Single-institution outcomes of surgical repair of infracardiac total anomalous pulmonary venous connection

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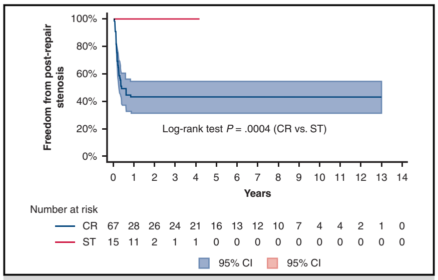
ABSTRACT

Objective: This contemporary study sought to describe the outcomes of patients undergoing biventricular repair of infracardiac total anomalous pulmonary venous connection.

Methods: A retrospective study was performed on patients with infracardiac total anomalous pulmonary venous connection who underwent sutureless technique or conventional repair between 2006 and 2018. Risk factors for survival and post-repair pulmonary vein stenosis (PVS) were assessed with Cox regression model. Time-to-event analysis was conducted using Kaplan-Meier estimates.

Results: This study included 82 consecutive patients with the median age of 21 days (interquartile range, 9-40 days). The median follow-up was 29 months (interquartile range, 12.5-59 months) and was available in 95% of the survivors at the end of the study period in 2019. Overall, 8 deaths (8.5%) occurred in the conventional repair group. There was a trend of higher mortality in the conventional repair group, although it did not reach a statistical difference ($P = .2$). Postrepair PVS occurred at a median of 2 months (interquartile range, 1.2-3.6 months) postoperatively and all occurred in the conventional repair group. Time-to-event analysis with the event of postrepair PVS showed significantly higher freedom from restenosis in the sutureless technique group ($P = .0004$). Adjusted hazard ratios from time-dependent Cox model described the association between postrepair PVS and pulmonary venous confluence of antler configuration (hazard ratio, 2.14; 95% confidence interval, 1.03-5.47; $P = .002$) and the use of sutureless technique (hazard ratio, 0.72; 95% confidence interval, 0.39-0.97; $P = .003$).

Conclusions: Sutureless technique is associated with a lower risk of postrepair PVS in patients with infracardiac total anomalous pulmonary venous connection. pulmonary venous confluence configuration of antler appearance appears to be associated with restenosis and mortality. (J Thorac Cardiovasc Surg 2021;161:1408-17)



Freedom from diagnosis of restenosis between patients with infracardiac TAPVC undergoing CR and ST.

CENTRAL MESSAGE

Our study indicates that PVC of antler configuration is associated with mortality and restenosis in infracardiac TAPVC. Patients undergoing conventional repair tend to have a high risk for restenosis.

PERSPECTIVE

Postrepair PVS remains an issue in patients with infracardiac TAPVC in the current era. Morphological classification of the PVC configuration appears to be of value due to its observed relevance to the prognosis. Our results modestly suggest a potential short-term benefit of primary sutureless technique as compared to the conventional left atrial-to-confluence anastomosis in this clinical setting.

See Commentaries on pages 1418 and 1419.

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Abbreviations and Acronyms

ASD	= atrial septal defect
CPB	= cardiopulmonary bypass
CR	= conventional repair
CTA	= computed tomography angiography
LA	= left atrial
PV	= pulmonary vein
PVC	= pulmonary venous confluence
PVO	= pulmonary vein obstruction
PVS	= pulmonary venin stenosis
ST	= sutureless technique
TAPVC	= total anomalous pulmonary vein connection

Scanning this QR code will take you to the table of contents to access supplementary information.

Pulmonary vein stenosis (PVS) after surgical repair of total anomalous pulmonary venous connection (TAPVC) causes incremental mortality and morbidity.[1] The prevalence of postrepair PVS ranges from 10% to 20%,[2] and patients with infracardiac connection subtype are reported to be at a high risk for restenosis.[3] Postrepair PVS is characterized by paucicellular fibrointimal proliferation and can vary from anastomotic stenosis to retrograde propagation of stenosis towards upstream pulmonary veins (PVs).[4,5] Given the high mortality and recurrent stenosis associated with reintervention for postrepair PVS, particularly when a progression of restenosis is observed in upstream PVs,[6,7] there has been a growing interest in using sutureless technique (ST) as a prophylactic method to reduce the incidence of restenosis.[8]

The rationale behind ST in the primary repair for TAPVC is to avoid mechanical stimuli to individual PVs and minimize suture line distortion arising from complex geometry, thereby decreasing postrepair PVS. However, the results of this technique are not universally promising, and the current published evidences on outcomes following ST versus conventional left atrial (LA)-to-confluence anastomosis is inconclusive.[9-12] This is largely attributed to the fact that majority of the existing studies consist of a case mix of all 4 subtypes of TAPVC, which may mask any potential beneficial impact of ST in the infracardiac variants. Thus, we hypothesized that the ST may be beneficial in this subset of patients. The primary objective of this study was to describe the experiences in the surgical repair of infracardiac TAPVC using both ST and conventional technique, and to provide insight into the relationship between confluence morphology and the clinical outcomes in terms of mortality and postrepair PVS.

METHODS

Study Design and Data Acquisition

This single-institution, retrospective study was approved by the Institutional Ethics Committee at Shanghai Children's Medical Center. One attending doctor and 1 follow-up nurse were in charge of the data collection. Perioperative data were obtained from the database that was established in 2000. This database includes surgical details, patient basic characteristics, and postoperative complications. Data after discharge were collected from the outpatient electronic medical records. Hence, there are no missing data with regard to the perioperative data. Our institutional follow-up protocol was that all survivors were required for outpatient follow-up visits at 1 month, 3 months, and 6 months after the initial operation, and then annually. Our follow-up staff maintained close contact with the patients via telephone, social media (eg, WeChat), or e-mail. When the survivors living far from Shanghai underwent follow-up in their local hospitals, attempts were made to obtain external records. If restenosis was suspected, patients were requested to come to our hospital for further evaluation.

