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Forty-year survival after Glenn procedure without Fontan procedure in patients with single ventricle

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Key question

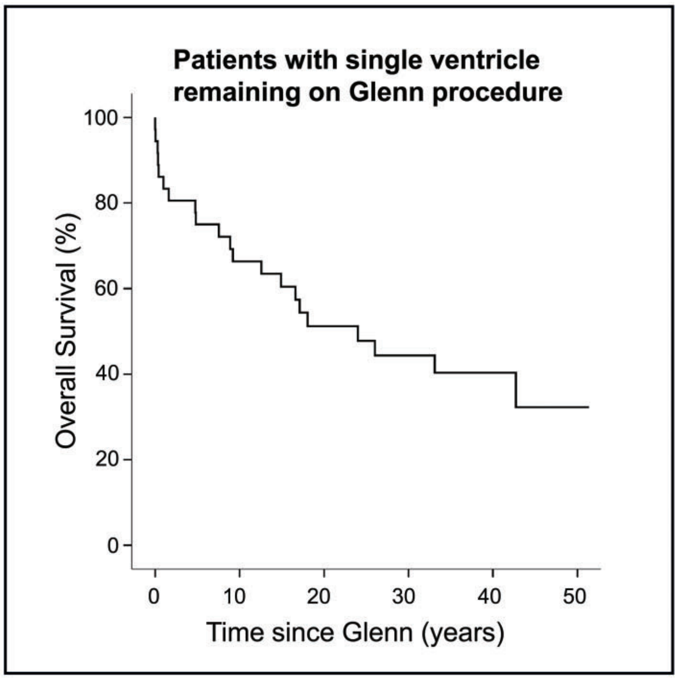
What is the very long-term outcome after the Glenn procedure without Fontan procedure in patients with single ventricle?

Key finding(s)

The 40-year overall survival after the Glenn procedure was 40%. Those with dominant left ventricle had better survival.

Take-home message

Very long-term survival of the entire cohort is not satisfactory. However, some of those with dominant left ventricle can survive long-term.



Abstract

OBJECTIVES: There are no data on long-term outcomes beyond 30 years after the Glenn procedure without the subsequent Fontan procedure in patients with single-ventricle physiology. Hence, this study aimed to clarify the very long-term outcomes of these patients.

METHODS: This single-centre, retrospective cohort study investigated the clinical outcomes of patients with single-ventricle physiology who underwent the Glenn procedure between 1970 and 1999. Those who underwent the subsequent Fontan procedure were excluded. The primary outcome was all-cause death. The secondary outcome was a composite of all-cause death, arrhythmic events, neurological events or infective endocarditis. The prognostic factors associated with the long-term outcomes were also evaluated.

RESULTS: In total, 36 patients were enrolled (median age at Glenn procedure: 6.2 years, 56% male). During a median follow-up of 17.6 years (interquartile range: 6.1–33.4), 21 patients died and 29 experienced the composite outcome. The 20-, 30- and 40-year overall survival after the Glenn procedure was 51.2%, 44.4% and 40.3%, respectively. The 20-, 30- and 40-year event-free survival was 36.0%, 25.5% and 14.5%, respectively. Patients with dominant left ventricular morphology had better overall survival than those with dominant right ventricular morphology (hazard ratio: 0.24, 95% confidence interval: 0.08–0.76, $P = 0.014$). None of the patients had liver cirrhosis but 1 had protein-losing enteropathy.

CONCLUSIONS: The 40-year overall survival after the Glenn procedure without the subsequent Fontan procedure in patients with single-ventricle physiology was 40.3%. Dominant left ventricular morphology may be associated with better long-term overall survival than dominant right ventricular morphology.

Keywords: Single ventricle • Glenn procedure • Cavopulmonary shunt • Fontan procedure • Survival

ABBREVIATION

IQR	Interquartile range

INTRODUCTION

The Glenn procedure, i.e. superior cavopulmonary anastomosis, is currently positioned as an intermediate palliative procedure prior to the Fontan procedure for patients with single-ventricle physiology [1]. The Fontan procedure, which is regarded as the definitive palliative procedure for such patients, can separate pulmonary and systemic blood flow completely by directing total systemic venous return to the pulmonary artery. Advances in surgical techniques have improved the survival of patients undergoing the Fontan procedure [2, 3]. However, noncardiac complications occurring late after the Fontan procedure, such as liver cirrhosis and protein-losing enteropathy, have raised concerns about the quality of life and their impact on long-term survival [3–6].

Clinicians occasionally encounter patients with single-ventricle physiology, particularly those with dominant left ventricular morphology, who have survived for a long time after the Glenn procedure alone and remain clinically stable without liver cirrhosis or protein-losing enteropathy. Some previous studies showed that patients remaining on a Glenn procedure had favourable long-term outcomes [7–9] and survival comparable to patients who underwent the subsequent Fontan procedure [10, 11]. Furthermore, neither liver cirrhosis nor protein-losing enteropathy was present in patients remaining on a Glenn procedure [8, 11].

Data on long-term outcomes of patients with single-ventricle physiology remaining on a Glenn procedure are limited to 20–30 years of follow-up. More long-term outcome data would be useful for clinical decision-making, particularly in paediatric patients. Therefore, we investigated the long-term outcomes up to 40 years after the Glenn procedure without the subsequent Fontan procedure in patients with single-ventricle physiology. Furthermore, we assessed factors associated with the long-term outcomes in these patients.

