Creatinine versus cystatin C to estimate glomerular filtration rate in adults with congenital heart disease: Results of the Boston Adult Congenital Heart Disease Biobank

Alexander R. Opotowsky, MD, MMSc,[a,b] Matthew Carazo, MD,[a,b] Michael N. Singh, MD,[a,b] Konstantinos Dimopoulos, MD, MSc, PhD,[c] David A. Cardona-Estrada, MD,[d] Ahmed Elantably, MD,[d] Sushrut S. Waikar, MD, MPH,[b] Finnian R. Mc Causland, MBBCh, MMSc,[b] Gruschen Veldtman, MD,[e] Jasmine Grewal, MD,[f] Catherine Gray, BS,[a] Brittani N. Loukas, PA-C,[a] and Saurabh Rajpal, MBBS, MD[g] *Boston, Salem, MA; London, United Kingdom; Cincinnati, Columbus, OH; and British Columbia, Canada*

Background Glomerular filtration rate is a key physiologic variable with a central role in clinical decision making and a strong association with prognosis in diverse populations. Reduced estimated glomerular filtration rate (eGFR) is common among adults with congenital heart disease (ACHD).

Methods We conducted a prospective cohort study of outpatient ACHD ≥18 years old seen in 2012-2017. Creatinine and cystatin C were measured; eGFR was calculated using either the creatinine or cystatin C Chronic Kidney Disease–Epidemiology Collaboration equation (CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$, respectively). Survival analysis was performed to define the relationship between eGFR and both all-cause mortality and a composite outcome of death or nonelective cardiovascular hospitalization.

Results Our cohort included 911 ACHD (39 ± 14 years old, 49% female). Mean CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$ were similar (101 ± 20 vs 100 ± 23 mL/min/1.73 m^2), but CKD-EPI$_{Cr}$ estimates were higher for patients with a Fontan circulation (n = 131, +10 ± 19 mL/min/1.73 m^2). After mean follow-up of 659 days, 128 patients (14.1%) experienced the composite outcome and 31 (3.4%) died. CKD-EPI$_{CysC}$ more strongly predicted all-cause mortality (eGFR <60 vs >90 mL/min/1.73 m^2: CKD-EPI$_{CysC}$ unadjusted HR = 20.2 [95% CI 7.6-53.1], *C*-statistic = 0.797; CKD-EPI$_{Cr}$ unadjusted HR = 4.6 [1.7-12.7], *C*-statistic = 0.620). CKD-EPI$_{CysC}$ independently predicted the composite outcome, whereas CKD-EPI$_{Cr}$ did not (CKD-EPI$_{CysC}$ adjusted HR = 3.0 [1.7-5.3]; CKD-EPI$_{Cr}$ adjusted HR = 1.5 [0.8-3.1]).

Patients reclassified to a lower eGFR category by CKD-EPI$_{CysC}$, compared with CKD-EPI$_{Cr}$, were at increased risk for the composite outcome (HR = 2.9 [2.0-4.3], $P < .0001$); those reclassified to a higher eGFR class were at lower risk (HR = 0.5 [0.3-0.9], $P = .03$).

Conclusions Cystatin C–based eGFR more strongly predicts clinical events than creatinine-based eGFR in ACHD. Creatinine-based methods appear particularly questionable in the Fontan circulation. (Am Heart J 2019;214:142-55.)

From the [a]Department of Cardiology, Boston Children's Hospital, Boston, MA, United States, [b]Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA, [c]Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College of Science and Medicine, London, United Kingdom, [d]Department of Medicine, North Shore Medical Center, Salem, MA, USA, [e]Adolescent and Adult Congenital Heart Disease Program, Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [f]Pacific Adult Congenital Heart Disease Clinic, Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada, and [g]Ohio State University Division of Cardiovascular Medicine and Nationwide Children's Hospital Heart Center, Columbus, OH, USA.

Funding sources: This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic health care centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health. This work was also supported by an investigator-initiated study research grant from Roche Diagnostics (Indianapolis, IN). A. R. O. and M. S. are supported by the Dunlevie Family Fund.