Patient Population and Definition

In total, 82 consecutive patients with infracardiac TAPVC and atrial septal defect (ASD) who underwent conventional repair (CR) ($n = 67$) or sutureless repair ($n = 15$) between February 1, 2006, and July 31, 2018, were included. Patients having a combined diagnosis with any other disease were excluded. Echocardiography and computed tomography angiography (CTA) were required for preoperative evaluation of anatomic morphology.[8] Echocardiography was performed on all patients. Eleven neonatal patients were hemodynamically unstable and underwent emergency operation without prior CTA. Seventy-one patients underwent urgent or selective operation. Emergency operation was defined as a lifesaving surgery performed within 12 hours of presentation. Urgent operation was defined as surgery performed between 12 and 24 hours of presentation. Selective operation was defined as surgery performed beyond 24 hours after admission. Preoperative pulmonary vein obstruction (PVO) was defined as the obstruction evaluated by a combination of oxygen saturation, echocardiography (a nonphasic flow velocity >1.8 m/s or ASD < 3 mm) and CTA. The 3 subtypes of preoperative PVO[8,13,14] included external stenosis (obstruction occurred within the route of anomalous connecting vein drainage), intrinsic stenosis (pulmonary ostial stenosis/PV hypoplasia), and restrictive ASD (<3 mm). Postrepair PVS was defined as anastomotic stricture or peripheral stenosis of individual PVs indicated by echocardiography showing a nonphasic flow velocity of > 1.8 m/s and further confirmed by CTA. In-hospital mortality was defined as death occurring before hospital discharge and late mortality was defined as death occurring after discharge. Neonatal patients were defined as patients younger than age 30 days. The configuration of pulmonary venous confluence (PVC) was classified into 2 types based on the CTA: inverted Christmas tree (symmetric or asymmetric) and antler appearance (Figure 1). The inverted Christmas tree appearance was defined as the left (right) upper and inferior PVs joined separately along the line of the vertical vein in a symmetric (A1 in Figure 1) or asymmetric way (A2 in Figure 1). The antler appearance was defined as that the left or right upper and inferior PVs joined to form a common vein respectively, and that these 2 common veins drained to form a confluence (Figure 1, *B*). All CTA data were reviewed by 2 blinded specialized cardiac radiologists (Drs Qian Wang and Yumin

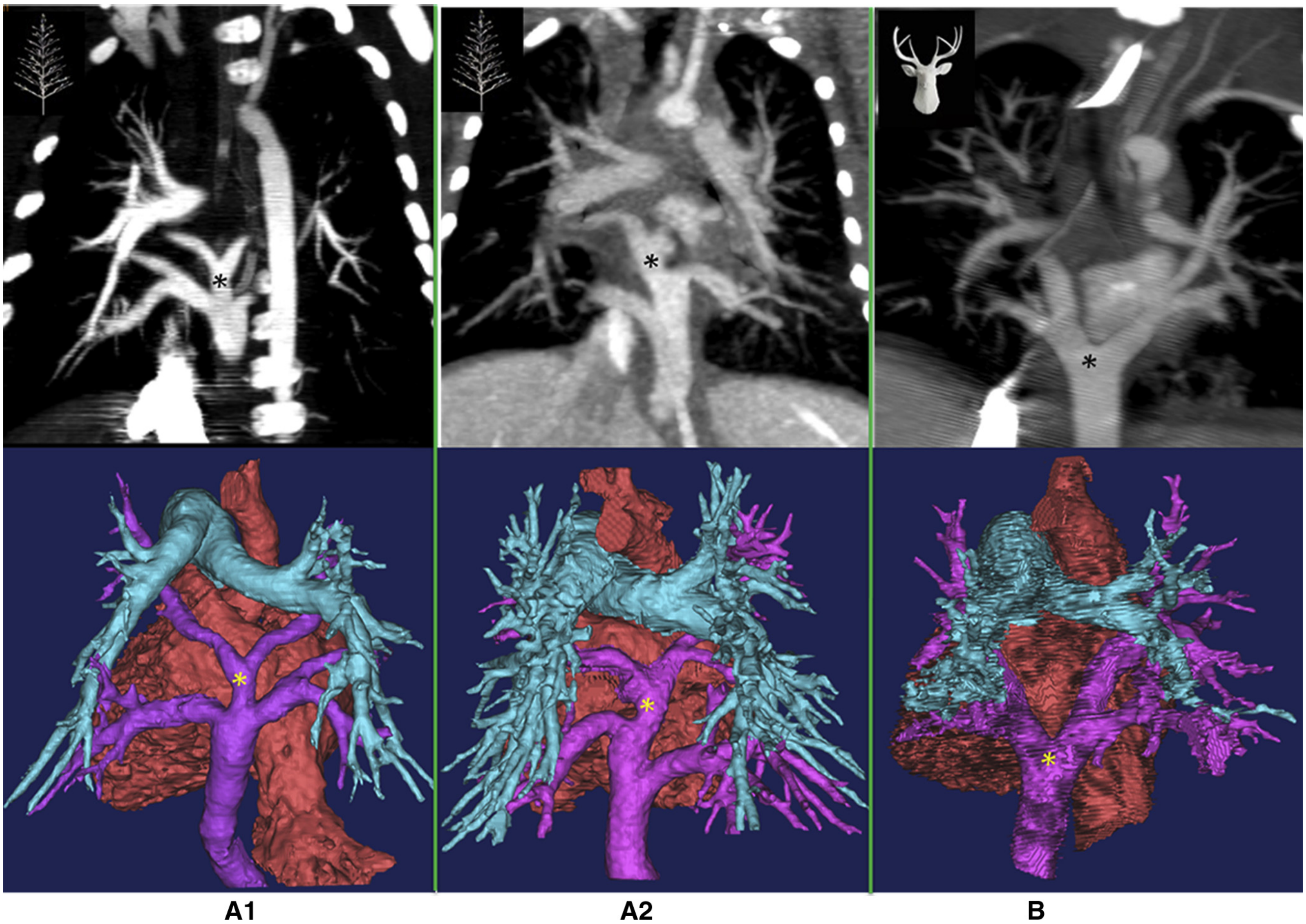


FIGURE 1. Pulmonary venous confluence configuration is classified into 2 types: inverted Christmas tree (A) and antler (B) appearance. The inverted Christmas tree appearance is defined as the left (*right*) upper and inferior pulmonary veins (PVs) join separately along the line of the vertical vein in a symmetric (A1) or asymmetric (A2) way. The antler appearance is defined as that the left or right upper and inferior PVs join to form a common vein respectively, and that these 2 common veins drain to form a confluence. *Pulmonary venous confluence.

Zhong), and the results of the categorization of the PVC configuration were shown in Figure E1.

Surgical Technique

Surgical repair was performed under standard cardiopulmonary bypass (CPB) with moderate hypothermia. Patent ductus arteriosus was ligated before the commencement of CPB if it existed. A temporal low-flow perfusion or circulatory arrest was adopted in a small portion of newborn infants to provide clear visualization. We only used suction to achieve a satisfactory exposure. The vertical vein was routinely ligated with hemoclips and ASD was closed with a pericardial patch. Given the lack of concrete evidence supporting the primary use of ST, CR was performed consistently within the study period and the ST was not performed until 2015. The choice of the surgical techniques was mainly due to both the surgeons and parents' decisions.

