Received: 28 August 2018 | Revised: 17 November 2018 | Accepted: 3 January 2019

DOI: 10.1111/chd.12746

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Creatinine-based estimation of glomerular filtration rate in patients with a Fontan circulation

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Funding information
National Health and Medical Research Council, Grant/Award Number: NHMRC Project Grant 1047923

Abstract

Background: Patients with a Fontan circulation are at risk of renal dysfunction. We analyzed cross-sectional data in pediatric and adult Fontan patients in order to assess the accuracy of commonly used serum creatinine-based methods in estimating glomerular filtration rate (GFR).

Methods: A total of 124 Fontan patients (58 children, 66 adults) were enrolled across three study centers. Measurement of GFR (mGFR) using in vivo ^{99m}Tc-DTPA clearance was performed. Various serum creatinine-based equations were used to calculate estimated GFR (eGFR).

Results: Mean mGFR was 108 ± 28 mL/min/1.73 m^2 in children and 92 ± 20 mL/min/1.73 m^2 in adults. Fourteen children (25%) and 28 adults (45%) had an mGFR

Abbreviations: BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DTPA, diethylenetriaminepentaacetate; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study; mGFR, measured glomerular filtration rate; NYHA, New York Heart Association.

<90 mL/min/1.73 m^2. There was no significant correlation between mGFR and eGFR (Schwartz) in children (r = 0.22, P = .1), which substantially overestimated mGFR (bias 50.8, 95%CI: 41.1-60.5 mL/min/1.73 m^2, P < .0001). The Bedside Schwartz equation also performed poorly in the children (r = 0.08, P = .5; bias 5.9, 95%CI: −2.9-14.6 mL/min/1.73 m^2, P < .0001). There was a strong correlation between mGFR and both eGFR (CKD-EPI) and eGFR (MDRD) in adults (r = 0.67, P < .0001 in both cases), however, both methods overestimated mGFR (eGFR(CKD-EPI):bias 23.8, 95%CI: 20-27.6 mL/min/1.73 m^2, P < .0001; eGFR (MDRD):bias 16.1, 95%CI: 11.8-20.4 mL/min/1.73 m^2, P < .0001). None of the children with an mGFR <90 mL/min/1.73 m^2 had an eGFR (Schwartz) <90 mL/min/1.73 m^2. Sensitivity and specificity of eGFR (CKD-EPI) and eGFR (MDRD) for mGFR <90 mL/min/1.73 m^2 in adults were 25% and 92% and 39% and 100%, respectively.

Conclusions: This study identifies the unreliability of using creatinine-based equations to estimate GFR in children with a Fontan circulation. The accuracy of formulas incorporating cystatin C should be further investigated and may aid noninvasive surveillance of renal function in this population.

KEYWORDS
Fontan procedure, glomerular filtration rate, kidney disease, renal function

1 | INTRODUCTION

The Fontan procedure has substantially improved survival for children born with complex congenital cardiac malformations not amenable to biventricular repair.[1] The focus in these patients is now shifting to the extracardiac manifestations resulting from this unique physiological state, characterized by elevated venous pressures and a reduced cardiac output. These inherent properties of the circulation, in addition to the use of multiple nephrotoxic medications, prolonged cardiopulmonary bypass, exposure to intravenous contrast agents, and longstanding cyanosis place the kidneys of a Fontan patient at undeniable risk.[2,3] We now know that up to half of adult Fontan patients will have evidence of chronic kidney damage in the form of a reduced measured glomerular filtration rate (mGFR) <90 mL/min/1.73 m.[2,4] It is likely that renal dysfunction will go undetected for some time in many Fontan patients, which may be partly due to the overestimation of GFR using serum-based formulas, and a lack of consensus on the best methods of surveillance.[5] Data are emerging on the use of cystatin C-based equations in Fontan patients, which may more accurately reflect true GFR in the Fontan cohort when compared to creatinine-based equations, possibly due to reduced lean muscle mass in these patients.[6,7] Nonetheless, the use of cystatin C in Fontan has not been completely validated, and creatinine-based methods remain the mainstay of routine GFR estimation at many centers worldwide. We analyzed cross-sectional data in pediatric and adult Fontan patients in order to assess the accuracy of commonly used serum creatinine-based methods for estimating GFR in this unique cohort.

2 | METHODS

2.1 | Study population

Data were collected between 2013 and 2015 as part of a cross-sectional study investigating end organ damage in the Fontan population. Patients were recruited for the cross-sectional study from the Australian and New Zealand Fontan Registry, the full design and administration of which has been described previously.[8] Patients were eligible for recruitment if they had consented to participate in Registry substudies and could attend one of three study centers (The Royal Children's Hospital, Melbourne, Australia; The Children's Hospital at Westmead, Sydney, Australia; Starship Children's Hospital, Auckland, New Zealand). Exclusion criteria included patients who were pregnant or breast-feeding, had a history of severe or end-stage renal impairment, or had previously declined to participate in substudies of the Registry. Patients were included in the current subanalysis if they had undergone measurement of serum creatinine as part of the study. The study was approved by local institutional ethics review boards. All patients underwent a complete history, physical examination, and assessment of New York Heart Association functional status. Additional medical and surgical data were obtained from the Registry database. Patients were separated based on age into children (<18 years) and adults (18 years) for the purpose of analysis.

