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Chronic kidney damage in the adult Fontan population

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ABSTRACT

Objectives: 1) To determine the accuracy of estimated GFR (eGFR) as compared to directly measured GFR (mGFR) in the adult Fontan population; 2) to determine the true prevalence of chronic kidney damage (CKD) as determined by uACR AND eGFR.
Methods: Prospective study of 81 patients Fontan patients (≥18 years) followed at St. Paul's Hospital, University of British Columbia. CKD-EPI and MDRD equations used to calculate eGFR, mGFR determined by ^{99m}Tc-DTPA renal dynamic imaging and urine albumin to creatinine ratios were calculated.
Results: The mGFR was 93 ± 27 ml/min/1.73 m^2: 28 (53%) had an mGFR < 90 ml/min/1.73 m^2 and 1 (2%) had an mGFR <60 ml/min/1.73 m^2. There was a modest correlation between mGFR and eGFR (EPI/MDRD) ($r = 0.50$, $p < 0.0001$ and $r = 0.54$, $p < 0.0001$ respectively). Both eGFR (EPI) (bias 27.0; 95% CI 18.0–27.7 ml/min/m^2, $p < 0.0001$) and eGFR (MDRD) (bias 15.5; 95% CI 7.6–17.4 ml/min/m^2, $p < 0.0001$) overestimated GFR as compared to mGFR. Among patients with an eGFR (EPI)/(MDRD) >90 ml/min/1.73 m^2, 50% and 46% respectively had an mGFR <90 ml/min/1.73 m^2. Significant albuminuria (>3 mg/mmol) was present in 33% and upwards of 32% of patients with a normal eGFR (MDRD/EPI) had evidence of CKD with uACR >3 mg/mmol. Using combined criteria of eGFR <90 ml/min/1.73 m^2 and/or uACR >3 mg/mmol, 46% of patients had evidence of CKD.
Conclusions: This study draws attention to the need for stringent CKD screening as an important proportion of CKD is currently not being detected. Mild undetected CKD, an early marker of end organ damage, may also be an early sign of Fontan failure that requires warrants further research.

1. Background

The Fontan procedure creates a unique circulation that separates the systemic venous circulation from the systemic arterial circulation in children born with univentricular physiology. This surgery has substantially decreased mortality and children are now surviving into adulthood [1,2]. The downside is that as a result of the surgically created Fontan circulation, patients are exposed to a high-pressure venous circulation and relative deprivation of cardiac output over a lifetime. In addition, along with possible previous episodes of acute kidney injury and neuro-hormonal/inflammatory changes, susceptibility to extra-cardiac organ damage including chronic kidney damage is increased (CKD). Certainly, extra-cardiac organ damage is being increasingly recognized in the Fontan population, however, there is limited published data examining CKD in this population.

Retrospective data has shown that moderate to severe kidney damage as diagnosed by estimated glomerular filtration rate (eGFR) alone is present in up to 10–15% of adult Fontan patients and is associated with up to a 5 fold increase in mortality [3]. Even a mild degree of CKD as determined by an eGFR between 60 and 90 ml/min/m^2 has been shown to be associated with a poor prognosis in the Fontan population. Glomerular filtration rate (GFR) is accepted as the best overall measurement of kidney function and an essential means for screening CKD. Accurate determination of GFR is important for the diagnosis and categorization of CKD. However, the accuracy of routine assessment of kidney function using estimated GFR (eGFR) in the Fontan population is unknown as some endogenous markers are likely to be suboptimal in select groups of patients. We question whether eGFR assessment is accurate in the Fontan population given the abnormal circulation, liver congestion, decreased muscle mass and abnormal protein metabolism. Furthermore, according to the KDIGO 2012 guidelines, CKD should be determined by BOTH eGFR assessment and urine albumin to creatinine ratio (uACR) [4]. Urine ACR alone is a marker of kidney damage and predicts adverse outcomes in many populations including the heart failure population [5–8]. However, uACR is not routinely assessed in the Fontan population and the true prevalence of CKD, using both uACR and GFR measurements, is unknown.

The objectives of this study were to: 1) to determine the accuracy of eGFR as compared to directly measured GFR (mGFR) in the adult Fontan population; 2) to determine the true prevalence of CKD as determined by uACR AND eGFR in the adult Fontan population.