Conventional Technique

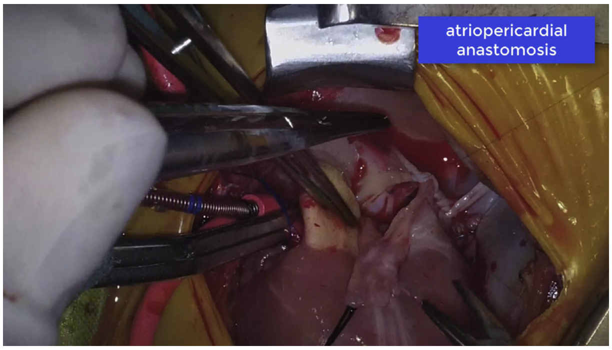
Through a right atriotomy, a tailored-to-match incision was required on the back wall of the LA. Then, a side-to-side anastomosis was performed between the confluence and the LA. For patients with small confluence, the incision was extended to the individual PVs to achieve an acceptably wide anastomosis.[8]

ST

A detailed description of ST has been previously published.[15] In brief, incisions were made in the confluence and usually extended into the individual PVs out toward the pleural pericardial reflection. A corresponding incision was made on the posterior LA wall. Then, a neoLA was created by anastomosing the LA to the posterior pericardium adjacent to the PV entrance to the pericardium (Video 1). Several steps were helpful for the success of this procedure: the LA incision was made large enough and usually extended into the appendage as well as the posterior atrial septum; incisions were made across the stenotic area of the individual PVs; shallow stitches were required at the pericardial edge where the PVs were close to the pleural pericardial reflection; and the stitch distance was not kept too wide, especially at the pericardial edge around the distal PV branch.

Statistical Analysis

Continuous data are presented as mean $\pm$ standard deviation or as median (interquartile range [IQR]) according to data distribution. Categorical data are presented as absolute numbers and percentages. Univariable comparisons between treatment groups were performed using Pearson's χ^2 test or Fisher exact test for categorical parameters, and Student t test or nonparametric Mann-Whitney U test for continuous



VIDEO 1. Operative procedure. Sutureless technique with commitment atrial septal defect (ASD) closure was performed in a 1.2-kg newborn infant with infracardiac total anomalous pulmonary venous connection (TAPVC) and ASD. Video available at: https://www.jtcvs.org/article/S0022-5223(20)31740-2/fulltext.

variables, as found appropriate. For mortality or restenosis, time-to-event analysis was conducted using Kaplan-Meier estimates, and comparisons were performed using the log-rank test. Cox proportional hazard regression model was used to explore the predictive variables for time to event outcomes. The proportional hazard assumption is satisfied for the outcome of mortality/freedom from restenosis from the time of initial operation to the last follow-up. Given that there were too few deaths or restenosis to have multiple variables in the multivariable models, we solely reported the univariate unadjusted proportional hazards. Hazard ratios of PVC configuration, preoperative PVO, and surgical technique were adjusted for baseline characteristics, including age, weight, oxygen saturation, emergency operation, and presurgical management. Further bootstrap method (using 1000 bootstrap replicated) for the HR (95% confidence interval) of risk factors was performed to validate the stable results of the cox regression. Statistical analyses were performed using SPSS statistics package, version 19 (IBM-SPSS Inc, Armonk, NY).

RESULTS

Baseline Characteristic

Of 82 patients, 80 came to our hospital owing to the first-onset symptom of cyanosis or respiratory distress. Only 2 newborn infants were referred to our hospital due to prenatal diagnosis. Preoperative median oxygen saturation was 80% (IQR, 70%-87%). Detailed information of the entire cohort is shown in Table 1. In total, 11 neonatal patients with obstructed PV drainage developed severe symptoms or increasing levels of lactate that were refractory to presurgical resuscitation, and they underwent emergency operations without CTA. Of the 82 patients, 13 developed worsening preoperative status after CTA, and they underwent urgent operations. Table 1 compares the baseline demographic characteristics between the 2 groups. There was a higher percentage of neonatal patients in the ST group compared with the CR group (14 out of 15, 92% vs 37 out of 67, 55%; $P = .02$).

Intraoperative Data and In-Hospital Clinical Outcome

The overall mean CPB and aortic crossclamp time were 96.7 ± 28.4 and 52.5 ± 17.7 minutes, respectively.

TABLE 1. Patient demographic characteristics at baseline*

Characteristic	Total (N = 82)	Conventional repair (n = 67)	Sutureless repair (n = 15)	*P* value†
Age at repair (d)	21 (9-40)	27 (10-45)	17 (6-22)	.03
Weight at repair (kg)	3.6 (3.2-4.1)	3.7 (3.2-4.3)	3.5 (3.0-3.8)	.2
Male sex	57 (70)	49 (73)	8 (53)	.2
Oxygen saturation (%)	80 (80-87)	80 (71-88)	80 (80-85)	.7
Preoperative intubation or infusion	36 (44)	29 (43)	7 (47)	.8
Preoperative PVO	45 (55)	36 (54)	9 (60)	.7
External stenosis	35 (78)	28 (78)	7 (78)	1.0
Intrinsic stenosis	8 (18)	6 (17)	2 (22)	.7
Restrictive ASD	2 (4)	2 (5)	0 (0)	1.0
Time of operation				
Emergency	11 (13)	9 (13)	2 (13)	1.0
Urgency	13 (16)	10 (15)	3 (20)	.7
Elective	58 (71)	48 (72)	10 (67)	.8
Preoperative CTA	71 (87)	58 (87)	13 (87)	1.0
Confluence morphology				
Symmetric inverted Christmas tree	42 (59)	35 (60)	7 (54)	.7
Asymmetric inverted Christmas tree	6 (8)	4 (7)	2 (15)	.3
Antler	23 (32)	19 (33)	4 (31)	1.0

Values are presented as median (interquartile range), mean ± standard deviation, or n (%). *PVO*, Pulmonary vein obstruction; *ASD*, atrial septal defect; *CTA*, computed tomography angiography. *Because 11 patients underwent emergency operation, CTA data were not available for these patients. As for other variables of basic characteristics, there are no missing data. †Comparison between patients undergoing conventional repair and patients undergoing sutureless repair.

TABLE 2. In-hospital procedural data and complications

Variable	Conventional repair (n = 67)	Sutureless technique (n = 15)	*P* value
CPB time (min)	93.6 ± 25.5	113.5 ± 37.8	.03
Aortic crossclamp time (min)	48.5 (40-58)	58 (45.5-72)	.03
Circulatory arrest	4 (6)	3 (20)	.1
Delayed sternal	27 (40)	11 (73)	.03
Time to delayed sternal (d)	3 (3-3)	3 (3-3)	1.0
Duration of ventilation (h)	92 (52.5-147.5)	138 (105.5-238)	.02
Low cardiac output	19 (28)	1 (7)	.1
Reintubation	3 (4)	0 (0)	1.0
Pulmonary hypertension crisis	12 (18)	0 (0)	.1
Hemidiaphragm plication	1 (1)	2 (13)	.1
Wound infection	1 (1)	0 (0)	1.0
Hemorrhage	2 (3)	0 (0)	1.0
Arrhythmia	3 (4)	0 (0)	1.0
CICU stay (d)	7 (6-11)	11 (7-14)	.1
Hospital stay (d)	17 (13-21)	21 (16-24)	.1
Restenosis	6 (9)	0 (0)	.6
In-hospital death	7 (10)	0 (0)	.3

Values are presented as median (interquartile range), mean ± standard deviation, or n (%). *CPB*, Cardiopulmonary bypass; *CICU*, cardiac intensive care unit.

