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Pulsatile Glenn as long-term palliation for single ventricle physiology patients

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Abstract

Objective: There are limited studies analyzing pulsatile Glenn as a long-term palliation strategy for single ventricle patients. This study sought to determine their outcomes at a single institution.

Design: A retrospective review was performed.

Setting: Study performed at a single pediatric hospital.

Patients: All single ventricle patients who underwent pulsatile Glenn from 1995 to 2016 were included.

Outcome measures: Pulsatile Glenn failure was defined as takedown, transplant, or death. Further palliation was defined as Fontan, 1.5, or biventricular repair. Risk factors were assessed by Cox multivariable competing risk analyses.

Results: Seventy-eight patients underwent pulsatile Glenn at age 9 months (interquartile range, 5-14). In total, 28% had heterotaxy, 18% had a genetic syndrome, and 24% had an abnormal inferior vena cava. There were 3 (4%) perioperative mortalities. Further palliation was performed in 41 (53%) patients with a median time-to-palliation of 4 years (interquartile range, 3-5). Pulsatile Glenn failure occurred in 10 (13%) patients with 8 total mortalities. Five- and 10-year transplant-free survival were 91% and 84%, respectively. At a median follow-up of 6 years (interquartile range, 2-8), 27 patients (35%) remained with PG (age 7 years [interquartile range, 3-11], oxygen saturation 83% ± 4%). Preoperative moderate-severe atrioventricular valve regurgitation (AVVR) (hazard ratio 7.77; 95% confidence interval 1.80-33.43; P =.005) and higher pulmonary vascular resistance (hazard ratio 2.59; 95% confidence interval 1.08-6.15; P =.031) were predictors of pulsatile Glenn failure after adjusting for covariates. Reaching further palliation was less likely in patients with preoperative moderate-severe AVVR (hazard ratio 0.22, 95% confidence interval 0.08-0.59; P =.002).

Conclusion: Pulsatile Glenn can be an effective tool to be used in challenging circumstances, these patients can have a favorable long-term prognosis without reducing their suitability for further palliation.

KEYWORDS

cavopulmonary connection, congenital heart disease, single ventricle

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1 | INTRODUCTION

The bidirectional Glenn (BDG) procedure or bidirectional cavopulmonary anastomosis is commonly performed as an intermediate palliative step for single ventricle patients prior to the creation of the Fontan procedure or total cavopulmonary connection.[1] However, BDG has been associated to secondary effects such as pulmonary arteriovenous malformations due to lack of hepatic blood flow into the lungs,[2] decrease in pulmonary artery (PA) growth,[3] and development of aortopulmonary collaterals.[4] Reported advantages of maintaining an additional source of pulmonary blood flow (APBF) include increased PA size,[5] protection of the pulmonary vascular bed,[6] and delaying the Fontan procedure.[7] When APBF is achieved through a patent right ventricular outflow tract, a potential advantage of this "pulsatile Glenn" (PG) include the decrease in development of pulmonary arteriovenous malformations by allowing prograde delivery of hepatic blood flow into the lungs.[8,9]

The actual benefits and potential adverse effects of PG are still a matter of debate.[7,10] At our institution, PG has been used to leave APBF for patients with associated comorbidities (eg, systemic venous anomalies, genetic syndromes) that may make them suboptimal Fontan candidates in the future. Some authors have raised the idea of using the PG as a long-term palliation[2,7,11] and we have anecdotally observed patients achieve long-term survival with few comorbidities. The goal of this study was to characterize the cohort of patients undergoing PG at our institution, define their long-term prognosis and management options, and determine the risk factors for its failure.

2 | METHODS

All patients who underwent a BDG (n = 708) at Texas Children's Hospital from January 1995 to April 2016 were retrospectively reviewed. From this cohort, only patients that had an APBF achieved through a patent right ventricular outflow tract (n = 78) were included. Demographic and clinical data were obtained by retrospective review of medical records, operative reports, and clinic notes. Follow-up was obtained by review of clinic notes and telephone calls to patients, families, and referring physicians. The study was approved by the Institutional Review Board at Baylor College of Medicine and informed consent was waived.