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2. Methods

2.1. Study population

This is a prospective study of adult patients (≥18 years) who underwent a Fontan operation. Patients actively followed in the Pacific Adult Congenital Heart Clinic at St. Paul's Hospital, University of British Columbia were approached for consent and enrolled between 2014 and 2016. Exclusion criteria included patients who were pregnant, declined to give consent or were hospitalized in the prior 60 days. The institutional ethics review board approved the study.

All patients underwent a complete history, physical examination and assessment of New York Heart Association functional class. Physical examination included resting oxygen saturation at room air (after 5 min of rest). The following data was also obtained from the patient records: underlying cardiac diagnoses, age at and type of Fontan procedure, other cardiac interventions, current cardiac medications, and history of all cardiac events that had occurred up until the time of last follow-up. Cardiac event composite included: thromboembolic complications, heart failure requiring additional therapy or hospitalization, refractory arrhythmias requiring pharmacologic or electrophysiology intervention and/or protein losing enteropathy. Standard investigations including electrocardiogram, cardiopulmonary stress testing, and echocardiogram were performed at or within 2 months of the clinical visit.

2.2. Kidney function assessment

All patients underwent outpatient blood collection for serum creatinine. GFR was estimated (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease Study (MDRD) equations. Directly measured GFR (mGFR) was determined by ^{99m}Tc-DTPA renal dynamic imaging. After measuring height and weight, drinking 300-to-500-mL water, and emptying the bladder, participants received a bolus injection of 185 MBq ^{99m}Tc-DTPA (purity 95–99%). The ^{99m}Tc-DTPA renal dynamic imaging measurement was carried out and after image acquisition, mGFR was automatically calculated with a computer by the Gates method. Urine albumin to creatinine ratio was calculated and averaged from two first morning voids.

2.3. Statistical analysis

All data was analyzed using SPSS version 18.0 (SPSS, Inc., Chicago, Illinois). No data sets were normally distributed, thus, nonparametric statistics were used throughout. Bias, precision, and accuracy were used to evaluate the performance of the MDRD and EPI equations as compared to mGFR. Bias was defined as the median results of differences between eGFR and mGFR (eGFR–mGFR). The interquartile range (IQR) of the differences was a marker of precision. Accuracy was calculated as the proportion of eGFR within 30% of mGFR (P_{30}). Classical Bland–Altman plots analysis was also used to compare mGFR and eGFR. Smoothed lines fit to plotted data for each patient, bias (eGFR–mGFR) against eGFR. The association of mGFR and any CKD with cardiovascular events was evaluated using logistic regression analysis. Data were considered statistically significant at $p < 0.05$. CKD prevalence was ascertained by the stringent criteria set forth by the Kidney Disease: Improving Global Outcomes guidance 2012.

3. Results

A total of 81 consecutive adult Fontan patients were enrolled in this study (Table 1). The mean eGFR of the overall population was 109 ± 19 ml/min/1.73 m^2 by the EPI equation and 100 ± 22 ml/min/1.73 m^2 by MDRD equation. Ten patients (12%) had an eGFR <90 ml/min/1.73 m^2, of which 3 patients had an eGFR <60 ml/min/1.73 m^2 as calculated by the EPI equation. Eighteen patients (22%) had an eGFR <90 ml/min/1.73 m^2, of which 4 patients had an eGFR <60 ml/min/1.73 m^2 as calculated by the MDRD equation.

Fifty-two adult Fontan patients underwent direct measurement of GFR. The mean mGFR was 93 ± 27 ml/min/1.73 m^2: 28 (53%) had an mGFR <90 ml/min/1.73 m^2 and 1 (2%) has an mGFR <60 ml/min/1.73 m^2. There was a moderately positive correlation between mGFR and eGFR (EPI) ($r = 0.50$, $p < 0.0001$) (Fig. 1a) and between mGFR and eGFR (MDRD) ($r = 0.54$, $p < 0.0001$) (Fig. 1b). Both eGFR (EPI) (bias 27.0; 95% CI 18.0–27.7 ml/min/m^2, $p < 0.0001$) and eGFR (MDRD) (bias 15.5; 95% CI 7.6–17.4 ml/min/m^2, $p < 0.0001$) overestimated GFR as compared to mGFR. However, there was less bias with the eGFR (MDRD) equation. Bland-Altman analysis demonstrated a consistent result (Fig. 1c and d). The proportion of individuals with an eGFR within 30% of the mGFR was 50% for eGFR (EPI) and 77% for eGFR (MDRD). Precision assessment was 25.5 for eGFR (EPI) and 27.8 for eGFR (MDRD). Results were consistent with analyses defined by the bias (eGFR-mGFR) versus eGFR, and the smoothed lines show the fit of the data (Fig. 2a and b). Among patients with an eGFR (EPI) >90 ml/min/1.73 m^2, 24 of 48 (50%) has an mGFR < 90 ml/min/1.73 m^2. Similarly 20 of 43 (46%) patients with an eGFR (MDRD) >90 ml/min/1.73 m^2 had an mGFR < 90 ml/min/1.73 m^2. In contrast, among patients with an eGFR (EPI) or eGFR (MDRD) >60 ml/min/1.73 m^2, none had an mGFR < 60 ml/min/1.73 m^2. Among the 52 patients with a directly measured GFR, the mGFR was 88 ± 19 ml/min/1.73 m^2 vs. 93 ± 19 ml/min/1.73 m^2, $p = 0.46$ in those who experienced a cardiovascular event vs. those who did not [OR 0.98 (0.96–1.0), $p = 0.45$].