PATIENTS AND METHODS

Ethical statement

The Ethics Committee of Tenri Hospital approved the protocol on 6 August 2021 (approval number: 1219) and waived the requirement for written informed consent owing to the retrospective nature of the study design.

Study population

This single-centre, retrospective cohort study included patients with single-ventricle physiology who underwent the Glenn procedure at Tenri Hospital (Tenri, Japan) between January 1970 and December 1999. The Glenn procedure included classic Glenn, bidirectional Glenn and bilateral bidirectional Glenn procedures. The databases of paediatric cardiology and cardiovascular surgery at our hospital were reviewed to identify all patients who underwent the Glenn procedure. This study excluded patients who underwent the Glenn procedure as a one-and-a-half ventricle repair and those who underwent the subsequent Fontan procedure after the Glenn procedure.

Data collection

Data on patient demographic, morphological and clinical characteristics at the time of Glenn procedure were collected from paper-based medical records. Diagnoses were made by experienced paediatric cardiologists on the basis of the findings of cardiac catheterization, including ventricular angiography. Ventricular dominance was classified as right ventricular, left ventricular or biventricular morphology based on the description in the medical records. Surgical information, including data on prior palliative procedures, concomitant procedures at the time of Glenn procedure and subsequent surgeries after the Glenn procedure, was obtained from the paper-based or electronic operation records. Arterial oxygen saturation, mean pulmonary artery pressure and dominant ventricular end-diastolic pressure were determined from the records of cardiac catheterization, which was performed before the Glenn procedure. Outcomes were also determined from the paper-based or electronic medical records. Data on the outcomes of patients who were not followed up at our hospital were collected in October 2021 by contacting the referring physicians, patients or their relatives via mailed questionnaires or telephone interviews.

Outcomes

The primary outcome was all-cause mortality. Operative mortality was defined as all-cause death within 30 days of the Glenn procedure or before hospital discharge. Late mortality was defined as all-cause death occurring 30 days after the procedure and after hospital discharge. The secondary outcome was a composite of all-cause death, arrhythmic events, neurological events or infective endocarditis. An arrhythmic event was defined as arrhythmia requiring resuscitation, electrical cardioversion, radiofrequency catheter ablation or permanent pacemaker implantation. A neurological event was defined as a stroke or brain abscess that was diagnosed based on clinical symptoms and findings of brain imaging, such as computed tomography and/or magnetic resonance imaging. Early postoperative electrical cardioversion (within 14 days of cardiac surgery) was excluded from the secondary outcome analysis because early postoperative arrhythmias are common after cardiac surgery and typically transient.

This study also investigated liver cirrhosis and protein-losing enteropathy, which are well-known complications of the Fontan circulation. Liver cirrhosis was defined based on the morphological changes such as an irregular or nodular surface, blunt margins, parenchymal heterogeneity and caudate lobe hypertrophy on ultrasonography, computed tomography and/or magnetic resonance imaging [5, 12]. Protein-losing enteropathy was defined based on clinical symptoms and laboratory findings of both hypoalbuminemia and elevated faecal alpha-1 antitrypsin [3]. In addition, pulmonary arterio-venous malformations, a well-known complication after the Glenn procedure [13, 14], were assessed using available data on cardiac catheterization including angiography, computed tomography, magnetic resonance imaging and/or contrast echocardiography with agitated saline, which was selectively injected into branch pulmonary arteries during cardiac catheterization [15, 16].

The reasons for not performing the subsequent Fontan procedure were determined from medical records. Detailed information on the current status of patients was obtained.

Statistical analysis

Categorical variables were presented as number and percentage. Continuous variables were presented as mean and standard deviation or median and interquartile range (IQR). Survival was estimated using the Kaplan–Meier method, and differences between groups were assessed by the log-rank test. Patients without evidence of death were censored at the date of the last available follow-up or contact. Overall survival was calculated from the date of the Glenn procedure to the date of all-cause death. Event-free survival was calculated from the date of the Glenn procedure to the date of the first event, which included any of the following: all-cause death, arrhythmic events, neurological events or infective endocarditis. Univariate Cox proportional hazards regression models were used to identify prognostic factors associated with long-term outcomes. Multivariate analysis was not performed because of the small sample size. All statistical analyses were conducted with SPSS 22.0 software (IBM Corp., Armonk, NY, USA). All reported *P*-values were two-tailed, and *P*-values <0.05 were considered statistically significant.

RESULTS

Study population

A total of 52 patients underwent the Glenn procedure at Tenri Hospital between January 1970 and December 1999. Three patients were excluded because they underwent the Glenn procedure as a one-and-a-half ventricle repair and 2 patients were excluded because of lost medical records. Among the remaining 47 patients, 11 patients were excluded because they eventually underwent the Fontan procedure after the Glenn procedure, with a median interval of 8.9 years (IQR: 3.6–15.4). Thus, 36 patients were finally enrolled in this study (Fig. 1). The median follow-up period after the Glenn procedure was 17.6 years (IQR: 6.1–33.4). The 20-, 30- and 40-year follow-up rates were 91.7%, 86.1% and 69.4%, respectively.