Submitted December 23, 2018; accepted April 26, 2019.

Reprint requests: Alexander R. Opotowsky, Boston Children's Hospital and Brigham and Women's Hospital, 300 Longwood Ave, Department of Cardiology, Boston, MA 02115
E-mail: alexander.opotowsky@cardio.chboston.org

0002-8703

https://doi.org/10.1016/j.ahj.2019.04.018

Patients with congenital heart disease (CHD) are increasingly likely to survive to adulthood. As a consequence, there is a burgeoning population of adults with CHD (ACHD),[1] and these patients have a high burden of risk factors for chronic kidney disease (CKD). Many of these relate to the underlying cardiovascular dysfunction such as venous congestion, neurohormonal and autonomic nervous system activation, and chronic hypoxemia.[2] Others relate to exposure to nephrotoxins and to interventions used to treat the underlying CHD. For example, both cardiac catheterization and surgery with cardiopulmonary bypass are associated with increased risk for acute kidney injury events, which in turn are associated with increased long-term risk for CKD.[3]

Glomerular filtration rate (GFR) is a fundamental, clinically relevant metric of kidney function. Clinical diagnosis and staging of CKD are largely based on estimated GFR (eGFR).[4] Reduced eGFR is strongly associated with various adverse outcomes in the general population as well as various diagnosis-based populations including patients with heart failure.[4,5] A number of equations have been developed to estimate steady-state GFR using the endogenous filtration markers creatinine and cystatin C.[6] These include the Cockcroft and Gault, Modification of Diet in Renal Disease (MDRD), and several Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) formulas. Accurate determination of eGFR has immediate clinical implications in ACHD. These include predicting the probability of kidney injury associated with cardiopulmonary bypass or after iodinated contrast administration for noninvasive imaging or catheterization; heart transplantation considerations; and appropriate selection and dosing of many antibiotics, antiarrhythmic drugs, and direct-acting oral anticoagulants.[7]

One large retrospective study enrolled ACHD patients between 1999 and 2006 and reported that creatinine-based MDRD eGFR was often reduced across a spectrum of congenital pathologies.[8] The accuracy of serum creatinine to estimate GFR depends on muscle mass, however, and some ACHD subsets are associated with reduced muscle mass.[9,10] No prior studies have compared various approaches to estimating GFR in large ACHD cohorts.

We studied 911 adults with CHD (1) to determine the correlation and agreement between various eGFR equations and (2) to compare the prognostic value of creatinine and cystatin C–based eGFR equations.

Methods

Study sample

We enrolled outpatients with CHD ≥18 years old between March 15, 2012, and June 28, 2017, at Boston Children's or Brigham and Women's Hospitals. Details of the Boston ACHD Biobank have been previously published.[11] The study was approved by Boston Children's Hospital's Institutional Review Board with a formal reliance agreement between the Partners HealthCare/Brigham and Women's Hospital and Boston Children's Hospital Institutional Review Boards. Informed consent was obtained from all participants.

Data collection and definitions

Demographic and clinical data, including medical comorbidities such as presence of diabetes and hypertension, were collected from medical records, as described previously.[11] Data were collected around the time of enrollment into the biobank, preferentially on the date of baseline biospecimen collection. In the absence of a relevant clinical intervention or event, we also included data obtained within 2 years of sample collection. We classified CHD patients into different pathophysiologic groups, as detailed in the Online Supplement. Patients were also classified on the basis of New York Heart Association (NYHA) functional class (I vs ≥II), presence of (defined as resting arterial oxygen saturation <92%), diagnosis severity classifed per the 32nd Bethesda conference guidelines, and the presence of a single-ventricle versus biventricular circulation.

Estimation of GFR

Details on blood collection, processing, and storage as well as about the assays used to measure creatinine and cystatin C are included in the Supplemental Methods. eGFR was calculated using published equations based on creatinine, cystatin C, or both (see Supplemental Methods for equations applied).[12-14] The primary analysis focused only on comparing the creatinine-based CKD-EPI equation ($CKD\text{-}EPI_{Cr}$) with the cystatin C-based CKD-EPI equation ($CKD\text{-}EPI_{CysC}$). Secondary analyses compared these with the MDRD and combined creatinine + cystatin C CKD-EPI ($CKD\text{-}EPI_{Cr + CysC}$) equations, with these results included in the Online Supplement. A subset of participants (n = 70) was also included in a prior analysis of kidney function in patients with a Fontan circulation.[15] For those participants, cystatin C was remeasured from stored samples.