Table 1
Patient characteristics.

Characteristic	Patients[a]
	n = 83
Age, years	28.4 ± 9.3
Male	49 (60%)
Fontan anatomy	
Atriopulmonary	13 (16%)
Lateral tunnel	30 (36%)
Extra-cardiac conduit	38 (46%)
Cardiac history	
Atrial arrhythmias	34 (41%)
Protein losing enteropathy	5 (6%)
Thromboembolism	20 (24%)
Heart Failure	13 (16%)
Systemic ventricle	
Normal	43 (52%)
Mildly depressed function	28 (34%)
Moderately/severely depressed function	12 (14%)
Morphologic right ventricle	21 (25%)
Morphologic left ventricle	60 (72%)
Indeterminate ventricle	2 (2%)
Systemic AV valve regurgitation	
≥ moderate	17 (20%)
Medications	
ACE/ARB	37 (44%)
Beta blocker	32 (38%)
Aspirin	30 (36%)
Warfarin	41 (49%)
Diuretic	8 (10%)

[a] Mean ± SD or n (%).

Fifty-two adult Fontan patients completed the uACR assessment with a mean uACR of 4.4 ± 10.1 mg/mmol (median 1.8 mg/mmol and range 0.2 to 70.0 mg/mmol). Among those who completed uACR, eGFR (MDRD) was 100 ± 22 ml/min/1.73 m^2 and eGFR (EPI) was 109 ± 21 ml/min/1.73 m^2.The prevalence of any degree of albuminuria greater or equal to 1 mg/mmol was 65% (n = 34/52). Significant albuminuria defined as >3 mg/mmol was present in 33% (n = 17/52) of all enrolled patients (Table 2). In the uACR ≤3 mg/mmol vs. >3 mg/mmol the eGFR (MDRD) was 101 ± 24 ml/min/1.73 m^2 vs. 98 ± 18 ml/min/1.73 m^2, $p = 0.62$ and eGFR (EPI) was 110 ± 22 ml/min/1.73 m^2 vs. 108 ± 19 ml/min/1.73 m^2, $p = 0.78$. Upwards of 32% of adult Fontan patients with a normal eGFR (MDRD) had evidence of kidney damage with uACR >3 mg/mmol and 30% with a normal eGFR (EPI) had a uACR >3 mg/mmol (Table 2). Using combined criteria of eGFR <90 ml/min/1.73 m^2 and/or uACR >3 mg/mmol, 46% of adult Fontan patients had evidence of CKD. Of the 34 patients that underwent both mGFR and uACR assessment, 14 had a normal mGFR >90 ml/min/1.73 m^2 and of these 6 (43%) had evidence of kidney damage with uACR >3 mg/mmol. In this group of patients that had mGFR evaluation up to 76% have evidence of CKD by mGFR <90 ml/min/1.73 m^2 and/or uACR >3 mg/mmol. Among the 52 patients with a uACR measurement, the uACR was 5.9 ± 14.9 mg/mmol vs. 3.4 ± 4.9 mg/mmol, $p = 0.38$ in those who experienced a cardiovascular event vs. those who did not [OR 1.0 (0.96–1.1), $p = 0.42$].