Circulatory arrest was required in 7 patients, and the mean time was 26.7 ± 14.4 minutes. The overall mean duration of postoperative ventilator support was 118.8 ± 74.8 hours. Three patients required reintubation due to hemodynamic instability after the first attempt of extubation. The median cardiac intensive care unit stay and hospitalization time of the entire cohort were 8 days (IQR, 6-12 days) and 17 days (IQR, 14-22 days), respectively. Delayed sternal closure was required in 38 patients with a median interval of 3 days (IQR, 3-3 days). Detailed comparisons of the operative characteristics and early postoperative complications between the 2 groups are provided in Table 2.

Seven in-hospital deaths occurred in the CR group; the causes were severe pulmonary artery hypertension secondary to postrepair PVS in 5 patients, low cardiac output in 1, and unknown cause in 1. One patient in the CR group developed anastomotic restriction, and proximal left and right upper PV restenosis 25 days postoperatively. We suggested reintervention; however, his parents were forced to decline the reoperation and withdraw from any treatment due to the lack of financial resources. This patient was discharged alive and lost follow-up. Univariable analysis indicated that preoperative PVO, PVC configuration of antler appearance, and longer CPB time were factors predicating for mortality (Table 3). Stratified by the different types of preoperative PVO, intrinsic stenosis was associated with a 6-fold increase in mortality (HR, 6.1; 95% confidence interval, 5.82-7.34; $P = .03$) compared with that for extrinsic stenosis and restrictive ASD.

Follow-up Outcome

The follow-up date in this series was as of December 1, 2019. Follow-up was available in 95% of the survivors discharged from the hospital. A detailed follow-up flow chart is shown in Figure E2. The median follow-up for all survivors was 29 months (IQR, 12.5-59 months), with 35 months (IQR, 13-65 months) for the CR group and 16 months (IQR, 11.5-17 months) for the ST group. There was 1 late death in the CR group. This patient developed restenosis and had to be re-hospitalized for ventilator support due to severe respiratory distress 4 months after the initial repair. Unfortunately, his parent signed to withdraw from medical treatment, and this patient died a few days after rehospitalization. Kaplan-Meier analysis revealed a trend for higher mortality in the CR group; however, this failed to reach statistical significance ($P = .2$) (Figure 2, *A*).

As depicted in Figure 2, *B*, the CR patients experienced significantly higher likelihood of restenosis at a median of postoperative 2 months (IQR, 1.2-3.6 months) compared with that for sutureless repair patients ($P = .0004$). There was a total of 37 patients developing restenosis among whom 32 patients developed during the follow-up and 5 developed before discharge (Figure 3), and these 37 events were used for further analysis. Progression of restenosis that extended from the LA-to-confluence anastomosis to the individual PVs were observed in 10 patients. Six patients underwent reintervention due to restenosis, among whom restenosis in the individual PVs was observed in 1 patient, and a combination of anastomotic stenosis and individual

CONG

TABLE 3. Adjusted and unadjusted analysis for mortality and postrepair pulmonary vein stenosis (PVS)

	Univariable unadjusted and adjusted analysis					
	Mortality			Postrepair PVS		
Variable	*P* value	Unadjusted hazard ratio*	95% confidence interval†	*P* value	Unadjusted hazard ratio*	95% confidence interval†
Gender	.572	0.66	0.16-2.77	.680	0.96	0.87-1.05
Age	.114	1.01	0.99-1.02	.328	0.99	0.93-1.01
Weight	.738	0.86	0.36-2.01	.320	0.96	0.87-1.06
Presurgical management	.146	2.81	0.70-11.28	.780	0.89	0.40-1.92
Preoperative PVO						
No	Reference			Reference		
Yes	.008	2.26	1.26-4.05	.016	2.14	1.17-4.95
PVC configuration						
Inverted Christmas-tree	Reference			Reference		
Antler	.019	2.13	1.09-7.31	<.001	4.20	2.05-8.62
Oxygen saturation	.086	0.94	0.88-1.01	.010	1.04	1.01-1.08
Emergency operation	.828	0.79	0.33-4.45	.009	2.91	1.30-6.49
CPB time	.041	1.02	1.00-1.53	.486	1.01	0.97-1.02
AXC time	.966	0.99	0.96-1.04	.131	1.02	0.99-1.03
Duration of ventilation	.586	1.01	0.98-1.03	.419	1.00	0.97-1.01
Delayed sternal	.399	1.85	0.44-3.78	.368	0.73	0.36-1.46
CICU stay	.597	0.81	0.38-1.75	.715	1.01	0.94-1.05
Hospital stay	.503	1.03	0.95-1.11	.529	1.01	0.99-1.03
Surgical technique						
CR	Reference			Reference		
ST	.406	2.71	0.57-3.64	.036	1.81	1.14-5.27
PVC configuration						
Inverted Christmas tree	Reference			Reference		
Antler	.032	1.97	1.65-4.16	.002	2.12	1.03-5.47
Preoperative PVO						
No	Reference			Reference		
Yes	.043	1.33	1.01-3.97	.604	1.81	0.64-4.22
Surgical technique						
CR	Reference			Reference		
ST	.063	0.92	0.54-1.42	.003	0.72	0.39-0.97

PVS, Pulmonary vein stenosis; *PVO*, pulmonary vein obstruction; *PVC*, pulmonary venous confluence; *CPB*, cardiopulmonary bypass; *AXC*, aortic crossclamp; *CICU*, cardiac intensive care unit; *CR*, conventional repair; *ST*, sutureless technique. *Hazard ratios of PVC configuration, preoperative PVO, and surgical technique were adjusted for age, weight, oxygen saturation, emergency operation, and presurgical management. †Bootstrap method (using 1000 bootstrap replicated) for the coefficients' 95% confidence interval of the risk factors were performed to validate the stable results of Cox regression.

PVS in 5 patients. Unfortunately, restenosis in 2 of the 6 patients were refractory to the reintervention. They developed recurrent restenosis between 1 and 3 months after the reoperation and were both in New York Heart Association class III or IV at the last follow-up. Nine of the other 22 patients with post-repair PVS had recurrent respiratory infection (n = 6) and worsening exercise tolerance (n = 3); however, they did not undergo timely reintervention due to family financial burden (n = 7) or parental refusal (n = 2). The remaining 13 patients with subclinical restenosis had ongoing follow-up. Rigorous surveillance was maintained among these patients, and reintervention was scheduled if possible. Univariable analysis indicated that preoperative percutaneous oxygen saturation, preoperative PVO, PVC configuration of antler appearance, and emergency operation were associated with restenosis, whereas ST was a protective factor of postrepair PVS (Table 3).

