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Prevalence, Predictors, and Outcomes of Cardiorenal Syndrome in Children with Dilated Cardiomyopathy: A Report from the Pediatric Cardiomyopathy Registry

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Abstract

Background—The association of cardiorenal syndrome (CRS) with mortality in children with dilated cardiomyopathy (DCM) is unknown.

Methods—With a modified Schwartz formula, we estimated glomerular filtration rates (eGFR) for children 1 year old with DCM enrolled in the Pediatric Cardiomyopathy Registry at the time

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of DCM diagnosis and annually thereafter, and defined CRS as an eGFR <90 mL/min/1.73 m². Children with and without CRS were compared on survival and serum creatinine concentrations (SCr). The association between eGFR and echocardiographic measures was assessed with linear mixed-effects regression models.

Results—Of 285 eligible children with DCM diagnosed at 1 year of age, 93 were evaluable. CRS was identified in 57 (61.3%). Mean (SD) eGFR was 62.0 (22.6) mL/min/1.73 m² for children with CRS and 108.0 (14.0) for those without ($P<0.001$); median SCr concentrations were 0.9 and 0.5 mg/dL, respectively ($P<0.001$). The mortality hazard ratio of children with CRS vs. no CRS was 2.4 (95% CI: 0.8–7.4). eGFR was positively correlated with measures of left ventricular function and negatively correlated with age.

Conclusions—CRS in children newly diagnosed with DCM may be associated with higher 5-year mortality. Children with DCM, especially those with impaired left ventricular function, should be monitored for renal disease.

Keywords

cardiomyopathy; cardiorenal syndrome; chronic kidney disease; pediatrics; heart failure

Introduction

Cardiorenal syndrome (CRS) describes a variety of acute and chronic conditions in which the primary failing organ can be either the heart or the kidney [1]. Although the term “CRS” was not introduced until 2004 by the National Heart, Lung, and Blood Institute Working Group, the association between worsening kidney function and worsening heart function was recognized in the 1980s [2]. The syndrome was first defined as a condition characterized by the initiation or progression of renal insufficiency secondary to heart failure. However, this definition did not describe the negative effects of decreased kidney function on the cardiovascular system [3].

CRS can be sub-classified into five types [4]. Although several studies have looked at acute CRS (type I) in infants undergoing cardiopulmonary bypass [5, 6], studies of children with chronic left ventricular (LV) dysfunction, such as dilated cardiomyopathy (DCM), are lacking.

In adults, chronic cardiac abnormalities resulting in impaired kidney function are associated with adverse outcomes and prolonged hospitalizations [3, 7], and the prevalence of CRS has been reported to be as high as 30% [8]. The prevalence of CRS in children with chronic systolic dysfunction is unknown. Price et al. reported that 48% (35/73) of children with acute decompensated heart failure had an increased serum creatinine (SCr) concentration of 0.3 mg/dL from baseline and that elevated concentrations were associated with increased mortality or the need for mechanical ventricular assistance [9]. However, this study did not report the prevalence of kidney dysfunction at the time of the primary heart disease diagnosis or describe kidney function in patients with compensated heart failure. Another recent study showed elevated levels of an additional renal biomarker, fibroblast growth

factor 23 (FGF23), were associated with heart failure severity in children [10]. To our knowledge, epidemiological data on CRS in children with DCM have not been published.

The North American Pediatric Cardiomyopathy Registry (PCMR) reported the incidence of cardiomyopathy to be 0.57 per 100,000 children. Dilated cardiomyopathy accounts for more than 50% of these cases [11, 12]. Among congenital and acquired heart diseases in children, DCM has one of the highest mortality rates [13]. Even with advanced medical care, the 5-year mortality rate for children with DCM has remained at 17% over the past two decades [13], and freedom from death or transplantation was 54% 5 years after diagnosis [12].

Whether kidney dysfunction contributes to mortality in these children is unknown.

Unfortunately, chronic kidney disease (CKD) is often underdiagnosed in children [14].

Children with CRS represent a unique high-risk subgroup of children with CKD because of the additive morbidity and mortality of CKD in addition to the risk of heart disease. In the absence of known predictive risk factors for CRS in children, recognizing kidney dysfunction in children with DCM seems to be challenging, especially because this group of children is followed mainly by pediatric cardiologists.

We sought to determine 1) the prevalence and outcomes of CRS in children with newly diagnosed DCM, 2) the accuracy of interpreting SCr concentration as a marker of CRS, and 3) the association between CRS and LV function.

