Long-term renal involvement in association with Fontan circulation

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ABSTRACT

Background: Multiorgan dysfunction is a concern of Fontan patients. To clarify the pathophysiology of Fontan nephropathy, we characterize renal disease in the long-term observational study.

Methods: Medical records of 128 consecutive Fontan patients (median age: 22 [range 15-37] years old) treated between 2009 and 2018 were reviewed to investigate the incidence of nephropathy and its association with other clinical variables.

Results: Thirty-seven patients (29%) showed proteinuria (n=34) or <90 mL/min/1.73 m^2 of estimated glomerular filtration rate (eGFR) (n=7), including 4 overlapping cases. Ninety-six patients (75%) had liver dysfunction (Forns index >4.21). Patients with proteinuria received the Fontan procedure at an older age (78 [26-194] *vs.* 56 [8-292] months old, p=0.02) and had a higher cardiac index (3.11 [1.49-6.35] *vs.* 2.71 [1.40-4.95] L/min/m^2, p=0.02), central venous pressure (12 [7-19] *vs.* 9 [5-19] mmHg, p<0.001), and proportion with >4.21 of Forns index (88% *vs.* 70%, p=0.04) than those without proteinuria. The mean renal perfusion pressure was lower in patients with a reduced eGFR than those without it (55 [44-65] *vs.* 65 [45-102] mmHg, p=0.03), but no other variables differed significantly. A multivariable analysis revealed that proteinuria was associated with an increased cardiac index (unit odds ratio 2.02, 95% confidence interval 1.12-3.65, p=0.02). Seven patients with severe proteinuria had a lower oxygen saturation than those with no or mild proteinuria (p=0.01, 0.03).

Conclusions: Proteinuria or a decreased eGFR differentially occurred in approximately 30% of Fontan patients. Suboptimal Fontan circulation may contribute to the development of proteinuria and reduced eGFR.

Introduction

The Fontan operation is a palliative procedure for pediatric patients with a functional single ventricle. Advances in surgical and medical management have increased the survival rates of these patients to reportedly over 75% at 25 years post-procedure [1], but the long-term survivors face burdens of the late effects.

The Fontan circulation is characterized by low cardiac output, high central venous pressure (CVP), and balanced low arterial oxygen saturation. These unique hemodynamics in Fontan patients result in more frequent complications than in patients with biventricular repair. Fontan-associated liver disease, protein-losing enteropathy, and plastic bronchitis are well-known long-term complications. The kidney is a commonly affected organ, and renal complications are often observed in patients with adult congenital heart disease (ACHD) [2,3]. A previous report indicated that renal disease is a predictor of mortality in patients with single-ventricle physiology [4]. However, the information on renal diseases in association with the Fontan circulation is limited [5-9].

To establish the diagnostic criteria and appropriate management of Fontan-associated kidney disease, we investigated the occurrence and characteristics of renal involvement in adolescent and young adult patients after the Fontan procedure. The present study indicated for the first time that the distinct pathophysiology of nephropathy from hepatorenal syndrome was in close association with pre- and post-Fontan hypoxemia.

Methods

Study population

This study enrolled a total of 196 patients who had undergone the Fontan procedure and were followed up at Kyushu University Hospital between October 2009 and August 2018. Patients ranging in age from 15-39 years old who had received blood tests and urinalyses were

included. Sixty-seven patients <15 or ≥40 years old or who lacked data on blood tests and urinalyses were excluded. One patient with hepatitis C virus infection was also excluded (**Fig. 1**). No patients required renal replacement therapy or had congenital anomalies of the kidney and urinary tract (CAKUT). Neither patients nor the public were involved in the design or conduct of this research. This retrospective study was approved by the Institutional Review Board of Kyushu University (#2019-525). The procedures used in this study adhered to the tenets of the Declaration of Helsinki.

Data collection

We collected the following information from medical records and imaging data: sex, the diagnosis of cardiac disease, type of the Fontan procedure, age at the procedure, time since the procedure was performed, cardiac catheterization and imaging data, clinical features, laboratory data, urine analysis, and the estimated glomerular filtration rate (eGFR) calculated using cystatin C. Cardiac index was calculated using the Fick method based on data by the cardiac catheterization. Blood and urine tests were performed at the first visit to outpatient clinics affiliated with Kyushu University Hospital, and catheterization was performed within a year before or after the first visit.

Assessing the renal function

The eGFR was calculated using the following equation for Japanese patients: $(104 \times [\text{Cystatin C}]^{-1.019} \times 0.996^{\text{Age}}$ [× 0.929 if female] – 8) [10]. A reduced eGFR and proteinuria were defined based on KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management in Chronic Kidney Disease as follows [11]: a normal eGFR was defined as ≥90 mL/min/1.73 m^2, while a reduced eGFR was divided into two categories of mild (60 to <90 mL/min/1.73 m^2) and moderate-to-severe (<60 mL/min/1.73 m^2). Proteinuria was defined as

the presence of ≥1+ protein on a urine dipstick test, a protein-to-urine creatinine ratio (PCR) of ≥0.15 g/g creatinine at urine quantitation, or an albumin-to-urine creatinine ratio (ACR) of ≥30 mg/g creatinine at urine quantitation. Severe proteinuria was defined as a protein value of ≥2+ on a urine dipstick test, a PCR of >0.5 g/g creatinine, or an ACR of >300 mg/g creatinine at urine quantitation. The mean renal perfusion pressure was calculated as the mean blood pressure – CVP (mmHg), which was measured during cardiac catheterization.

Liver dysfunction

We collected data on the Forns index, aspartate aminotransferase to platelet ratio index (APRI), and Fibrosis-4 (Fib-4) index in addition to hepatobiliary system enzymes and liver fibrosis markers. In our study, a Forns index >4.21 was used to define liver dysfunction in order to exclude the effects of anticoagulation and renal impairment [12-14]. This index was calculated using the following formula: 7.811 – 3.131 ×ln [platelet count (10^9/L)] + 0.781 × ln [γ-glutamyl transpeptidase (γ-GTP) (IU/L)] + 3.467× ln [Age (years old)] – 0.014 × [cholesterol (mg/dL)].

Statistical analyses

Descriptive statistics were used for demographic, clinical, operative, and outcome variables. Medians with ranges and counts with percentages were used for continuous and categorical variables, respectively. Wilcoxon's rank-sum test and chi-squared test were used for comparing continuous and qualitative variables, respectively. To identify determinants of proteinuria, reduced eGFR, and liver dysfunction, uni- and multi-variable regression analyses were performed. P <0.05 was considered to indicate statistical significance. All analyses were performed using the JMP Pro15 software program (version 15.1.0 for Windows; JMP Inc. SAS Institute Inc., Cary, NC, USA).