2.2 | Assessment of renal function

All patients underwent venous blood sampling for serum creatinine, measured in micromoles per liter (μmol/L) and converted to milligrams per deciliter (mg/dL). Creatinine values were measured using either an enzymatic assay or the Jaffe method. Blood sampling was performed at the time of cannulation for ^{99m}Tc-DTPA clearance following the administration of prehydration with 20 mL/kg of oral water, which was consumed in the 1 hour preceding the study. Various serum creatinine-based equations were used for the estimation of GFR (Table 2), including the Schwartz, Bedside Schwartz, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease Study (MDRD) equations. Measured GFR (mGFR) was determined by in vivo ^{99m}Tc-DTPA clearance using multiple time-point blood samplings and a single reference standard.

2.3 | Statistical analysis

All data were analyzed using GraphPad Prism 7 (GraphPad Software, Inc, San Diego, California). Variables are presented as count (percentage), mean ± standard deviation (SD), or median (interquartile range (IQR)). Nonparametric statistics were used for data that were not normally distributed. Bias and accuracy were used to evaluate the performance of the Schwartz, CKD-EPI, and MDRD equations as compared to mGFR. Bias was defined as the median results of differences between eGFR and mGFR (eGFR-mGFR). Accuracy was calculated as the proportion of eGFR within 30% of mGFR. Linear regression analysis and Bland-Altman plots were used to compare mGFR and eGFR. Correlations between normally distributed variables were calculated using Pearson's correlation (*r*). Data were considered significant at $P < .05$. Separate analyses were performed for children and adult patients due to varying degrees of validation of individual creatinine-based methods of GFR estimation in each. Subanalysis based on the type of creatinine assay was also undertaken in both the children and adult patients.

3 | RESULTS

A total of 124 Fontan patients (58 children, 66 adults) were enrolled across three major study centers. Patient characteristics (Table 1) were representative of the Registry.[9]

3.1 | Children

Mean serum creatinine was 0.60 ± 0.12 mg/dL (53 ± 11 μmol/L) using the Jaffe method ($n = 21$) and 0.57 ± 0.15 mg/dL (50 ± 13 μmol/L) using the enzymatic assay ($n = 37$) ($P = .3$). The mean eGFR (Schwartz) was 158 ± 31 mL/min/1.73 m^2 (150 ± 31 mL/min/1.73 m^2 using the Jaffe method and 163 ± 31 mL/min/1.73 m^2 using the enzymatic assay, $P = .1$). No patients had an eGFR (Schwartz) <90 mL/min/1.73 m^2. The mean eGFR (Schwartz$_{bedside}$) was 114 ± 22 mL/min/1.73 m^2 (108 ± 17 mL/min/1.73 m^2 using the Jaffe method and 117 ± 24 mL/min/1.73 m^2 using the enzymatic assay, $P = .1$). Nine patients (16%) had an eGFR (Schwartz$_{bedside}$) <90 mL/min/1.73 m^2.

Fifty-seven children underwent measurement of GFR using ^{99m}Tc-DTPA clearance. The mean mGFR was 108 ± 28 mL/min/1.73 m^2. Fourteen patients (25%) had an mGFR <90 mL/min/1.73 m^2 and no patient had an mGFR <60 mL/min/1.73 m^2. There was a weak positive correlation between mGFR and eGFR (Schwartz) that was not significant ($r = 0.22$, $P = .1$) (Figure 1A). However, in children in whom the Jaffe method was used for measurement of serum creatinine there was a significant correlation between mGFR and eGFR (Schwartz) ($r = 0.48$, $P = .03$, vs $r = 0.18$, $P = .27$ using the enzymatic assay). Use of eGFR (Schwartz) significantly overestimated GFR when compared to mGFR (bias 50.8, 95%CI: 41.1-60.5 mL/min/1.73 m^2, $P < .0001$) (Figure 1C). The proportion of individuals with an eGFR (Schwartz) within 30% of the mGFR was 30% (17/57), and 54% (31/57) had an eGFR (Schwartz) outside 50% of the mGFR. Use of the eGFR (Schwartz$_{bedside}$) equation reduced the degree of overestimation of mGFR (bias 5.9, 95%CI: −2.9-14.6 mL/min/1.73 m^2, $P < .0001$) when compared to the Schwartz equation (Figure 1D), but also failed to correlate significantly with mGFR ($r = 0.08$, $P = .5$) (Jaffe: $r = 0.33$, $P = .2$; enzymatic: $r = 0.11$, $P = .5$) (Figure 1B). The proportion of individuals with an eGFR (Schwartz$_{bedside}$) within 30% of the mGFR was 70% (40/57), and 9% (5/57) had an eGFR (Schwartz$_{bedside}$) outside 50% of the mGFR. Difference (eGFR-mGFR) vs eGFR (Schwartz) and eGFR (Schwartz$_{bedside}$) is displayed in Figure 1E and F, respectively, highlighting that the difference increased with increasing eGFR.