At our institution, the decision to perform a PG is made by the surgeon and cardiologist after assessing the anatomy and patient's risk factors (Figure 1). The reasons to maintain right ventricular outflow patency are to delay the next procedure while maintaining viable surgical alternatives in marginal Fontan candidates, to increase pulmonary blood flow, and to potentially prevent pulmonary arteriovenous malformations. It is routine practice to place a single-lumen catheter in the internal jugular vein at the beginning of a BDG or PG procedure to measure PA pressures at the end of the procedure. The line is generally removed on postoperative day 1. BDG pressure was defined as the first recorded PA pressure on arrival to the intensive care unit.

Echocardiographic data such as atrioventricular valve regurgitation (AVVR) and ventricular dysfunction were collected from the last transthoracic echocardiogram before surgery, at the time of discharge, and at last PG follow-up, defined as (1) before further palliation (n = 41) or (2) at last follow-up (n = 27). AVVR and ventricular dysfunction were classified as none-mild or moderate-severe. Abnormal inferior vena cava was defined as any of the following: left-sided, an interrupted drainage with or without azygos or hemiazygos continuation, or a separate hepatic vein drainage.

Cardiac catheterization data (ie, PA pressure, PA oxygen saturation, pulmonary vascular resistance (PVR), and pulmonary flow:systemic flow (Qp:Qs) ratio) were collected at the pre-PG period from 59 patients at a median 3 months (Interquartile Range (IQR), 1-5) before surgery, and from the last catheterization with a PG physiology (n = 56) at a median 3 years (IQR, 2-5) after surgery. Of note, the institutional practice is to selectively perform catheterization studies prior to BDG.

Two mutually exclusive primary outcomes were defined: (1) *further palliation* (ie, patients who underwent a Fontan palliation, 1.5

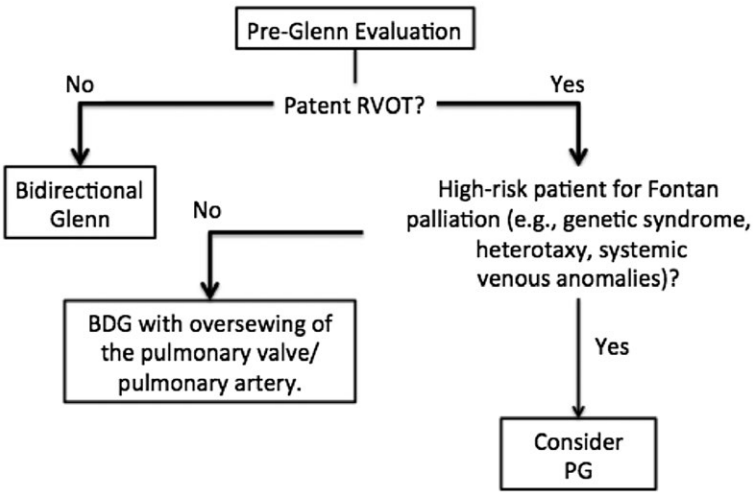

FIGURE 1 Pulsatile Glenn pathway. Abbreviations: BDG, bidirectional Glenn; PG, pulsatile Glenn; RVOT, right ventricular outflow tract

ventricular, or a biventricular repair); (2) *failure* (ie, patients who underwent takedown of the PG, transplantation, or death).

Secondary outcomes included transplant-free survival, the development of pulmonary arteriovenous malformations, and the development of perioperative and long-term complications. Complications included nosocomial infections (ie, pneumonia, surgical site infection), need for mechanical circulatory support, pleural effusion requiring intervention or ≥14 days of chest tube drainage, pericardial effusion requiring intervention, thromboembolic events, acute ischemic stroke, seizures, and arrhythmias requiring medical management or placement of a permanent pacemaker.

2.1 | Statistical analysis

Categorical variables were analyzed using Fisher's test or chi-square test, as appropriate. The independent-samples Mann-Whitney U test and Wilcoxon signed-rank test were performed for continuous and ordinal variables, as appropriate.

The risk of failure and further palliation was determined using competing risks analyses. Univariable analyses were performed using Gray's test or a univariable Cox model, as appropriate. Multivariable Cox proportional hazards models were performed including the significant variables after univariate analysis. The results of the competing risk analyses are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Transplant-free survival was estimated using the Kaplan-Meier survival function estimates.