Results

Patients' characteristics

The details of the 128 analyzed patients are summarized in **Table 1**. The median age at the first visit to Kyushu University Hospital was 22 (range: 15-37) years old. Thirty-two patients had heterotaxy syndrome (right atrial isomerism in 19, left atrial isomerism in 13). Eleven patients (9%) received a classic Fontan procedure (atrio-pulmonary connection [APC]), 46 (36%) after a lateral tunnel, and 71 (55%) after an extracardiac conduit. None of the patients in our study had fenestration. The median age at the Fontan procedure was 64 (range: 8-292) months old, and the median post-procedure duration was 17 (10-29) years. Current medications included warfarin in 109 patients (85%), acetylsalicylic acid in 101 (79%), angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin II receptor blockers (ARBs) in 94 (73%), β-blockers in 60 (47%), diuretics in 24 (19%), and digoxin in 5 patients (4%). The median and range of the Forns index in these patients were 5.02 and 2.52-6.89, and 96 (75%) had liver dysfunction with a Forns index of >4.21.

Renal function and urinalysis

Among 128 patients with a median (ranges) blood urea nitrogen (BUN) value of 14 (7-23) mg/dL, serum creatinine of 0.69 (0.40-1.09) mg/dL, and cystatin C of 0.67 (0.45-1.36) mg/L, along with a cystatin C-based eGFR of 127.6 (61.9-194.0) mL/min/1.73 m^2, 37 (29%) had renal disease with proteinuria or a reduced eGFR. Seven patients had <90 mL/min/1.73 m^2 of eGFR but no one showed <60 mL/min/1.73 m^2 of eGFR (**Supplemental Fig. 1**). Thirty (81%) or 3 (8%) patients had proteinuria or a reduced eGFR alone, and 4 (11%) had both. Seven patients showed severe proteinuria. Nine had microscopic hematuria, but none showed macroscopic hematuria.

Liver dysfunction, proteinuria, and reduced eGFR

The swimmer plots depict the age at the Fontan procedure (**Fig. 2A**) and the follow-up duration since the procedure (**Fig. 2B**) of all individuals. Liver dysfunction (Forns index >4.21), proteinuria, and a reduced eGFR are presented as heat map images. When all subjects were divided into two groups by the median age at the Fontan procedure or the median follow-up time after the procedure, the proportions of patients with liver dysfunction at the time of the study were higher in patients who underwent the procedure at or over the median age than in those who received it under the median age (78% *vs.* 66%, p=0.02), or in patients with a follow-up duration at or over the median value than in those with a shorter follow-up duration (76% *vs.* 66%, p=0.02). The proportion of patients with proteinuria was larger in patients who underwent the Fontan procedure at or over the median age than in those who received it under the median age (38% *vs.* 16%, p=0.009) but not in patients with a follow-up duration at or over the median value versus in those with a shorter follow-up duration. The proportion of patients with a reduced eGFR did not differ markedly between the two groups of patients concerning the age at the Fontan procedure or the duration since the procedure. The proportion of patients with severe or non-severe proteinuria did not differ markedly between the two groups of patients concerning the age at the Fontan procedure or the duration since the procedure. Among the 37 patients with renal disease and 96 with liver dysfunction, 33 had both. Among the 7 patients with a reduced eGFR and 34 with proteinuria, 4 had both (**Supplemental Fig. 1**). These findings indicate the distinct association of liver dysfunction with proteinuria or a decreased eGFR in Fontan patients.

Factors associated with proteinuria

When we compared clinical variables between patients with and without proteinuria (n=34 and 94) (**Table 2**), those with proteinuria were older at the Fontan procedure (median 78 *vs.* 56 months old, p=0.02) than those without it. Proteinuria-positive patients also had a significantly higher CVP (median 12 *vs.* 9 mmHg, p <0.001) and cardiac index (median 3.11 *vs.* 2.71 L/min/m^2, p=0.02) than proteinuria-negative patients. The median levels of serum alanine aminotransferase (p=0.04), γ-GTP (p=0.002), and hepatic fibrosis markers, including hyaluronic acid (p <0.001) and type IV collagen (p=0.006), were higher in proteinuria-positive patients than in proteinuria-negative patients. Patients with proteinuria had a higher proportion of liver dysfunction than those without proteinuria (30 [88%] *vs.* 66 [70%], p=0.04). Additionally, patients with proteinuria had a significantly higher proportion of diuretic usage compared to those without proteinuria (11 [32%] *vs.* 13 [14%], p=0.02). However, the administration of other medications did not show significant differences between the two groups of patients. A multivariable logistic regression analysis revealed that an increased cardiac index was associated with proteinuria (cardiac index: unit odds ratio [uOR] 2.02, 95% confidence interval [CI] 1.12-3.65, p=0.02) (**Table 3**). Among the 7 patients with severe proteinuria (**Supplemental Table 1**), 4 (57%) had <90% of percutaneous oxygen saturation (SpO_2) and liver dysfunction. The median SpO_2 levels were lower in patients with severe proteinuria than in those with mild proteinuria (p=0.03) or without proteinuria (p=0.01) (**Fig. 3**).

Factors associated with a reduced eGFR

When we compared clinical variables between patients with a reduced eGFR (<90 mL/min/1.73 m^2, n=7) and a normal eGFR (≥90 mL/min/1.73 m^2, n=121) (**Table 2**), reduced-eGFR patients had a higher pulmonary vascular resistance index (1.99 [1.32-2.82] *vs.* 1.22 [0.23-4.38] wood unit. m^2, p=0.04) and lower mean renal perfusion pressure (55 [44-

65] *vs.* 65 [45-102] mmHg, p=0.03) than normal-eGFR patients, although the cardiac index and CVP levels did not differ markedly between the groups of patients. The median levels of serum creatinine (0.87 *vs.* 0.68 mg/dL, p=0.02) and cystatin C (1.05 *vs.* 0.66 mg/L, p <0.001) were higher in reduced-eGFR patients than in normal-eGFR patients. Regarding medications, as with the results for proteinuria, a significant difference was observed only in the use of diuretics (5 [71%] *vs.* 19 [16%], p=0.003). A multivariable logistic regression analysis indicated only an inverse trend in the association of an increased cardiac index with a reduced eGFR (p=0.05, **Table 4**).

