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Mid-Term Results and Risk Factors For 10 Years of Functional Single Ventricle Associated With Total Anomalous Pulmonary Venous Connection

Bin Li, MD, Aijun Liu, MD, Ming Yang, MD, Junwu Su, MD, Xiangming Fan, MD

Pediatric Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

ABSTRACT

Background: There are few surgical treatment results in elderly patients with functional single ventricle (FSV) and total anomalous pulmonary venous connection (TAPVC). We retrospectively analyzed 10 years of mid-term surgical treatment results and risk factors of these age-specific people.

Methods: Between March 2008 and December 2018, 43 consecutive patients with FSV and TAPVC received initial surgical palliation in our center. There were 20 cases of supracardiac TAPVC, 21 of cardiac type, and two cases of mixed type. Initial surgical palliation procedures involved pulmonary artery banding (PAB) for patients, modified Blalock-Taussing shunt (mBTs) for five patients, and bidirectional Glenn (BDG) for 34 patients. TAPVC repair was performed in 12 patients during BDG.

Results: The 1-year and 5-year overall survival rates were 69.7% and 62.8%, respectively. In TAPVC repair group and non-TAPVC repair group, the 1-year overall survival rates after initial surgical palliation were 41.7 and 80.5%, respectively, and the 3-year ones were 25% and 77%, respectively. There were significant differences in the type of TAPVC ($P < 0.001$), preoperative pulmonary venous obstruction ($P = 0.001$), and overall mortality ($P = 0.001$) between these two groups. Cox univariate and multivariable analysis indicated concomitant TAPVC repair was the only risk factor for mortality.

Conclusions: The mid-term results of surgical treatment of FSV and TAPVC, especially for patients who underwent concomitant TAPVC repair, remain poor. TAPVC repair may be a priority over single-ventricular palliative surgery for patients with FSV and TAPVC.

INTRODUCTION

Functional single ventricle (FSV) associated with extracardiac total anomalous pulmonary venous connection (TAPVC) makes surgical treatment more challenging. Extracardiac TAPVC, especially in patients with pulmonary hypertension associated with pulmonary venous obstruction (PVO), leads to poor prognosis in FSV patients with TAPVC who undergo single ventricle palliative surgery. Therefore, urgent simultaneous or staged surgical intervention should be performed in infancy and even in the neonatal period [Okamoto 2021; Sugano 2019; Yong 2019; Hoashi 2013].

There is rare surgical treatment in elderly patients with FSV and TAPVC in previous literature. In our study, patients with FSV and TAPVC admitted to our center for surgical treatment were older, with the median age of 32 months (ranging 2-256 months). Thirty-seven out of the 43 patients (86%) who underwent their first single-ventricular palliative surgery in their lives were age 1. The main reason for the older patients in our group was delayed diagnosis or parents' inability to afford financial expenses. For these patients, surgical intervention might be the only method to improve the prognosis. In this paper, we shared the experiences of surgical treatment of specific-aged patients with FSV and TAPVC, and we hope to provide some help in the surgical treatment of similar cases.

METHODS

Patient characteristics: We screened and reviewed patients diagnosed with FSV and TAPVC by echocardiography or CT scan from our center's inpatient database. We collected the clinical data of patients with FSV and TAPVC at initial surgical palliation procedures in our center. Patients with FSV and TAPVC without undergoing surgery were excluded. The project was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

Among all 43 patients, there were four patients for initial surgical palliation procedures in our center including pulmonary artery banding (PAB), five for modified Blalock-Taussing shunt (mBTs), and 34 for bidirectional Glenn procedure (BDG). Of 34 patients undergoing BDG surgery, 12 patients with extracardiac TAPVC underwent simultaneous correction. Other procedures included atrioventricular valvuloplasty (four cases) and PAB (three cases) to limit excessive pulmonary blood flow during BDG. Subsequently, of these 43 patients, BDG was performed on three patients and Fontan on five. Among them, there were two cases of BDG and three cases of Fontan in our center; in other centers, there was one case of BDG and two cases of Fontan.

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Correspondence: Xiangming Fan, Pediatric Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, 100029, China (e-mail: fanxiangming@126.com).

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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). The continuous data between the two groups (TAPVC repair group and non-TAPVC repair group) were continuously compared by the student unpaired t test or the Mann-Whitney U test, and categorical data were compared 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. All P values < 0.05 were considered significant.

