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Outcomes of total anomalous pulmonary venous drainage repair in neonates and the impact of pulmonary hypertension on survival



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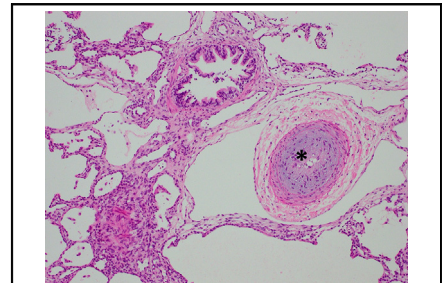
ABSTRACT

Background: Mortality after repair of total anomalous pulmonary venous drainage (TAPVD) in neonates has remained high. Analysis of risk factors may help identify therapeutic targets to improve survival.

Methods: Retrospective analysis of all neonates who underwent simple TAPVD repair.

Results: Between 1973 and 2021, 175 neonates underwent TAPVD repair, at a median age of 6 days (interquartile range, 2-15 days) and a mean weight of 3.2 ± 0.6 kg. TAPVD was supracardiac in 42.3% of the patients (74 of 175), cardiac in 14.3% (25 of 175), infracardiac in 40% (70 of 175), and mixed type in 3.4% (6 of 175), with obstruction in 65.7% (115 of 175). Pulmonary hypertension (PHT) crisis occurred in 12% (21 of 175). Early mortality was 9.7% (17 of 175) and late mortality was 5.1% (8 of 158), with most deaths occurring within 1 year (75%; 6 of 8). Survival was 86.5% (95% CI, 80.3%-90.8%) at 1 year and 85.8% (95% CI, 79.6%-90.3%) at 5, 10, 15, and 20 years. Survival was lower in patients with obstructed TAPVD, patients with emergent surgery, and those with PHT crisis. PHT crisis (hazard ratio [HR], 4.93; 95% CI, 1.95-12.51; $P = .001$), urgency of surgery (HR, 2.51; 95% CI, 1.11-5.68; $P = .027$), and higher pulmonary artery pressure-to-systemic blood pressure percentage ratio (HR, 1.06; 95% CI, 1.01-1.11; $P = .026$) were identified as risk factors for mortality. Histopathological analysis of 17 patients (9.7%; 17 of 175) showed signs of pulmonary arterial hypertension with media hypertrophy in 58.8% (10 of 17).

Conclusions: Mortality after TAPVD repair occurred mainly within the first year of life. Urgency of surgery and persistent PHT appears to be risk factors for mortality. Lung biopsy might be useful for identifying patients at risk and guiding newer treatment modalities. (JTCVS Open 2022;12:335-43)



Lung tissue of obstructed total anomalous pulmonary venous drainage with severe media hypertrophy of the pulmonary artery (*).

CENTRAL MESSAGE

Mortality after neonatal total anomalous pulmonary venous drainage repair has not improved over time. Identification of patients with pulmonary artery disease could help guide treatment strategies and potentially improve outcomes.

PERSPECTIVE

Long-term survival after neonatal total anomalous pulmonary venous drainage repair was excellent for those survived beyond 1 year of age. Mortality occurred mainly within the first year of life. Urgency of surgery and persistent pulmonary hypertension were identified as risk factors for mortality. Lung biopsy could help identify patients with evolving pulmonary arterial hypertension and guide new treatment modalities.

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Abbreviations and Acronyms

ECMO	= extracorporeal membrane oxygenation
HI	= hemodynamic index
HR	= hazard ratio
IQR	= interquartile range
MAP	= mean systemic arterial pressure
PAH	= pulmonary arterial hypertension
PAP	= mean pulmonary arterial pressure
PHT	= pulmonary hypertension
TAPVD	= total anomalous pulmonary venous drainage

Numerous diagnostic and therapeutic advancements over the past several decades have led to increasingly better outcomes after surgery for most congenital heart defects. However, although outcomes have improved for patients with total anomalous pulmonary venous drainage (TAPVD), mortality has remained high, at 9% to 30%,¹⁻¹⁰ and the improvement in outcomes has lagged in those who require repair during the neonatal period.⁵ Evolution in repair techniques toward reduced handling of the pulmonary veins and the use of primary pericardial anastomosis have reduced the rate of recurrent pulmonary venous obstruction and lowered reoperation rates; however, neonates remain at risk, with substantial mortality.^{5,11-14} The fact that operative and perioperative refinements have not significantly improved neonatal survival may indicate that intrinsic patient characteristics influence outcomes. Therefore, an analysis of risk factors could help identify potential treatment targets to improve survival in these patients.

The aim of this study was to determine the outcomes of simple TAPVD repair in neonates over a time span of almost 50 years and to identify risk factors for mortality. In particular, we investigated whether pulmonary hypertension (PHT) could affect survival of these patients.