Associations of liver dysfunction with proteinuria or a reduced eGFR

When clinical variables were compared between patients with and without liver dysfunction (**Supplemental Table 2**), patients with liver dysfunction were older at the Fontan procedure (median age 71 *vs.* 44 months old, p=0.003) and had a longer post-procedure duration (median 17 *vs.* 16 years, p=0.004) than those without it. All APC-type Fontan patients had liver dysfunction. There was no significant difference in the CVP or cardiac index between the two groups. The median levels of serum creatinine (0.70 *vs.* 0.64 mg/dL, p=0.03) and cystatin C (0.70 *vs.* 0.65 mg/dL, p=0.02) were higher in patients with liver dysfunction than in those without it. Proteinuria but not a reduced eGFR occurred more frequently in patients with liver dysfunction than seen in those without it (30 [31%] *vs.* 4 [13%], p=0.04). A multivariable logistic regression analysis revealed the association of liver dysfunction with the post-procedure duration (uOR 1.36, 95% CI 1.09-1.70, p=0.007) but not with the development of proteinuria (uOR 2.91, 95% CI 0.84-10.1, p=0.09) (**Supplemental Table 3**).

Discussion

Approximately 30% of adolescent and young adult Fontan patients had renal disease with proteinuria or a modest reduction of eGFR differentially. The older age at the Fontan procedure and post-Fontan hypoxemia might affect the development and severity of proteinuria, but not a reduced eGFR. Multivariable analyses indicated that a relatively high cardiac index was the sole independent predictor of proteinuria, and an inversely decreased cardiac index showed a trend toward an association with a reduced eGFR. This observational study demonstrated the different presentations of proteinuria and a decreased eGFR after the Fontan procedure. Hypoxemia, elevated CVP, and unbalanced cardiac output may be considered to form the pathophysiological bases of Fontan nephropathy, which is distinct from hepatorenal syndrome.

Fontan patients reportedly present with albuminuria more frequently than healthy controls [7]. In addition, among ACHD populations, albuminuria was found to have a high prevalence in Fontan patients [15]. A small cross-sectional study showed that 43% of Fontan patients had a pathological micro-albumin/creatinine ratio (MCR) (>20 μg/mg creatinine), irrespective of a normal eGFR, indicating a strong positive correlation between the MCR and Fontan pressure [5]. In the present study, 27% of patients had proteinuria, including albuminuria, although the MCR was not assessed.

The major concern is the pathophysiology of proteinuria after the Fontan procedure. Venous congestion induces tubular dysfunction or chronic tubulointerstitial damage leading to increased proteinuria [16]. The present study demonstrated that proteinuria-positive patients had a higher CVP than proteinuria-negative patients. Elevated CVP results in an increase in glomerular filtration pressure, leading to an elevation in microalbuminuria, which serves as an early indicator of glomerulopathy [17]. Elevated venous pressure may thus contribute to the development of proteinuria in Fontan circulation. Furthermore, older age at the Fontan procedure was a predictor of proteinuria. The SpO_2 from the bidirectional Glenn

(BDG) to Fontan procedure generally remains below 90%. In cases where there are pulmonary arteriovenous fistulas (PAVFs) after BDG, the SpO_2 may be even lower [18,19]. Additionally, severe proteinuria was associated with desaturation at the time of the current study. This may suggest a potential effect of prolonged hypoxemia on the kidney during childhood and residual cyanosis after the Fontan procedure, as proteinuria is a pivotal manifestation of cyanotic nephropathy [20-22]. Chronic hypoxemia may cause secondary erythrocytosis and hyperviscosity, resulting in decreased glomerular blood flow, pathological glomerular changes, and the appearance of proteinuria [17]. In this context, long-term uncompensated hypoxemia before and after the procedure may induce and exacerbate proteinuria in Fontan patients.

Several cohort studies have shown that 22%-23% of adult Fontan patients presented with decreased eGFR values, and 1% had an eGFR <60 mL/min/1.73 m^2 [7,9]. Also, the occurrence of an eGFR <90 mL/min/1.73 m^2 in the young Fontan population reportedly ranged from 10% to 20% [6,8]. In the present study, only 5% of enrolled patients had a reduced eGFR, and none had moderate to severe renal dysfunction. Pujol C et al. [4] demonstrated that there is an association between high mortality and renal disease (either structural or functional kidney damage, or eGFR <60 mL/min/1.73 m^2) in older patients (aged over 40 years) with single-ventricle physiology. Further cohort studies with longer observation periods are needed to clarify the effect of aging on progressive renal dysfunction.

Renal perfusion accounts for approximately 20%-25% of the total cardiac output in normal healthy circulation [23,24]. The Fontan circulation characterized by low cardiac output therefore inevitably leads to low renal perfusion. A small study showed a strong association between reduced pulmonary blood flow/elevated CVP and a decreased eGFR in pediatric Fontan patients [8]. This finding is consistent with our study, where we observed an association between increased PVRI and reduced eGFR. Adult Fontan patients with a

reduced eGFR are more likely to develop adverse outcomes than those with normal renal functions [7]. The association of decreased cardiac output with a reduced eGFR did not reach statistical significance in the present study, possibly due to our relatively small sample size and stable hemodynamics in young patients. Decreased eGFR is attributable to the unique property of the Fontan circulation, which influences long-term complications. CVP was not significantly associated with a reduced eGFR in our study. However, Mullens et al. reported that venous congestion is an important factor for declined renal function in biventricular circulation [25]. Further studies are needed to clarify the long-term effect of elevated CVP on renal function in Fontan circulation. In future studies, the measurements of kidney size, patterns of renal blood flow, and the Renal Resistive Index using ultrasound, which is known to increase in Fontan patients [26], will be incorporated.

The present study revealed that proteinuria was associated with hypoxemia and relatively high cardiac output, along with liver dysfunction. Causes of high cardiac output in Fontan patients include the presence of veno-venous collaterals and PAVFs, high cardiac output heart failure with elevated CVP [27], as well as potential hepatic influences. Previous reports showed that hepatic fibrosis appeared to start within a decade after the Fontan operation [28], and liver stiffness increased 5-10 years after the procedure [29]. This was consistent with our findings that the appearance of liver dysfunction was associated with the duration since Fontan surgery. The significant association between proteinuria and cardiac output reflected the augmented effect of relatively high-output circulation due to liver dysfunction [30,31]. Inflammatory cytokines, oxidative stress, hypercoagulability, and increased insulin resistance caused by liver damage augment kidney damage [32]. The age-dependent link of proteinuria with liver dysfunction may account for the effect of unique Fontan circulation as well as the long-term metabolic effects. Liver dysfunction may be a contributing factor to proteinuria in

Fontan patients. More precise studies are needed to clarify the complex crosstalk between the liver and kidney of Fontan patients.