All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, North Carolina). Categorical data are expressed as frequencies (percentages), continuous data are expressed as medians and IQR unless otherwise specified. A P value <.05 was determined to be statistically significant.

3 | RESULTS

The cohort included 78 patients (37 females, 47%) with a median age at surgery of 9 months (IQR, 5-14). A total of 14 (18%) patients had a genetic syndrome, 22 (28%) had heterotaxy, 15 (19%) had dextrocardia, and 19 (24%) had an abnormal inferior vena cava (10 separate hepatic venous drainage, 6 left sided inferior vena cava return (5 with levocardia), and 3 interrupted inferior vena cava; 16 (84%) had heterotaxy). The demographic characteristics are shown in Table 1.

Prior to PG, 35 (45%) had a PA band, 36 (46%) had native right ventricular outflow tract obstruction, 6 (7%) had both, and 1 (1%) had tricuspid valve stenosis and right ventricular hypoplasia. Thirteen (17%) had a modified Blalock-Taussig shunt and 2 (3%) had previously been intervened due to pulmonary atresia (ie, pulmonary valvotomy and pericardial patch augmentation of outflow tract; radio-frequency perforation and outflow tract stenting). On preoperative echocardiography, 6 (7%) patients had moderate-severe ventricular dysfunction and 12 (15%) had moderate-severe AVVR.

TABLE 1 Demographic characteristics of the overall cohort (N = 78)

Characteristics	N (%)
Age, months, median (interquartile range)	9 (5-14)
Gender	
Female	37 (47)
Fundamental diagnoses	
CAVSD with associated	
DORV	23 (29)
D-TGA	1 (1)
Unbalanced isolated CAVSD	
Trisomy 21	9 (12)[a]
No genetic syndrome	1 (1)
L-TGA/Ebstein's anomaly	1 (1)
D-TGA/Multiple VSDs	3 (4)
Double inlet left ventricle	8 (10)
DORV	
Remote VSD	9 (12)
Subpulmonary VSD	2 (3)
Subaortic VSD	1 (1)
Doubly committed VSD	1 (1)
DORV/mitral atresia or stenosis	5 (6)
DORV/ventricular inversion	7 (9)
Tricuspid atresia	6 (8)
PA-IVS status post-RVOT opening	2 (2)
Genetic anomalies	
Down syndrome	10 (13)
Other genetic syndromes[b]	2 (3)
Nonsyndromic chromosomal gains	2 (3)
Anatomic abnormalities	
Heterotaxy	22 (28)
Dextrocardia	15 (19)
AIVC	19 (24)
Ventricular dominance	
Right	26 (33)
Left	27 (35)
Biventricular	25 (32)

Abbreviations: AIVC, abnormal inferior vena cava; CAVSD, complete atrioventricular septal defect; DORV, double outlet right ventricle; PA-IVS, pulmonary atresia and intact ventricular septum; RVOT, right ventricular outflow tract; TGA, transposition of the great arteries; VSD, ventricular septal defect.

[a]Seven (78%) were left ventricular dominant and 2 (22%) were right ventricular dominant.

[b]DiGeorge syndrome and Opitz C syndrome.

Preoperative hemodynamic evaluation was available in 59 (76%) patients. Preoperative PVR for the entire cohort was 1.8 Wood units/m^2 (IQR, 0.6-2.5), PA pressure was 16 mm Hg (IQR, 14-20), and Qp:Qs was 1.1 (IQR, 0.7-1.9).

Pulmonary blood flow was controlled through a PA band alone in 35 (45%) patients, native right ventricular outflow tract obstruction in 21 (27%), both in 21 (27%), and 1 (1%) had enough prograde flow limitation due to tricuspid stenosis and right ventricular hypoplasia and did not require intervention. Thirty-three (42%) patients underwent concomitant intracardiac repair: 17 atrial septectomies, 9 atrioventricular valve repairs, 6 total anomalous pulmonary venous return repairs, 6 subaortic resections, 3 pulmonary vein stenosis repairs, and 4 other type of procedures (ie, enlargement of a ventricular septal defect, right ventricular outflow tract resection, modified Maze procedure). All modified Blalock-Taussig shunts were taken down and pulmonary arterioplasties were performed in 10 patients.

