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# Comparison of creatinine and cystatin C for estimation of glomerular filtration rate in pediatric patients after Fontan operation

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## Abstract

**Background:** There are several limitations when using creatinine to estimate glomerular filtration rate, especially in children with chronic medical conditions who are at high risk of kidney dysfunction. Cystatin C has been the recent focus of research as a replacement biomarker for creatinine. Our objective was to compare the 2 biomarkers in pediatric single-ventricle heart disease patients who have undergone the Fontan operation. We hypothesized that there would be poor correlation and agreement between the 2 estimates of renal function.

**Methods:** This was a single center retrospective chart review of 20 patients who had previously undergone Fontan operation. Demographic and clinical data were collected from medical records. Blood samples were collected as part of routine clinical care and simultaneously measured for serum creatinine and cystatin C. Glomerular filtration rate was calculated using the creatinine-based bedside Schwartz formula and cystatin C-based Zapatelli equation. Spearman correlation and Bland-Altman analysis were used to assess correlation and agreement.

**Results:** The median Schwartz-derived estimated glomerular filtration rate was 98.94 mL/min/1.73 $m^2$ while the median Zappitelli-derived estimated glomerular filtration rate was 84.76 mL/min/1.73 $m^2$. The mean difference was −19.27 suggesting poor agreement. There was weak to moderate correlation between the Schwartz and cystatin C estimated glomerular filtration rate.

**Conclusion:** The bedside Schwartz formula may be an overestimate of glomerular filtration rate in pediatric single-ventricle heart disease patients who have undergone the Fontan operation. While larger studies are necessary, cystatin C is a promising biomarker to replace creatinine and better estimate kidney function in this population.

KEYWORDS
acute kidney injury, chronic kidney disease, cystatin C, Fontan

## 1 | INTRODUCTION

The Fontan operation is commonly the third operation in a series of palliative surgeries for single-ventricle heart disease. The Fontan operation is a palliative procedure that creates a circulatory system characterized by elevated central venous pressures and results in a host of comorbidities. Central venous hypertension and low cardiac output have been shown to decrease renal perfusion

  

in this cohort.[1] Cardiopulmonary bypass itself is a risk factor for acute kidney injury. As a result, acute kidney injury following the Fontan operation is a common occurrence, ranging from 42% to 52% of patients.[1,2] The presence of acute kidney injury following the Fontan procedure is associated with greatly increased morbidity, including prolonged mechanical ventilation and increased length of hospital stay.[2] Fontan survivors are also at increased risk for developing chronic kidney disease later on in life with a prevalence of up to 50% after 10 years.[3]

Exogenous agents such as inulin, Ethylenediaminetetraacetic acid, and iohexol are the gold standard for assessing glomerular filtration rate. These molecules are freely filtered through the glomerulus and are neither secreted nor reabsorbed.[4] While these ideal filtration markers are accurate, they are impractical for routine clinical use due to complexity and cost. Creatinine-based estimates of renal function have several limitations. Serum creatinine is modulated by age, gender, medications, muscle mass, and hydration status.[5] These drawbacks have led to a recent search to identify alternative methods to assess renal function.

Cystatin C is a reversible protein inhibitor of cysteine proteases produced by all nucleated cells. It is considered to be an ideal marker to estimate glomerular filtration rate, as it is generated at a constant rate and almost exclusively renally eliminated without tubular secretion or reabsorption.[6] In addition, cystatin C does not appear to be affected by age, gender, body muscle mass, inflammatory state, or nutritional conditions.[7] Many studies have shown cystatin C is an earlier and more sensitive marker for acute kidney injury than serum creatinine.[8-12] Cystatin C may be particularly more informative of renal function in Fontan patients because of their lower muscle mass. Limited to no data exists on the comparison of creatinine-based estimated glomerular filtration rate and cystatin C estimated glomerular filtration rate in children with single-ventricle heart disease following the Fontan operation. The purpose of this study was to compare cystatin C-derived estimated glomerular filtration rate and creatinine-derived estimated glomerular filtration rate in pediatric single-ventricle heart disease patients who have undergone the Fontan operation. We hypothesized that there would be poor correlation and agreement between the 2 measures of renal function.

## 2 | MATERIALS AND METHODS

We performed a retrospective chart review of outpatient children with single-ventricle heart disease who had undergone Fontan palliation at Children's Hospital Colorado from July 2016 to June 2018. The study was approved by the University of Colorado Multiple Institutional Review Board with a waiver of informed consent.