Methods

The PCMR is a National Heart, Lung, and Blood Institute-funded registry established to describe the epidemiologic features and clinical course of cardiomyopathies in children up to 18 years old and to promote the development of cause-specific treatments [15]. The registry has entered data from over 3500 children diagnosed since 1990 with different types of cardiomyopathies enrolled by almost 100 pediatric cardiomyopathy centers in United States and Canada.

Data in the PCMR were derived from two different cohorts. The first was a retrospective cohort identified from a review of medical records for diagnoses made between January 1, 1990 and December 31, 1995. The second was a prospective cohort of cases diagnosed after December 31, 1995. Children with specific secondary causes of myocardial abnormalities, such as congenital heart disease, endocrine disorders known to cause myocardial damage, history of chemotherapy or pharmacology-associated cardiotoxicity, chronic arrhythmia, and pulmonary parenchymal or vascular disease, were excluded. Once a patient was enrolled in the PCMR, an enrollment form with demographic, clinical, and diagnostic data from the first 30 days after diagnosis was submitted (defined as baseline data). Follow-up forms completed by annual chart review were also submitted. LV ejection fraction was captured only later in the study and available for fewer than half of the subjects. Each participating center obtained Institutional Review Board or Ethics Committee approval for the study.

Cardiomyopathy is a general term describing various phenotypes of heart muscle disease with different physiologies and prognoses. To avoid the confounding effect of these

different phenotypes, we included only children with a diagnosis of DCM. The analysis used the PCMR database as of November, 2011.

Design and Measurements

Patients with a diagnosis of DCM who had at least one SCr concentration reported in the registry to calculate eGFR were analyzed. Subjects less than one year of age at registry entry and those with an eGFR > 150 mL/min/1.73m² were excluded.

We used only the baseline data to determine the prevalence of CRS in children at the time of DCM diagnosis and classified these baseline SCr concentrations as normal or abnormal.

Patients with DCM in the PCMR met at least 1 of the following criteria: 1) strict echocardiographic criteria for DCM (LV dilation [i.e., LV end-diastolic dimension (LVEDD) >2 standard deviations (SD) above normal for body surface area] and depressed LV systolic function [LV fractional shortening (LVFS) or LV ejection fraction (LVEF) >2 SD below normal for age]); 2) pathologic findings consistent with DCM at autopsy or by endomyocardial biopsy; or 3) other clinical evidence of DCM provided by the cardiologist [15].

We defined CRS as an estimated glomerular filtration rate (eGFR) of <90 mL/min/1.73 m², as per the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative stratification of decreased eGFR [16]. The eGFR was calculated using the modified Schwartz formula [17, 18]:

$$eGFR_{(mL/min/1.73m^2)} = 0.413 \times \text{height}_{(cm)} / SCr_{(mg/dL)}.$$

We excluded children less than 1 year old because Schwartz reported this formula in CKD only for children more than 1 year old.

Whether glomerular hyperfiltration, regardless of proteinuria, is a sign of kidney injury is unknown, and neither the definition nor the implications of hyperfiltration are clear in clinical practice. Furthermore, hyperfiltration has been defined with different thresholds ranging from an eGFR between 120 and 150 mL/min/1.73 m² [19-21]. Unfortunately, the PCMR does not collect urinalysis data. Thus, we excluded children with an eGFR greater than 150 mL/min/1.73 m² from our analysis.

We compared demographic and clinical characteristics and survival rates between children with and without CRS. The accuracy of describing SCr concentrations as “normal” or “abnormal” as documented in the medical record was analyzed to evaluate the recognition of decreased eGFR among health care providers.

We used both the baseline and the annual follow-up data to determine the prevalence of CRS annually for 5 years after DCM diagnosis, to evaluate the effect of CRS on 5-year mortality rates, and to assess the association between eGFR and the values and Z scores for six echocardiographic measures: LVFS, LVEF, LVEDD, LV end-systolic dimension

(LVESD), LV end-diastolic posterior wall thickness (PWT), end-diastolic septal thickness (IVS), as well as the calculated PWT:LVEDD ratio (a measure of LV remodeling, with small values reflecting disproportionate left ventricular dilation relative to wall thickness). Z scores were calculated to body surface area.

Statistical Methods

Categorical data are presented as counts and percentages and were analyzed with Chi-square and Fisher's exact tests. Skewed distributions are described with medians and interquartile ranges (IQR) and were compared with a Wilcoxon rank sum test. Normal distributions are described with means and SD and compared with Student's *t* test. Agreement between the classification of SCr by primary providers as normal or abnormal and the gold standard of eGFR being normal, i.e. eGFR more or equal to 90 mL/min/1.73 m², or abnormal, i.e. eGFR less than 90 mL/min/1.73 m² was assessed with the kappa statistic (*k*).