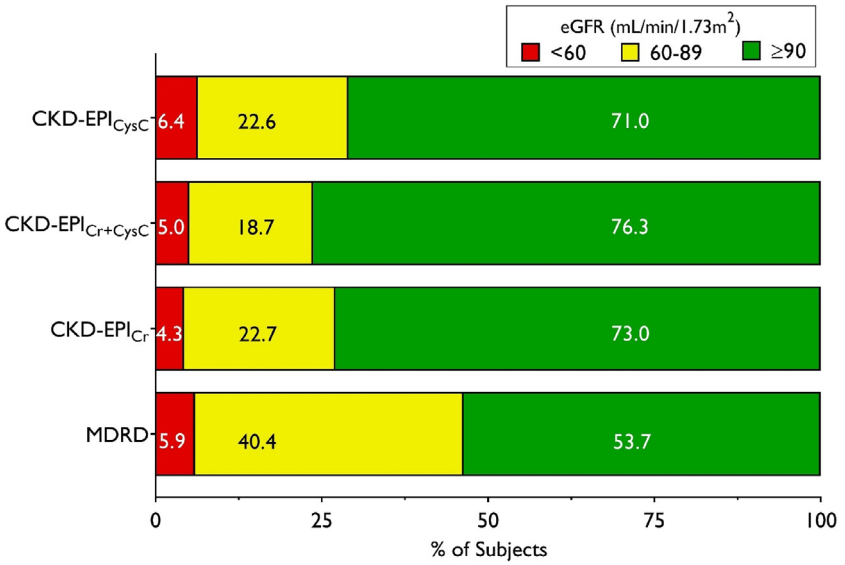
Outcomes

The primary outcomes of interest were (1) all-cause mortality and (2) a composite outcome of either all-cause mortality or nonelective cardiovascular hospitalization. *Nonelective cardiovascular hospitalization* was defined as at least overnight admission for heart failure, arrhythmia or symptoms of arrhythmia, thromboembolism, cerebral hemorrhage, or cardiovascular disease–related events (eg, protein-losing enteropathy in the context of single-ventricle Fontan circulation).

Data analysis

We categorized each eGFR variable by clinically relevant cutoffs (<60, 60-89, ≥90 mL/min/1.73 m^2).[4] Summary data for continuous variables are presented as mean ± SD and median (25th-75th percentile) for non-normally distributed variables. The 2-sided unpaired

Figure 1



Prevalence of chronic kidney disease, as defined by reduced eGFR, in adults with congenital heart disease using various equations to estimate glomerular filtration rate.

Student *t* or Wilcoxon rank sum test, as appropriate for distribution, was used to compare continuous variables between 2 groups. The χ^2 or Fisher exact test was used to analyze categorical variables between groups. When comparing values across the 3 categories of eGFR, continuous and categorical variables were assessed with tests for trend, analysis of variance for linear trend, and the Mantel-Haenszel extension of the χ^2 test, respectively. Pearson correlation and Bland-Altman analysis were used to assess correlation and agreement between eGFR equations. The log-rank test was used to perform univariate survival analysis stratified by eGFR category. Time-to-event analyses were conducted from the date of biospecimen collection to the date of the first clinical event, with censoring of event-free individuals at the most recent clinical follow-up date when event status was known. Least absolute shrinkage and selection operator (LASSO) regression was used to identify the variables, from the list of demographic and clinical variables in Table I, most strongly associated with the composite outcome, selecting those up to the first nadir in the 50-fold cross-validation predicted residual sum of squares. The following variables were selected: history of atrial arrhythmia, NYHA functional class, cyanosis, and ventricular systolic function. Cox regression using forward selection with a criterion of $P < .05$ for entry produced the same set of key variables. Multivariable survival analysis was performed using Cox regression, including the variables identified in the analyses above plus the eGFR variable. The *C*-statistic was calculated using Harrell's method.[16] The assumption of proportional hazards was assessed for each model, and there was no apparent violation. eGFR was also analyzed as a continuous variable using restricted cubic splines to assess for a nonlinear relationship between the various methods to calculate eGFR and outcomes. Prognostic reclassification, including net reclassification index, was assessed using dichotomous 1-year composite outcome probabilities of ≤2.5%, >2.5%-10%, >10%-20%, >20%-30%, and >30%. These probabilities were estimated with logistic regression inclusive of any patient who had experienced an event within 1 year or who had at least 1 year of event-free follow-up time. For this analysis, the baseline predictive risk model included history of atrial arrhythmia, NYHA functional class, cyanosis, ventricular function, and continuous CKD-EPI$_{Cr}$ eGFR. The updated model included the same variables, replacing CKD-EPI$_{Cr}$ with CKD-EPI$_{CysC}$. Goodness-of-fit for these logistic regression models was assessed using the Hosmer-Lemeshow test with deciles of expected and observed events.