Regarding the association between medication and renal involvement, ACE-Is/ARBs, which are inhibitors of the renin-angiotensin-aldosterone system (RAAS), have the risk of acute kidney injury, while they also possess an effect in reducing proteinuria and are employed in the treatment of chronic kidney disease [33,34]. We did not observe any significant differences in proteinuria or reduced eGFR based on the presence or absence of RAAS inhibitors, while there were significant differences in proteinuria or reduced eGFR based on the presence or absence of diuretics in this study. Diuretics lead to increased activity of the sympathetic nervous system and the RAAS, resulting in a reduced eGFR. However, the alleviation of congestion by diuretics can contribute to an increased eGFR due to the reduction of renal venous pressure [33]. Additionally, in patients who are taking warfarin as anticoagulation therapy, such as our Fontan patients, it's also important to exercise caution regarding the development of anticoagulant-related nephropathy [35,36]. The pharmacokinetics in Fontan patients remain unclear, posing a challenge for future research.

This study's limitations include its relatively small sample size from a single institution, the absence of long-term outcome information, the lack of an assessment of the renal function in the pre-and peri-operative periods, and an unclear timing of the onset of kidney and liver disease after the Fontan procedure. In addition, we did not assess the renal histology, the association between renal disease and medication, or renal interstitial damage using β2-microglobulin. Liver dysfunction was assessed using the liver fibrosis index because of the lack of imaging findings or biopsy assessments. In addition, we did not evaluate hemodynamics by cardiac catheterization in all patients and observed that the assessment of veno-venous collaterals and PAVFs using contrast echocardiography or CT was insufficient in this study.

Conclusions

Proteinuria is the major presentation of Fontan nephropathy, not a reduced eGFR, suggesting a distinct impact on the pathophysiology of renal complication. The optimal cardiac output may be the pivotal factor in preventing the development of Fontan-associated nephropathy rather than aging and liver damage.

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Contributors Statement Page

Dr. Mamoru Muraoka carried out the primary analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr. Hazumu Nagata and Dr. Kenichiro Yamamura conceptualized and designed the study, drafted the manuscript, and critically reviewed and revised the manuscript. Dr. Ichiro Sakamoto, Dr. Ayako Ishikita, Dr. Akiko Nishizaki, and Prof. Hiroyuki Tsutsui managed the patients and critically reviewed and revised the manuscript. Dr. Yoshimi Eguchi, Dr. Shoji Fukuoka, Dr. Kiyoshi Uike, Dr. Yusaku Nagatomo, Dr. Yuichiro Hirata, and Dr. Kei Nishiyama assisted in implementing the examinations and interventions and critically reviewed and revised the manuscript. Prof. Shouichi Ohga helped complete the project and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Disclosures

The authors declare no conflicts of interest in association with the present study.

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Figure legends

Fig. 1 Flow chart of the enrolled subjects.

Fig. 2 Swimmer's plots sorted by the oldest age at the Fontan procedure (A) and the time since the procedure (B) in patients with or without liver dysfunction, proteinuria, and a reduced estimated glomerular filtration rate (eGFR). A red asterisk indicates patients with proteinuria, a reduced eGFR, and liver dysfunction. Blue indicates those having proteinuria and a reduced eGFR but no liver dysfunction. The slanted line in the proteinuria column indicates patients with severe proteinuria.

Fig. 3 The comparison between patients with no proteinuria, mild proteinuria, and severe proteinuria by percutaneous oxygen saturation (SpO_2).

Fig. 4 A schematic model of the causative effects on the development of Fontan-associated renal disease differentially consisting of renal dysfunction or proteinuria. The solid arrow indicates the possible effect size, and the dashed arrow indicates the borderline trend in this study and verification in previous reports. Accompanied marks represent the results from Table 2 (*), Table 3 (†), Supplemental Table 2 (‡), Figure 2 (§), and Figure 3 (#).

Table 1. Patients' characteristics

	n=128
Sex, male	70 (54%)
Primary cardiac diagnosis	SV 38 (30%), TA 22 (17%), DORV 21 (16%), DILV 14 (11%), uAVSD 12 (9%), PA/IVS 9 (7%), HLHS 6 (5%), ccTGA 4 (3%), TGA 1 (1%), TOF 1 (1%)
Heterotaxy	32 (RAI 19, LAI 13)
Primary Fontan procedure	APC 11 (9%), LT 46 (36%), EC 71 (55%)
The age at the Fontan procedure, months old	64, 8-292
The age at the first visit, years old	22, 15-37
Post-procedure duration, years	17, 10-29
Hemodynamics	
Mean blood pressure, mmHg	75, 55-111
SpO_2, %	95, 76-99
CVP, mmHg	10, 5-19
PVRI, wood unit. m^2	1.26, 0.23-4.38
Cardiac index, L/min/m^2	2.82, 1.40-6.35
Mean renal perfusion pressure, mmHg	64, 44-102
EF, %	61, 37-79
AVVR	None 39, Mild 69, Moderate 11, Severe 1, ND 8
Laboratory data	
Hemoglobin, g/dL	15.5, 9.3-19.0
Platelet, $\times 10^4/\mu L$	16.4, 4.9-50.8
BUN, mg/dL	14, 7-23
Creatinine, mg/dL	0.69, 0.40-1.09
Cystatin C, mg/L	0.67, 0.45-1.36
Alb, g/dL	4.6, 3.0-5.5
TB, mg/dL	1.1, 0.2-5.1
ALT, IU/L	22, 4-142
ChE, IU/L	277, 132-501
γ-GTP, IU/L	63, 18-355
Hyaluronic acid, ng/mL	31, 9-428
Type IV collagen, ng/mL	161, 67-403
Forns index	5.02, 2.52-6.89
APRI	0.39, 0.12-1.68
Fib-4 index	0.70, 0.25-2.25
BNP, pg/mL	20.2, 4.0-370.6
eGFR	
≥90 mL/min/1.73 m^2	121 (95%)
<90 mL/min/1.73 m^2	7 (5%)
Urinalysis	
Proteinuria	None 94 (73%), Positive 34 ([27%]; severe positive 7 [5%])
Microscopic hematuria	None 119 (93%), Positive 9 (7%)
Current medication	Warfarin 109 (85%), Acetylsalicylic acid 101 (79%), ACE-Is/ARBs 94 (73%), β-blockers 60 (47%), Diuretics 24 (19%), Digoxin 5 (4%)