The median cardiopulmonary bypass time was 100 minutes (IQR, 66-148); 44 (56%) required cross-clamp with a median duration of 51 minutes (IQR, 35-75); and 18 (23%) required circulatory arrest with a median of duration of 23 minutes (IQR, 12-29). PG in 3 (4%) patients consisted of a Kawashima connection (interrupted IVC with azygos or hemiazygos continuation) and 15 (19%) had bilateral cavopulmonary anastomoses.

Glenn pressure on arrival to the intensive care unit was available for 71 (91%) patients, with a median of 15 mm Hg (IQR, 13-19). Median intensive care unit length of stay was 3 days (IQR, 1-34), median postoperative hospitalization was 7 days (IQR, 6-11), median intubation duration was 1 day (IQR, 0-1), and median thoracostomy duration was 3 days (IQR, 2-5). Fourteen (18%) patients were extubated in the operating room; these patients did not have a significantly different Glenn pressure (median 15 [IQR, 13-17] mm Hg) compared to nonextubated patients (median 15 [IQR, 13-19] mm Hg) (P =.768). The Glenn pressure on postoperative day 1 was a median of 15 (IQR, 12-16) mm Hg, which was not statistically different from the Glenn pressure on arrival (P =.089). A total of 23 (29%) patients had postoperative complications (Table 2). Mean oxygen saturation at discharge was 86% ± 5%.

Follow-up cardiac catheterization was available for 56 (72%) patients at the PG stage at a median of 3 years (IQR, 2-5) after surgery. Three (5%) of these patients had pulmonary arteriovenous malformations and 31 (55%) had collaterals; 8 patients underwent collateral coiling. Pulmonary arteriovenous malformations were more common in patients with heterotaxy (P =.025), dextrocardia (P =.004), and abnormal inferior vena cava (P =.013).

TABLE 2 Complications in the perioperative period

Perioperative outcomes/complications	N (%)
Perioperative outcomes	
PG takedown	1 (1)
Perioperative mortality	3 (4)
Perioperative complications	
Nosocomial infection[a]	8 (10)
Pleural effusion	7 (9)
Arrhythmia[b]	6 (8)
Deep vein thrombosis	2 (3)
ECMO usage	1 (1)
Acute ischemic stroke	1 (1)
Seizures	1 (1)
Mediastinal hemorrhage	1 (1)
Iatrogenic diaphragmatic hernia	1 (1)
Pericardial effusion	1 (1)

Abbreviations: ECMO, extracorporeal membrane oxygenation; PG, pulsatile Glenn.

[a]Two of these infections were incision site infections.

[b]Supraventricular tachycardia (n = 1), second-grade atrioventricular block (n = 1), atrial tachycardia (n = 2), isolated junctional rhythm (n = 1), and junctional rhythm with first-grade atrioventricular block (n = 1).

3.1 | Further palliation and failure

During follow-up, 41 (53%) patients underwent further palliation: Fontan completion (n = 37), 1.5 ventricular repair (n = 3), and biventricular repair (n = 1). Median time-to-palliation was 4 years (IQR, 2-8). Overall, 10 (13%) patients had PG failure: 8 died (3 [4%] perioperative and 5 [6%] late mortalities), 3 (4%) had PG takedowns, and 1 (1%) required heart transplant. Median time-to-failure was 6 months (IQR, 1 month-5 years). The 5 late mortality cases occurred at median of 14 months (range, 2 months-9 years) postoperatively. There were no mortalities after the further palliation procedures. One patient underwent PG takedown perioperatively with reconstruction of the superior vena cava and loosening of the PA band; currently followed for 17 months. The remaining 2 takedowns occurred after 2 months and 9 months, both patients died 8 and 3 months after takedown, respectively. The heart transplantation occurred after 10 years due to progressive ventricular dysfunction.

At a median follow-up of 6 years (IQR, 2-8 years), 35% (n = 27) remained with the PG with a median age of 7 years (IQR, 3-11; range, 6 months-18 years). These patients had a mean oxygen saturation of 83% ± 4%, and 74% (n = 20) were New York Heart Association functional class I at last follow-up. The different outcomes of the cohort are displayed in the competing risk analysis in Figure 2. Overall 5- and 10-year transplant-free survival was 91% (95% CI 84%-98%) and 84% (95% CI 73%-96%), respectively (Figure 3). One (1%) patient, who remained with a PG circulation, presented with an acute ischemic stroke 10 years after surgery.