All patients are seen annually at Fontan follow-up clinic and undergo simultaneous testing of creatinine and cystatin C as well as a urinalysis with urine protein to creatinine ratio. Initially, these labs were only performed on patients with a prior episode of acute kidney injury, however, when there were abnormalities in creatinine in patients with no prior episodes, we began evaluating all patients given the known limitations of creatinine. Any patient with an abnormality in this testing (ie, presence of chronic kidney disease) is referred to nephrology for followup and a more comprehensive assessement. For this retrospective chart review, demographic and clinical data were collected from medical records and single-ventricular function was abstracted from the report. Blood samples were collected as part of routine clinical care and measured for both serum creatinine and cystatin C. Serum creatinine was measured using the Vitros chemistry analyzer using the Vitros Creatinine slide method.[13] Glomerular filtration rate was then calculated using the bedside Schwartz equation as follows.[14]

$$0.4text13\times(\text{height in centimeters/serum creatinine})$$

Cystatin C was measured using the latex-enhanced immunoturbidometric assay. Glomerular filtration rate was the calculated using the Zappitelli Formula as follows.[15]

$$75.9text4\times(\text{Cys C})^{-1.1text7}$$

### 2.1 | Statistical analysis

Summary data for continuous variables is presented as median with interquartile range. Categorical variables were summarized as number with percent. Spearman correlation and Bland-Altman analysis were used to assess correlation and agreement between the bedside Schwartz glomerular filtration rate and cystatin C glomerular filtration rate equations.

## 3 | RESULTS

Over the study period, 20 patients underwent simultaneous creatinine and cystatin C testing, which in the past year became part of routine surveillance in the Fontan follow-up clinic. The median age was 9 years (interquartile range: 5.25-12.5 years) and 50% were male. All patients had previously undergone the Fontan procedure at a median age of 3.09 years (interquartile range: 2.59-3.91 years) (Table 1).

Most patients ($n$ = 15%, 75%) had experienced at least 1 prior episode of acute kidney injury. Some patients experienced more than 1 episode of acute kidney injury. Of the 3 patients with acute kidney injury after the Fontan operation, only 1 patient had not had a prior acute kidney injury episode. The distribution of acute kidney injury episodes after each surgery is summarized in Table 2. The median Schwartz glomerular filtration rate was 98.94 mL/min/1.73 $m^2$ (interquartile range: 90.85-116.46 mL/min/1.73 $m^2$) and the median cystatin C glomerular filtration rate was 84.76 mL/min/1.73 $m^2$ (IQR: 65.86-98.82 mL/min/1.73 $m^2$). There was weak to moderate linear correlation between the Schwartz and cystatin C glomerular filtration rate with ($r$ = 0.48) (Figure 1). The Bland-Altman plot is shown

**TABLE 1** Fontan patient demographics and clinical characteristics

| Variable | |
|---|---|
| Age at follow-up (years) | 9 (5.25-12.5) |
| Age at Fontan procedure (years) | 3.09 (2.59-3.91) |
| Sex (male) | 10 (50%) |
| Weight (kg) | 27.95 (21.93-42.35) |
| Height (cm) | 126.4 (109.7-151.62) |
| Systemic ventricle (left) | 9 (45%) |
| Ventricular function | |
| Normal | 17 (85%) |
| Mildly reduced | 1 (5%) |
| Moderate to severely reduced | 2 (10%) |
| Prior acute kidney injury (yes) | 15 (75%) |
| Schwartz glomerular filtration rate (mL/min/1.73 $m^2$) | 98.94 (90.85-116.46) |
| Cystatin C glomerular filtration rate (mL/min/1.73 $m^2$) | 84.76 (65.86-98.82) |
| Nephrotoxic medications | |
| Aspirin | 18 (90%) |
| ACEi/ARB | 7 (35%) |
| Diuretics | 5 (25%) |

*Note*. Variables are presented as median with interquartile range and categorical variables are presented as number (*n*) with percent (%).
Abbreviation: ACEi, angiotensin converting enzyme inhibitor.

**TABLE 2** Distribution of prior acute kidney injury episodes

| | Number (15) |
|---|---|
| Total number of patients with AKI | 15 (78%) |
| Number of patients with AKI post Norwood | 10 (67%) |
| Number of patients with AKI post Glenn | 6 (40%) |
| Number of patients with AKI post Fontan | 3 (20%) |
| Number of patients with >1 episode of AKI[a] | 6 (40%) |

[a]In these patients, the Norwood was always the first episode.

in Figure 2 demonstrating the difference in the means between the creatinine estimated glomerular filtration rate and cystatin C estimated glomerular filtration rate. The mean difference was −19.27 (95% confidence interval: −71, 32) suggesting poor agreement between the 2 measures of estimated glomerular filtration rate.