Patient characteristics and surgical procedures

Baseline clinical characteristics and surgical details are presented in Table 1. Among 28 patients who underwent the classic Glenn procedure, 6 had a bilateral superior vena cava and underwent ligation of either the left ($n = 5$) or right ($n = 1$) superior vena cava. Thirteen patients (36%) underwent subsequent surgeries after the Glenn procedure. The subsequent surgical procedures were as follows: aortopulmonary shunt ($n = 5$), atrioventricular valve repair ($n = 3$), Blalock–Taussig shunt ($n = 2$), pulmonary valvotomy ($n = 2$), right ventricular outflow tract reconstruction ($n = 2$) and others ($n = 5$).

Operative mortality

Among the 36 patients enrolled in this study, 21 died after the Glenn procedure. Two patients (5.6%) died within 30 days of the procedure or before hospital discharge. One patient died of intractable bleeding on the day of the Glenn procedure; the other died of hypoxic–ischaemic encephalopathy caused by a ventilator-associated event 14 days after the Glenn procedure.

Late outcomes

There were 19 late deaths. None of the patients underwent heart transplantation. The causes of late deaths were as follows: heart failure ($n = 10$); sudden death ($n = 3$); postoperative death due to subsequent surgeries after the Glenn procedure ($n = 3$, atrioventricular valve repair, tricuspid valve replacement and cardiac resynchronization therapy performed 1, 13 and 24 years after the Glenn procedure, respectively); stroke ($n = 1$); ventricular fibrillation ($n = 1$); and unknown cause ($n = 1$). In 4 of the 10 patients who died of heart failure, obstruction ($n = 3$) or stenosis ($n = 1$) of the Glenn shunt was diagnosed before haemodynamic deterioration. The median survival time was 24 years. The 20-, 30- and 40-year overall survival was 51.2%, 44.4% and 40.3%, respectively (Fig. 2A).

A total of 42 clinical events including all-cause death occurred in 29 patients. The clinical events other than all-cause death were as follows: resuscitation from ventricular fibrillation ($n = 2$); electrical cardioversion for atrial tachycardia ($n = 4$) and atrial fibrillation ($n = 1$); radiofrequency catheter ablation for atrial tachycardia ($n = 3$); stroke ($n = 3$); brain abscess ($n = 5$); and infective endocarditis ($n = 3$). The 20-, 30- and 40-year event-free survival was 36.0%, 25.5% and 14.5%, respectively (Fig. 2B).

No patients were diagnosed with liver cirrhosis. One patient was diagnosed with protein-losing enteropathy based on technetium-99m-labeled human serum albumin scintigraphy findings and an elevated faecal alpha-1 antitrypsin clearance 4 years after the Glenn procedure. However, the pressure in the

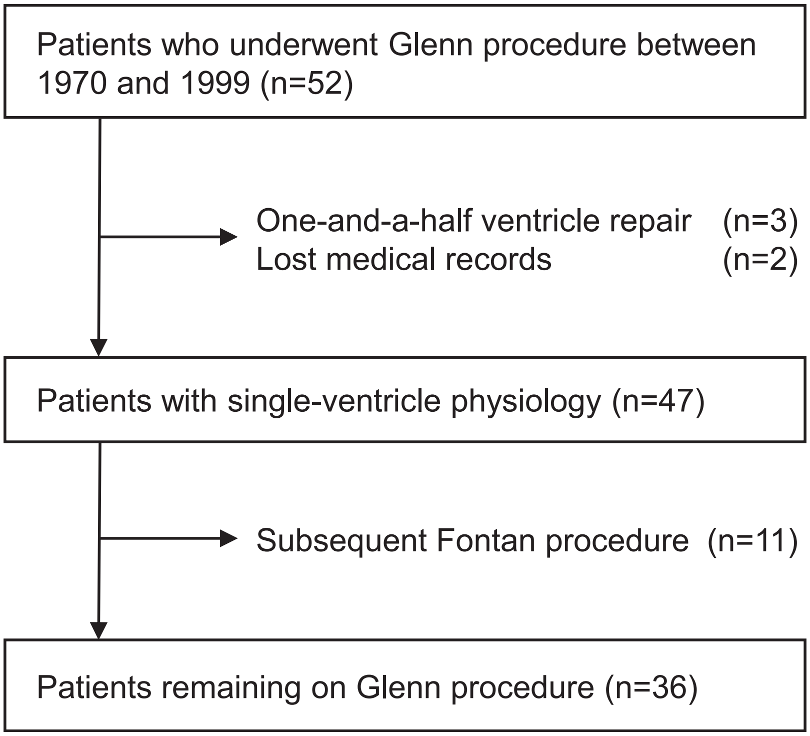


Figure 1: Study flow chart.

inferior vena cava was only 5 mmHg at the time of the diagnosis of protein-losing enteropathy. The patient died of heart failure 14 years after the diagnosis of protein-losing enteropathy.

Six patients (17%) were diagnosed with pulmonary arterio-venous malformations by computed tomography ($n = 2$) or contrast echocardiography ($n = 4$). Pulmonary arterio-venous malformations were present in the right lung in 4 patients after right-sided classic Glenn procedure, in the left lung in 1 patient after left-sided classic Glenn procedure and in both lungs in 1 patient after bidirectional Glenn procedure.