A total of 21 (27%) patients had an exercise test performed at a median of 10 (IQR, 8-12) years after the PG; 14/21 (67%) after a further palliation and 7/21 (33%) with a PG circulation. Patients who underwent further palliation achieved a maximum METS median of 13 (IQR, 11-13) compared to a median of 9 (5-10) in patients who continued with the PG circulation (P =.004). Patients who underwent further palliation achieved a median heart rate of 85% predicted (IQR, 81%-97%) compared to a median of 78% predicted (IQR, 60%-82%) in patients who remained with the PG circulation (P =.052).

On univariate analysis, older age at PG operation (P =.037), preoperative moderate-severe AVVR (P <.001), Down syndrome (P =.044), and higher preoperative PVR (P =.042) were significant risk factors for failure (Table 3). On preoperative hemodynamic

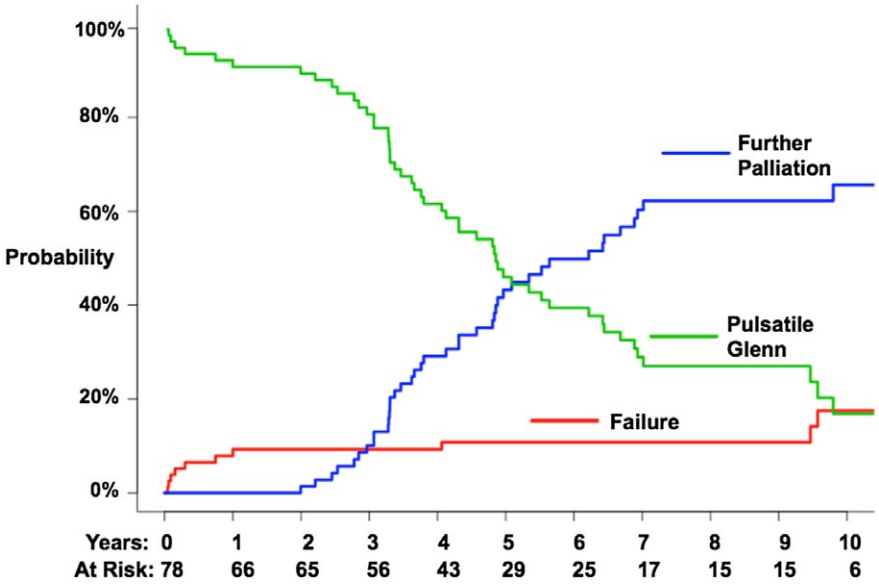

FIGURE 2 Competing risk analysis. Cumulative incidence of further palliation (Fontan circulation, 1.5 or biventricular repair) and failure (death, transplantation, or takedown); and the survival curve of remaining pulsatile Glenn circulation patients. Abbreviation: CI, cumulative incidence [Colour figure can be viewed at wileyonlinelibrary.com]

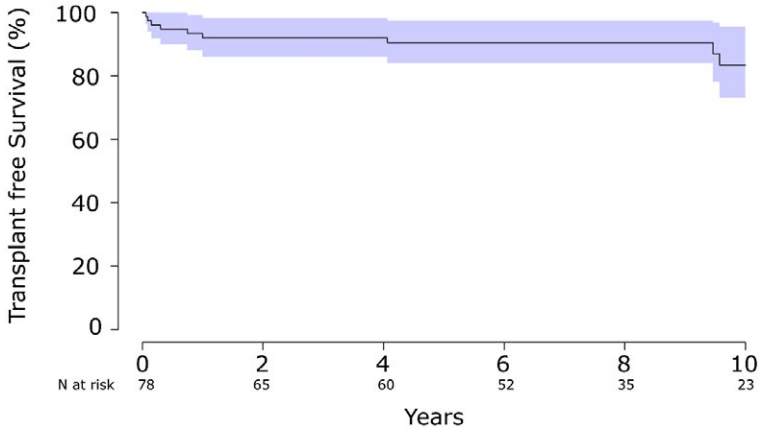

FIGURE 3 Transplant-free survival [Colour figure can be viewed at wileyonlinelibrary.com]