4. Discussion

This study is the first to examine the reliability of commonly used eGFR equations in comparison with directly measured GFR in the

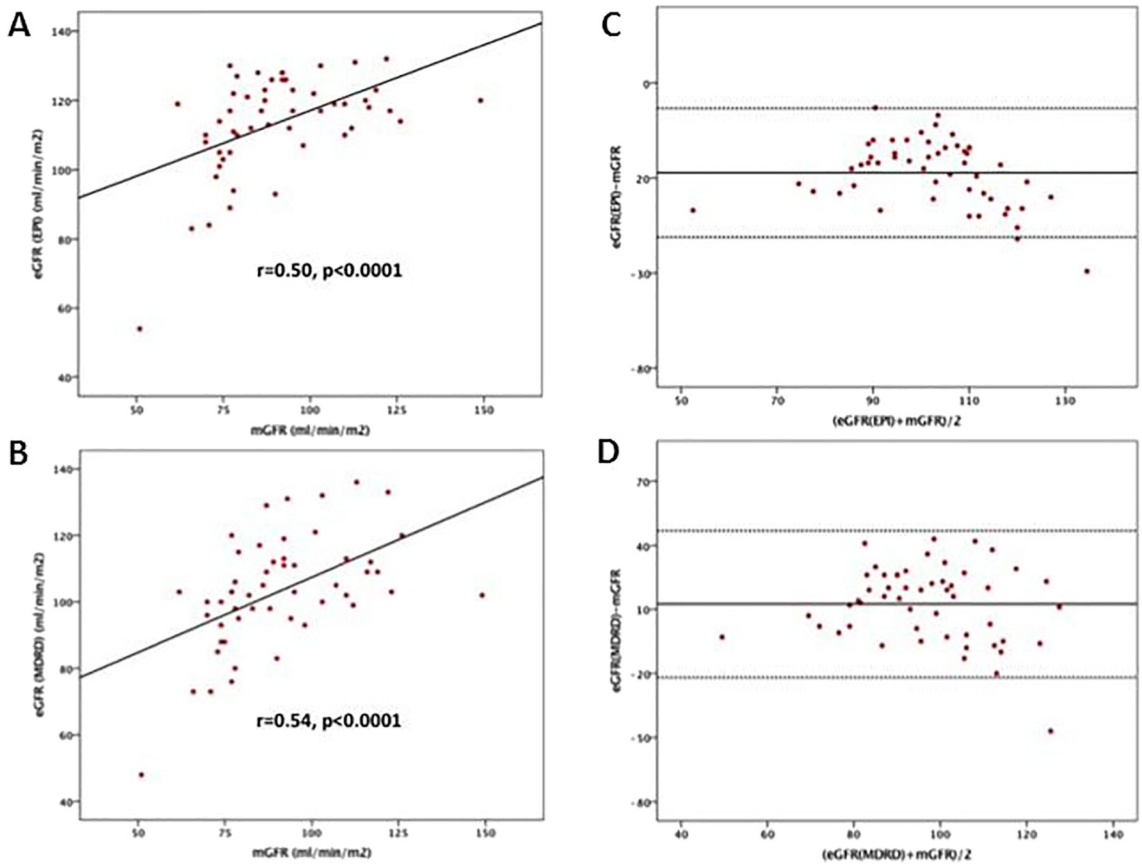

Fig. 1. Regression Analysis and Bland-Altman Plot A & B. Comparison of mGFR with eGFR (EPI) and eGFR (MDRD) respectively. **C&D**. Bias plots compare mGFR with eGFR (EPI) and eGFR (MDRD) respectively. The difference between eGFR and mGFR was regressed against the mean of eGFR and mGFR.

adult Fontan population. We found that approximately 50% of adult Fontan patients have a mild reduction in GFR when ascertained by a direct measurement. In fact, 45–50% of these adult Fontan patients with a mild reduction in mGFR were not identified when the GFR was estimated. This study is also the first to determine the prevalence of CKD in the adult Fontan population as per the widely accepted KDIGO Guidelines using both eGFR AND uACR. We found that at least 30% of adult Fontan patients were not identified as having CKD when using eGFR alone with a total of 46% displaying evidence of CKD as determined by eGFR AND uACR criteria. The prevalence of CKD could be as high as 75% when using mGFR instead of eGFR assessment in combination with uACR.