Reasons for not performing the subsequent Fontan procedure

Five patients were unable to undergo the Fontan procedure because of death after the Glenn procedure: operative death in 2 patients and death within 6 months of the Glenn procedure in 3 patients. One patient died from an atrioventricular valve repair performed 1 year after the Glenn procedure. Other reasons included high pulmonary artery pressure ($n = 2$), ventricular systolic dysfunction ($n = 1$), pulmonary atresia with hypoplasia of left pulmonary artery ($n = 2$), lung resection for congenital lung anomaly and consequent left pulmonary vein obstruction ($n = 1$), impaired respiratory function due to thoracic deformity ($n = 1$) and the paediatric cardiologist's decision that it was risky to perform the Fontan procedure ($n = 2$). Reasons for not performing the subsequent Fontan procedure in the remaining 21 patients were not described in the medical records.

Factors associated with long-term outcomes

The results of univariate Cox proportional hazards regression models for overall survival are shown in Table 2. Patients with dominant left ventricular morphology had significantly better long-term overall survival than those with dominant right ventricular morphology. The 40-year overall survival was 73.3% for patients with dominant left ventricular morphology, whereas the 20- and 30-year overall survival was 38.5% and 23.1% for patients with dominant right ventricular morphology, respectively (log-rank $P = 0.008$, Fig. 3A). No other factors including the type of Glenn procedure were associated with long-term overall survival in these patients (Table 2 and Fig. 4A).

The results of univariate Cox proportional hazards regression models for long-term event-free survival are shown in Table 3. Patients with dominant left ventricular morphology had significantly better long-term event-free survival than those with dominant right ventricular morphology, although clinical events were commonly observed even in patients with dominant left ventricular morphology. The 20-, 30- and 40-year event-free survival was 49.5%, 41.3% and 24.8% for patients with dominant left ventricular morphology, respectively, whereas the 20-, 30- and 40-year event-free survival was 25.7%, 9.6% and 0% for patients with dominant right ventricular morphology, respectively (log-rank $P = 0.013$, Fig. 3B). No other factors including the type of Glenn procedure were associated with long-term event-free survival in these patients (Table 3 and Fig. 4B).

Current status of patients

Nine patients were confirmed to be alive as of October 2021. Dominant ventricular morphology was right in 2 patients and left in 7 patients. Seven patients underwent the classic Glenn procedure, and 2 patients underwent the bidirectional Glenn procedure. Detailed information on the current status was available in 6 patients (Table 4). Central venous pressure was estimated to be normal in 5 patients and intermediate in 1 patient based on

Table 1: Baseline characteristics and surgical procedures

Variable	Patients ($n = 36$)
Age at Glenn (years)	6.2 (2.8–9.5)
Male	20 (56)
Body weight at birth (g)	3150 (2809–3275)
Body weight at Glenn (kg)	15.6 (11.5–21.9)
Heterotaxy syndrome	11 (31)
Morphological group	
CAVV	13 (36)
DORV	9 (25)
TA	8 (22)
PA/IVS	3 (8)
PA/VSD	1 (3)
ccTGA	1 (3)
DILV	1 (3)
Ventricular dominance	
Right	17 (47)
Left	15 (42)
Biventricular	3 (8)
Undetermined	1 (3)
Haemoglobin (g/dl)	18.9 ± 2.5
Preoperative hemodynamics	
Arterial oxygen saturation (%)	71.4 ± 6.9
Mean pulmonary artery pressure[a] (mmHg)	11.7 ± 2.7
Dominant ventricular end-diastolic pressure[b] (mmHg)	8.1 ± 3.0
Prior palliative procedures	
Blalock–Taussig shunt	3 (8)
Aortopulmonary shunt	3 (8)
Closed transventricular pulmonary valvotomy	1 (3)
Type of Glenn procedure	
Classic Glenn	28 (78)
BDG	4 (11)
Bilateral BDG	4 (11)
Concomitant procedures at Glenn	
Atrioventricular valve repair	4 (11)
Atrial septectomy	2 (6)
Anomalous pulmonary venous connection repair	2 (6)
Others	3 (8)
Contralateral pulmonary blood flow in classic Glenn	
Antegrade	21 (58)
Antegrade and PDA	1 (3)
Antegrade and prior aortopulmonary shunt	1 (3)
PDA	3 (8)
Prior aortopulmonary shunt	1 (3)
Aortopulmonary collateral artery	1 (3)

Categorical variables are presented as number (%) and continuous variables are presented as mean ± standard deviation or median (interquartile range).

[a]Data are available in 13 patients.

[b]Data are available in 35 patients.

BDG: bidirectional Glenn; CAVV: common atrioventricular valve; ccTGA: congenitally corrected transposition of the great arteries; DILV: double-inlet left ventricle; DORV: double-outlet right ventricle; PA/IVS: pulmonary atresia with intact ventricular septum; PA/VSD: pulmonary atresia with ventricular septal defect; PDA: patent ductus arteriosus; TA: tricuspid atresia.

echocardiographic findings of inferior vena cava diameter and its respiratory changes. There were no patients whose central venous pressure was estimated to be high. Of the 6 patients, 3 patients were employed as a full-time worker ($n = 2$) or a part-time worker ($n = 1$).