We further assessed the relationship between albuminuria and reduced eGFR, and analyzed the independent prognostic value of each. For these analyses, we excluded patients with an albumin-to-creatinine ratio (ACR) ≥30 mg/g after they had performed an exercise test on the same day because strenuous exertion can lead to transient albuminuria, as described previously.[17]

Analyses were performed with SAS 9.4 (SAS Institute, Inc, Cary, NC), R version 3.4.1, and GraphPad Prism (GraphPad Software, Inc, La Jolla, CA). A 2-sided *P* value < .05 was considered statistically significant.

Table I. Demographic and clinical characteristics of 911 adults with congenital heart disease by (A) CKD-EPI creatinine and (B) CKD-EPI cystatin C eGFR categories

A		$CKD\text{-}EPI_{Cr}$ eGFR (mL/min/1.73 m^2)			
Variable	All	<60	60-89	≥90	*P* value
n	911	39	207	665	
Age (y)	38.6 ± 13.6	58.7 ± 11.0	47.2 ± 13.6	34.7 ± 11.3	<.0001
Sex (male)	462 (50.7)	13 (33.3)	94 (45.4)	355 (53.4)	.0115
Race (white)	666 (73.1)	30 (76.9)	155 (74.9)	481 (72.3)	.6626
BMI (kg/m^2)	27.0 ± 5.7	29.4 ± 8.3	26.9 ± 4.7	26.8 ± 5.8	.0074
BMI >30	231 (25.5)	15 (38.5)	46 (22.2)	170 (25.8)	.0979
Hypertension	133 (14.6)	19 (48.7)	44 (21.3)	70 (10.5)	<.0001
Diabetes mellitus	38 (4.2)	10 (25.6)	10 (4.8)	18 (2.7)	<.0001
Stroke	39 (4.3)	1 (2.6)	9 (4.4)	29 (4.4)	.8637
Cirrhosis	20 (2.2)	0 (0.0)	7 (3.4)	13 (2.0)	.2995
Atrial fibrillation or flutter	203 (22.3)	26 (66.7)	56 (27.1)	121 (18.2)	<.0001
Pulmonary hypertension	38 (4.2)	7 (18.0)	16 (7.7)	15 (2.3)	<.0001
Cyanosis	53 (6.5)	4 (11.1)	19 (10.1)	30 (5.0)	.0251
NYHA functional class					
I	686 (75.7)	16 (41.0)	143 (69.8)	527 (79.6)	<.0001
≥II	220 (24.3)	23 (59.0)	62 (30.2)	135 (20.4)	
Systemic ventricular systolic function					
Normal	643 (74.9)	21 (58.3)	139 (72.0)	483 (76.7)	.0562
Mildly reduced	152 (17.7)	9 (25.0)	36 (18.7)	107 (17.0)	
Moderately or severely reduced	64 (7.5)	6 (16.7)	18 (9.3)	40 (6.4)	
Disease complexity					
Simple	197 (21.7)	8 (20.5)	48 (23.3)	141 (21.2)	.0506
Moderate	387 (42.5)	21 (53.9)	99 (48.1)	267 (40.2)	
Severe	326 (35.8)	10 (25.6)	59 (28.6)	257 (38.7)	
Medications					
ACEi/ARB	264 (29.0)	16 (41.0)	69 (33.3)	179 (26.9)	.0490
β-Blocker	277 (30.4)	26 (66.7)	74 (35.8)	177 (26.6)	<.0001
Aspirin	304 (33.4)	19 (48.7)	81 (39.1)	204 (30.7)	.0091
Warfarin	197 (21.6)	26 (66.7)	49 (23.7)	122 (18.4)	<.0001
Loop diuretic	161 (17.7)	31 (79.4)	53 (25.6)	77 (11.6)	<.0001