evaluation, patients who eventually had a failed PG, were further palliated, and maintained a PG at last follow-up had a preoperative PVR median of 2.6 (IQR, 2.3-3.1), 1.8 (IQR, 1.3-2.5), and 1.4 (IQR, 0.9-2.2) Wood units/m^2, respectively (P =.033); a preoperative PA pressure of 19 (IQR, 17-21), 15 (IQR, 14-19), and 15 (IQR, 13-21) mm Hg, respectively (P =.248); and a preoperative Qp:Qs of 0.8 (IQR, 0.7-1.5), 1.2 (IQR, 0.8-1.9), and 0.9 (IQR, 0.7-2.2), respectively (P =.784). Preoperative moderate-severe AVVR was present in 60%, 7%, and 11% of cases which eventually failed, were further palliated, or remain with PG as current palliation, respectively.

After adjusting for significant covariates, (Table 4) preoperative moderate-severe AVVR (HR 7.77; 95% CI 1.81-33.43; P =.006) and high PVR (HR 2.59; 95% CI 1.09-6.16; P =.031) remained significant predictors of PG failure. Preoperative moderate-severe AVVR (HR 0.22, 95% CI 0.08-0.59; P =.009) was the only significant risk factor for not reaching further palliation on a Cox regression model.

4 | DISCUSSION

For decades, the Fontan procedure has been considered the last stage in palliation for single ventricle patients.[1,12] However, we believe that not every patient is necessarily best suited with a Fontan circulation. Patients may have certain conditions that may make them nonideal Fontan candidates such as high mean PA pressure (>15 mm Hg), high PVR, small branch PAs, presence of vascular abnormalities, chronic lung disease, or inadequate ventricular function.[2,3,13,14]

Our results demonstrate that a PG can successfully bridge patients to Fontan or to a complete/partial anatomical repair or function as an indefinite long-term alternative for patients who remain stable and are not ideal Fontan candidates. The latter is evidenced by how one-third of patients continue being palliated with a PG at a median age of 7 years (IQR, 3-11), with the oldest patient being 18 years old. Most of these patients are clinically stable: 74% are asymptomatic and have a mean oxygen saturation of 84% ± 4%. This

TABLE 3 Univariate analysis of relationship between risk factors and primary outcomes

	PG Failure			Further palliation		
Risk factors	**Failure N (%)**	**No failure N (%)**	***P* value**	**Palliation N (%)**	**No palliation N (%)**	***P* value**
Heterotaxy	1 (10)	21 (31)	.097	12 (29)	10 (27)	.393
Any genetic anomaly	3 (30)	11 (16)	.240	4 (10)	10 (27)	.069
Down syndrome	3 (30)	7 (10)	**.045**	3 (7)	7 (19)	.110
Dextrocardia	2 (20)	13 (19)	.912	6 (15)	9 (24)	.064
AIVC drainage	2 (20)	17 (25)	.710	8 (20)	11 (30)	.160
Right ventricular dominance	5 (50)	22 (32)	.243	11 (27)	16 (43)	.068
Moderate-severe AVVR pre-Glenn	6 (60)	6 (9)	**<.001**	3 (7)	9 (24)	**.009**
Ventricular dysfunction	1 (10)	5 (7)	.503	3 (7)	3 (8)	.964
Concomitant PA reconstruction	7 (70)	10 (15)	.290	10 (24)	9 (24)	.470
Concomitant cardiac repair	7 (70)	38 (56)	.171	22 (54)	24 (65)	.063
Age, months	13 (10–18)	8 (5–14)	**.037**	8 (5–11)	10 (6–16)	.198
Preoperative PVR	2.6 (2.3–3.1)	1.6 (1.1–2.3)	**.042**	1.8(1.3–2.5)	1.7 (0.9–2.5)	.151

Bold values indicate statistical significance. Abbreviations: AVVR, atrioventricular valve regurgitation; AIVC, abnormal inferior vena cava; PA, pulmonary artery; PVR, pulmonary vascular resistance.