DISCUSSION

The main results of the present study were as follows: (i) the 20-, 30- and 40-year overall survival after the Glenn procedure without the subsequent Fontan procedure in patients with single-ventricle physiology was 51.2%, 44.4% and 40.3%, respectively; (ii) few patients developed liver cirrhosis or protein-losing enteropathy; and (iii) patients with dominant left ventricular morphology had better long-term overall survival than those with dominant right ventricular morphology.

Long-term overall survival

The long-term overall survival of patients with single-ventricle physiology remaining on a Glenn procedure was not comparable with the previously reported survival of those who underwent the Fontan procedure. A previous cohort study showed that the 20-year overall survival of patients who underwent a lateral tunnel Fontan procedure was 90% [2]. Another cohort study showed that the 32-year overall survival of patients who underwent an extracardiac conduit Fontan procedure was 84% [17]. Since only patients who have survived the period between the Glenn and the Fontan procedure can undergo the Fontan procedure, such bias should be considered when comparing outcomes between patients with and without the Fontan procedure. However, recent studies have reported that operative mortality for the bidirectional Glenn procedure is as low as 0.7–1.8% [18–20] and 1-year survival after the procedure exceeds 90% [19, 21]. Therefore, the strategy of proceeding with the Fontan procedure is likely to be the best option today for patients with single-ventricle physiology.

In the majority of patients in this study, the reasons for not performing the subsequent Fontan procedure were unknown. These patients may not necessarily have been ineligible for the Fontan procedure. Of 30 patients who survived 1 year after the Glenn procedure, only 11 patients eventually underwent the Fontan procedure. This number seems too small. We speculate that the paediatric cardiologists working at our hospital in those days may have thought that not all patients with single-ventricle physiology eventually needed to undergo the Fontan procedure and may not have recommended the Fontan procedure for patients who remained clinically stable after the Glenn procedure. There may have been other good candidates for the Fontan procedure, and these patients may have had better outcomes with the Fontan procedure. In contrast, for patients who were not good candidates for the Fontan procedure, the outcomes of this study would have been acceptable.

Clinical events and complications

Although arrhythmic and neurological events were common in this study, few patients developed liver cirrhosis or protein-losing enteropathy. These results are consistent with those of previous studies [7, 8, 11]. The latter result seems particularly important.

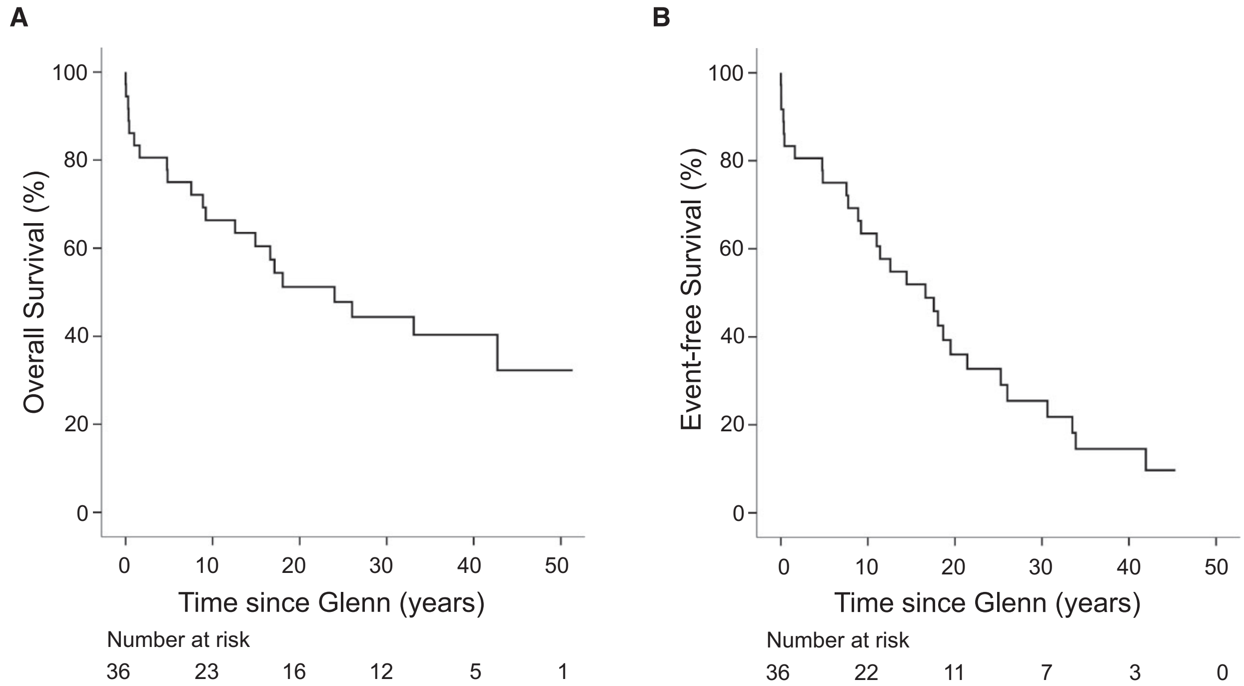


Figure 2: Kaplan–Meier curves for (**A**) overall survival and (**B**) event-free survival after the Glenn procedure.