To estimate survival, time to heart transplantation, and the composite of the earliest occurring of death or transplantation as a function of CRS status, we utilized an adjusted-risk-set method that accommodates left-truncated data [22], which allows the cases without available eGFR at the time of diagnosis (baseline) but later available eGFR value to enter the Kaplan-Meier plots and Cox regression models at the time of the first eGFR available for each case. This approach was adopted to increase the power of analyses given the relatively small number available eGFR values (ability to assign CRS classification) at the time of diagnosis. Simple linear mixed-effects regression models were applied to study the association between the response variable eGFR and the raw values and Z scores of echocardiographic measures of LV size and function. Multivariable mixed-effects models were applied in order to adjust for age while evaluating the correlation between serial eGFR and echocardiographic measures.

Outliers were detected using jackknife residuals and normality was tested with the Kolmogorov-Smirnov test. Two LVFS observations were recognized as outliers and were excluded.

Alpha was set at 0.05. The analyses were conducted using SAS versions 9.2 and 9.3 (SAS Institute Inc., Cary, North Carolina) and Microsoft EXCEL 2010 (Redmond, Washington). Kaplan-Meier plots were created using the statistical software package R.

Results

Between January 1990 and November 2011, 3559 children were registered in the PCMR. Of these, 2141 (60%) had a diagnosis of DCM, but only 484 (23%) had at least one SCr concentration reported in baseline or annual data. eGFR could be calculated for 105 children in the baseline data after excluding children less than 1 year of age and 219 eGFRs were calculated from annual data (Figure 1).

At baseline, the 105 children with vs. the 180 without assessable eGFRs did not differ with respect to age, race, weight, and height (supplemental Table 1 in the Online Appendix). In addition, the two groups did not differ with respect to history of congestive heart failure

(CHF), the need for hospitalization, the need for heart transplant evaluation, or on any echocardiographic measure.

The distribution of eGFR in 105 children with accessible eGFR (before exclusion of values >150 mL/min/1.73 m²) in the baseline data stratified into six eGFR ranges is depicted in Figure 2.

Of 105 children with baseline eGFR data, 12 (11.5%) had eGFRs greater than 150 mL/min/1.73 m² and were excluded, leaving 93 children who met all inclusion and exclusion criteria. Of these, 57 (61.3%) had an eGFR less than 90 mL/min/1.73 m² (the CRS group). Creatinine and blood urea nitrogen serum concentrations were significantly higher in children with CRS than in those without CRS. The groups did not differ in age, sex, race, weight, height, history of CHF, echocardiographic measures, the need for hospitalization, or days of hospitalization (Table 1).

Although the groups differed significantly in mean eGFR and SCr concentrations at the time of DCM diagnosis, they did not differ when SCr concentrations were classified as normal or abnormal by the participating centers' laboratory criteria (43% abnormal for CRS and 32% abnormal non-CRS). We used eGFR to define SCr concentrations as normal (eGFR = 90 to 150 mL/min/1.73 m²) or abnormal (eGFR <90 mL/min/1.73 m²) to validate the accuracy of the primary care providers in recognizing SCr being normal or abnormal (Figure 3). There was little to no agreement between the SCr classification by providers and the classification based on eGFR ($k=0.09$; 95% CI: -0.009-0.28) (Figure 3).

We also enriched the dataset by classifying 122 additional patients as CRS or non-CRS based on their follow-up data and utilizing an adjusted-risk-set approach (see Methods). Thus, the enriched dataset included 215 patients. Median follow-up was 3.8 (IQR: 0.6-5.0) years for children without CRS and 4.9 (IQR: 1.6-6.9) years for children with CRS. Of the 215 patients, 18 died (14 of 105 in the CRS group and 4 of 110 in the non-CRS group, $P=0.14$) and 57 underwent heart transplant (31 of 105 in the CRS group and 26 of 110 in the non-CRS group, $P=0.69$; Table 2). The hazard ratio for patients with CRS was 2.4 (95% CI: 0.8-7.4) for death, 0.9 (95% CI: 0.5-1.6) for transplant, and 1.1 (95% CI: 0.7-1.8) for the composite of death and transplant (Table 2; Figure 4).

Using all available data, children with DCM had significantly improved eGFRs, less dilation, and a trend toward improved LV function over time since DCM diagnosis (Table 3). The z-scores for both posterior wall thickness and end-diastolic septal thickness became more negative over time, but the thickness-to-dimension ratio did not change, consistent with change in LV mass commensurate with the change in LV volume rather than adverse ventricular remodeling.