ACE-Is, angiotensin converting enzyme inhibitors; ALT, alanine aminotransferase; APC, atrio-pulmonary connection; APRI, aspartate aminotransferase to platelet ratio index; ARBs, angiotensin II receptor blockers; AVVR, atrioventricular valve regurgitation; Alb, albumin; BNP, b-type natriuretic peptide; BUN, blood urea nitrogen; CVP, central venous pressure; ChE, cholinesterase; DILV, double inlet left ventricle; DORV, double outlet right ventricle; EC, extracardiac conduit; EF, ejection fraction; Fib-4, Fibrosis-4; HLHS, hypoplastic left

heart syndrome; LAI, left atrial isomerism; LT, lateral tunnel; ND, not described; PA/IVS, pulmonary atresia with intact ventricular septum; PVRI, resistance of pulmonary vascular index; RAI, right atrial isomerism; SV, single ventricle; SpO_2, percutaneous oxygen saturation; TA, tricuspid valve atresia; TB, total bilirubin; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; ccTGA, congenitally corrected transposition of the great arteries; eGFR, estimated glomerular filtration rate; uAVSD, unbalanced atrioventricular septum defect; γ-GTP, γ-glutamyl transpeptidase; variables : median (range)

Table 2. Clinical variables between proteinuria and none and between reduced-eGFR (<90 mL/min/1.73 m^2) patients and normal-eGFR (≥90 mL/min/1.73 m^2) patients

Table 2. Clinical variables between proteinuria and none and between reduced-eGFR (<90 mL/min/1.73 m^2) patients and normal-eGFR (≥90 mL/min/1.73 m^2) patients

	Proteinuria	None		Reduced eGFR	Normal eGFR	
	n=34	n=94	*p value*	n=7	n=121	*p value*
The age at the Fontan procedure, months old	78, 26-194	56, 8-292	**0.02**	69, 26-165	63, 8-292	0.96
APC, n (%)	4 (12)	7 (7)	0.48	0 (0)	11 (9)	0.99
Post-procedure duration, years	17, 10-26	16, 10-29	0.74	18, 12-19	16, 10-29	0.65
Mean blood pressure, mmHg	74, 59-102	75, 55-111	0.53	65, 58-80	75, 55-111	0.05
SpO_2, %	94, 76-99	95, 80-99	0.28	94, 82-98	95, 76-99	0.99
CVP, mmHg	12, 7-19	9, 5-19	**<0.001**	10, 8-19	10, 5-19	0.24
PVRI, wood unit. m^2	1.18, 0.31-2.82	1.29, 0.23-4.38	0.32	1.99, 1.32-2.82	1.22, 0.23-4.38	**0.04**
Cardiac index, L/min/m^2	3.11, 1.49-6.35	2.71 1.40-4.95	**0.02**	1.70, 1.60-3.01	2.83, 1.40-6.35	0.14
Mean renal perfusion pressure, mmHg	62, 44-87	65, 45-102	0.09	55, 44-65	65, 45-102	**0.03**
Hemoglobin, g/dL	15.7, 9.3-18.6	15.2, 10.3-19.0	0.42	16.4, 9.3-19.0	15.3, 10.3-19.0	0.10
Platelet, $\times 10^4/\mu L$	14.5, 4.9-33.0	16.9, 7.2-50.8	0.07	15.3, 11-31.5	16.4, 4.9-50.8	0.96
BUN, mg/dL	15, 7-21	13, 7-23	0.11	17, 11-19	13, 7-23	0.13
Creatinine, mg/dL	0.71, 0.44-1.02	0.68, 0.40-1.09	0.54	0.87, 0.54-1.09	0.68, 0.40-1.02	**0.02**
Cystatin C, mg/L	0.71, 0.45-1.14	0.66, 0.50-1.36	0.39	1.05, 0.91-1.36	0.66, 0.45-0.93	**<0.001**
Alb, g/dL	4.6, 3.0-5.4	4.6, 3.6-5.5	0.40	4.5, 3.9-5.4	4.6, 3.0-5.5	0.80
TB, mg/dL	1.2, 0.4-2.5	1.0, 0.2-5.1	0.42	1.2, 0.7-1.9	1.0, 0.2-5.1	0.53
ALT, IU/L	24, 12-51	21, 6-142	**0.04**	26, 22-44	22, 6-142	0.07
ChE, IU/L	281, 214-401	272, 132-501	0.25	255, 175-365	280, 132-501	0.23
γ-GTP, IU/L	80, 19-322	54, 18-355	**0.002**	137, 42-167	60, 18-355	0.37
Hyaluronic acid, ng/mL	45, 12-428	28, 9-215	**<0.001**	56, 12-90	31, 9-428	0.20
Type IV collagen, ng/mL	180, 67-403	153, 94-326	**0.006**	184, 140-293	157, 67-403	0.06
Liver dysfunction (Forns index >4.21), n (%)	30 (88)	66 (70)	**0.04**	6 (86)	90 (74)	0.68
APRI	0.49, 0.18-1.68	0.35, 0.12-1.68	**0.007**	0.56, 0.18-1.09	0.38,0.12-1.60	0.24
Fib-4 index	0.83, 0.30-2.25	0.66, 0.25-2.00	**0.002**	0.79, 0.30-1.50	0.70, 0.25-2.25	0.53
BNP, pg/mL	22.7, 5.5-370.6	20.0, 4.0-284.8	0.11	17.2, 5.8-135.1	20.4, 4.0-370.6	0.72
Warfarin, n (%)	29 (85)	80 (85)	0.78	7 (100)	102 (84)	0.59
Acetylsalicylic acid, n (%)	25 (74)	76 (81)	0.53	6 (86)	95 (79)	0.68
ACE-Is/ARBs, n (%)	25 (74)	69 (73)	0.99	7 (100)	87 (72)	0.19
β-blockers, n (%)	19 (56)	41 (44)	0.22	3 (43)	57 (47)	0.99
Diuretics, n (%)	11 (32)	13 (14)	**0.02**	5 (71)	19 (16)	**0.003**
Digoxin, n (%)	1 (3)	4 (4)	0.76	0 (0)	5 (4)	0.58

ACE-Is, angiotensin converting enzyme inhibitors; ALT, alanine aminotransferase; APC, atrio-pulmonary connection; APRI, aspartate aminotransferase to platelet ratio

index;
ARBs, angiotensin II receptor blockers; BNP, b-type natriuretic peptide; BUN, blood urea nitrogen; Alb, albumin; CVP, central venous pressure; ChE, cholinesterase; Fib-4, Fibrosis-4; PVRI, resistance of pulmonary, vascular index; SpO_2, percutaneous oxygen saturation; TB, total bilirubin; eGFR, estimated glomerular filtration rate; γ-GTP, γ-glutamyl transpeptidase; variables: median (range), or number, (%). Bold *p values* represent <0.05.