DISCUSSION

This retrospective analysis of 82 patients treated either by CR or ST is among the largest analyses in the setting of infracardiac TAPVC, providing valuable information

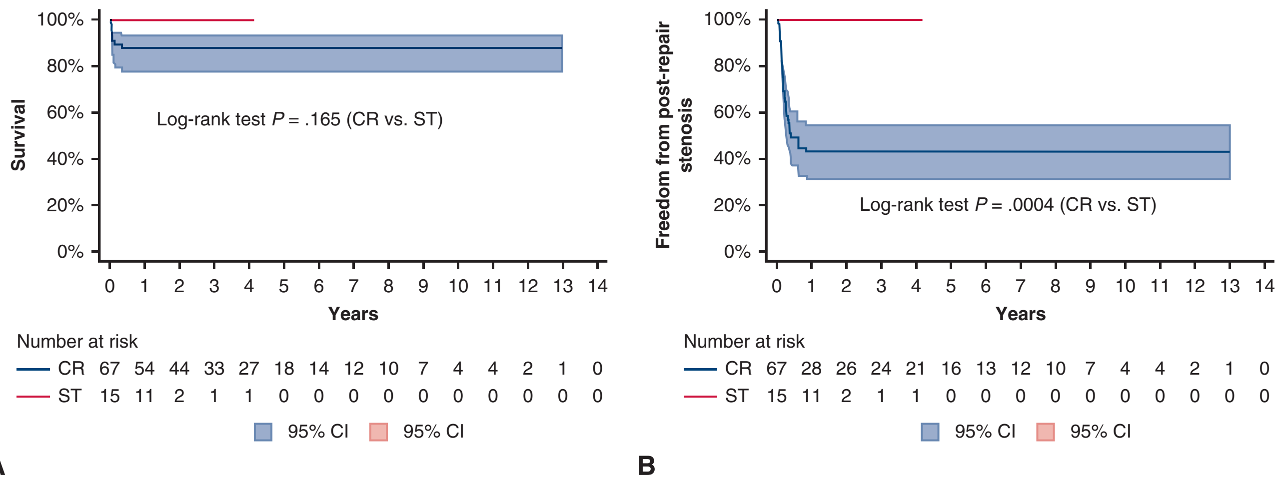


FIGURE 2. A, Kaplan-Meier curves of survival between patients with infracardiac total anomalous pulmonary venous connection (TAPVC) undergoing conventional repair (*CR*) and sutureless technique (*ST*). B, Freedom from diagnosis of postrepair pulmonary vein stenosis between patients with infracardiac TAPVC undergoing CR and ST. *CI*, Confidence interval.

regarding surgical outcomes in this subgroup population. Patients with infracardiac TAPVC who underwent LA-to-confluence anastomosis had a high risk of mortality and postrepair PVS. Our results modestly suggest a potential short-term benefit of the primary ST in this clinical setting, which supports the contention[16] that ST can optimize the outcomes of TAPVC repair. Our study first introduced a classification of PVC morphology in the infracardiac subtype and suggested an association between the antler configuration and adverse outcomes.

Current Knowledge of Postrepair PVS

Postrepair PVS most often occurs within the first year after initial repair of TAPVC and portends a guarded prognosis.[1,2] Existing evidence[5,17] indicates the role of endothelial-to-mesenchymal transitions in the pathologic process of restenosis. Various reasons may be responsible for the development of restenosis: intrinsic genetic predisposition,[18] direct surgical trauma to the veins, increased anastomotic tension, and distortion of the individual PVs arising from the complex geometry of a suture line. Reasons other than direct surgical trauma to the veings are likely related to anastomotic imperfection that will cause geometric constraints on tissues and result in increased anastomotic tension as well as changes in flow pattern. The vessel endothelium will sense such local haemodynamic characteristics (eg, shear stress) and respond by initiating acute changes in structural remodeling within an early period after operation.[19,20]

Confluence Morphology and Restenosis

The morphological heterogeneity of confluence and PV dimensions complicates the LA-PVC anastomosis, which may contribute to postrepair PVS.[21] In our series, the antler appearance of PVC configuration was strongly associated with restenosis. There are several possible explanations for this. First, there may be more spatial distance between the confluence and LA in the antler configuration. A direct LA-to-confluence anastomosis would lead to twisting of individual PVs or increased anastomotic tension. This corresponds to the findings[22] that CR would result in increased incidence of restenosis when the LA was relatively far away from the confluence. Second, there is a high likelihood of geometric constraints on tissue due to the complex geometry of the suture line that follows the divided edges of the PVs around irregularly shaped incisions in confluence. This will result in complex geometry of atrial-vein connections and lead to distortion or angulation of the veins, which potentially alters the flow pattern and contributes to the aforementioned PV remodeling. Furthermore, the small thick-walled extrapulmonary veins loss of distensibility in obstructed infracardiac TAPVC[23] is vulnerable to intimal proliferation and fibrosis. As such, hemodynamic changes after anastomotic imperfections may induce and aggravate postrepair PVS.

Primary Use of ST

Early favorable outcomes using the ST[24] have encouraged more surgeons to intuitively pursue the adoption of this technique for a primary repair of TAPVC because it potentially mitigates some of the aforementioned risk factors. However, there are conflicting results regarding the primary use of ST in patients with TAPVC. Buitrago and colleagues,[25] Zhang and colleagues,[10] and Mueller and colleagues[3] observed the diminished postrepair PVS using