Table 2: Univariate Cox proportional hazards regression models for overall survival

Variable	HR	95% CI	*P*-Value
Age at Glenn[a] (years)	1.01	0.90–1.12	0.925
Male sex	0.95	0.40–2.24	0.898
Weight at Glenn[a] (kg)	1.00	0.94–1.06	0.912
Heterotaxy syndrome	1.91	0.77–4.71	0.162
LV morphology (versus RV morphology)	0.24	0.08–0.76	0.014
Arterial oxygen saturation[a] (%)	0.96	0.91–1.02	0.148
Dominant ventricular end-diastolic pressure[a] (mmHg)	1.14	0.98–1.34	0.099
Prior palliative procedure	0.62	0.18–2.12	0.450
BDG (versus classic Glenn)	1.16	0.42–3.20	0.774
Glenn era (versus 1970–1979)			
1980–1989	0.45	0.15–1.40	0.169
1990–1999	1.21	0.39–3.81	0.740
Any concomitant surgeries	1.14	0.44–2.93	0.794

[a]For every 1-unit increase.

BDG: bidirectional Glenn; CI: confidence interval; HR: hazard ratio; LV: left ventricular; RV: right ventricular.

Current central venous pressure in this study was estimated not to be high according to the guidelines from the American Society of Echocardiography [22], suggesting that keeping central venous pressure low can prevent liver cirrhosis and protein-losing enteropathy in patients with single-ventricle physiology over the long term. These ideas may be also applied to patients undergoing the Fontan procedure. The fenestrated Fontan procedure has been reported to be effective in lowering central venous pressure and maintaining cardiac output in early postoperative management of the Fontan procedure [23, 24]. We suspect that a patent fenestration could minimize the long-term problems caused by high venous pressure on the abdominal viscera and may enable patients after the Fontan procedure to survive longer, even at the expense of worsening cyanosis. Further studies are needed to investigate the effects of a patent fenestration on long-term outcomes.

All pulmonary arterio-venous malformations after the classic Glenn procedure were present in the lung on the side of the Glenn procedure and none in the contralateral lung, corroborating previous reports indicating that a lack of hepatic venous blood plays a role in the development of pulmonary arterio-venous malformations [15, 16]. Although the incidence of pulmonary arterio-venous malformations has been reported to increase with time after the Glenn procedure [13, 15], the incidence in this cohort was lower than previously reported [13–16]. A possible explanation for this difference is that some of the patients who died in the early years of this study may have had undiagnosed pulmonary arterio-venous malformations. If so, undiagnosed pulmonary arterio-venous malformations may have negatively affected their clinical course.

Impact of ventricular morphology on long-term survival

As expected, the patients with dominant left ventricular morphology had better long-term overall survival than those with dominant right ventricular morphology. Although there are no reports on the impact of ventricular morphology on the long-term survival of patients remaining on a Glenn procedure, there are some relevant studies. A study showed that the 10-year survival after the Glenn procedure was 100% for patients with tricuspid atresia [25]. Another study showed that dominant right ventricle was an independent risk factor for death prior to the Fontan procedure in patients after the bidirectional Glenn procedure [26]. Similarly, in patients after the Fontan procedure, dominant right ventricular morphology was associated with