A lower eGFR was associated with lower fractional shortening and higher LVEDD Z score, LVESD Z score, and LV mass Z score (Table 4, model 1). For example, mean eGFR increased 0.6 mL/min/1.73 m² for every one SD increase in LVFS Z score. The same associations remain significant after adjusting for age. However, eGFR was not associated with echocardiographic measures of wall thickness (LV posterior wall thickness and end-diastolic septal thickness). The negative association between eGFR and age was persistent

and significant, regardless of the echocardiographic measure used in the model (Table 4, model 2). Accordingly, eGFR increases as LVFS improves and as LV dilation diminishes, and decreases as age increases.

Discussion

The coexistence of compromised kidney function and heart failure in adults is associated with poor prognosis and prolonged hospitalization [3, 8]. Chen et al., using a multifactorial regression model, found that a blood urea nitrogen concentration greater than 43 mg/dL was the best predictor of mortality in adults admitted for acute decompensating heart failure [23], a fact reflecting the marked impact of deteriorating kidney function in this population.

Dilated cardiomyopathy is the most common form of cardiomyopathy and the main cause of cardiac transplant in children. Although much CRS-related research has been conducted in adults, similar research in children is limited [24], and most reports have studied the implications of CRS in children after cardiopulmonary bypass [5, 25]. We found no studies reporting the prevalence, outcome, and predictors of CRS in children with DCM.

Using the modified Schwartz formula to calculate eGFR and defining CRS as an eGFR <90 mL/min/1.73 m², we found that the prevalence of CRS in children newly diagnosed with DCM was 61.3% (57/93). However, Schwartz derived this formula to calculate eGFR in children with known CKD, and it has not been validated in children with DCM. Because the PCMR does not have eGFR data for healthy children, we used data published by Fadrowski et al., who reported the 25th and 50th percentiles for eGFRs in 3256 healthy children to be 84.4 and 96.6 mL/min/1.73 m² using the modified Schwartz formula [26]. Assuming Fadrowski's data are normally distributed, we calculated that 36.3% of healthy controls have eGFRs of 90 mL/min/1.73 m² or less. Thus, we may assume that 36.3% of children with DCM will have an eGFR of 90 mL/min/1.73 m² or lower without decreased kidney function. Given that we found the prevalence of CRS to be 61.3%, we suggest that 25% (61.3% minus 36.3%) may be a reasonable estimate of the true prevalence of CRS in children with DCM. Interestingly, this estimate is consistent with the 25% to 30% prevalence of kidney dysfunction in adults with chronic heart failure [3, 9, 11, 26]. The prevalence of CRS in our cohort decreased over time; it was higher during the first (44.2%) and second (45.0%) years after diagnosis (Table 3) than it was among Fadrowski's healthy cohort (36.3%). After the second year, the prevalence of CRS in our cohort was lower than that in Fadrowski's cohort; however, our sample was much smaller after the first 2 years (Table 3).

Unfortunately, the PCMR data suggest that in children with DCM, reporting physicians inconsistently evaluated kidney function and more often than not misinterpreted the markers of kidney dysfunction, such as SCr concentrations. Concentrations of SCr were reported for only 484/2141 (22.6%) children with DCM over 11 years of data collection. The agreement between our classification of SCr concentrations by eGFR as normal or abnormal and the classification by reporting physicians was poor ($\kappa=0.09$). This lack of agreement represents a major deficiency in assessing children with DCM for CRS. However, the poor recognition

of kidney dysfunction is not surprising and is consistent with the general under-diagnosis and under-treatment of CKD in the United States [27].

Using the modified Schwartz formula, in addition to the associated normal reference ranges of SCr concentrations, could help identify children with abnormal kidney function. Furthermore, recognizing abnormal kidney function could potentially result in treatment options that would preserve residual kidney function, such as limiting iatrogenic damage from nephrotoxic agents and encouraging the more judicious use of diuretics.

Increasing evidence indicates that renal insufficiency in adults with heart failure is an important independent risk factor for death [3, 28, 29]. In our study, the CRS group had qualitatively higher mortality rates (31% vs. 14% at 5 years). However, these differences were not statistically significant, most likely because of the small number of deaths (only 18 deaths in annual data) in children with and without CRS. Accordingly, we cannot conclude that CRS is associated with increased mortality in children. The rate of successful heart transplants was also similar between the two groups.

Left ventricular diameter improved significantly and LV thickness-to-dimension ratio remained stable in survivors in the years after DCM diagnosis. There was a trend toward improvement in LV function but it did not reach statistical significance. Concurrently, eGFR also improved with time after diagnosis. Thus, eGFR may be associated directly with the degree of systolic dysfunction, although other variables may modify this association. However, an alternative explanation is that survivor bias led to the appearance of better LV function and less LV dilation at later follow-up visits relative to the baseline data that included all subjects.