Linear regression analyses were performed comparing alternative creatinine-based eGFR formulas with mGFR in children. These equations yielded similar results, with weak and largely nonsignificant correlations with mGFR (see Table 2).

3.2 | Adults

Mean serum creatinine was 0.80 ± 0.13 mg/dL (71 ± 12 μmol/L) using the Jaffe method ($n = 23$) and 0.78 ± 0.17 mg/dL (69 ± 15 μmol/L) using the enzymatic assay ($n = 43$) ($P = .5$). The mean eGFR was 116 ± 16 mL/min/1.73 m^2 using the CKD-EPI equation (107 ± 17 mL/min/1.73 m^2 using the Jaffe method and 118 ± 18 mL/min/1.73 m^2 using the enzymatic assay, $P = 0.02$) and 108 ± 22 mL/min/1.73 m^2 using the MDRD equation (96 ± 17 mL/min/1.73 m^2 using the Jaffe method and 112 ± 24 mL/min/1.73 m^2 using the enzymatic assay, $P = .004$). Nine patients (14%) had an eGFR (CKD-EPI) <90 mL/min/1.73 m^2, and no patient had an eGFR (CKD-EPI) <60 mL/min/1.73 m^2. Fifteen patients (23%) had an eGFR (MDRD) <90 mL/min/1.73 m^2, of whom one patient (2%) had an eGFR (MDRD) <60 mL/min/1.73 m^2.

Sixty-two adult Fontan patients underwent measurement of GFR using ^{99m}Tc-DTPA clearance. The mean mGFR was 92 ± 20 mL/min/1.73 m^2. Twenty-eight patients (45%) had an mGFR <90 mL/min/1.73 m^2 and 2 patients (3%) had an mGFR <60 mL/min/1.73 m^2.

TABLE 1 Patient characteristics

	Children (*n* = 58)	Adults (*n* = 66)
Male, *n* (%)	37 (64%)	31 (47%)
Age (years)	12.8 ± 2.6	27.1 ± 8.2
Years post-Fontan	8.4 ± 3.1	19.9 ± 6.3
Anatomical comorbidities, *n* (%)		
Dextrocardia/mesocardia	4 (7%)	6 (9%)
Isomerism/heterotaxy	6 (10%)	4 (6%)
Ventricular morphology, *n* (%)		
Left	31 (53%)	50 (76%)
Right	20 (35%)	13 (20%)
Biventricular/indeterminate	7 (12%)	3 (5%)
Primary morphological diagnosis, *n* (%)		
TA	15 (26%)	21 (32%)
DILV	7 (12%)	15 (23%)
DORV	5 (9%)	9 (14%)
CAVC	7 (12%)	5 (8%)
HLHS	11 (19%)	2 (3%)
ccTGA	4 (7%)	5 (8%)
PA-IVS	3 (5%)	3 (5%)
Other	6 (10%)	6 (9%)
Prior BCPS, *n* (%)	57 (98%)	30 (45%)
Age at Fontan	4.4 (3.5-5.1)	5.1 (3.3-8.3)
Fontan type, *n* (%)		
AP	0 (0%)	18 (27%)
LT	0 (0%)	24 (36%)
ECC	58 (100%)	24 (36%)
Fenestrated, *n* (%)	24 (41%)	14 (21%)
Current medications, *n* (%)		
ACEI/ARB	25 (43%)	22 (33%)
Beta-blocker	4 (7%)	13 (20%)
Diuretic	6 (10%)	9 (14%)
Aspirin	29 (50%)	25 (38%)
Warfarin	29 (50%)	36 (55%)
NYHA classification, *n* (%)		
I	46 (79%)	42 (64%)
II	9 (16%)	21 (32%)
III	3 (5%)	3 (5%)
Pacemaker in situ, *n* (%)	1 (2%)	12 (18%)

Data are presented as, *n* (%), mean ± SD or median (IQR).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AP, atriopulmonary; ARB, angiotensin receptor blocker; BCPS, bidirectional cavopulmonary shunt; CAVC, common atrioventricular canal; ccTGA, congenitally corrected transposition of the great arteries; DILV, double-inlet left ventricle; DORV, double-outlet right ventricle; ECC, extracardiac conduit; HLHS, hypoplastic left heart syndrome; LT, lateral tunnel; NYHA, New York Heart Association; PA-IVS, pulmonary atresia with intact ventricular septum; SD, standard deviation; TA, tricuspid atresia.