METHODS**Study Design**

This single-institution retrospective study was approved by the institutional Human Research Ethics Committee (HREC no. 42425; 14/08/2017), with a waived need for informed written consent. The study cohort included all patients who underwent TAPVD repair within first month of life between 1973 and 2021. Patients with single ventricle anatomy or additional complex cardiac procedures were excluded. Data were collected retrospectively from the hospital records either as paper charts or digital records. If available, postoperative hemodynamic data, including average mean systemic arterial pressure (MAP), mean pulmonary arterial pressure (PAP), and central venous pressure, were recorded hourly for the first 36 hours after surgery.

Survival and risk factors for mortality were analyzed. For patients with available hemodynamic data, the PAP/MAP ratio was calculated hourly. The highest ratio obtained at any time point was used to calculate the hemodynamic index (HI), as (PAP/MAP)/weight.¹⁵ Follow-up was obtained from correspondence with cardiologists and general practitioners.

Definitions

Emergent surgery was defined as life-saving surgery performed within the first 24 hours of diagnosis in hemodynamically unstable patients; urgent surgery, as surgery performed within 24 to 48 hours of diagnosis in hemodynamically stable patients. All other surgeries were classified as nonurgent. Prematurity was defined as birth at <37 weeks of gestation. Pulmonary venous obstruction was determined clinically and by echocardiography. Obstructed TAPVD was defined as a restriction of pulmonary venous drainage at any level. Postoperative PHT crisis was recorded by staff when there was acute rise in PAP accompanied by an apparent reduction in cardiac output, as manifested by a significant drop in systemic arterial pressure or when there was strong clinical suspicion due to acute drop in systemic arterial pressure with high central venous pressure and decreased lung compliance in those patients without a pulmonary arterial line. Acute kidney injury was defined as a >50% increase in serum creatinine level from preoperative baseline. Early mortality was defined as death within 30 days after surgery or before discharge from the hospital; late mortality, as death beyond 30 days after surgery and after hospital discharge.

Operative Technique

The procedures were performed with varying degrees of hypothermia (18-32 °C), and blood cardioplegia was used for cardiac arrest. Periods of circulatory arrest were used as needed. Repair was done either by a side-to-side anastomosis between the pulmonary venous confluence and the left atrium or with a primary sutureless technique by fashioning a pericardial anastomosis.¹⁶

Statistical Analysis

Descriptive statistics include mean $\pm$ SD for normal continuous data, median with interquartile range (IQR) for skewed continuous data, and frequency with percentage for categorical data. The *t*-test was used to compare normally distributed continuous variables, and the Mann-Whitney *U* test was used to compare nonnormally distributed continuous variables between groups. The χ^2 test and Fisher exact test were used to compare categorical data.

The distributions of survival and freedom from reoperation were estimated using Kaplan-Meier methodology. Distributions of time to event in selected patient groups were compared using the log-rank test. Cox proportional hazard modeling was used to determine risk factors for mortality and reoperation. Risk factors with a *P* value $\leq .1$ on univariable analysis were included in a multivariable analysis. Statistical significance was set at *P* < .05, and CIs were set at 95%. Data analysis was performed with Stata version 17 (StataCorp).

RESULTS**Patient and Procedure Characteristics**

Between 1973 and 2021, 175 neonates underwent simple TAPVD repair (Table 1), including 10.3% (18 of 175) born prematurely. Anomalous drainage was supracardiac in 42.3% of the patients (74 of 175), cardiac in 14.3% (25 of 175), infracardiac in 40% (70 of 175), and mixed type in 3.4% (6 of 175). Obstruction occurred in 65.7% of the patients (115 of 175). Preoperative mechanical ventilation was required in 64.6% (113 of 175); extracorporeal membrane oxygenation (ECMO), in 4% (7 of 175). Indications for early repair of cardiac TAPVD were either obstructed drainage (36%; 9 of 25) or heart failure despite medical treatment (64%; 16 of 25).

The median age at surgery was 6 days (IQR, 2-15 days), and mean weight was 3.2 ± 0.6 kg. Emergent surgery was necessary in 28% of the patients (49 of 175); urgent

TABLE 1. Characteristics of the 175 neonates who underwent simple TAPVD repair

Characteristic	Value
Males/females, n (%)	116 (66.3)/59 (33.7)
Prematurity, n (%)	18 (10.3)
Age, d, median (IQR)	6 (2-15)
Weight, kg, mean $\pm$ SD	3.2 $\pm$ 0.6
TAPVD type, n (%)	
Supracardiac	74 (42.3)
Cardiac	25 (14.3)
Infracardiac	70 (40)
Mixed	6 (3.4)
Urgency, n (%)	
Emergent	49 (28)
Urgent	75 (42.9)
Nonurgent	51 (29.1)
PHT crisis, n (%)	21 (12)
Postoperative ECMO, n (%)	13 (7.4)

IQR, Interquartile range; TAPVD, total anomalous pulmonary venous drainage; PHT, pulmonary hypertension; ECMO, extracorporeal membrane oxygenation.