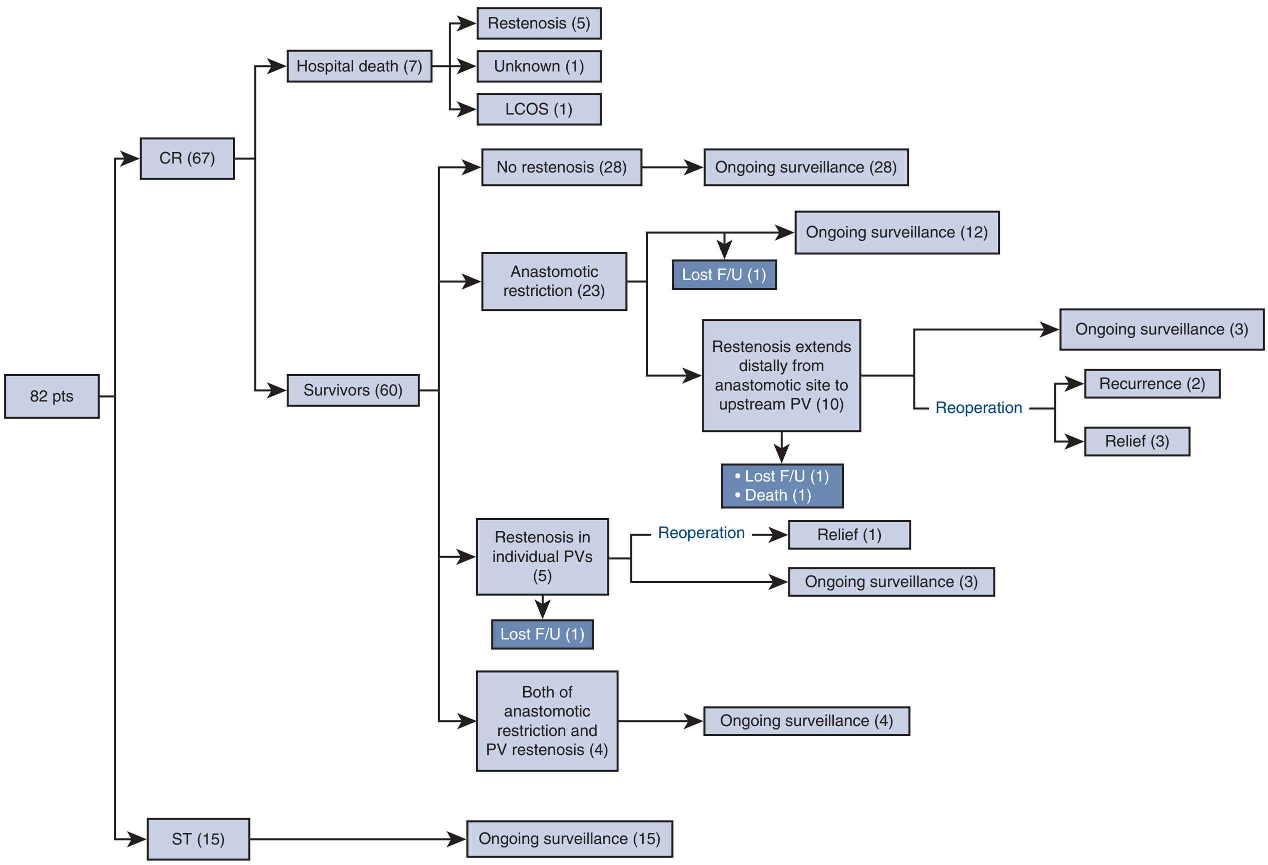


FIGURE 3. Outcome and follow-up schema for the entire cohort. None of the patients undergoing sutureless technique (*ST*) develop restenosis in a short follow-up period. A total of 37 patients in the conventional repair (*CR*) group develop restenosis, among whom 5 experienced in-hospital death and 1 experienced late death. Three of the 37 patients were lost follow-up. Six of the 37 patients had reoperation among whom 2 developed recurrent stenosis. Twenty-two patients who developed restenosis did not undergo reoperation and had ongoing surveillance. *pts*, Patients; *LCOS*, low cardiac output syndrome; *PV*, pulmonary vein; *F/U*, follow-up.

ST, whereas Yun and colleagues[11] and Yanagawa and colleagues[15] only reported noninferior results in the ST group. A recent study[12] indicates that ST is still burdened by a substantial risk of restenosis, which is in line with the findings that ST is still associated with progressive peripheral[26] and anastomotic[27] restenosis.

The bulk of existing studies have included a case mix of all four subtypes of TAPVC. It is not uncommon to detect in these underlying data that a lower prevalence of restenosis among a small number of patients with infracardiac variant undergoing sutureless repair is neutralized by the equivalence between ST and CR in the occurrence of restenosis amongst patients with other subtypes. This corresponds to our previous finding[8] that the benefit of ST is apparent in patients with preoperative PVO (a considerable proportion of patients diagnosed as infracardiac subtype) but not in those without. Further, it also corresponds to the recent finding that ST is not advantageous in supracardiac TAPVC.[28] Hence, it can be speculated that such a case mix may mask a potential beneficial influence of ST in a distinct subtype of TAPVC.

This study lacked the power to draw a firm conclusion in favor of the primary use of ST due to the small sample size with a short follow-up duration. Nevertheless, the study provides some valuable insight into this issue. The majority of restenosis occurred within the postoperative 1 year in the CR group. It is plausible to infer that vessel remodeling via the flow-mediated endothelial mechanotransduction related to the anastomotic imperfection probably occurs within an early postoperative period, which corresponds to most of the published data[1,2,26] that the highest hazard for restenosis can usually be found within postoperative 6 months. For recurrent PVS pathology, although it is difficult to conclude that the ST is superior to CR in terms of decreasing restenosis because most of the survivors in the ST group had <1-year follow-up, the freedom-from-restenosis curve indicated a trend of higher incidence of restenosis using the CR within an early period of the follow-up. This suggests that CR may be associated with a suboptimal prognosis in infracardiac TAPVC.

Potential Benefits and Drawbacks of ST

The general consensus for the benefit of ST is that this technique can avoid surgical trauma to the vein endothelium. Another potential benefit is that ST may optimize the flow dynamics by minimizing the distortion of individual PVs because of the following: LA is sutured to the less pliable posterior pericardium rather than to the thin PVs that lack a myocardial muscular layer[29] and are disposed to twist; the ST provides a simple oval suture line instead of an irregular contour of incision included in a suture line; and ST can maximize the confluence size and create a large neo-LA, which may be associated with a more benign postoperative course with respect to pulmonary and cardiac function issues related to pulmonary hypertension. In this regard, Fujimoto and colleagues[30] suggested that a small LA may be related to the intrapulmonary vein stenosis and pulmonary hypertension.

A potential disadvantage of ST is bleeding, including intrapleural bleeding due to perforation at the pleural pericardial reflection and bleeding from the gap between the confluence and pericardium into the posterior mediastinum. Another disadvantage is thrombogenicity at the exposed pericardial surface. The phrenic nerve is easily identifiable in the primary operation, so concerns regarding its injury may be overestimated. Finally, whether anastomoses performed in a static heart will result in a satisfactory pulmonary venous flow pattern in a beating heart requires further confirmation.

Limitations

The results of this study should be interpreted in view of several limitations. First, although this study was among the largest series of cases with infracardiac TAPVC, there was a discrepancy in number between CR and ST groups. As a result, the findings supporting the short-term benefit of ST are constrained due to the lack of power and retrospective nature of the study. Thus, the results should only be regarded as hypothesis-generating. The small proportion of patients in the ST group with a shorter follow-up duration could also be a source of errors. Second, we could not analyze the association of other PVC morphologies (except for inverted Christmas tree or antler configuration) with outcomes. Third, our findings are from a single institution so the generalizability of the results may be limited, and the association between PVC configuration and postoperative outcomes may be influenced by other confounders that were not measured.