RESULTS

Patient characteristics: From March 2008 to December 2018, 97 patients were diagnosed as FSV combined with TAPVC in our center inpatient database. Fifty-four patients who did not undergo surgery were excluded because their parents could not afford financial expenses, nor could they accept the risk and prognosis of surgery, and there was no indication for surgery due to severe pulmonary hypertension. Finally, our retrospective study included 43 patients (Figure 1) with a median weight and age of 12 (5-44) kg and 32 (2-256) months who underwent their first surgical palliative care at our center. (Figure 1) According to whether TAPVC had been repaired, patients were divided into the TAPVC repair group and non-TAPVC repair group. (Table 1)

Among these cases, there were 20 cases of supracardiac TAPVC, 21 of cardiac type, and two of mixed type. In the TAPVC repair group, all of the 12 patients had extracardiac TAPVC (supracardiac and mixed type) and TAPVC repair was performed during BDG surgery. In the non-TAPVC repair group, there were 10 cases of supracardiac TAPVC whose single ventricle palliative surgery were PAB or mBTs, and 21 cases of cardiac type (Table 1). There was no infracardiac TAPVC in our study. There was a significant difference in the type of TAPVC between these two groups (P < 0.001) (Table 1).

Preoperative chest echocardiography determined that blood flow velocity greater than 1.2m/s was PVO, and only the TAPVC group (3/43, 6.9%) showed a statistically significant difference between the two groups (P = 0.001). There were no significant differences in age, gender, weight, function single ventricle, heart position, right atrial isomerism, endocardial cushion defect, pulmonary valve morphology, abnormal systemic venous return, cardiopulmonary bypass time, and aortic cross-clamp time between the two groups (Table 1).

Results of surgical treatment in patients with FSV and TAPVC are summarized in Figure 1. In the TAPVC repair group, postoperative echocardiography showed that the blood flow velocity of the pulmonary venous anastomosis was all

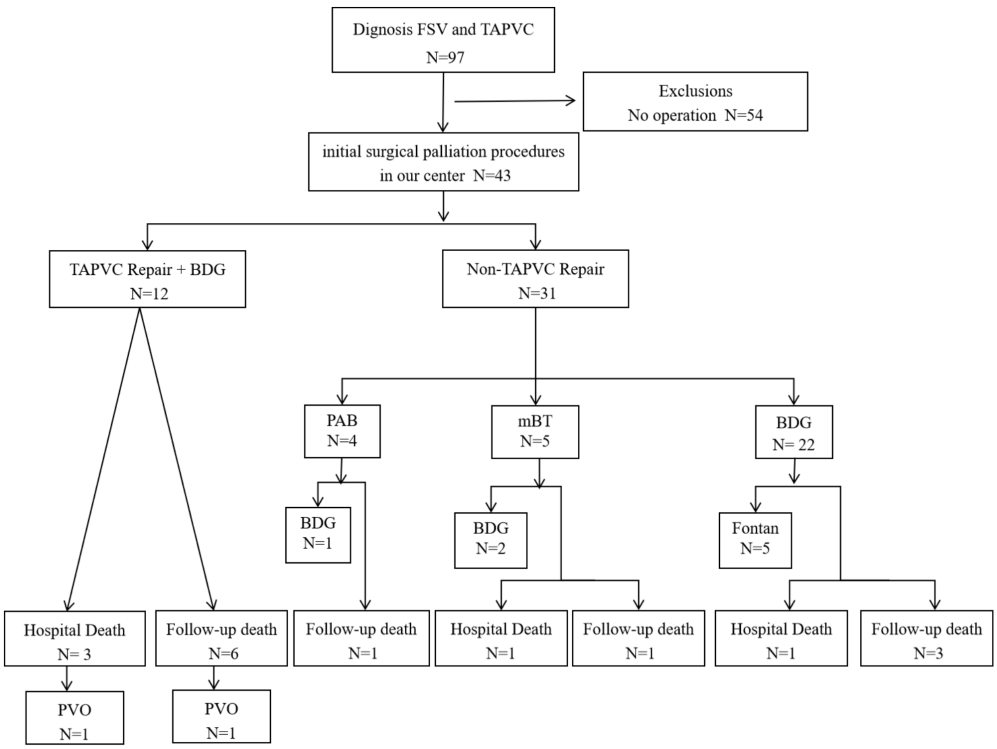

Figure 1. Diagram of surgical treatment in FSV patients with TAPVC in our study. TAPVC, total anomalous pulmonary venous connection; FSV, functional single ventricle; BDG, bi-directional Glenn; PAB, pulmonary artery banding; mBTs, modified Blalock-Taussig shunt; PVO, pulmonary venous obstruction