surgery, in 42.9% (75 of 175). Repair of supracardiac and infracardiac TAPVD was done by direct anastomosis in 86.1% of cases (124 of 144) and by pericardial repair in 13.9% (20 of 144, including 13 infracardiac and 7 supracardiac TAPVD). The median cardiopulmonary bypass and cross-clamp times were 78 minutes (IQR, 53-111 minutes) and 39 minutes (IQR, 33-52 minutes), respectively. Circulatory arrest was used in 44% of the patients (77 of 175), for a mean duration of 31 ± 12 minutes. Postoperative ECMO was needed in 7.4% (13 of 175). The chest was electively left open in 22.3% (39 of 175). Postoperative PHT crisis occurred in 12% of the patients (21 of 175), and 3.4% (6 of 175) experienced cardiac arrest. Acute kidney injury developed in 23.4% (41 of 175). The median duration of ventilation was 87 hours (IQR, 48-137 hours), median length of intensive care unit stay was 124 hours (IQR, 73-182 hours), and median length of hospital stay was 14 days (IQR, 10-22 days).

Survival

The median duration of follow-up was 9 years (IQR, 1.4-20.4 years). Early mortality was 9.7% (17 of 175); late mortality, 5.1% (8 of 158). Late mortality was due to a cardiopulmonary cause in 87.5% of cases (7 of 8), most occurring within 1 year (85.7%; 6 of 7). Only 2 deaths occurred beyond 1 year after surgery; 1 patient died 1.3 years postsurgery of heart failure in the context of progressive pulmonary hypertension, and 1 patient died from a brain tumor at 23.6 years after undergoing TAPVD repair.

Estimated survival for the entire cohort was 86.5% (95% CI, 80.3%-90.8%) at 1 year and 85.8% (95% CI,

79.6%-90.3%) at 5, 10, 15 and 20 years, with no significant changes over time (Figure 1, A). Survival was significantly lower in patients with obstructed pulmonary venous drainage, at 81.3% (95% CI, 72.8%-87.4%) at 1 year and 80.4% (95% CI, 71.8% to 86.6%) at 5, 10, 15, and 20 years (Figure 1, B). Survival was even worse in patient who required emergent surgery, at 71.4% (95% CI, 56.6%-82%) at 1 year and 69.3% (95% CI, 54.4%-80.2%) at 5, 10, 15, and 20 years (Figure 1, C). Mortality was highest in patients with recorded postoperative PHT crisis who had a survival of 57.1% (95% CI, 33.8%-74.9%) at 1, 5, 10, 15 and 20 years (Figure 1, D). There was no difference in survival based on TAPVD type (log-rank $P = .53$).

On multivariable analysis, PHT crisis (hazard ratio [HR], 4.93; 95% CI, 1.95-12.51; $P = .001$) and urgency of the procedure (HR, 2.51; 95% CI, 1.11-5.68, $P = .027$) were identified as risk factors for mortality (Table 2, Figure 2).

Postoperative Hemodynamic Data

Postoperative PAP was not measured in the patients operated on before 1994 ($n = 58$). Between 1994 and 2021, 117 patients were treated, and postoperative PAP was measured with a pulmonary arterial line in 92 of them (78.6%). Of these, 11 patients (12%; 11 of 92) were on postoperative ECMO support and thus were excluded from the hemodynamic analysis. Hourly PAP/MAP ratio and HI were calculated. Hemodynamic data during the first 36 hours after surgery are displayed in Table 3. There were 7 deaths (8.6%; 7 of 81) in this subgroup of patients. Patients who died had a higher average PAP, with 27.2 mm Hg (IQR, 20.4-28 mm Hg) ($P = .046$), and a higher PAP/MAP ratio ($P = .02$), and HI ($P = .04$) compared with patients who survived. A higher average PAP/MAP percentage ratio (HR, 1.06; 95% CI, 1.01-1.11; $P = .026$) was identified as a risk factor for mortality.

Pulmonary Histopathology

A lung biopsy was performed in 9 patients (5.1%; 9 of 175), of whom 6 required ECMO support (66.7%; 6 of 9) and 6 (66.7%; 6 of 9) died eventually. Another 8 patients underwent postmortem inspection of their lung tissue during autopsy. Among all patients with lung tissue available for examination (9.7%; 17 of 175), the histopathological analysis showed signs of pulmonary hypertension, with media hypertrophy in 58.8% (10 of 17), lymphangiectasia in 52.9% (9 of 17), and thickened pulmonary veins in 5.9% (1 of 17). Three patients (17.6%; 3 of 17) had either normal histology or only mild changes.