## 4 | DISCUSSION

We compared the correlation and agreement of cystatin C and creatinine when used to estimate glomerular filtration rate in 20 children with single-ventricle heart disease who have undergone Fontan operation. Limited data on the effect of the Fontan circulation on renal function and CKD exist. The Zappitelli equation utilizing

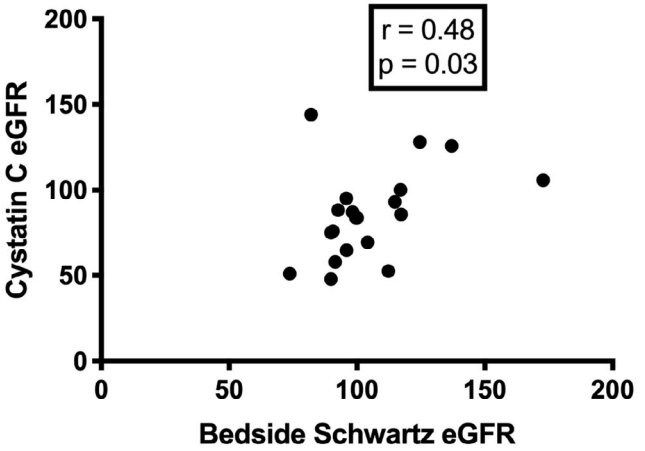


**FIGURE 1** Comparison of Glomerular filtration rate estimates by the bedside Schwartz equation and the cystatin C Zappitelli equation
The cystatin C-based estimating equation generally results in a lower estimated glomerular filtration rate.

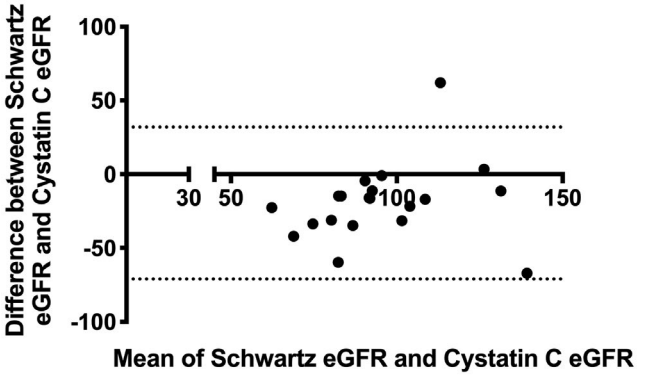


**FIGURE 2** Bland-Altman plot of the difference in estimated glomerular filtration rate by Schwartz and cystatin C compared to the mean of the 2 measurements
There is generally poor agreement between the 2 measures. The dotted lines represent the 95% confidence limits.

cystatin C generally resulted in a lower estimated glomerular filtration rate when compared to the creatinine-based bedside Schwartz formula with poor agreement between the 2 biomarkers. The median Schwartz-derived estimated glomerular filtration rate was 98.94 mL/min/1.73 $m^2$, suggesting normal kidney function while the median Zappitelli-derived estimated glomerular filtration rate was 84.76 mL/min/1.73 $m^2$ suggesting mild kidney dysfunction.

In children with chronic medical conditions, who are also high risk for kidney dysfunction, cystatin C-based estimated glomerular filtration rate has proven to be more accurate compared to creatinine. Over 10 equations exist to estimate glomerular filtration rate in the pediatric population. Some use creatinine or cystatin C individually, while others use a combination of the 2 biomarkers. The most widely used equation is the creatinine-based bedside Schwartz equation.[16] While this equation has been shown to be a good estimate of glomerular filtration rate in children with chronic kidney disease, it is often an overestimate of glomerular filtration rate in other populations.[16,17]

