of FSV patient is to successful achieve the Fontan circulation. Depending on the anatomy, patients with single ventricle have four physiological modes, which are determined by excessive or insufficient pulmonary blood flow, that are inadequate pulmonary blood flow, excessive pulmonary blood flow with or without systemic outflow obstruction, and balanced pulmonary blood flow[11]. The primary goal of treatment for these patients is to establish a stable pulmonary blood flow as early as possible, and to avoid the adverse effects of continuous high blood flow and high pressure on pulmonary

vascular bed, so that the Fontan circulation can be achieved in the later stage. Functional single ventricle patients combined with TAPVC makes the surgical treatment more complicated. Extracardiac TAPVC, especially with PVO, can cause pulmonary hypertension which makes patients in a worse situation. Surgical outcome of patients with FSV and TAPVC have a poor prognosis. Therefore, urgent simultaneous or staged surgical intervention should be performed in the infant stage or even the neonatal period. In our group of cases, the patients with FSV and TAPVC who came to our center for surgical treatment are all older. The median age were 32 months, range from 2 to 256 months. We retrospectively analyzed mid-term results and risk factors of petients with FSV and TAPVC in our center.

The management of patients with FSV and TAPVC remains challenging, a rate of in-hospital death increase significantly and the overall survival rate is low in this group[6]. Concomitant TAPVC repair significantly increased the risk for mortality. It was reported that operative mortalities of patients with FSV and TAPVC repair was 30% to 55%[12,13], and the 5-year survival rate was 30%-60%[2,4,10,14]. Overall survival at 1 and 5 years were 89.5% and 83.3%, respectively (Figure 2). One year survival is 58.3% in TAPVC repair group and 87.1% in non-TAPVC repair group. Three years survival is 40% in TAPVC repair group and 87.1% in non-TAPVC repair group (Figure 3). In our study, totally mortality rate in TAPVC repair group was higher than that in non-TAPVC repair group (58.3% vs 12.9%, $p = 0.002$, HR:0.430) (Table 1). Type of TAPVC ($p< 0.001$) and preoperative PVO ($p = 0.001$) were significant difference between these two groups. In our study, univariate analysis identified that preoperative PVO ($p = 0.047$) and concomitant TAPVC repair ($p = 0.007$) were risk factors for mortality. Only concomitant TAPVC repair was risk factors for mortality by multivariate analysis (Table 2).

Type of TAPVC also affects the prognosis of patients with FSV and TAPVC. Nakayama Y and colleagues found that subcardiac and mixed TAPVC influenced the early surgical outcome of patients with FSV and TAPVC repair[7]. Nakata T and colleagues identified mixed TAPVC increased mortality of patients with FSV and TAPVC repair[14]. In our study, intracardiac and supracardia TAPVC are the main types of TAPVC (41/43, 95.3%). There are statistical differences between the two groups in the type of TAPVC ($p< 0.001$) (Table 1), but it is not a risk factor affecting mortality (Table 2). We consider that small proportion of mixed TAPVC may be the main reason.

Pulmonary venous obstruction is another factor that increases risk of mortality in patients with FSV and TAPVC[1,7]. Increased pulmonary vascular resistance due to PVO is unfavorable for achieving a successful Fontan circulation. Of 41 patients with FSV and extracardiac TAPVC, preoperative PVO was considered to be a risk factor for death[1]. Any significant PVO needs to be relieved at the first palliative stage, which can be staged or concurrent surgery[11]. In our study, all 6 patients with PVO were addressed during BDG procedure. Four of them died, but there was no direct correlation with PVO (Figure 1). No cases of postoperative pulmonary vein stenosis were found. Univariate analysis, but not multivariate analysis, indentified preoperative PVO as significant risk factors for mortality (Table 2). Cumulative survival rate in patients with preoperative PVO was lower than that in patients with no preoperative PVO ($p = 0.03$, HR:0.535) (Figure 4).

Study limitations

The number of cases in this retrospective analysis is small. Compared with treatment of FSV and TAPVC in the neonatal or early childhood period, our group of patients is relatively old. There may be some deviations in the assessment of surgical risk factors.

5 | CONCLUSION

The results of surgical treatment of FSV patients with TAPVC are not ideal. COX univariate analysis suggests that concomitant TAPVC repair and preoperative PVO are risk factors. Multivariate analysis identified concomitant TAPVC repair is the only risk factor.

CONFLICE OF INSTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

Li Bin, Liu Aijun and Su Junwu designed and conceived the study. Yang Ming collected the data. Li Bin and Su Junwu analyzed and interpreed the data. All authors approved the manuscript.

FOUNDATION ITEM

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