Figure 3 exemplifies the histopathological findings in 3 consecutive neonates who underwent simple TAPVD repair. Patient 1 had unobstructed supracardiac TAPVD with nonurgent repair, and the pulmonary tissue demonstrated no pathological changes. Patient 2 had obstructed

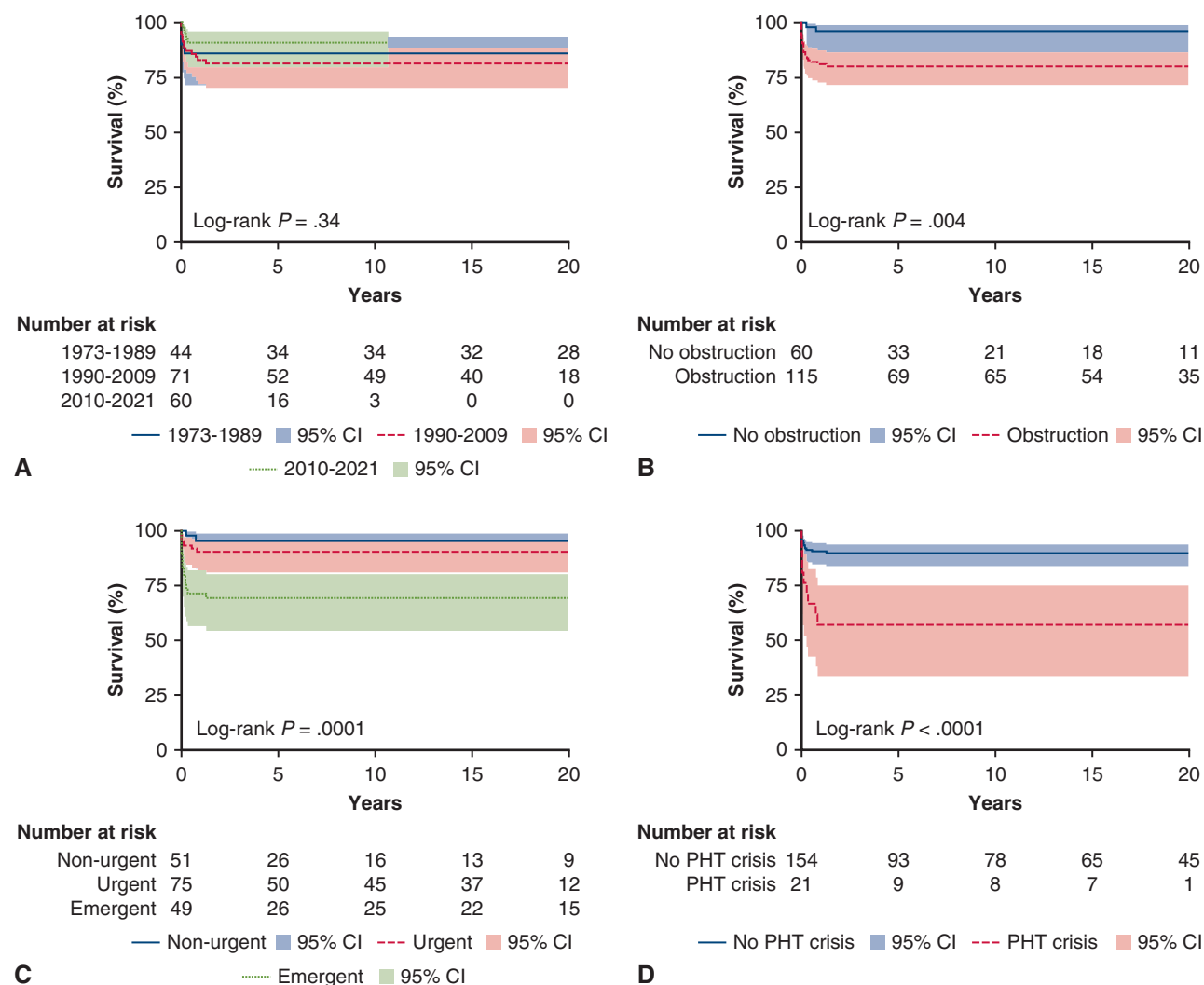


FIGURE 1. Kaplan–Meier curves comparing estimated survival over the years (A), in patients with and without obstructed pulmonary venous drainage (B); patients with emergent, urgent, and nonurgent repairs (C); and patients with and without postoperative pulmonary hypertensive (PHT) crisis (D). Shaded areas represent 95% confidence bands. CI, Confidence interval.

TABLE 2. Univariable and multivariable Cox models for mortality and pulmonary vein reoperation

Variable	Mortality			Reoperation		
	Univariable	Multivariable		Univariable	Multivariable	
	<i>P</i> value	HR (95% CI)	<i>P</i> value	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age at surgery	.036	0.96 (0.91-1.02)	.22	.32		
Prematurity	.004	1.65 (0.44-6.25)	.46	<.001	4.05 (1.07-15.27)	.04
Weight <2.5 kg	.004	3.02 (0.93-9.81)	.07	.02	0.61 (0.22-1.64)	.33
Obstruction	.012	0.97 (0.16-5.93)	.98	.38		
Urgency	<.001	2.57 (1.13-5.84)	.02	.96		
CPB time	.06	1.01 (0.99-1.01)	.06	.02	1.0 (0.99-1.02)	.51
Cross-clamp time	.245			.01	1.01 (0.98-1.04)	.44
PHT crisis	<.001	4.82 (1.91-12.15)	.001	.03	4.27 (1.25-14.59)	.02
PV reoperation	.056	1.61 (0.57-4.54)	.37			

Significant *P* values are in bold type. HR, Hazard ratio; CI, confidence interval; CPB, cardiopulmonary bypass; PHT, pulmonary hypertension; PV, pulmonary vein.