Table 3. Risk factors of proteinuria

	Unit odds ratio	95% confidence interval	*p value*
Cardiac index, L/min/m^2	2.02	1.12-3.65	**0.02**
Hyaluronic acid, ng/mL	1.01	0.99-1.03	0.06
CVP, mmHg	1.18	0.97-1.43	0.09
The age at the Fontan procedure, months old	1.01	0.99-1.02	0.16

CVP, central venous pressure. Bold *p values* represent <0.05.

Table 4. Risk factors for the development of a reduced eGFR (<90 mL/min/1.73 m^2)

	Unit odds ratio	95% confidence interval	*p value*
Cardiac index, L/min/m^2	0.11	0.01-1.01	0.05
Mean renal perfusion pressure, mmHg	0.85	0.72-1.03	0.10
PVRI, wood unit. m^2	1.69	0.55-5.20	0.64

eGFR, estimated glomerular filtration rate; PVRI, resistance of pulmonary vascular index.
Bold *p values* represent <0.05.

Fig .1

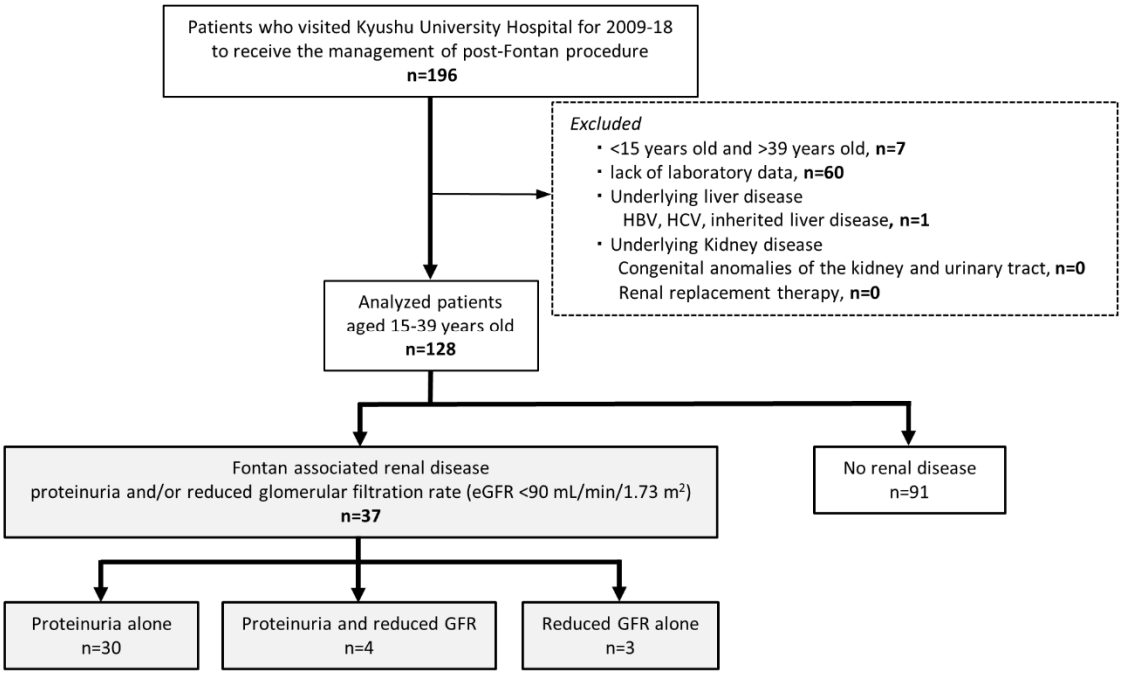

Patients who visited Kyushu University Hospital for 2009-18
to receive the management of post-Fontan procedure
n=196
Excluded
・<15 years old and >39 years old, n=7
・lack of laboratory data, n=60
・Underlying liver disease
HBV, HCV, inherited liver disease, n=1
・Underlying Kidney disease
Congenital anomalies of the kidney and urinary tract, n=0
Renal replacement therapy, n=0
Analyzed patients
aged 15-39 years old
n=128
Fontan associated renal disease
proteinuria and/or reduced glomerular filtration rate (eGFR <90 mL/min/1.73 m2)
n=37
No renal disease
n=91
Proteinuria alone
n=30
Proteinuria and reduced GFR
n=4
Reduced GFR alone
n=3