There was a positive correlation between mGFR and eGFR (CKD-EPI) ($r = 0.67$, $P < .0001$) (Figure 2A) and between mGFR and eGFR (MDRD) ($r = 0.67$, $P < .0001$) (Figure 2B). These correlations were similar for each of the creatinine assays (CKD-EPI: $r = 0.73$, $P < .001$ using the Jaffe method and $r = 0.69$, $P < .0001$ using the enzymatic assay, MDRD: $r = 0.68$, $P < .001$ using the Jaffe method and $r = 0.73$, $P < .0001$ using the enzymatic assay). Both equations overestimated GFR when compared to mGFR: eGFR (CKD-EPI) (bias 23.8, 95%CI:

TABLE 2 Creatinine-based estimation of GFR (eGFR) using various formulas vs measured GFR (mGFR) using ^{99m}Tc-DTPA clearance

Name (Reference)	Formula	Mean ± SD (mL/min/1.73 m^2)[a]	Correlation with mGFR (r, P)[b]
Children (<18 years) (n = 58)			
Schwartz[26-28]	$k \times Ht/S_{Cr}$	158 ± 31	0.22, .1
Schwartz$_{crea}$[29]	$42.3\ (Ht/S_{Cr})^{0.780}$ (Ht in meters)	93 ± 14	0.09, .5
Schwartz$_{bedside}$[19]	$0.413 \times (Ht/S_{Cr})$	113 ± 22	0.08, .5
Counahan-Barratt[30]	$0.43 \times (Ht/S_{Cr})$	118 ± 23	0.08, .5
Léger[31]	$(0.641 \times Wt)/S_{Cr} + (0.00131 \times Ht^2)/S_{Cr}$	108 ± 25	0.17, .2
FAS$_{crea}$(Ht)[32]	$107.3/[S_{Cr}/Qcrea(Ht)]$	114 ± 23	0.15, .3
CKD-EPI[20]	$141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{age} \times (1.018^{female}) \times (1.159^{Black})$	150 ± 18	0.22, .1
MDRD[33,34]	$175 \times S_{Cr}^{-1.154} \times age^{-0.203} \times (0.742^{female}) \times (1.212^{Black})$	190 ± 58	0.18, .2
Cockroft-Gault[35]	$((140-age) \times Wt)/(72 \times S_{Cr}) \times (0.85^{female})$	137 ± 40 mL/m^2	0.32, **.02**
Cockroft-Gault$_{IBW}$[35]	$((140-age) \times IBW)/(72 \times S_{Cr}) \times (0.85^{female})$	141 ± 36 mL/m^2	0.32, **.02**
Children (12-18 years) (n = 36)[c]			
Cockroft-Gault[35]	$((140-age) \times Wt)/(72 \times S_{Cr}) \times (0.85^{female})$	146 ± 44 mL/m^2	0.42, **.01**
Adults (n = 66)			
CKD-EPI[20]	$141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{age} \times (1.018^{female}) \times (1.159^{Black})$	116 ± 16	0.67, **<.0001**
MDRD[33,34]	$175 \times S_{Cr}^{-1.154} \times age^{-0.203} \times (0.742^{female}) \times (1.212^{Black})$	108 ± 22	0.67, **<.0001**
Schwartz$_{bedside}$[19]	$0.413 \times (Ht/S_{Cr})$	92 ± 17	0.62, **<.0001**
Cockroft-Gault[35]	$((140-age) \times Wt)/(72 \times S_{Cr}) \times (0.85^{female})$	128 ± 34 mL/m^2	0.49, **<.0001**
Cockroft-Gault$_{IBW}$[35]	$((140-age) \times IBW)/(72 \times S_{Cr}) \times (0.85^{female})$	119 ± 29 mL/m^2	0.61, **<.0001**

k = 0.55 for children and adolescent girls, 0.7 for adolescent boys; Ht = height (in cm unless otherwise specified); S_{Cr} = serum creatinine (mg/dL unless otherwise specified); Wt = weight (kg); FAS = Full Age Spectrum; $Qcrea(Ht) = 3.94 - 13.4 \times Ht + 17.6 \times Ht^2 - 9.84 \times Ht^3 + 2.04 \times Ht^4$ (Ht in m); κ = 0.7 for females, 0.9 for males; α = −0.329 for females, −0.411 for males; $\min(S_{Cr}/\kappa, 1)$ = minimum of S_{Cr}/κ or 1; max = maximum of S_{Cr}/κ or 1; BSA = body surface area, calculated using the Dubois method[36]; IBW: ideal body weight, calculated using the Devine formula[37]. P-values <.05 are in highlighted in bold text.

[a]Units are mL/min/1.73 m^2 unless otherwise specified.

[b]Adults (n = 62) and children (n = 57) for correlation with mGFR.

[c]All equations analyzed in the Children (<18 years) group were also analyzed in the Children (12-18 years) group, with results only included in the table if P < .05.

20-27.6 mL/min/1.73 m^2, P < .0001) and eGFR (MDRD) (bias 16.1, 95%CI: 11.8-20.4 mL/min/1.73 m^2, P < .0001). There was less bias with the eGFR (MDRD) equation (P = .01). Bland-Altman analyses are displayed in Figure 2C and D. The proportion of individuals with an eGFR within 30% of the mGFR was 55% (34/62) for eGFR (CKD-EPI) and 69% (43/62) for eGFR (MDRD). As seen in the children, the difference between eGFR and mGFR was greater with higher eGFR (Figure 2E and F).