B	$CKD\text{-}EPI_{CysC}$ eGFR (mL/min/1.73 m^2)			
Variable	<60	60-89	≥90	*P* value
n	58	206	647	
Age (y)	53.0 ± 14.1	46.6 ± 14.3	34.8 ± 11.2	<.0001
Sex (male)	23 (39.7)	96 (46.6)	343 (53.0)	.0180
Race (white)	42 (72.4)	149 (72.3)	475 (73.4)	.7636
BMI (kg/m^2)	29.9 ± 7.9	28.1 ± 6.1	26.3 ± 5.2	<.0001
BMI >30	23 (39.7)	68 (33.2)	140 (21.8)	<.0001
Hypertension	21 (36.2)	42 (20.4)	70 (10.8)	<.0001
Diabetes mellitus	17 (29.3)	8 (3.9)	13 (2.0)	<.0001
Stroke	3 (5.2)	7 (3.4)	29 (4.5)	.8296
Cirrhosis	3 (5.2)	7 (3.4)	10 (1.6)	.0247
Atrial fibrillation or flutter	43 (74.1)	66 (32.0)	94 (14.5)	<.0001
Pulmonary hypertension	10 (17.2)	17 (8.3)	11 (1.7)	<.0001
Cyanosis	8 (16.0)	21 (11.1)	24 (4.1)	<.0001
NYHA functional class				
I	21 (36.2)	127 (62.3)	538 (83.5)	<.0001
≥II	37 (63.8)	77 (37.8)	106 (16.5)	

(continued on next page)

Table I (*continued*)

Systemic ventricular systolic function				
Normal	29 (55.8)	137 (71.0)	477 (77.7)	<.0001
Mildly reduced	14 (26.9)	32 (16.6)	106 (17.3)	
Moderately or severely reduced	9 (17.3)	24 (12.4)	31 (5.1)	
Disease complexity				
Simple	12 (20.7)	42 (20.4)	143 (22.1)	.7455
Moderate	27 (46.6)	86 (41.8)	274 (42.4)	
Severe	19 (32.8)	78 (37.9)	229 (35.5)	
Medications				
ACEi/ARB	24 (41.4)	80 (38.8)	160 (24.7)	<.0001
β-Blocker	39 (67.2)	92 (44.7)	146 (22.6)	<.0001
Aspirin	25 (43.1)	104 (50.5)	175 (27.1)	<.0001
Warfarin	40 (69.0)	55 (26.7)	102 (15.8)	<.0001
Loop diuretic	46 (79.3)	70 (34.0)	45 (7.0)	<.0001

Demographic and clinical characteristics of the study sample are presented, stratified by the (A) creatinine-based and (B) cystatin C–based CKD-EPI eGFR categories. Continuous variables are presented as mean ± SD. The analysis of variance test was used to compare trends for continuous variables between groups. Categorical variables are presented as n (% of total sample) for the leftmost column and n (% of row total with that characteristic) for each eGFR category. The Mantel-Haenszel extension of the χ^2 test for trend was used to analyze categorical variables. *Cyanosis* was defined as resting oxygen saturation <92%. Missing data: n = 5 for NYHA FC, n = 6 for BMI, and n = 89 for oxygen saturation/cyanosis status. *ACEi*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker.