CONCLUSIONS

Patients with infracardiac TAPVC who undergo CR are more likely to experience postrepair PVS. Our results indicate that PVC of antler configuration is associated with mortality and restenosis. This study contributes some valuable information regarding contemporary outcomes of surgical repair of infracardiac TAPVC. Our results modestly suggest a potential short-term benefit of primary ST; however, further studies are necessary to determine whether ST has a clear superiority to CR.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. White BR, Ho DY, Faerber JA, Katcoff H, Glatz AC, Mascio CE, et al. Repair of total anomalous pulmonary venous connection: risk factors for postoperative obstruction. *Ann Thorac Surg*. 2019;108:122-9.
2. Kalfa D, Belli E, Bacha E, Lambert V, di Carlo D, Kostolny, et al. Outcomes and prognostic factors for postsurgical pulmonary vein stenosis in the current era. *J Thorac Cardiovasc Surg*. 2017;156:278-86.
3. Mueller C, Dave H, Pretre R. Primary correction of total anomalous pulmonary venous return with a modified sutureless technique. *Eur J Cardiothorac Surg*. 2013;43:635-40.
4. Kovach AE, Magcalas PM, Ireland C, McEnany K, Oliveira AM, Kieran MW, et al. Paucicellular fibrointimal proliferation characterize pediatric pulmonary vein stenosis: clinicopathologic analysis of 213 samples from 97 patients. *Am J Surg Pathol*. 2017;41:1198-204.
5. Zhu J, Ide H, Fu YY, Teichert AM, Kato H, Weisel RD, et al. Losartan ameliorates “upstream” pulmonary vein vasculopathy in a piglet model of pulmonary vein stenosis. *J Thorac Cardiovasc Surg*. 2014;148:2550-7.
6. Caldarone CA, Najm HK, Kadletz M, Smallhorn JF, Freedom RM, Williams WG, et al. Relentless pulmonary vein stenosis after repair of total anomalous pulmonary venous drainage. *Ann Thorac Surg*. 1998;66:1515-20.
7. Balasubramanian S, Marshall AC, Gauvreau K, Peng LF, Nugent AW, Lock JE, et al. Outcomes after stent implantation for thetreatment of congenital and postoperative pulmonary vein stenosis in children. *Circ Cardiovasc Interv*. 2012;5:109-17.
8. Shi G, Zhu Z, Chen J, Ou Y, Hong H, Nie Z, et al. Total anomalous pulmonary venous connection: the current management strategies in a pediatric cohort of 768 patients. *Circulation*. 2017;135:48-58.
9. Honjo O, Atlin CR, Hamilton BC, AI-Radi O, Viola N, Coles JG, et al. Primary sutureless repair for infants with mixed total anomalous pulmonary venous drainage. *Ann Thorac Surg*. 2010;90:862-8.
10. Zhang C, Ou Y, Zhuang J, Chen J, Nie Z, Ding Y. Comparison of sutureless and conventional technique to repair total anomalous pulmonary venous connection. *Semin Thorac Cardiovasc Surg*. 2016;28:473-84.
11. Yun TJ, Coles JG, Konstantinov IE, AI-Radi OO, Wald RM, Guerra V, et al. Conventional and sutureless techniques for management of the pulmonary veins: evolution of indications from postrepair pulmonary vein stenosis to primary pulmonary vein anomalies. *J Thorac Cardiovasc Surg*. 2005;239:167-74.
12. Tremblay C, Yoo SJ, Mertens L, Seed M, Jacques F, Slorach C, et al. Sutureless versus conventional pulmonary vein repair: a magnetic resonance pilot study. *Ann Thorac Surg*. 2018;105:1248-54.
13. Liufu R, Shi G, Zhu F, Guan Y, Lu Z, Chen W, et al. Superior approach for supracardiac total anomalous pulmonary venous connection. *Ann Thorac Surg*. 2018;105:1429-35.
14. Walsh MJ, Ungerleider RM, Aiello VD, Spicer D, Giroud JM. Anomalous pulmonary venous connections and related anomalies: nomenclature, embryology, anatomy, and morphology. *World J Pediatr Congenit Heart Surg*. 2013;4:30-43.

15. Yanagawa B, Alghamdi AA, Dragulescu A, Viola N, AI-Radi OO, Mertens LL, et al. Primary sutureless repair for "simple" total anomalous pulmonary venous connection: midterm results in a single institution. *J Thorac Cardiovasc Surg*. 2011;141:1346-54.
16. Wu Y, Xin L, Zhou Y, Kuang H, Jin X, Li Y, et al. Is sutureless technique beneficial in the primary repair of total anomalous pulmonary venous connection? A systematic review and meta-analysis. *Pediatr Cardiol*. 2019;40:881-91.
17. Kato H, Fu YY, Zhu J, Wang L, Aafaqi S, Rahkonen O, et al. Pulmonary vein stenosis and the pathophysiology of "upstream" pulmonary veins. *J Thorac Cardiovasc Surg*. 2014;148:245-53.
18. Latson LA, Prieto LR. Congenital and acquired pulmonary vein stenosis. *Circulation*. 2007;115:103-8.
19. Kovacic JC, Dimmeler S, Harvey RP, Finkel T, Aikawa E, Krenning G, et al. Endothelial to mesenchymal transition in cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:190-209.
20. Chistiakov DA, Orekhov AN, Bobryshev YV. Effects of shear stress on endothelial cells: go with the flow. *Acta Physiol*. 2017;219:382-408.
21. Seale AN, Uemura H, Webber SA, Partridge J, Roughton M, Ho SY, et al. Total anomalous pulmonary venous connection: morphology and outcomes from an international population-based study. *Circulation*. 2010;122:2718-26.
22. Peng Y, Ge Y, Zhang H, Liu J, Hong H, Lu Y. Positional relationship between the pulmonary venous confluence-vertical vein and atria in infracardiac total anomalous pulmonary venous connection. *Pediatr Cardiol*. 2016;37:372-7.
23. Haworth SG. Total anomalous pulmonary venous return. Prenatal damage to pulmonary vascular bed and extrapulmonary veins. *Br Heart J*. 1982; 48:513-24.
24. Lacour-Gayet F, Rey C, Planche C. Pulmonary vein stenosis. Description of a sutureless surgical technique using the pericardium in situ [in French]. *Arch Mal Coeur Vaiss*. 1996;89:633-6.
25. Buitrago E, Panos AL, Ricci M. Primary repair of infracardiac total anomalous pulmonary venous connection using a modified sutureless technique. *Ann Thorac Surg*. 2008;86:320-2.
26. Lo Rito M, Gazzaz T, Wilder T, Saedi A, Chetan D, Van Arsdell GS, et al. Repair type mode of pulmonary vein stenosis in total anomalous pulmonary venous drainage. *Ann Thorac Surg*. 2015;100:654-62.
27. Agematsu K, Okamura T, Takiguchi Y, Harada Y. Pulmonary vein obstruction after primary sutureless pericardial repair of a total anomalous pulmonary venous connection. *Interact Cardiovasc Thorac Surg*. 2018;27: 624-5.
28. Zhu Y, Qi H, Jin Y. Comparison of conventional and primary sutureless surgery for repairing supracardiac total anomalous pulmonary venous drainage. *J Cardiothorac Surg*. 2019;14:34.
29. Douglas YL, Jongbloed MR, DeRuiter MC, Gittenberger-de Groot AC. Normal and abnormal development of pulmonary veins: state of the art and correlation with clinical entities. *Int J Cardiol*. 2011;147:13-24.
30. Fujimoto Y, Urashima T, Kawachi F, Akaike T, Kusakari Y, Ida H, et al. Pulmonary hypertension due to left heart disease causes intrapulmonary venous arterialization in rats. *J Thorac Cardiavasc Surg*. 2017;154:1742-53.