Among adult patients with an eGFR (CKD-EPI) >90 mL/min/1.73 m^2, 21 of 57 (37%) had an mGFR <90 mL/min/1.73 m^2. Similarly, 17 of 51 (33%) with an eGFR (MDRD) > 90 mL/min/1.73 m^2 had an mGFR <90 mL/min/1.73 m^2. An eGFR (CKD-EPI) <90 mL/min/1.73 m^2 was 25% sensitive and 92% specific for an mGFR <90 mL/min/1.73 m^2, while an eGFR (MDRD) <90 mL/min/1.73 m^2 was 39% sensitive and 100% specific for an mGFR <90 mL/min/1.73 m^2, ie, an mGFR <90 mL/min/1.73 m^2 was correctly identified in 7 of 28 (25%) cases using eGFR (CKD-EPI) and in 11 of 28 (39%) using eGFR (MDRD).

4 | DISCUSSION

This study is the largest of its kind to compare creatinine-based eGFR with mGFR in a representative cross-sectional sample of pediatric and adult patients with a Fontan circulation. Given that adults with congenital heart disease have an up to 3-fold increased risk of mortality in the presence of chronic kidney disease (CKD), the accuracy of commonplace methods used for surveillance and monitoring of renal dysfunction is crucial and must be scrutinized in this physiologically unique subpopulation.[3,10] The Schwartz equations are currently the most commonly used equations in children for the estimation of GFR, and the CKD-EPI and MDRD equations are well validated in adults.[11-16]

Although it has been suspected that creatinine-based equations may be especially inaccurate in estimating GFR in children with a Fontan circulation, this study is the first in this population to directly compare results to mGFR and definitively highlight this inaccuracy. We