We also found significant associations between eGFR and several echocardiographic measures, including a positive correlation with LVFS. This significant correlation supports the clinical conclusion that eGFR increases or decreases as LV function improves or worsens, respectively. The literature is not consistent regarding the association between eGFR and different echocardiographic measures; some studies report a correlation [30, 31] and others do not [32]. Likewise, studies of novel tubular injury markers, such as kidney injury molecule-1 and N-Acetyl- β -(D)-glucosaminidase also have conflicting results [33]. In healthy children, eGFR increases during infancy and remains steady during childhood and adolescence [34]. In order to eliminate the possibility that the correlation between eGFR and LV function is confounded by age, we created a multivariate model (Table 4, model 2) including age as a covariate. The model showed that eGFR and LV function were still correlated after adjusting for age supporting the presumptive association between heart and kidney functions.

Many mechanisms have been proposed to contribute to the pathogenesis of kidney dysfunction in patients with impaired systolic function. These include salt and water retention, venous congestion with associated elevation of central venous pressure, anemia, and other systemic co-morbidities [35]. However, patients with known endocrine conditions or primary essential hypertension were excluded from this cohort. Further, CRS cannot be interpreted simply as being secondary to decreased renal perfusion that, in turn, is secondary

solely to decreased systolic function as in our cohort. Studies in adults have shown that elevated central venous pressure is important in developing CRS with elevated pressure in the efferent arterioles of the glomeruli. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness study, right atrial pressure, an indicator of venous congestion, correlated with SCr; cardiac index did not [36]. Animal models have showed that eGFR was not always significantly affected after massive myocardial infarction with impaired systolic function [37], suggesting that other humoral and/or neurological regulators may be involved in the development of CRS. Another potential pathogenic pathway is the maladaptive stimulation of the renin-angiotensin-aldosterone system that leads to additional fluid retention, systemic vascular resistance, and oxidative stress. A chronic inflammatory state has also been described that potentiates further injury to the kidney, including glomerulosclerosis and tubulointerstitial fibrosis [38]. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockade, and aldosterone antagonists have been used as treatment for heart failure in both adults and children. There are no studies in pediatric heart failure to assess the use of ACE inhibitors and angiotensin receptor blockers in the presence of CRS, and these studies are also lacking in the adult literature. If these agents are used in the presence of both DCM-related heart failure and CRS in children, proper adjustment of ACE inhibitor dose is recommended based on rise in SCr, eGFR, and the presence of hypotension [39]. The impact of these medications on the progression of CRS in pediatric DCM needs further assessment due to the potential for clinical benefit but also the potential for harm due to side effects.

Limitations of the Study

Our study is limited by the fact that we used data from a registry designed primarily to characterize children with different forms of cardiomyopathy. As a result, data on kidney function markers were expected to be easily missed and not reported, which reduced the number of records available for analysis and precluded the evaluation of the longitudinal progression or recovery of kidney function in the DCM cohort. Also, different centers may use different assays to measure SCr concentrations, which might increase the variability in these concentrations without any real clinical or pathological reason for this variability. In addition, our cohort includes only children with DCM who had at least one SCr concentration measurement, which may bias the study if children at high risk for kidney insufficiency tend to have SCr concentrations measured more often. Finally, as mentioned previously, observed improvements in echocardiographic parameters over time may be due, at least in part, to survivor bias.

Conclusions

Our results highlight the likely prevalence of CRS in children with DCM and the association between the heart and kidney function using SCr, a simple and commonly used marker of kidney function. Using more sensitive and early markers of renal injury, such as serum Cystatin-C, urinary microalbumin, and perhaps the novel renal tubular injury markers, could expand our knowledge of CRS in children with different pathological forms of cardiomyopathy. It has been suggested that children with renal disease should be cared for by a multidisciplinary team including pediatric cardiologists, among others [40]. Perhaps the

care team for children with DCM should include pediatric nephrologists which could lead to earlier testing and diagnosis of CRS in this population.

Cardiorenal syndrome is likely to be common in children with a recent diagnosis of DCM. Currently, it appears that CRS is underreported and misdiagnosed by cardiologists caring for these children. Despite the fact that mortality is higher in children with CRS than without, the difference was not statistically significant, so conclusions cannot be definitive. Because CRS concentrations are correlated with LV function, we suggest that baseline assessment and surveillance of kidney function should be conducted as part of routine care of children with DCM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Analysis cohort selection

Sample selection from the Pediatric Cardiomyopathy Registry (PCMR) data to study the prevalence of cardiorenal syndrome (CRS) as defined by estimated glomerular filtration rate (eGFR) in children with dilated cardiomyopathy (DCM). SCr = serum creatinine.