lower than 1.2m/s, indicating that there was no postoperative pulmonary venous stenosis. There were three hospital deaths and six follow-up deaths. PVO occurred in two patients in the TAPVC repair group. BDG surgery was performed on 22 patients in the non-TAPVC repair group. Other procedures, such as PAB, were performed on four patients and mBTs on five. Of these patients in the non-TAPVC repair group, BDG and Fontan procedures were performed on three and five patients in the later stage, respectively. There were two hospital deaths and five follow-up deaths in this group. There was a significant difference in the overall mortality between these two groups (P = 0.001) (Table 1). Causes of death were pulmonary bleeding in one, congestive heart failure in five, pulmonary hypertension in four, infection in two, and hypoxemia in four. Subsequently, BDG and Fontan were respectively performed on two patients and three patients in our center, while they were respectively performed on one patient and two patients in other centers. The follow-up period was 40 ± 29 months. Three patients were lost to follow up, and the follow-up rate was 93%.

Risk analysis for death: Univariate analysis identified concomitant TAPVC repair (P = 0.001, HR:5.412 , 95%

Table 1. Patient characteristics at initial surgical palliation procedures in our center

Variable	TAPVC repair (N = 12)	Non-TAPVC repair (N = 31)	P-value
Gender			
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
Function Single Ventricle			
DIV	9 (75)	20 (64.5)	0.419
TA	1 (8.3)	7 (22.5)	
MA	2 (16.7)	2 (6.5)	
UAVCD	-	2 (6.5)	
Heart position			
Levocardia	9 (75)	22 (71)	0.328
Dextrocardia	3 (25)	9 (29)	
TAPVC type			
Cardiac	-	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 venous obstruction	3 (25)	-	0.001
Pulmonary valve			
Atresia	2 (16.7)	6 (19.4)	0.846
Stenosis	10 (83.3)	22 (71.0)	
Unrestricted	-	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
Total mortality	75%	22.6%	0.001

mean±standard deviation or medians and interquartile ranges (IQRs) for continuous variables, and frequencies and proportions for categorical variables.
TAPVC, total anomalous pulmonary venous connection; DIV, double inlet ventricle; TA, tricuspid atresia; MA, mitral atresia; UAVCD, unbalanced common atrioventricular canal defect

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Table 2. Risk factor for death

Variable	Univariate Models		Multivariate Models	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Gender				
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 (months)				
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		
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 venous obstruction	0.571 (0.270-1.210)	0.144		
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)	0.001	5.501 (1.929-15.693)	0.019
Atrioventricular valvuloplasty	1.098 (0.392-3.075)	0.858		

CI: confidence interval; TAPVC, total anomalous pulmonary venous connection

CI:1.578-18.566) as a significant risk factor for mortality. Age, gender, weight, type of TAPVC, right atrial isomerism, endocardial cushion defect, pulmonary valve morphology, abnormal systemic venous return, and atrioventricular valvuloplasty were not correlated with death. Multivariate analysis only identified concomitant TAPVC repair (P = 0.019, HR:5.501, 95% CI:1.929-15.693) as a significant risk factor for mortality. (Table 2)

Survival: The 1-year and 5-year overall survival rates were 69.7% (95% CI: 61.9% to 88.8%) and 62.8% (95% CI: 51.8% to 81.9%), respectively. (Figure 2) Cumulative survival rate of patients in the non-TAPVC repair group was better than that in the TAPVC repair group (P = 0.001, HR:0.182). The 1-year survival rate was 41.7% (95% CI: 15.2% to 66.4%) in the TAPVC repair group and 80.5% (95% CI: 61.4% to 90.6%) in the non-TAPVC repair group. The 3-year survival rate was 25% (95% CI: 4% to 48.8%) in the TAPVC repair group and 77% (95% CI: 57.4% to 88.2%) in the non-TAPVC repair group. (Figure 3) Cumulative survival rate of patients with preoperative PVO was lower than that of patients without preoperative PVO, but there was no statistical difference between the two groups (P = 0.114, HR:2.497). (Figure 4)

DISCUSSION

In the previous literature, these FSV and TAPVC patients were treated with urgent simultaneous or staged surgical

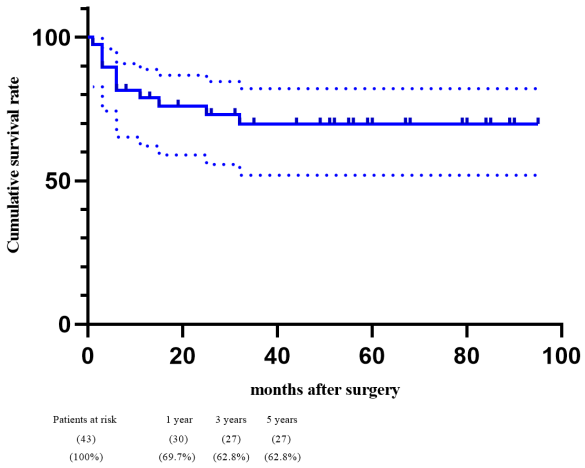

Figure 2. Overall survival rate for FSV patients with TAPVC. The dotted area indicates 95% confidence limits.