Outcomes of simple total anomalous pulmonary venous drainage repair in neonates

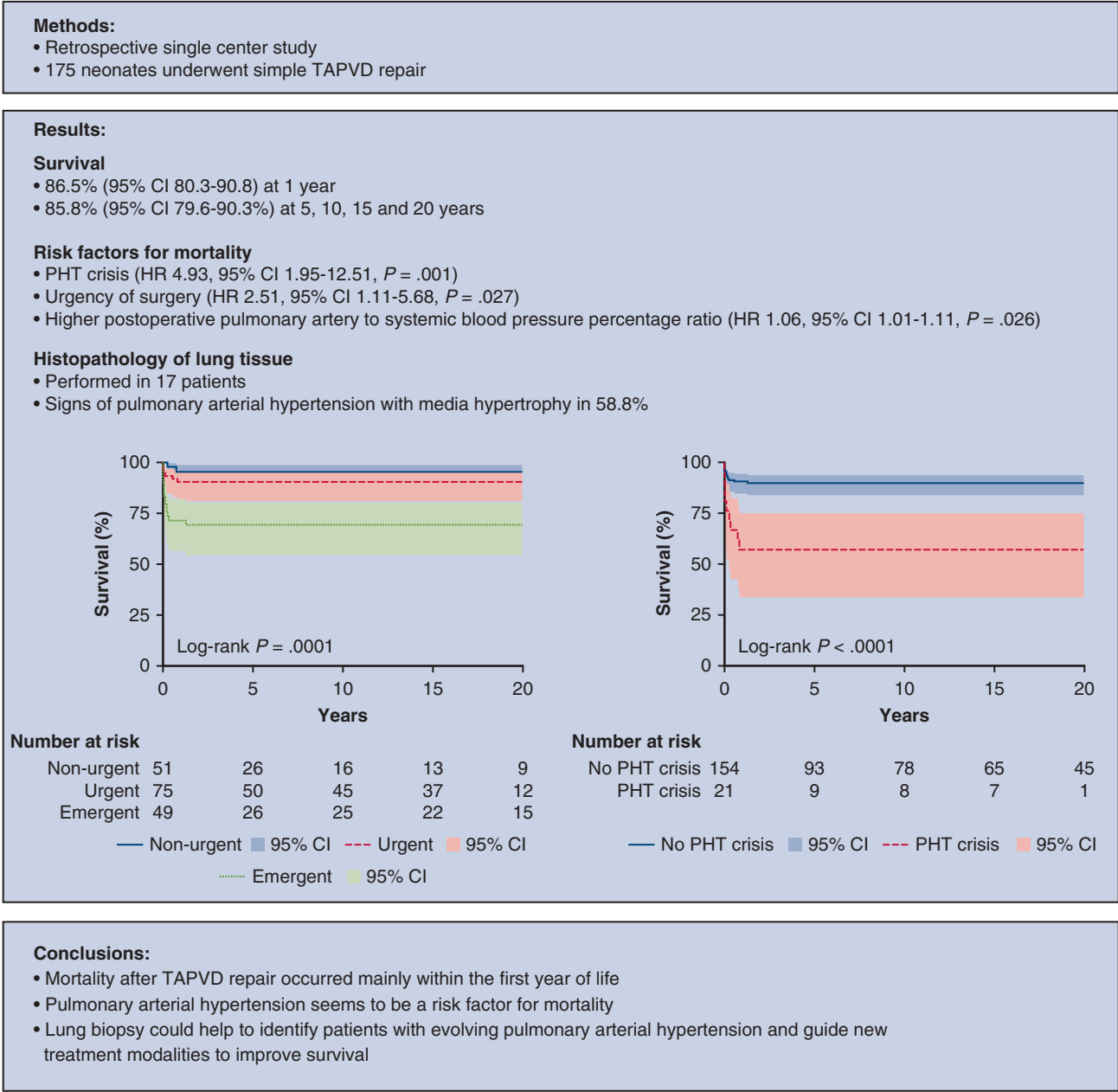


FIGURE 2. Outcome analysis of 175 neonates who underwent simple total anomalous pulmonary venous drainage (TAPVD) repair identified pulmonary hypertensive (PHT) crisis, urgency of surgery, and higher postoperative pulmonary artery–to–systemic blood pressure percentage ratio as risk factors for mortality. A significant number of patients ($n = 17$) with lung tissue available for analysis showed signs of pulmonary arterial hypertension. CI, Confidence interval; HR, hazard ratio.