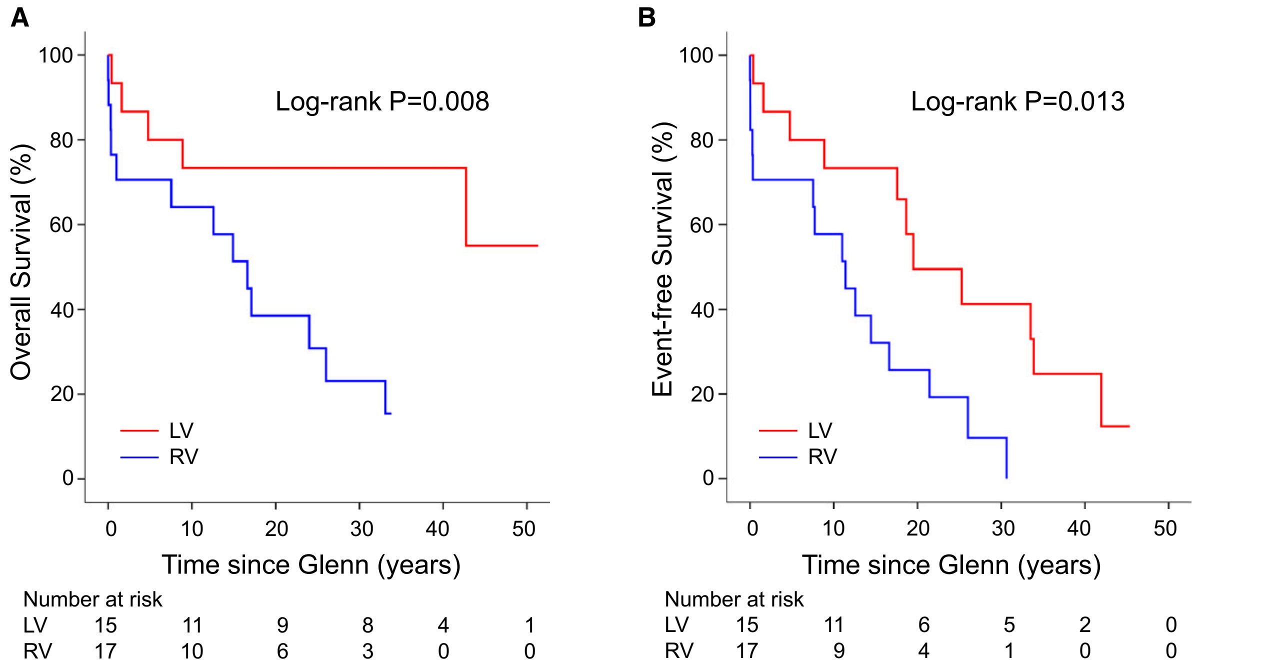


Figure 3: Kaplan–Meier curves for (**A**) overall survival and (**B**) event-free survival after the Glenn procedure according to ventricular dominance. LV: dominant left ventricular morphology; RV: dominant right ventricular morphology.

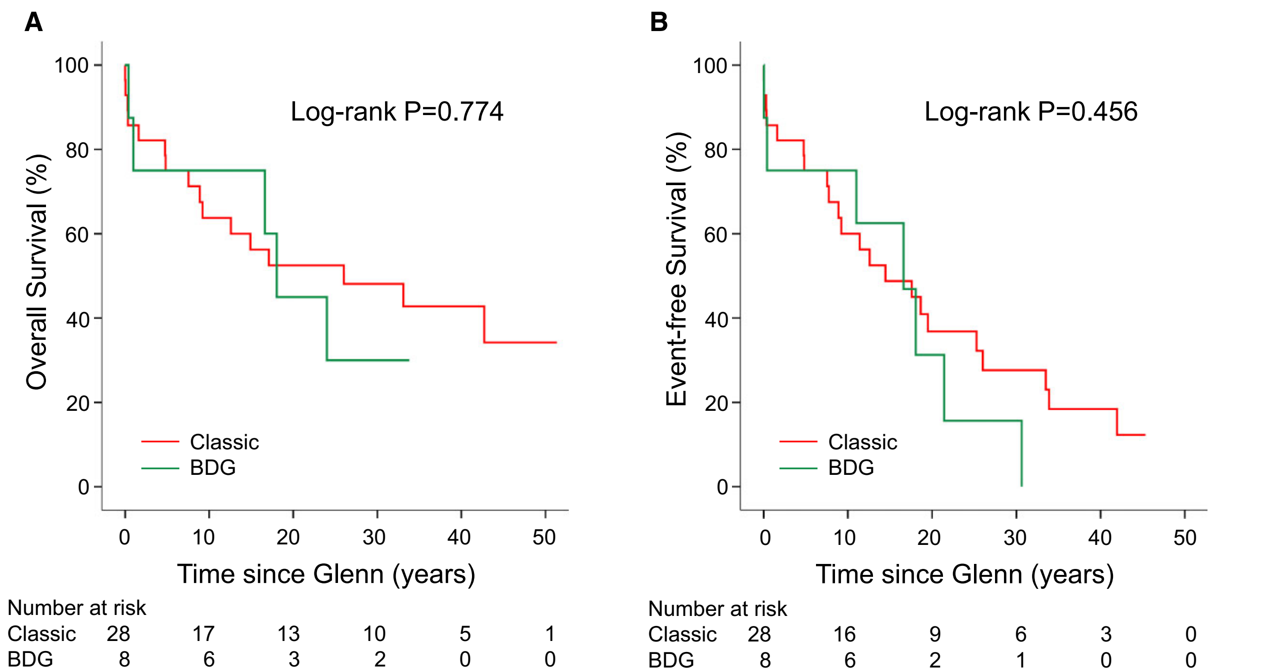


Figure 4: Kaplan–Meier curves for (**A**) overall survival and (**B**) event-free survival after the Glenn procedure according to type of Glenn procedure. BDG: bidirectional Glenn; Classic: classic Glenn.

poorer outcomes than dominant left ventricular morphology [2, 27]. An echocardiographic study showed that single ventricles with dominant right ventricular morphology had reduced systolic and diastolic function compared with single ventricles with dominant left ventricular morphology [28]. The results of our study and abovementioned studies may reflect these inherent differences between right and left ventricular performance.

Limitations

This study has several limitations. First, because this was a single-centre, retrospective cohort study, the sample size was small and the reasons for not performing the subsequent Fontan procedure were unclear in the majority of patients. Especially the latter one is the weakest point of this study. If the patients had been divided

Table 3: Univariate Cox proportional hazards regression models for event-free survival

Variable	HR	95% CI	*P*-Value
Age at Glenn[a] (years)	1.02	0.93–1.12	0.728
Male sex	0.82	0.39–1.73	0.605
Weight at Glenn[a] (kg)	1.00	0.96–1.05	0.885
Heterotaxy syndrome	2.06	0.92–4.60	0.078
LV morphology (versus RV morphology)	0.35	0.14–0.83	0.017
Arterial oxygen saturation[a] (%)	0.95	0.90–1.01	0.124
Dominant ventricular end-diastolic pressure[a] (mmHg)	1.07	0.93–1.22	0.343
Prior palliative procedure	0.78	0.30–2.06	0.619
BDG (versus classic Glenn)	1.39	0.58–3.30	0.458
Glenn era (versus 1970–1979)			
1980–1989	0.60	0.25–1.43	0.247
1990–1999	1.38	0.49–3.92	0.545
Any concomitant surgeries	1.13	0.50–2.55	0.777

[a]For every 1-unit increase.