Figure 2. Distribution of estimated glomerular filtration (eGFR) rate

The distribution of eGFR in 105 children, measured at the time of diagnosis of cardiomyopathy.

Figure 3. Accuracy analysis of reporting serum creatinine

Modified Latin Square of 2×2 table for reporting Serum Creatinine (SCr) values as normal or abnormal compared to the actual status estimated glomerular filtration rate (eGFR) using the modified Schwartz formula. PCMR = Pediatric Cardiomyopathy Registry.

Figure 4. Kaplan-Meier estimates of time to death, time to cardiac transplantation and time to death or cardiac transplantation in children with dilated cardiomyopathy (DCM), by cardiorenal syndrome (CRS) status at baseline
eGFR = estimated glomerular filtration rate.

- Kaplan-Meier estimates of time to death in 215 children with DCM by CRS status at baseline (logrank $P=0.14$). Follow-up times are censored at the time of cardiac transplantation, where applicable.
- Kaplan-Meier estimates of time to cardiac transplantation in 215 children with DCM by CRS status at baseline (logrank $P=0.69$).
- Kaplan-Meier estimates of time to death or cardiac transplantation in 215 children with DCM by CRS status at baseline (logrank $P=0.68$).

Table 1
Characteristics of Children in the Pediatric Cardiomyopathy Registry Older than 1 Year with a Diagnosis of Dilated Cardiomyopathy, with and without Cardiorenal Syndrome as Defined by Estimated Glomerular Filtration Rate at the Time of Diagnosis of Cardiomyopathy

Characteristic at Diagnosis of Cardiomyopathy	CRS Group (eGFR <90 mL/min/1.73 m ²) <i>n</i> = 57 (61.3%)	Non-CRS Group (eGFR = 90 to 150 mL/min/1.73 m ²) <i>n</i> = 36 (38.7%)	<i>P</i> Value
Age at diagnosis, median (IQR), years	10.9 (2.1-14.5)	8.0 (3.0-14.3)	0.81 ^a
Sex, <i>n</i> (%)			0.20 ^c
Male	32 (56.1)	25 (69.4)	
Female	25 (43.9)	11 (30.6)	
Race, <i>n</i> (%)			0.37 ^c
White	30 (54.6)	22 (62.9)	
Black	11 (20.0)	7 (20.0)	
Hispanic	10 (18.2)	2 (5.7)	
Other	4 (7.3)	4 (11.4)	
Height, mean (SD), cm	128.0 (39.6)	128.3 (37.9)	0.98 ^b
Height for age, mean (SD), Z score	-0.4 (2.1)	0.0 (1.7)	0.31 ^b
Weight, median (IQR), kg	32.0 (11.3-60.0)	26.7 (12.3-49.8)	0.60 ^a
Weight for age, mean (SD), Z score	-0.1 (1.7)	-0.3 (1.6)	0.69 ^b
CHF at diagnosis, <i>n</i> (%)			0.95 ^c
Positive	44 (77.2)	28 (77.8)	
Negative	13 (22.8)	8 (22.2)	
Hospitalization within 30d of diagnosis, <i>n</i> (%)			0.35 ^c
Yes	50 (96.2)	32 (91.4)	
No	2 (3.8)	3 (8.6)	
Days of hospitalization within 30d of diagnosis, median (IQR)	13.5 (8.0-19.0)	13.0 (10.0-27.0)	0.58 ^a
Heart transplant evaluation, <i>n</i> (%)			0.45 ^c
Yes	10 (28.6)	7 (38.9)	
No	25 (71.4)	10 (61.1)	
NYHA class, <i>n</i> (%) [In patients with CHF]			0.26 ^c
II	3 (1 3.6)	4 (3 6.4)	
III	8 (36.4)	4 (36.4)	
IV	11 (50.0)	3 (27.2)	
Canadian Functional Assessment, <i>n</i> (%) [In patients with CHF]			0.86 ^c
II	1 (12.5)	0 (0)	
III	3 (37.5)	1 (50)	
IV	4 (50)	1 (50)	