infracardiac TAPVD and required preoperative intubation and urgent repair. Biopsy showed mild media hypertrophy consistent with initial changes of pulmonary arterial hypertension (PAH). The veins were unremarkable. The patient was started on PAH medication and had an uneventful recovery. Patient 3 had a severely obstructed supracardiac TAPVD that necessitated emergent surgery with preoperative ECMO

cannulation. Lung biopsy demonstrated severe media hypertrophy of the pulmonary arteries consistent with severe PAH. The veins showed no abnormalities. The patient’s clinical status improved remarkably on PAH medication; however, the patient eventually died after 4 months in the hospital from progressively worsening PAH with ongoing PHT crisis despite maximum medical therapy.

TABLE 3. Postoperative hemodynamic data for the first 36 hours after surgery in survivors and deceased patients

Variable	Survivors (N = 74)	Deceased (N = 7)	P value
PAP, mm Hg, median (IQR)	20.6 (18.1-24.6)	27.2 (20.4-28)	.046
MAP, mm Hg, median (IQR)	49.8 (46.3-52.7)	46.8 (44-47.4)	.13
CVP, median (IQR)	7.1 (6.2-8.2)	6.6 (5.2-7.7)	.55
PAP/MAP, median (IQR)	0.42 (0.36-0.49)	0.6 (0.43-0.73)	.02
HI, median (IQR)	0.2 (0.15-0.26)	0.28 (0.21-0.78)	.04

Significant *P* values are in bold type. PAP, Mean pulmonary arterial pressure; IQR, interquartile range; MAP, mean systemic arterial pressure; CVP, central venous pressure; HI, hemodynamic index.

Reoperation for Pulmonary Vein Obstruction

Twenty patients (11.4%; 20 of 175) required reoperation due to recurrent pulmonary vein obstruction at the anastomosis site (35%; 7 of 20), stenosis of pulmonary veins (55%; 11 of 20), or both complications (10%; 2 of 20). The median time to reoperation was 5 months (IQR, 0.1-1.2 years). Freedom from reoperation was 90.0% (95% CI, 85.2% to 94.5%) at 1 year, 89.5% (95% CI, 83.4% to 93.4%) at 5 years, 88.3% (95% CI, 81.8% to 92.7%) at 10 years, 87.2% (95% CI, 80.2% to 91.9%) at 15 years, and 84.1% (95% CI, 75.6%-89.8%) at 20 years (Figure 4, A). There was no significant difference in freedom from reoperation between patients with direct anastomosis (*n* = 124) and those with pericardial anastomosis (*n* = 20) (log-rank *P* = .63); however, freedom from pulmonary vein reoperation was significantly lower in premature neonates (Figure 4, B). On multivariable analysis, prematurity (HR, 4.05; 95% CI, 1.07-15.27; *P* = .04) and PHT crisis (HR, 4.27; 95% CI, 1.25-14.59; *P* = .02) were identified as risk factors for pulmonary vein reoperation (Table 2). In patients requiring pulmonary vein reoperation due to pulmonary vein stenosis, prematurity was the sole significant risk factor identified (HR, 4.59; 95% CI, 1.41-14.92; *P* = .011).

DISCUSSION

TAPVD requires repair during the neonatal period when patients are symptomatic. Obstructed pulmonary venous return is a known risk factor for mortality, as well as for recurrent obstruction with the need for reoperation.^{1,2,8,9,11} Although obstruction can be difficult to quantify, symptoms usually dictate the urgency of the repair, and there is a clear association between urgency of the procedure and survival.^{2,3} This risk factor is difficult to modify, however. Prenatal diagnosis can facilitate timely treatment, but in the absence of heterotaxy syndrome, the diagnosis is frequently made only once the child begins to exhibit symptoms.¹⁷ Therefore, mortality for neonatal TAPVD repair has not changed much despite significant improvements in overall outcome.^{12,13} The reported survival ranges between 70% and 91%.¹⁻⁹ In our series covering a time span of almost 50 years, survival was 85.8%, and we did not find a significant change in neonatal survival over time.

Mortality after repair occurred either early before hospital discharge or mostly within 1 year of life. For those patients who survived the first year, long-term survival was excellent. No patient in our series died from a cardiopulmonary cause beyond 16 months, in agreement with the reports from other groups.⁶ Although long-term health in these patients is good, neurodevelopmental difficulties have been reported later in life.^{18,19}