Equations including cystatin C have proven to be better estimates of glomerular filtration rate than creatinine alone.[17,18] A 2013 retrospective study by Nehus et al measured glomerular filtration rate with the gold standard, nuclear medicine, in 142 children and young adults who received an organ transplant or had a malignancy. Compared to the Nuclear medicine glomerular filtration rate gold standard, creatinine-based equations significantly overestimated glomerular filtration rate in the cohort, while cystatin C-based equations were reasonably accurate.[17] These findings were attributed to the lower muscle mass in children of this cohort. Similar to the findings from Nehus et al, the Schwartz equation is likely an overestimate of kidney function in our cohort due to lower muscle mass and therefore lower levels of serum creatinine. Children who have received Fontan palliation tend to be shorter with significant lean muscle deficits compared to their peers later in life and thus cystatin C may be a better estimate of kidney function in children with chronic medical conditions as the serum levels are not affected by muscle mass.[19] While the findings in several studies detail the benefit of cystatin C, none of these studies specifically discuss patients following the Fontan procedure.[16-18]

Single ventricle heart disease patients are at an increased risk of acute kidney injury every time they undergo cardiopulmonary bypass surgery as well as chronic kidney disease later in life. A recent study by Hasson et al looked at a heterogeneous population of pediatric congenital heart disease patients undergoing multiple surgeries. In their cohort, odds of acute kidney injury after a third surgery was 2.4 times more likely if they had an acute kidney injury after either of the first 2 surgeries.[20] There is a high prevalence of chronic kidney disease in the adult Fontan population with over 50% of patients having reduced glomerular filtration rate or microalbuminuria.[21] Signs of early kidney dysfunction can be seen in younger Fontan children as well. A study by Sharma et al looking at children with a median age of 13, found that 10% of survivors post-Fontan palliation had estimated glomerular filtration rate <90 and higher median parathyroid hormone levels compared to controls, indicating early chronic kidney disease. Similar to our study, they measured creatinine and cystatin C at a single point in time to estimate glomerular filtration rate. They found that although median serum creatinine concentration was slightly lower among Fontan subjects compared to controls, they had a higher median cystatin C level.[22]

Several studies have shown that equations using cystatin C significantly improved the risk classification in patients with chronic kidney disease.[18] Cystatin C equations strengthen the relationship between estimated glomerular filtration rate categories and risk of death from renal disease or cardiovascular causes.[18] A 2017 study by Opotowsky et al measured cystatin C, creatinine, and several urinary biomarkers in adult Fontan patients and measured time to first non-elective cardiovascular hospitalization or death. They found an association between cystatin C-based glomerular filtration rate and risk of adverse outcome. The same association with creatinine-based glomerular filtration rate could not be made, suggesting cystatin C is a more informative biomarker in Fontan patients.[23]

These findings are important for management and risk stratification of children at high risk for acute kidney injury and chronic kidney disease such as our cohort. Creatinine-based estimated glomerular filtration rate may be falsely reassuring in children with low muscle mass, and inaccurately predict risk of adverse outcomes in future. Our study did not compare the formula-based estimated glomerular filtration rates to a gold standard measurement that utilizes exogenous agents such as iohexol or inulin. Many patients are also on several chronic nephrotoxic medications including angiotensin converting enzyme inhibitors and aspirin. Chronic diuretics are also often used. In the setting of acute illness necessitating hospitalization, additional nephrotoxins are often added thereby increasing risk for acute kidney injury, which may be associated with substantial morbidity and mortality in the setting of pre-existing chronic kidney disease. Adjunctive therapeutic drug monitoring in addition to creatinine and cystatin C-based measurements should be considered when possible.

There are several limitations in this study. First, this was a single center retrospective study. Second the study population was small, consisting of 20 patients, many with a single time point of creatinine and cystatin c measurement. Given the retrospective nature of this study, we were not able to include a comparison with the gold standard of glomerular filtration rate testing.

In conclusion, in single-ventricle heart disease patients who have undergone Fontan operation there is poor agreement between the estimated glomerular filtration rates with the mean Zappitelli equation glomerular filtration rate being almost 20 mL/min/1.73 $m^2$ lower than the Schwartz-derived glomerular filtration rate. Larger studies in single-ventricle congenital heart disease patients with a history of acute kidney injury and risk for chronic kidney disease that include routine surveillance of both creatinine, cystatin C, and invasive glomerular filtration rate testing are necessary.

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## CONFLICT OF INTEREST

Dr. Katja Gist is a consultant for BioPorto. None of the other authors have any conflicts to disclose.

## AUTHOR CONTRIBUTIONS

*Collected data, wrote the manuscript:* Kirelik
*Collected data:* Fisher
*Wrote a portion of the manuscript, edited content:* DiMaria, Soranno
*Supervised the 1st author in data collection, manuscript preparation and edited the manuscript for content:* Gist

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