Characteristic at Diagnosis of Cardiomyopathy	CRS Group (eGFR <90 mL/min/1.73 m ²) <i>n</i> = 57 (61.3%)	Non-CRS Group (eGFR = 90 to 150 mL/min/1.73 m ²) <i>n</i> = 36 (38.7%)	<i>P</i> Value
Characteristic at Diagnosis of Cardiomyopathy	CRS Group (eGFR <90 mL/min/1.73 m ²) <i>n</i> = 57 (61.3%)	Non-CRS Group (eGFR = 90 to 150 mL/min/1.73 m ²)	<i>P</i> Value
Kidney function markers			
BUN, median (IQR), (mg/dL)	19.5 (14.0-28.0)	13.5 (11.0-16.5)	0.0002^a
Creatinine, median (IQR), mg/dL	0.9 (0.6-1.0)	0.5 (0.3-0.6)	<0.0001^a
eGFR, mean (SD), mL/min/1.73 m ²	62.0 (22.6)	108.0 (14.0)	<0.0001^b
Reported PCMR creatinine concentration, <i>n</i> (%)			0.32 ^c
Normal	32 (57.1)	23 (67.7)	
Abnormal	24 (42.9)	11 (32.3)	
Echocardiographic measures			
LVFS, mean (SD), %	15.1 (7.0)	16.4 (8.4)	0.48 ^b
LVEF, mean (SD), % ^d	29.2 (11.6)	31.3 (10.7)	0.64 ^b
LVEDD, mean (SD), cm	5.8 (1.6)	5.5 (1.1)	0.39 ^b
LVEDD, mean (SD), Z score	4.4 (2.5)	4.2 (2.7)	0.81 ^b
LVESD, mean (SD), Z score	5.9 (2.8)	5.8 (3.0)	0.95 ^b
PWT, mean (SD), Z score	-0.3 (1.9)	-0.6 (1.9)	0.58 ^b
IVS, mean (SD), Z score	-0.9 (1.9)	-0.4 (1.3)	0.34 ^b
LV Mass, mean (SD), Z score	2.5 (2.2)	2.5 (1.9)	0.99 ^b
Ratio of PWT:LVEDD, median (IQR)	0.12 (0.10-0.16)	0.12 (0.10-0.15)	0.75 ^a
Log ratio of PWT:LVEDD, mean (SD)	-2.1 (0.4)	-2.1 (0.3)	0.65 ^b

CRS, cardiorenal syndrome; eGFR, estimated glomerular filtration rate; IQR, interquartile range; CHF, congestive heart failure; NYHA, New York Heart Association; BUN, blood urea nitrogen; PCMR, Pediatric Cardiomyopathy Registry; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; PWT, posterior wall thickness; IVS, end-diastolic septal thickness.

^aWilcoxon rank sum test

^bStudent's t test

^cChi-square test

^dSample sizes for LVEF are *n*=16 and *n*=11 for the CRS and non-CRS groups, respectively.

Table 2
Adjusted Risk Set Mortality and Heart Transplantation Rates in Children with Dilated Cardiomyopathy over Age 1 Year by Cardiorenal Syndrome as Defined by Initial Estimated Glomerular Filtration Rate

Outcome	CRS Group (eGFR <90 mL/min/1.73 m ²)	Non-CRS Group (eGFR = 90 to 150 mL/min/1.73 m ²)	Hazard Ratio (95% CI)	Cox Regression <i>P</i> Value
<i>n</i>	105	110		
Median (IQR) follow-up time since diagnosis, yrs	3.8 (0.6-5.0)	4.9 (1.6-6.9)		
Total no. of deaths	14	4	2.4 (0.8-7.4)	0.14
6-month death rate since diagnosis (95% CI)	7 14.6% (4.0-23.0%)	2 7.3% (0.0-16.5%)		
5-year death rate since diagnosis (95% CI)	13 31.4% (14.6-45.0%)	4 13.8% (0.2-25.5%)		
Total no. of transplants	31	26	0.9 (0.5-1.6)	0.69
6-month transplant rate since diagnosis (95% CI)	11 22.7% (10.0-33.6%)	7 23.8% (9.0-37.8%)		
5-year transplant rate since diagnosis (95% CI)	26 50.7% (34.5-62.9%)	21 53.7% (35.4-66.7%)		
Total no. with death or transplant	45	30	1.1 (0.7-1.8)	0.68
6-month death/transplant rate since diagnosis (95% CI)	18 34.0% (20.0-45.5%)	9 29.5% (11.4-43.9%)		
5-year death/transplant rate since diagnosis (95% CI)	39 66.2% (51.6-76.4%)	25 60.1% (42.6-72.2%)		

CRS, cardiorenal syndrome; eGFR, estimated glomerular filtration rate; IQR, interquartile range

Table 3

All Available Baseline and Up to Five-year Post-cardiomyopathy Diagnosis Annual Values of Estimated Glomerular Filtration Rate (eGFR), Prevalence of Cardioresenal Syndrome (CRS), and Left Ventricular Echocardiographic Measures in 215 Children with Dilated Cardiomyopathy who had an eGFR Value at Least One Time Point Paired with an Echo Measure