Fig. 2

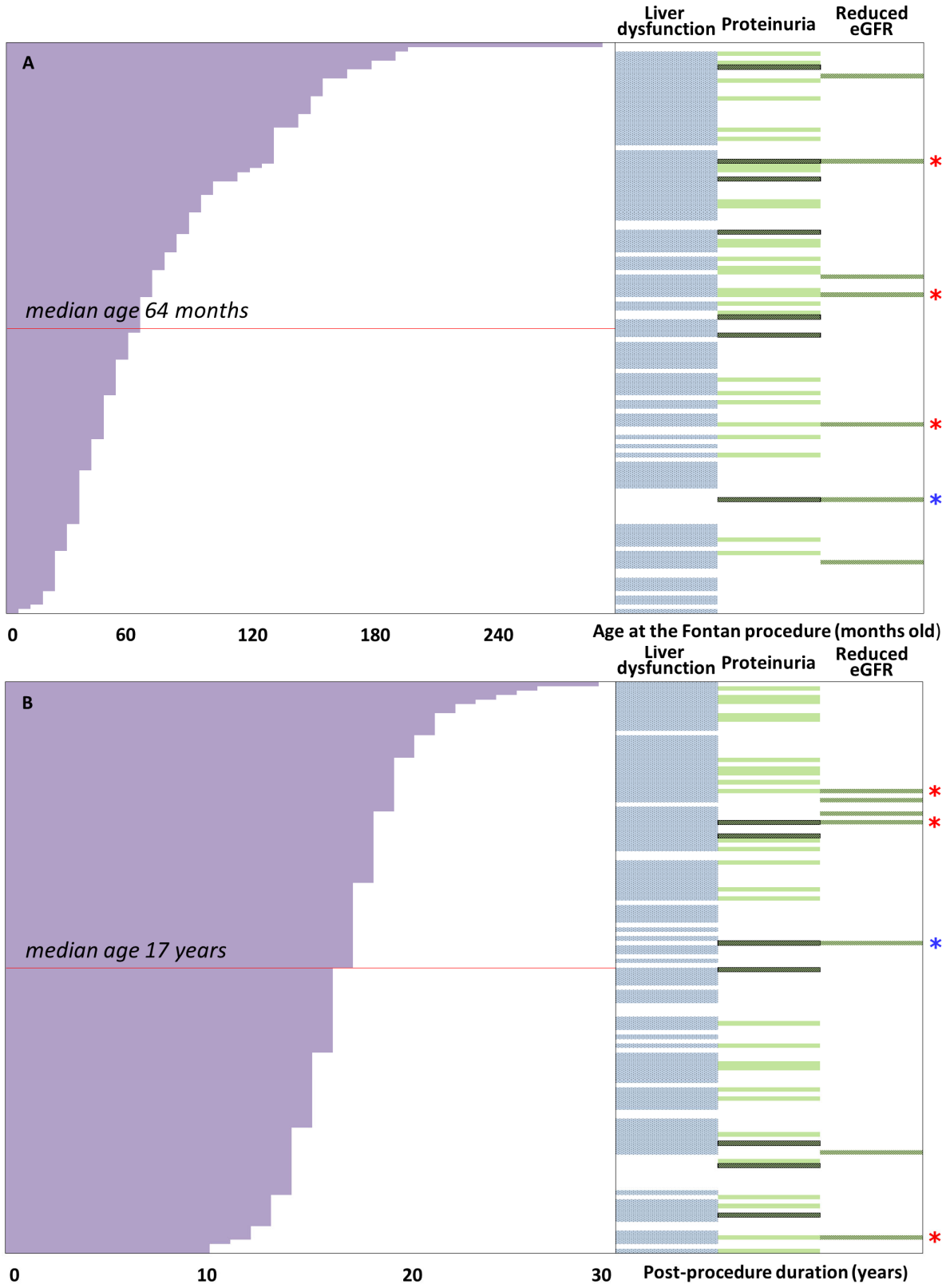

Liver dysfunction
Proteinuria
Reduced eGFR
A
median age 64 months
0
60
120
180
240
Age at the Fontan procedure (months old)
Liver dysfunction
Proteinuria
Reduced eGFR
B
median age 17 years
0
10
20
30
Post-procedure duration (years)

Fig. 3

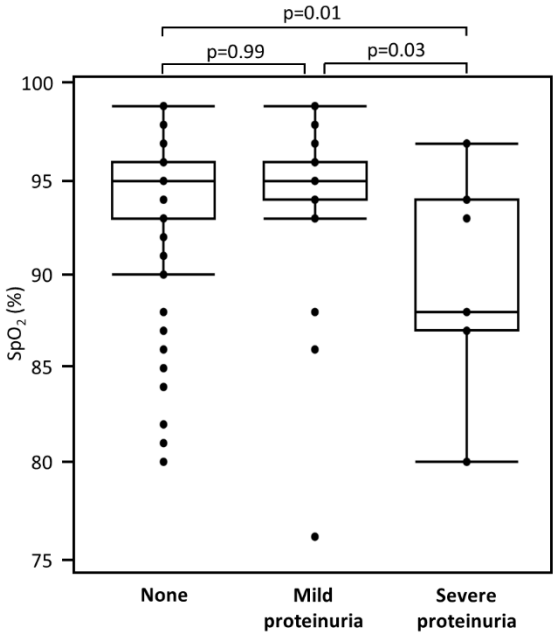
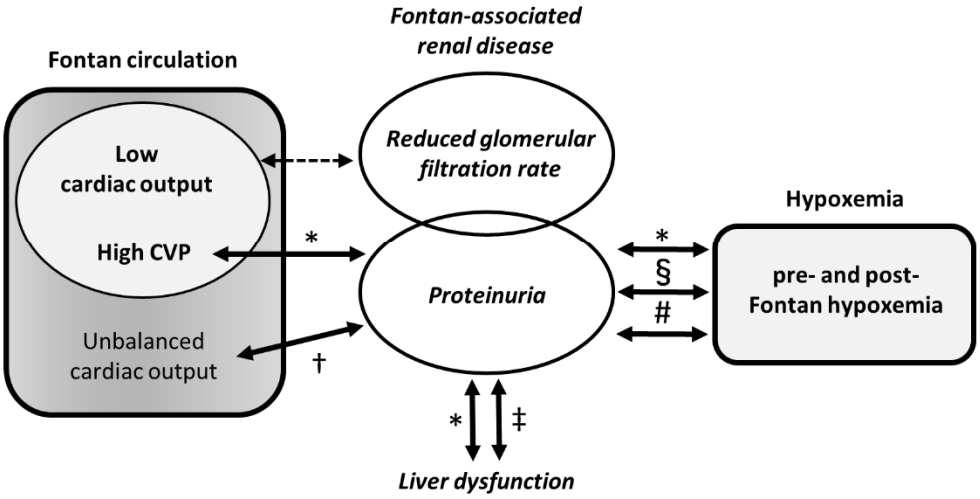

p=0.01
p=0.99
p=0.03
100
95
90
85
80
75
SpO2 (%)
None
Mild proteinuria
Severe proteinuria