BDG: bidirectional Glenn; CI: confidence interval; HR: hazard ratio; LV: left ventricular; RV: right ventricular.

into 2 groups based on good or poor candidates for the Fontan procedure, this study would have provided a therapeutic perspective for each group. Second, current central venous pressure was not directly measured by cardiac catheterization but estimated by echocardiography. However, estimation of central venous pressure by measuring inferior vena cava diameter and its respiratory changes has been established [22] and widely used in daily clinical practice. Third, the patients in this study did not regularly undergo imaging of the liver. Many patients with congestive hepatopathy are asymptomatic [29]. Therefore, there may have been patients with undiagnosed liver cirrhosis. Fourth, comprehensive statistical analysis was limited by the small sample size. The impact of ventricular dominance could not be analysed using multivariate models. Heterotaxy syndrome was not a prognostic factor in this study, although it has been reported as a prognostic factor in patients with single-ventricle physiology [3, 26]. This difference may be due to type II error. Finally, surgical and medical management has changed over the past 40 years. The bidirectional Glenn procedure is currently performed around 6 months of age [26, 30], and the classic Glenn procedure is no longer used today. Therefore, the results of this study may not be fully applicable in current practice. Nevertheless, the underlying

Table 4: Details of current status of patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at present (years)	50	45	47	45	59	37
Age at Glenn (years)	10	6	2	11	10	7
Sex	Female	Female	Male	Female	Male	Female
Morphological group	DILV	TA	CAVV	CAVV	TA	PA/IVS
Ventricular dominance	Left	Left	Left	Right	Left	Left
Type of Glenn	Classic	Classic	Classic	BDG	Classic	Classic
Contralateral PBF in classic Glenn	APBF	APBF	APBF + APCA	–	APBF	APBF
PAVMs	None	Right lung	None	None	None	Right lung
NYHA functional class	II	II	II	III	II	III
Oxygen saturation (%)	85	80	85	86	82	63
Haemoglobin (g/dl)	17.4	20.1	18.7	14.9	21.8	11.6
Total protein (g/dl)	6.8	6.5	7.9	6.8	6.7	7.3
Albumin (g/dl)	4.2	4.1	4.1	4.2	4.0	4.3
Creatinine (mg/dl)	0.8	0.9	0.9	0.8	1.3	0.9
BNP (pg/ml)	158.6	32.1	36.7	250.6	250.3	182.0
IVC diameter[a] (mm)	11	17	10	15	11	15
IVC collapse with a sniff[a,b]	Present	Present	Present	Present	Present	Absent
LC findings on ultrasonography	None	None	NA	None	None	None
LC findings on CT	None	None	NA	None	NA	NA
Current medication						
	DOAC	Aspirin	Aspirin	DOAC	Warfarin	Aspirin
	β-Blocker	ARB	ARB	β-Blocker	Aspirin	Digoxin
				ACEI	β-Blocker	
				Diuretics	ARB	
				Digoxin	Diuretics	
				Aprindine	Amiodarone	

[a]Evaluated by echocardiography.

[b]A decrease of >50% in IVC diameter with a sniff.

ACEI: angiotensin-converting enzyme inhibitor; APBF: antegrade pulmonary blood flow; APCA: aortopulmonary collateral artery; ARB: angiotensin receptor blocker; BDG: bidirectional Glenn; BNP: B-type natriuretic peptide; CAVV: common atrioventricular valve; CT: computed tomography; DILV: double-inlet left ventricle; DOAC: direct oral anticoagulant; IVC: inferior vena cava; LC: liver cirrhosis; NA: not available; NYHA: New York Heart Association; PA/IVS: pulmonary atresia with intact ventricular septum; PAVMs: pulmonary arterio-venous malformations; PBF: pulmonary blood flow; TA: tricuspid atresia.

pathophysiology of the diseases remains unchanged; therefore, some lessons can be learned from this study.

CONCLUSIONS

The 40-year overall survival after the Glenn procedure without the subsequent Fontan procedure in patients with single-ventricle physiology was 40.3%. Few patients developed liver cirrhosis or protein-losing enteropathy. Dominant left ventricular morphology may be associated with better long-term overall survival than dominant right ventricular morphology.

Conflict of interest: none declared.

Data Availability Statement

Data are not available. The Ethics Committee of Tenri Hospital approved data collection and its use only for registered researchers of this study. Therefore, the data used in this study cannot be shared outside Tenri Hospital.

Author contributions

Makoto Miyake: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing—original draft; Writing—review & editing. **Jiro Sakamoto:** Investigation. **Hirokazu Kondo:** Investigation; Writing—review & editing. **Atsushi Iwakura:** Investigation; Resources. **Hiraku Doi:** Investigation; Resources; Supervision. **Toshihiro Tamura:** Supervision; Writing—review & editing.

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