Although patients in our cohort who presented with obstructed TAPVD had lower survival, multivariable regression identified the urgency of the procedure and postoperative PHT crisis as risk factors for mortality. Patients with PHT crisis had the lowest survival, at 57.1% after 1 year. To better understand the significance of pulmonary vascular disease for mortality, we analyzed the postoperative hemodynamic data of patients in whom PAP was monitored after the procedure. Although we increasingly placed pulmonary artery lines in recent years, it was not done consistently for all patients and was not done in the historic era. We ultimately analyzed the hemodynamic data of 81 patients (46.3%; 81 of 175) after excluding those on ECMO (*n* = 11). This certainly resulted in a cohort that was missing some patients at particularly high risk for elevated PAP. Nevertheless, we found significantly higher average PAP, PAP/MAP ratio, and HI in patients who died compared with those who survived, and a higher PAP/MAP percentage ratio was identified as a risk factor for mortality. The underlying cause of higher postoperative PAP can be multifactorial, however, and thus we set out to investigate whether disease of the pulmonary vasculature itself might contribute to the inferior outcome in some patients. We reviewed the histopathological reports from lung biopsies as well as from autopsy studies and found a significant proportion of patients with media hypertrophy in their pulmonary arteries consistent with PAH, but only 1 patient with abnormal pulmonary veins. However, we emphasize that lung biopsies were performed in only a minority of patients, mainly in those who were not doing well clinically, and thus these findings cannot be generalized. More data are needed to determine how many patients are affected by changes in the pulmonary vasculature.

In a small series of 3 consecutive patients, we analyzed pulmonary tissue from biopsies taken at the time of repair

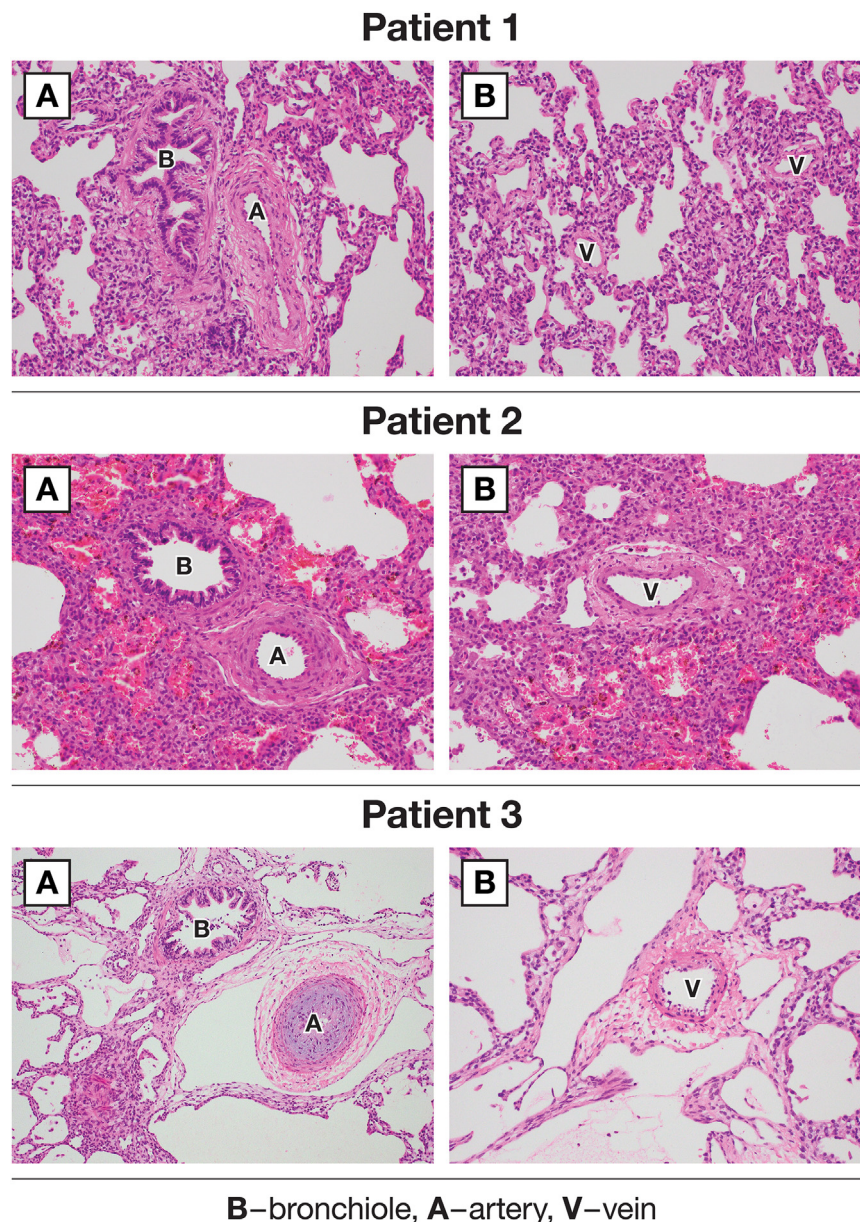


FIGURE 3. Pulmonary tissue of 3 consecutive patients with hematoxylin and eosin staining showing bronchioles and pulmonary arteries (A) and pulmonary veins (B) for each patient. In patient 1, both (A) and (B) show normal histology in this patient with unobstructed supracardiac total anomalous pulmonary venous drainage (TAPVD) and nonurgent repair. For patient 2, (A) shows mild media hypertrophy in the artery and (B) shows normal vein histology. This patient had an obstructed infracardiac TAPVD necessitating preoperative intubation and urgent repair. For patient 3, (A) shows severe media hypertrophy in the artery, resulting in an almost obliterated vessel lumen, whereas (B) shows no abnormalities in the vein. This patient had a severely obstructed supracardiac TAPVD necessitating emergent surgery with preoperative cannulation for extracorporeal membrane oxygenation. B, Bronchiole; A, artery; V, vein.