	Time since Diagnosis of Cardiomyopathy					P Value
	Diagnosis	1 year	2 years	3 years	4 years	5 years
eGFR						0.009
<i>N</i>	93	52	40	25	14	10
Mean (SD)	79.8 (29.9)	85.9 (33.2)	96.0 (26.6)	93.0 (25.4)	95.4 (33.3)	104.2 (29.0)
CRS prevalence						0.030
<i>n/N</i>	58/93	23/52	18/40	7/25	2/14	2/10
%	62.3%	44.2%	45.0%	28.0%	14.3%	20.0%
LVFS, %						0.097
<i>n</i>	77	44	29	18	7	8
Mean (SD)	15.6 (7.6)	22.1 (10.4)	21.3 (9.7)	23.0 (10.9)	19.7 (8.9)	21.7 (7.3)
LVEDD Z score						0.002
<i>n</i>	77	42	32	18	8	7
Mean (SD)	4.3 (2.6)	3.4 (2.8)	4.1 (2.6)	4.3 (2.9)	4.6 (2.1)	3.2 (1.6)
LVESD Z score						0.009
<i>n</i>	68	42	28	16	7	7
Mean (SD)	5.9 (2.9)	4.4 (3.3)	5.2 (3.2)	5.0 (3.8)	5.7 (2.6)	4.2 (1.9)
LV PWT Z score						0.001
<i>n</i>	54	33	27	19	7	6
Mean (SD)	-0.4 (1.9)	-1.2 (1.5)	-1.5 (2.3)	-1.3 (1.9)	-0.6 (2.3)	-1.0 (1.6)
LV IVS Z score						<.001
<i>n</i>	50	33	26	17	7	5
Mean (SD)	-0.7 (1.7)	-0.9 (1.2)	-0.9 (1.4)	-1.2 (1.2)	-0.5 (1.1)	-2.1 (0.5)
LV Mass Z score						<.001
<i>n</i>	54	33	27	18	7	6
Mean (SD)	2.5 (2.1)	1.1 (1.8)	1.7 (2.7)	1.7 (2.3)	2.9 (2.0)	1.1 (1.4)
PWT:LVEDD Z score						0.429

Time since Diagnosis of Cardiomyopathy						P Value
	Diagnosis	1 year	2 years	3 years	4 years	5 years
n	58	33	27	18	7	7
Mean (SD)	-1.9 (1.5)	-1.9 (1.3)	-2.4 (1.1)	-2.5 (1.4)	-2.2 (1.5)	-2.0 (1.2)

LVFS, left ventricular fractional shortening; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LV PWT, left ventricular posterior wall thickness; LV IVS, left end-diastolic septal thickness.

Table 4
Results from Linear Mixed Effects Regression Models of Estimated Glomerular Filtration Rate (eGFR) on LV Size and Function (Model 1) and with Adjustment for Age at eGFR Measurement (Model 2)

Predictor	No. of Obs	Model 1	Model 2	
		Echocardiographic variable	Echocardiographic variable	Age eGFR assessed, years
LVFS, %				
Estimate (95% CI)	212	0.64 (0.16, 1.11)	0.60 (0.13, 1.06)	-0.90 (-1.56, -0.25)
P value		0.008	0.012	0.007
LVEDD Z score				
Estimate (95% CI)	212	-1.58 (-3.03, -0.14)	-2.11 (-3.54, -0.68)	-1.11 (-1.77, -0.45)
P value		0.032	0.004	<.001
LVESD Z score				
Estimate (95% CI)	196	-1.40 (-2.73, -0.08)	-1.80 (-3.11, -0.48)	-1.11 (-1.82, -0.41)
P value		0.038	0.008	0.002
LV PWT Z score				
Estimate (95% CI)	171	-1.48 (-3.89, 0.93)	-1.63 (-4.01, 0.74)	-0.79 (-1.55, -0.03)
P value		0.23	0.18	0.042
LV IVS Z score				
Estimate (95% CI)	163	-1.33 (-4.44, 1.79)	-1.77 (-4.88, 1.35)	-0.96 (-1.77, -0.15)
P value		0.40	0.27	0.020
LV Mass Z score				
Estimate (95% CI)	170	-2.42 (-4.37, -0.49)	-2.86 (-4.84, -0.89)	-0.91 (-1.66, -0.16)
P value		0.014	0.005	0.017
PWT:LVEDD Z score				
Estimate (95% CI)	176	-0.41 (-14.4, 13.6)	-0.22 (-3.28, 2.84)	-0.75 (-1.47, -0.03)
P value		0.95	0.89	0.040

LVFS, left ventricular fractional shortening; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LV PWT, posterior wall thickness; LV IVS, end-diastolic septal thickness.