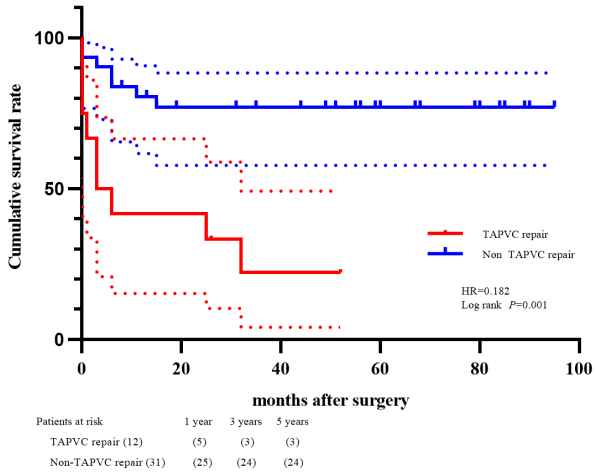

Figure 3. Survival rate for TAPVC repair and non-TAPVC repair. The dotted area indicates 95% confidence limits.

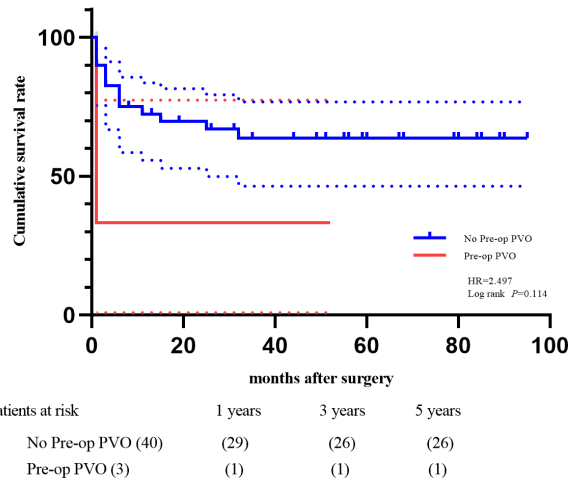

Figure 4. Survival rate for pre-op PVO and no pre-op PVO. The dotted area indicates 95% confidence limits. PVO, pulmonary venous obstruction

intervention in infancy and even in the neonatal period [Okamoto 2021; Sugano 2019; Yong 2019; Hoashi 2013]. However, surgical outcomes of treatment of patients with FSV and TAPVC had a high rate of mortality and poor prognosis. Elderly patients with FSV and TAPVC were rarely treated with surgery. In our study, patients with FSV and TAPVC who were admitted to our center for surgical treatment were older, with the median age of 32 months. Thirty-seven of the 43 patients who underwent their first single-ventricular palliative surgery in their lives were age 1. For these patients, surgical intervention might be the only method to improve the prognosis. Here, we retrospectively analyzed and shared our mid-term surgical treatment results and risk factors of specific-aged patients in the last decade.

The management of patients with FSV and TAPVC remained challenging, and the rate of in-hospital death increased significantly in this group, with a low overall survival rate. The 1-year and 5-year overall survival rates of our patients were 69.7% (95% CI: 61.9% to 88.8%) and 62.8% (95% CI: 51.8% to 81.9%), respectively (Figure 2). Compared with previous reports that operative mortality of patients with FSV and TAPVC repair was 30% to 55% [Hancock 2005; Sachdev 2006] and that 5-year survival rate was 30%-60% [Sugano 2019; Hoashi 2013; Gaynor 1999; Nakata 2009], the survival rate of our group generally was higher. However, relative to other reports, we performed a lower proportion of TAPVC repair and Fontan procedure. Fontan procedure was performed on five cases (Figure 1). Moreover, TAPVC repair was not performed during palliative surgery, such as BT and PAB. There were six and five follow-up deaths in the TAPVC repair group and non-TAPVC repair group, respectively. For the follow-up death patients in the non-TAPVC repair group, it was unclear whether TAPVC repair yielded a better surgical outcome during their first single-ventricular palliative surgery. In addition to PAB surgery, single-ventricular palliative surgery increased pulmonary blood flow and thus the risk of pulmonary venous return obstruction in patients with uncorrected TAPVC but without preoperative PVO. Moreover, it was confirmed that pulmonary vein wall was thickened and arterialized in patients with FSV and TAPVC by autopsy [Gaynor 1999]. This pathological change of pulmonary veins led to an increase in pulmonary vascular resistance, thus affecting the prognosis of these patients. Therefore, in combination with our retrospective study, we suggest that TAPVC repair be performed with single-ventricular palliative surgery, simultaneously or by stage, more actively in older patient with FSV. TAPVC repair may be a priority over single-ventricular palliative surgery.