to look for early changes in the vasculature. Among these 3 patients, in both patients with obstructed TAPVD, the pulmonary arteries demonstrated mild to severe media hypertrophy, suggesting early changes in PAH. This suggests that some neonates have pulmonary artery disease early in life, which should be considered, particularly in patients with obstructed drainage. Those patients could potentially

benefit from early treatment of PHT once residual pulmonary venous obstruction has been ruled out and a wide confluence anastomosis has been confirmed. This is particularly important because postoperative pulmonary venous obstruction itself is a risk factor for mortality, and residual obstruction should be addressed early.^{20,21} However, media hypertrophy in the pulmonary arteries could explain the

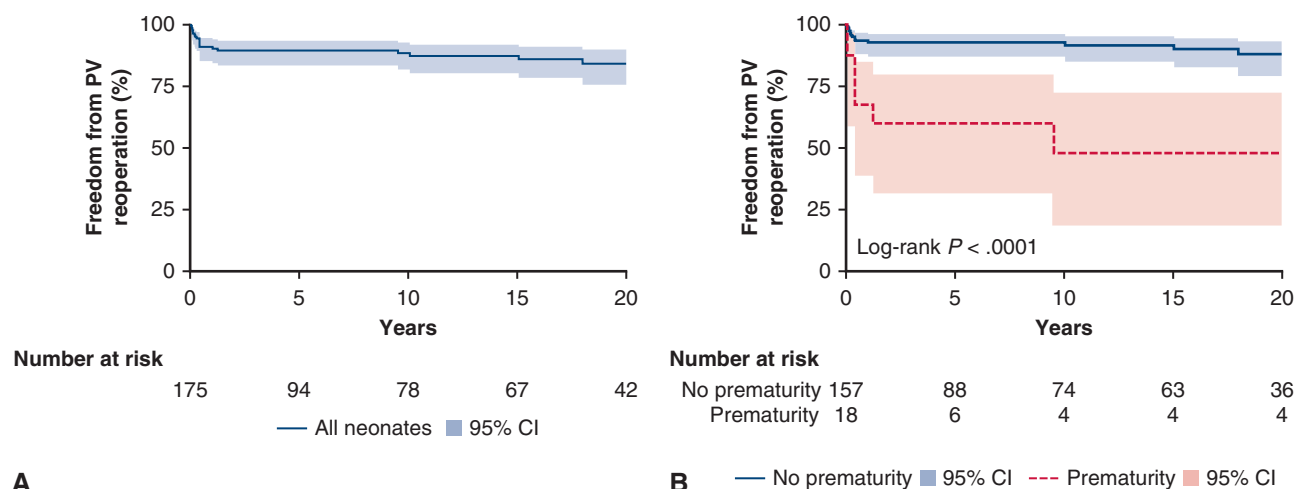


FIGURE 4. Kaplan-Meier estimated freedom from pulmonary vein (PV) reoperation for all neonates (A) and comparing patients born prematurely and born at term (B). Shaded areas represent 95% confidence bands. CI, Confidence interval.

observed beneficial effects of nitric oxide use in the postoperative course of patients with obstructed TAPVD.^{10,22} Although it is unclear from our data how well those patients with pulmonary artery disease respond to medical treatment and if the changes in the pulmonary vasculature are reversible, this might be a future treatment target to further improve outcomes after neonatal TAPVD repair. Therefore, routine lung biopsy at time of repair could help identify patients with early pulmonary artery disease and trigger timely medical treatment. Further investigations are needed to understand how many patients are affected by early changes and whether preemptive treatment might be warranted.

Limitations

This study is limited by its retrospective design. The histopathological results came from a highly selected subset of patients. Biopsy was performed mostly due to failure to progress in the absence of residual obstruction. Furthermore, autopsy results from deceased patients were included. Therefore, it is unclear how many patients are affected by those changes, and whether these changes are present from the beginning or develop later. Unfortunately, in this study we could not analyze the effects of PAH medication on outcome.

CONCLUSIONS

In our cohort, survival after simple neonatal TAPVD repair did not improve over time. Mortality occurred mainly within the first year of life, after which long-term survival was excellent. Urgency of surgery and persistent PHT were risk factors for mortality. Lung biopsy could help identify patients with evolving PAH and guide new treatment modalities to improve survival.

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.

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