The etiology of CKD in the Fontan population is multi-factorial and certainly the prevalence of CKD is much higher than what would be expected for a similarly aged normal population. Although the Fontan palliated heart does not represent the classic heart failure model, the complex underlying interaction of the heart, kidneys and vasculature leads to a cardio-renal type syndrome [9,10]. The pathophysiology is complex and related to chronic venous congestion, pre-sinusoidal hepatic congestion, neurohormonal activation, decreased cardiac output, inflammation, and oxidative stress. The relatively increased right-sided pressures can lead to decreased effective arterial blood volume and cardiac output. This in turn yields diminished renal blood flows with neurohormonal changes that ultimately have a further negative impact on renal and cardiac function. Certainly increased right atrial pressures and venous congestion have been shown to be associated with a decrease in GFR in the structurally normal heart. In addition, exposure to multiple surgeries and nephrotoxins over time lead to episodes of acute kidney injury that are also known to predispose patients to CKD. The effect of all the above may be more profound in the Fontan population given the absence of a sub-pulmonic ventricle and inability to augment cardiac output in the setting of systemic vasodilation. Similarly, albuminuria can occur via various mechanisms including damage to the glomerular basement membrane secondary to increased central venous pressure, renal congestion, endothelial dysfunction and inflammatory cytokine activation and reduced tubular reabsorption of albumin as a consequence of tubular dysfunction [11–15]. Systemic venous congestion is known to increase efferent arteriolar pressure and decrease in afferent arteriolar blood flow that increases filtration pressure within the glomerulus also causing albuminuria.

We report that assessment of kidney function by eGFR alone, as is the routine clinical practice in the majority of adult congenital heart disease clinics, greatly underestimates the true prevalence of CKD in an adult Fontan population. Estimated GFR methods suggest that 12% and 22% of Fontan patients have reduced eGFR (<90 ml/min/1.73 m^2) as determined by eGFR (EPI) and eGFR (MDRD) respectively. However, our study shows that using these routine equations to estimate GFR fails to identify an important proportion of individuals with CKD. We found that over 50% of those with a normal estimated GFR in fact have a mildly reduced GFR when measured directly. Specifically, among patients with a normal eGFR by EPI or MDRD equations, 50% and 46% respectively had evidence of kidney damage with direct measurement. The correlation of eGFR and mGFR was modest at best, with the MDRD equation demonstrating less bias as compared to the EPI equation. Routine assessment of GFR by direct measurement is not feasible and likely not required as we did not find eGFR estimates to be missing moderate to severe CKD. A single mGFR evaluation in adulthood may be sufficient to identify mild CKD so that special consideration can be given to avoiding acute kidney injury and kidney protection.

When the assessment of CKD is expanded as per the KDIGO recommendations to include urine ACR, it becomes apparent that the adult Fontan patients have evidence of early end organ damage that is