Fig. 4


Fontan-associated
renal disease
Fontan circulation
Low
cardiac output
High CVP
Unbalanced
cardiac output
Reduced glomerular
filtration rate
Proteinuria
Liver dysfunction
Hypoxemia
pre- and post-
Fontan hypoxemia
*
†
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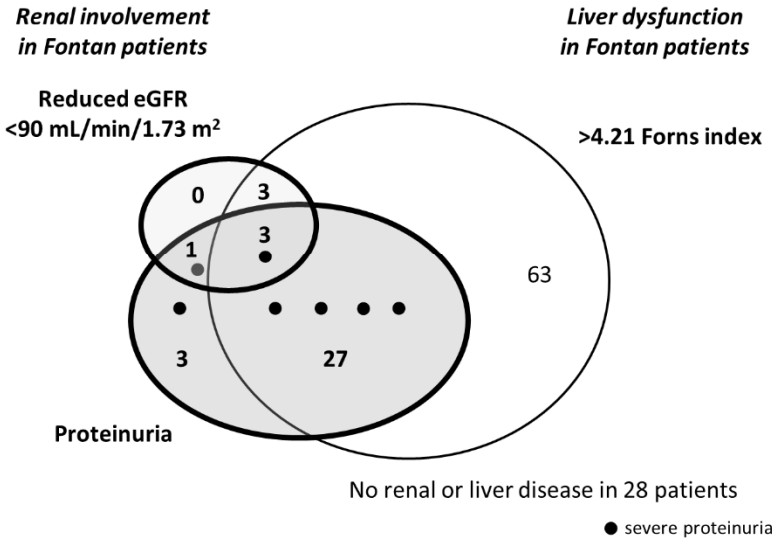
*
‡

Supplemental Fig. 1



Supplemental Table 1. Characteristics of all 7 patients with severe proteinuria

Case	Age, years old	Sex	The age at the Fontan procedure, months old	Post-procedure duration, years	SpO_2, %	CVP, mmHg	Cardiac index, L/min/m^2	Liver dysfunction (Forns index > 4.21)	Reduced eGFR (< 90 mL/min/1.73 m^2)
1	18	F	62	13	**87**	15	3.95	**5.27**	140.8
2	19	M	67	14	93	12	1.93	4.02	124.8
3	20	F	35	17	94	12	3.01	3.76	**84.0**
4	23	M	114	14	**88**	15	ND	**6.89**	146.4
5	26	F	87	18	**80**	19	5.49	**5.70**	149.2
6	29	F	129	18	97	10	1.70	**4.73**	**86.7**
7	30	M	177	16	**87**	10	1.49	**4.81**	107.8

CVP, central venous pressure; F, Female; M, Male; ND, not described; SpO_2, percutaneous oxygen saturation; eGFR, estimated glomerular filtration rate

Supplemental Table 2. Clinical variables between patients with and without liver dysfunction (Forms index > 4.21)

	Liver dysfunction	Non-liver dysfunction	
	n = 96	n = 32	*p value*
The age at the Fontan procedure, months old	71, 87–194	44, 14–292	**0.003**
APC, n (%)	11 (11)	0 (0)	0.06
Post-procedure duration, years	17, 10–29	16, 10–21	**0.004**
Mean blood pressure, mmHg	75, 55–108	75, 58–111	0.69
SpO_2, %	95, 76–99	95, 81–100	0.31
CVP, mmHg	10, 5–19	9, 5–16	0.21
PVRI, wood unit. m^2	1.26, 0.31–4.38	1.26, 0.23–2.80	0.97
Cardiac index, L/min/m^2	2.84, 1.40–6.35	2.60, 1.56–4.77	0.31
Mean renal perfusion pressure, mmHg	64, 44–101	65, 49–102	0.44
Hemoglobin, g/dL	15.7, 10.8–19.0	14.6, 9.3–17.2	**0.002**
Platelet, $\times 10^4/\mu L$	14.5, 4.9–25.5	26.2, 9.8–50.8	**< 0.001**
BUN, mg/dL	14,7–23	13, 7–19	0.91
Creatinine, mg/dL	0.70, 0.44–1.09	0.64, 0.40–0.89	**0.03**
Cystatin C, mg/L	0.70, 0.45–1.36	0.65, 0.52–0.97	**0.02**
Alb, g/dL	4.6, 3.0–5.5	4.6, 4.1–5.3	0.69
TB, mg/dL	1.1, 0.4–5.1	0.8, 0.2–1.8	**0.03**
ALT, IU/L	23, 6–142	20, 13–44	**0.03**
ChE, IU/L	270, 132–452	296, 197–501	0.06
γ-GTP, IU/L	69, 18–355	43, 21–181	**< 0.001**
Hyaluronic acid, ng/mL	34, 11–428	23, 9–81	**0.005**
Type IV collagen, ng/mL	163, 67–326	151, 110–403	0.17
APRI	0.45, 0.19–1.68	0.20, 0.12–0.66	**< 0.001**
Fib-4 index	0.82, 0.37–2.25	0.35, 0.25–0.78	**< 0.001**
BNP, pg/mL	22.4, 4.0–370.6	12.9, 5.8–79.9	**0.04**
Warfarin, n (%)	81 (84)	28 (88)	0.75
Acetylsalicylic acid, n (%)	75 (78)	26 (81)	0.78
ACE-Is/ARBs, n (%)	69 (72)	25 (78)	0.64
β-blockers, n (%)	45 (47)	15 (47)	0.99
Diuretics, n (%)	22 (23)	2 (6)	**0.04**
Digoxin, n (%)	4 (4)	1 (3)	0.78

Proteinuria, n (%)	30 (31)	4 (13)	**0.04**
Reduced eGFR (< 90 mL/min/1.73 m^2), n (%)	6 (6)	1 (3)	0.68

ACE-Is, angiotensin converting enzyme inhibitors; ALT, alanine aminotransferase; APC, atria-pulmonary connection; APRI, aspartate aminotransferase to platelet ratio index; ARBs, angiotensin II receptor blockers; Alb, albumin; BNP, b-type natriuretic peptide; BUN, blood urea nitrogen; CVP, central venous pressure; ChE, cholinesterase; Fib-4, Fibrosis-4; PVRI, resistance of pulmonary vascular index; SpO_2, percutaneous oxygen saturation; TB, total bilirubin; eGFR, estimated glomerular filtration rate; γ-GTP, γ-glutamyl transpeptidase; Variables: median (range), or number, (percentage). Bold *p values* represent < 0.05.

Supplemental Table 3. Risk factors of liver dysfunction (Forns index > 4.21)

	Unit odds ratio	95% confidence interval	*p value*
Post-procedure duration, years	1.36	1.09–1.70	**0.007**
The age at the Fontan procedure, months old	1.01	0.99–1.02	0.05
Presence of Proteinuria	2.91	0.84–10.1	0.09
BNP, pg/mL	1.01	0.99–1.02	0.47

BNP, b-type natriuretic peptide. Bold *p values* represent < 0.05.