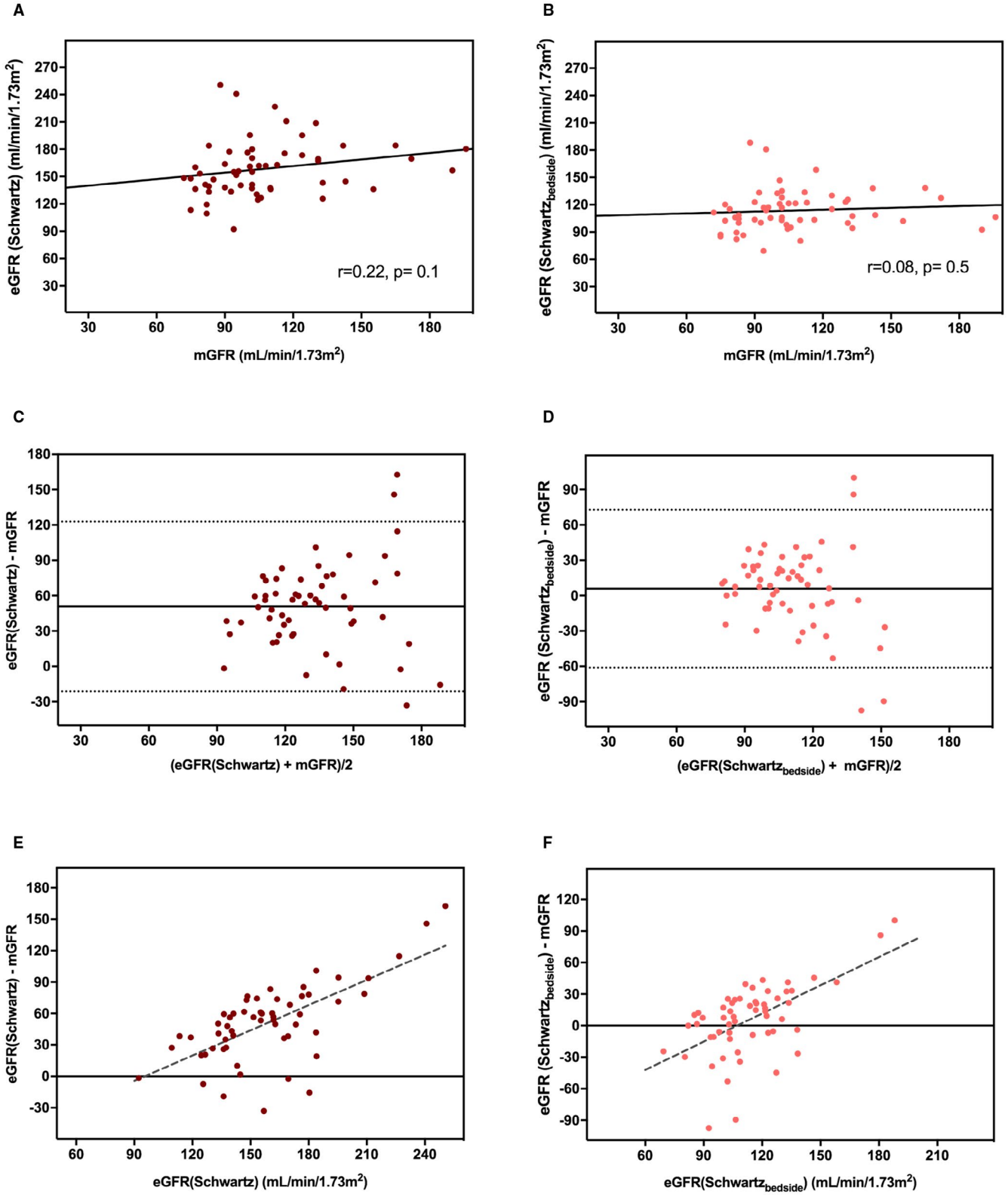

FIGURE 1 Children. Regression analysis (A and B). Comparison of mGFR with eGFR (Schwartz) and eGFR (Schwartz$_{bedside}$), respectively. Bland-Altman plots (C and D). Comparison of mGFR with eGFR (Schwartz) using a bias plot, showing mean bias and upper and lower limits of agreement. Difference between eGFR and mGFR plotted against the mean of eGFR and mGFR. Relationship between eGFR and difference (eGFR-mGFR) (E and F). Horizontal line at zero indicates no difference between two methods

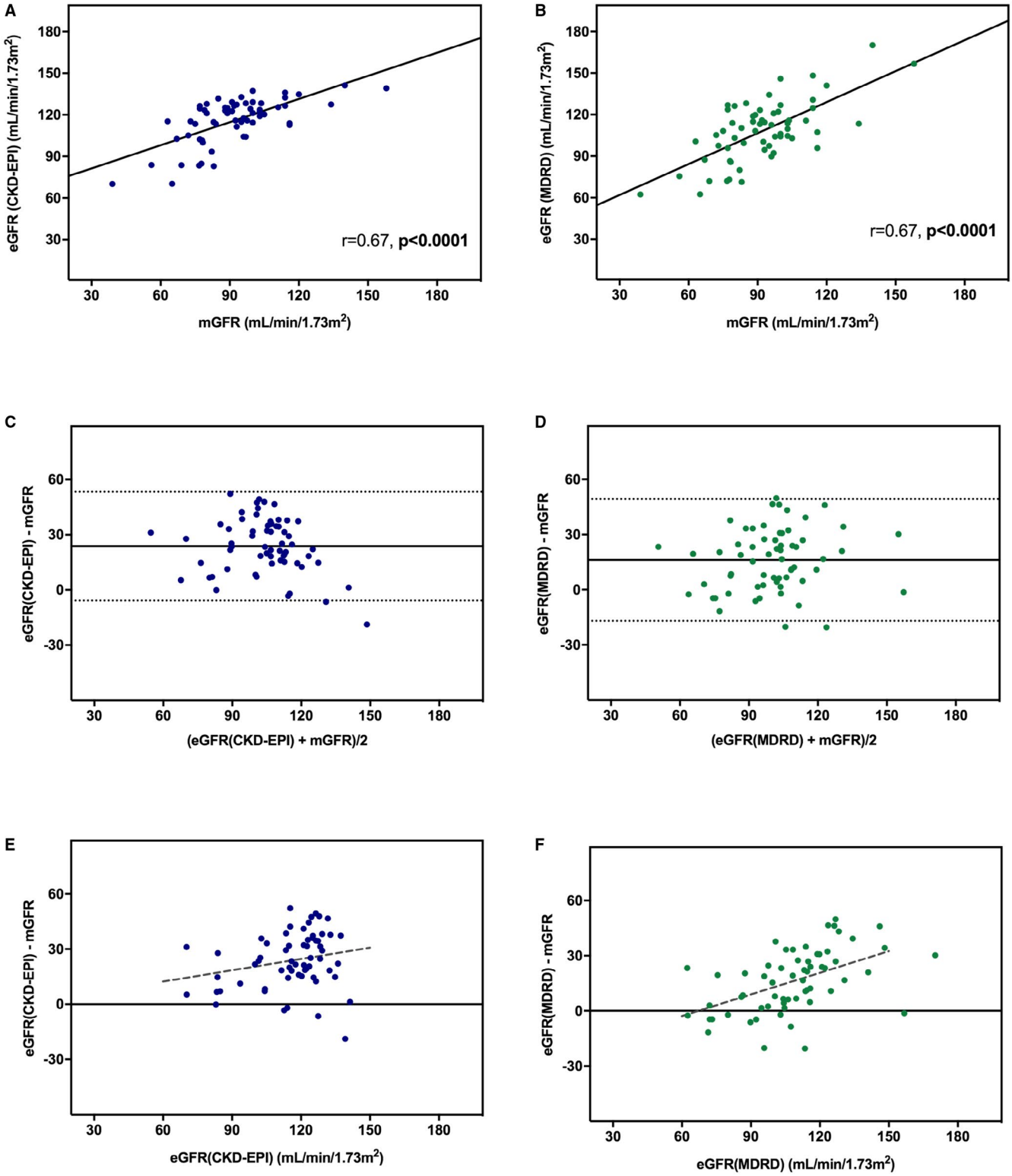

FIGURE 2 Adults. Regression analysis (A and B). Comparison of mGFR with eGFR (CKD-EPI) and eGFR (MDRD), respectively. Bland-Altman plot (C and D). Comparison of mGFR with eGFR (CKD-EPI) and eGFR (MDRD) using bias plots, showing mean bias and upper and lower limits of agreement. Difference between eGFR and mGFR plotted against the mean of eGFR and mGFR. Relationship between eGFR and difference (eGFR-mGFR) (E and F). Horizontal line at zero indicates no difference between the two methods