Different from risk factors of mortality in patients with FSV and TAPVC reported in previous literature, such as pulmonary atresia [Sugano 2019; Nakayama 2012], pulmonary artery stenosis [Yong 2019], preoperative PVO [Okamoto 2021; Nakayama 2012], right ventricular dominance [Yong 2019; Yong 2018], infracardiac or mixed TAPVC [Nakayama 2012], low weight and younger age [Jang 2010], concomitant

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TAPVC repair was the only risk factor for mortality identified by cox univariate and multivariate analysis (Table 2). Type of TAPVC also affected the prognosis of patients with FSV and TAPVC. Extracardiac TAPVC, which is often associated with pulmonary venous obstruction and variable pulmonary venous return, is an adverse event for single-ventricular palliative surgery, especially for BDG and Fontan. In our study, cardiac and supracardia TAPVC were the main types of TAPVC (41/43, 95.3%). In the TAPVC repair group, types of TAPVC were all extracardiac TAPVC (supracardiac in 10 and mixed type in two). There was a statistical difference between the TAPVC repair group and non-TAPVC repair group in the type of TAPVC ($P < 0.001$) (Table 1), but it was not a risk factor for mortality (Table 2).

Increased pulmonary vascular resistance caused by PVO is detrimental to a successful BDG or Fontan circulation [Okamoto 2021]. Any significant PVO needs to be addressed in the neonatal period [Friesen 2002]. There are still problems of late detection, late diagnosis, and late medical treatment in China. Patients with FSV and TAPVC with PVO either died in the neonatal period or infancy or were not intervened in the early stage. In our study, only three patients with preoperative PVO were all in the TAPVC repair group (Table 1) and were treated during BDG procedure. Unfortunately, two of them died, but it was not directly correlated with PVO (Figure 1). The proportion of PVO in our group of cases (3/43, 6.9%) was lower than that reported in the previous literature. The 1-year survival rate was 41.7% (95% CI: 15.2% to 66.4%) in the TAPVC repair group and 80.5% (95% CI: 61.4% to 90.6%) in the non-TAPVC repair group. The 3-year survival rate was 25% (95% CI: 4% to 48.8%) in the TAPVC repair group and 77% (95% CI: 57.4% to 88.2%) in the non-TAPVC repair group (Figure 3). No cases of postoperative pulmonary venous stenosis were found. Preoperative PVO was not identified as a risk factor for mortality (Table 2), although cumulative survival rate in patients with preoperative PVO was lower than in patients with no preoperative PVO ($P = 0.114$, HR:2.497) (Figure 4). Patients with PVO demonstrated a lower 1-year survival rate without surgical intervention.

Limitation: This is a retrospective analysis about surgical outcome in a small number of patients with FSV and TAPVC. Compared with treatment of FSV and TAPVC in infancy or even the neonatal period, our patients are relatively older. Delayed diagnosis of patients with FSV and TAPVC lead some patients to miss the effective surgical treatment or die naturally, thus possibly resulting in the natural screening of patients and some deviations in the assessment of surgical risk factors. Enhanced community screening for fetal congenital heart disease and the popularization of parental knowledge also play an important role in the prompt surgical treatment of these patients, which may improve their prognosis. Moreover, TAPVC repair needs to be performed with single-ventricular palliative surgery, simultaneously or by staged, more actively in older patients with FSV. TAPVC repair may be a priority over single-ventricular palliative surgery.

CONCLUSION

Surgical treatment results of patients with FSV and TAPVC are unsatisfactory. Concomitant TAPVC repair is identified as the only risk factor for mortality. TAPVC repair may be a priority over single-ventricular palliative surgery for patients with FSV and TAPVC.

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