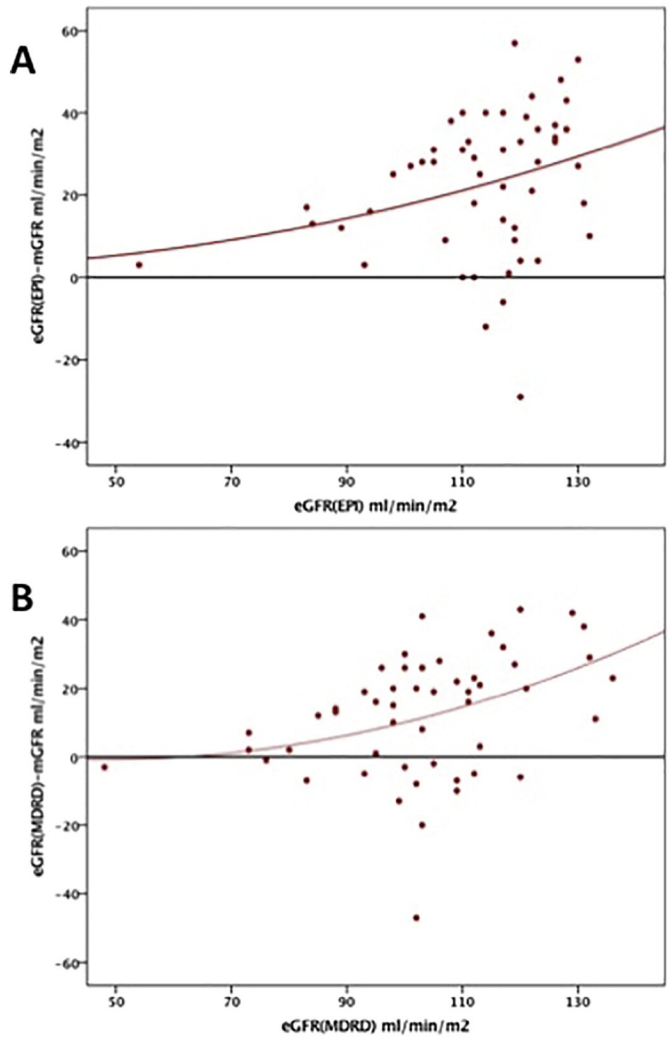

Fig. 2. Relationship between eGFR and bias (calculated as eGFR-mGFR). Solid horizontal line indicates no difference. Smoothed line shows the fit of the data. A. eGFR (EPI) B. eGFR (MDRD).

currently not being detected. Approximately 30% of patients with a normal eGFR by EPI or MDRD have evidence of significant albuminuria. Previous studies have also shown that microalbuminuria is prevalent in patients with a Fontan circulation [16,17]. As per KDIGO guidelines, when taking eGFR <90 ml/min/1.73 m^2 and/or significant albuminuria as a diagnosis of CKD, 46% of our population are affected by CKD as compared to 12–22% when using eGFR assessment alone. This prevalence increases further when taking into account that eGFR itself underestimated true kidney function, so that the prevalence of mild CKD could be as high as 75% in this complex population.

An increased urine albumin excretion is a recognized and accepted early marker of kidney damage and its quantification is used for monitoring patients with CKD as well as for estimating the risk of kidney disease progression. Albuminuria, defined as values >3 mg/mmol has been shown to be associated not only with CKD progression, but also with an increased risk of cardiovascular death in the general population [5,8,18–19]. The greater prevalence of albuminuria and its association with worsening outcomes in heart failure patients has also been well demonstrated [6,7,11]. Several studies have shown a 40–80% increase in the adjusted risk for all-cause mortality and hospital admission. Other studies have also shown that mortality risk increases with increasing albumin excretion even in the normal range, suggesting that this parameter is a continuous measure of risk [8,20]. The association of uACR with outcomes in the Fontan population has not been established, however, the overwhelming evidence in several other populations is highly suggestive that its prognostic value would hold true in this population and should be the focus of future study. Certainly in our study we found a trend towards an association between a lower mGFR or increasing uACR with adverse cardiovascular events. This was limited as the event adjudication was retrospective and the number of Fontan patients relatively small.

Traditionally recognized mostly late presentations of the "failing/failed" Fontan circulation include progressive edema, refractory pleural effusions, ascites, decreasing exercise tolerance, cachexia and/or protein losing enteropathy. Previously under-recognized non-cardiac sequelae of the failing Fontan circulation are now being appreciated. Extra-cardiac organ disease including kidney, liver, and lymphatic issues have all been implicated in the Fontan failure trajectory. Our study demonstrates that the adult Fontan population has a high prevalence of end organ kidney damage, albeit mild. Certainly, manifest kidney dysfunction in the adult Fontan population is one of the final common pathways associated with mortality or cardiac transplantation. Fontan circulation failure usually presents insidiously over years. In contrast to other forms of operated complex congenital heart disease, Fontan patients have lived with less than ideal cardiac output their entire lives, and may neither recognise nor show overt manifestations of progressive decline until deterioration is marked. As such, routine assessment may be missing those patients at higher risk of decompensation over the longer term. Detection of early extra-cardiac organ dysfunction could serve as a marker of early Fontan failure and predict adverse outcomes. Detecting early CKD by uACR, with no other explanation for an increased uACR, may identify patients that are starting to travel down the path of chronic Fontan failure. Targeting therapies at this stage may be effective in interrupting/slowing the Fontan failure trajectory and reducing associated adverse events and will be the focus of future study.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest

Table 2
CKD classification.

			Persistent albuminuria categories		
			Normal to mildly increased	Moderately increased	Severely increased
			<3 mg/mmol	3–30 mg/mmol	>30 ml/mmol
GFR categories (ml/min/1.73 m^2)[a]	Normal or high	≥90	28/32	12/13	1/1
Description and range	Mildly decreased	60–89	5/1	3/2	0
	Mild/moderately decreased	45–59	1/1	1/1	0
	Moderate to severely decreased	30–44	0	0	0
	Severely decreased	15–29	1/1	0	0
	Kidney failure	<15	0	0	0

[a] eGFR for each category is displayed as eGFR (MDRD)/eGFR (EPI).

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