Key Words: total anomalous pulmonary venous connection, pulmonary venous confluence, sutureless technique, pulmonary vein stenosis

		CT Reviewer #1		
	Configuration	A1	A2	B
CT Reviewer #2	A1	42	0	0
	A2	0	6	0
	B	0	0	23

There is no inter-observer difference. Configuration **A1** and **A2** refer to symmetric and asymmetric inverted Christmas tree. Configuration **B** refers to antler appearance.

FIGURE E1. Results of 2 blinded specialized radiologists in categorizing the subtypes of the pulmonary venous confluence configurations. There was no interobserver difference. *CT*, Computed tomography; *A1*, symmetric inverted Christmas tree; *A2*, asymmetric inverted Christmas tree; *B*, antler appearance.

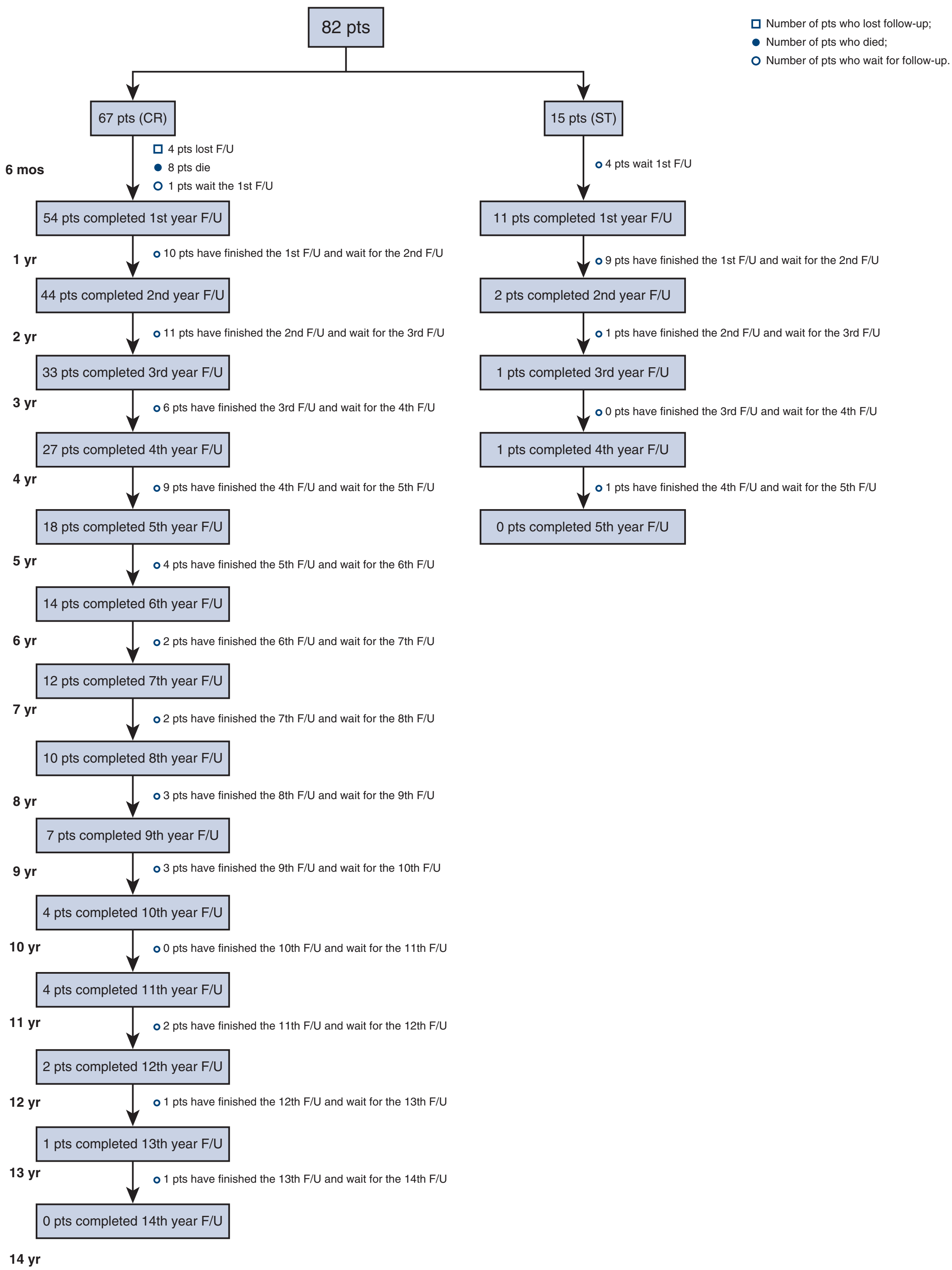


FIGURE E2. Seven of the 82 patients experienced in-hospital death. Of the 75 alive patients after discharge, 1 patient experienced late death and 3 were lost to follow-up. All of the remaining 71 patients are available for follow-up. Number of patients who have completed follow-up at each time point is provided. Further, in the conventional repair (*CR*) group, follow-up was complete for 95% (57 out of 60) of patients at 1 month, 85% (51 out of 60) of patients at 3 months, and 75% (45 out of 60) of patients at 6 months. In the sutureless technique (*ST*) group, follow-up was complete for 100% (15 out of 15) of patients at 1 month, 93% (14 out of 15) of patients at 3 months, and 67% (10 out of 15) of patients at 6 months. *pts*, Patients; *F/U*, follow-up; *yr*, year; □, number of pts who lost F/U after discharge; ●, number of pts who experienced in-hospital and late death; ○, number of pts who have finished the previous F/U and wait for the next coming F/U.