found that one-quarter of children had an mGFR <90 mL/min/1.73 m^2 at a mean age of 13 years (mean 8 years post-Fontan). However, none of these children were identified using the Schwartz formula, which substantially overestimated mGFR. The Bedside Schwartz equation performed slightly better in the children, identifying close to two thirds of those with an mGFR <90 mL/min/1.73 m^2. Importantly, we could not demonstrate any significant correlation between either of the Schwartz formulas and mGFR in the children. Less commonly used equations yielded similar results (Table 2), with the Cockroft-Gault formula the only one of these with a demonstrable significant (although weak) correlation with mGFR in patients aged <18 years.[17] This equation, however, is not recommended for routine use in pediatric patients with significant error noted in children with varying renal pathologies.[18] The inaccuracies of creatinine-based estimates of GFR in children are well known, especially in children with reduced muscle mass.[9,10] In spina bifida patients, who are known to have severely reduced muscle mass, creatinine-based eGFR is problematic and has been shown to overestimate mGFR.[10] However, incorporation of cystatin C into eGFR calculations resulted in a more accurate estimation of GFR in this group of children. The concordance of eGFR and mGFR was assessed in a group of patients prior to hematopoietic cell transplantation, with varying primary disease processes including malignancy, immunodeficiency, and bone marrow failure.[11] The eGFR (Schwartz) equation showed a mean bias of 57 mL/min/1.73 m^2, similar to that seen in our cohort of children. Mean bias was reduced to 14.1 using the Bedside Schwartz equation, and incorporation of cystatin C again resulted in a more accurate estimation of GFR, reducing the mean bias to −3.6 mL/min/1.73 m^2. Similar to these two cohorts, Fontan patients are known to have reduced muscle mass compared to control groups.[7,12] This finding alone is unlikely to explain the discrepancy of eGFR and mGFR found in children in this study, given the improved accuracy of eGFR in the adults.

Almost half of the adult patients had an mGFR <90 mL/min/1.73 m^2 at a mean age of 27 years, and a mean of 20 years post-Fontan. This figure is consistent with that found by Lee et al, who reported a 53% prevalence of mGFR <90 mL/min/1.73 m^2 in adult patients of a similar age.[4] Similar to the findings of the aforementioned study was the observed tendency of both the CKD-EPI and MDRD equations to overestimate GFR, with the MDRD equation responsible for a lesser degree of overestimation in both theirs and the current study. This comes in contrast to previously reported mean differences between eGFR (MDRD) and mGFR in large studies of adult patients (ranging from −5.5 to 0.9 mL/min/1.73 m^2 in patients with known CKD, and from −29 to 3.3 mL/min/1.7 $3m^2$ in patients without known CKD) demonstrating a propensity for underestimation of mGFR.[13-17] The CKD-EPI equation has also demonstrated a slight tendency to underestimate GFR in adult patients without known CKD.[18] Although the degree of correlation between the CKD-EPI and MDRD methods and mGFR was essentially the same in this study, we demonstrated the MDRD equation to be superior to CKD-EPI in accuracy, sensitivity, and specificity when estimating mGFR. Our data and those of Lee et al suggest that the MDRD equation is the creatinine-based method of choice for routine surveillance of renal function in Fontan adults. The caveat of this is the relatively low sensitivity of this method for identifying an eGFR <90 mL/min/1.73 m^2, meaning that results less than 110 mL/min/1.73 m^2 should raise suspicion and warrant further investigation.

The precise reason for the relative inaccuracy of creatinine-based eGFR in the children vs the adults in the current study is unclear. The effect of active linear growth and the resulting difficulty in estimating muscle mass during this period may play a role in this discrepancy, especially when used in those with altered body composition such as Fontan patients. The primary issue, however, is likely to be inherent in the development of the eGFR equations. Many of these equations were developed in populations with known CKD and a GFR <75-90 mL/min/1.73 m^2, with varying degrees of validation in patients with normal renal function.[19,20] We found that eGFR by all equations was less accurate at higher mGFR. A higher mean eGFR in the children therefore translates to greater inaccuracy of estimation of mGFR when compared to the adults.