TABLE 4 Relationship between risk factors and primary outcomes

	PG Failure			Further palliation		
Risk factors	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age at surgery (per month)	1.01	0.96–1.04	.783	—	—	—
AVVR pre-PG	7.77	1.81–33.43	**.005**	0.22	0.08–0.59	**.003**
Preoperative PVR (per wood unit/m^2)	2.59	1.09–6.16	**.031**	—	—	—
Down syndrome	0.58	0.0–835.84	.884	—	—	—

Bold values indicate statistical significance. Abbreviations: AVVR, atrioventricular valve regurgitation; CI, confidence interval; HR, hazards ratio; PG, pulsatile Glenn; PVR, pulmonary vascular resistance.

finding is supported by previous reports of adequate oxygenation levels with PG.[2,16,17] The additional pulmonary blood flow may allow them to have more acceptable oxygen saturations in the long-term compared to a traditional BDG.[21]

Furthermore, a patent right ventricular outflow tract maintains an anatomy conductive for further palliation. One (1%) underwent a biventricular repair and 3 (4%) underwent 1 ½ ventricular repairs. Additionally, the Fontan operation can be significantly delayed along with its potential consequences such as liver failure, thromboembolic events, bleeding, protein-losing enteropathy, and arrhythmias.[10,11]

The creation of PG did not completely prevent the formation of pulmonary arteriovenous malformations, with a 4% cumulative incidence. The idea that the incidence of pulmonary arteriovenous malformations would have been different if these patients had undergone a traditional BDG is still controversial.[21] The incidence of arteriovenous malformations in series of patients after BDG has been reported to be 0%-3%.[8,10,16,18,22,23]

At our institution, PG is considered the preferred method to provide APBF to single ventricle patients with anomalous systemic venous anatomy and/or who are considered poor future Fontan candidates. It is unclear whether PGs are a better alternative than BDG for patients with normal venous anatomy and no other comorbidities. Previous groups have attempted to determine how APBF influences late and overall mortality compared to BDG. Most groups have found comparable overall mortality between patients with APBF and those without.[5,10,11,16-19,22] Of note, most cohorts found in the literature had a mixed source of APBF.[5,8,10,11,16-19] Given the findings of this study, this approach could represent a feasible temporary alternative for single ventricle patients in challenging circumstances given the relatively

low incidence of complications and mortality, the latter which is comparable to the results of previous PG cohorts[2,16,17] and BDG cohorts.[28,29] This study was focused on describing the outcomes of marginal Fontan candidates managed with PG instead of a traditional BDG. It was decided not to include traditional BDG patients because we consider them a relatively different population to include in a single study.

As expected, preoperative moderate-severe AVVR and higher PVR were predictive risk factors for PG failure.[31,32] Our group previously described how a PVR >3 Wood units/m^2 is associated with an increased mortality in single ventricle patients. Of note, this previous study also showed how Down syndrome was not an independent risk factor for mortality when accounting for PVR.[33]

This study has several limitations, mostly related to its retrospective and descriptive nature. At our institution, the PG repair is only performed in specific conditions, which creates a selection bias and makes extrapolation of our results challenging. However, PG is usually performed in the cohort that could be considered higher risk (eg, heterotaxy, venous anomalies, genetic syndromes).[34] Results may, therefore, be better for lower risk cohorts. The lack of a comparable control group does not allow us to make conclusions regarding the potential use of PG as routine palliation in patients without associated comorbidities. Furthermore, even though patients seem to have adequate oxygen saturations and functional status years after their PG, exercise testing was not consistently performed and it can be expected that patients may have lower exercise tolerance than fully saturated patients following a nonfenestrated Fontan procedure.

5 | CONCLUSION

PG can be an effective tool to be used in challenging circumstances. Patients who remain clinically stable can be followed indefinitely as a long-term palliation. The creation of a PG does not preclude further palliation and may serve as an adequate intermediate step in patients in which a biventricular, 1.5 repair, or a Fontan operation may be performed at a later stage, further delaying the Fontan circulation and its potential complications. Moderate-severe AVVR and a high PVR prior to the PG repair are the main predictors of a negative prognosis in these complex single ventricle patients.

AUTHOR CONTRIBUTIONS

MACP study concept, study design, data collection, drafted and wrote the manuscript, performed data interpretation and analysis.

RZV data collection and preparation of manuscript.

HZ data analysis.

HAD study design, data interpretation, and preparation of manuscript.

IA data interpretation and preparation of manuscript.

JSH study design and preparation of manuscript.

CDF study concept and design, preparation of manuscript.

CMM data interpretation, study concept and design, and preparation of manuscript. All authors read and approved the last version of the manuscript.

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