The type of creatinine assay used should be taken into account when interpreting results of creatinine-based eGFR equations. The use of an enzymatic assay results in a lower creatinine value compared to the older Jaffe method, and hence generally results in a relatively higher estimation of GFR.[21] This is consistent with our findings, with estimations using the enzymatic assay-derived creatinine measurements comparatively higher than those using measurements obtained via the Jaffe method. Interestingly, we found that eGFR (Schwartz) calculated in children using Jaffe method-derived creatinine measurements correlated significantly with mGFR, while the use of enzymatic assay-derived measurements did not. This is likely due to the fact that the original formula was based upon serum creatinine values determined by the older Jaffe method. The Jaffe method has now been replaced by an enzymatic assay at many centers worldwide, which is thought to provide more accurate creatinine measurements, particularly at lower serum creatinine concentrations.[22] Use of the enzymatic assay in adults resulted in a stronger correlation between mGFR and eGFR (MDRD), but not with eGFR (CKD-EPI).

There is increasing evidence supporting the use of cystatin C, a protein encoded by CST3, as a biomarker for renal and cardiovascular disease.[21] Use of cystatin C alone or in combination with creatinine has been shown to strengthen the association between eGFR and risk of death and end-stage renal disease across a broad population of patients with CKD.[23] Combination of serum cystatin C with creatinine has been demonstrated to more precisely estimate GFR in a number of studies, when compared to the use of creatinine or cystatin C alone.[24,25] In contrast to creatinine, cystatin C is not affected by muscle mass, and could be the key to accurate estimation of GFR independent of altered body composition in Fontan patients.[22] Equations incorporating this biomarker may improve accuracy of eGFR compared to creatinine-based equations, with a recent study by Opotowsky et al demonstrating an association between cystatin C-based eGFR and risk of adverse outcomes in Fontan patients (and no such relationship observed between creatinine-based eGFR and adverse outcomes).[6] However, it has been hypothesized that this biomarker may be associated with unfavorable hemodynamics

in general and may not more accurately estimate GFR in Fontan patients when compared to serum creatinine.[6] Further studies comparing cystatin C-based eGFR calculations, including those incorporating both cystatin C and serum creatinine, with directly measured GFR are required to establish the accuracy of these methods in the Fontan population.

Additional biomarkers including kidney injury molecule 1 (KIM-1), N-acetyl-glucosaminidase (NAG), and neutrophil gelatinase-associated lipocalin have been investigated in the Fontan population, with an aim to distinguish varying mechanisms of renal dysfunction, such as glomerular and tubular injury.[6] At this stage, their role in routine care is unclear. Microalbuminuria is also widely prevalent in Fontan patients, with rates potentially exceeding that observed in cyanotic congenital heart disease.[23] The relationship between microalbuminuria to both GFR deterioration and adverse outcomes in Fontan patients has not yet been established. Angiotensin-converting enzyme inhibitors may exhibit a renoprotective effect in Fontan patients, with reduced degree of proteinuria observed in those on one of these medications, consistent with their established efficacy in patients with nondiabetic nephropathy.[23,24] Their role in Fontan-associated nephropathy should be further investigated.

4.1 | Limitations

This study was conducted across three major sites, and although a standardized protocol was used, findings may be subject to some variation in investigative techniques used across these three centers. Most notably, the use of two different assays for serum creatinine measurement was a weakness of this study, although this did allow us to analyze the effect of these two methods on the subsequent findings. The multicenter nature of this study, however, enabled us to include a large cohort of patients from across Australia and New Zealand.

5 | CONCLUSIONS

The findings of the current study are likely to have implications on the detection and monitoring of renal dysfunction in the Fontan cohort, with significant inaccuracy noted in the use of creatinine-based equations compared to mGFR in children. If performed at all, creatinine-based eGFR should be interpreted with caution in children with a Fontan circulation, especially when underpinning clinical decisions such as medication dosage, intravenous contrast tolerance, and those informing decisions based on cardiac transplantation. The use of creatinine-based equations to calculate eGFR is more accurate in adults with a Fontan circulation, however, also tends to overestimate the measured values. Further investigation into the accuracy of GFR estimation methods incorporating cystatin C in the Fontan population should be undertaken and may aid routine noninvasive surveillance of renal function in these patients. Formal measurement of GFR should be considered in those who require an accurate assessment of kidney function.

ACKNOWLEDGMENTS

The authors acknowledge Aneta Kotevski's role in project setup as well as all the technicians, clinical, and support staff who assisted in data acquisition. This project was supported by a grant from the National Health and Medical Research Council (NHMRC Project Grant 1047923). The authors acknowledge support provided to the Murdoch Childrens Research Institute by the Victorian Government's Operational Infrastructure Support Program. Yves d'Udekem is a NHMRC Clinician Practitioner Fellow (1082186).

CONFLICTS OF INTEREST

Yves d'Udekem is consultant for MSD and Actelion. Robert Weintraub serves on an advisory board for Actelion. The remaining authors have nothing to disclose.

DISCLOSURES

All authors have approved the final version of this manuscript.

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How to cite this article: Wilson TG, d'Udekem Y, Winlaw DS, et al. Creatinine-based estimation of glomerular filtration rate in patients with a Fontan circulation. *Congenital Heart Disease*. 2019;14:454–463. https://doi.org/10.1111/chd.12746