Funding sources

This work was conducted with support from Harvard Catalyst/The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102, Harvard University, and its affiliated academic healthcare centers), an investigator-initiated study research grant from Roche Diagnostics (Indianapolis, IN), and the Dunlevie Family Fund. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

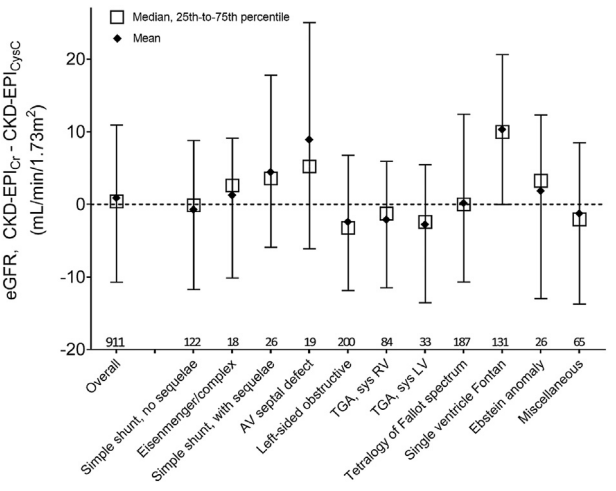
Description of the cohort

Over the study period, 911 patients with CHD were enrolled in whom both creatinine and cystatin C were measured. Average age was 38.6 ± 13.6 years, and 49.2% of patients were female. Most patients had moderately or severely complex diagnoses (Table I). The most common underlying diagnoses were left-sided obstructive lesions (n = 200, 22.0%), tetralogy of Fallot (n = 187, 20.5%), single-ventricle physiology with a Fontan palliation (n = 131, 14.4%), simple shunt lesion without clinical sequelae (n = 122, 13.4%), and transposition of the great arteries with a systemic right ventricle (n = 84, 9.2%). A total of 144 (14.6%) patients had hypertension and 38 patients (4.6%) had diabetes.

Cross-sectional analysis of eGFR

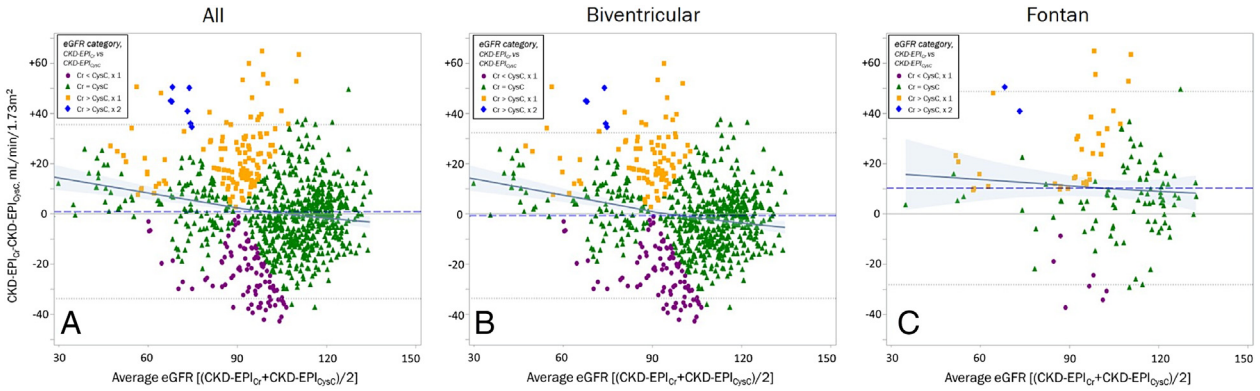
Mean creatinine was 0.9 ± 0.2 mg/dL (median 0.8 [25th-75th percentiles, 0.7-1.0]), and mean cystatin C was 0.9 ± 0.2 mg/L (median 0.8 [0.7-0.9]). In the overall cohort, mean CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$ were similar (100.8 ± 20.4 vs 99.9 ± 23.0, mean difference+ 0.9 ± 17.3 mL/min/1.73 m^2) as was CKD-EPI$_{Cr + CysC}$ (101.5 ± 21.7 mL/min/1.73 m^2), whereas MDRD eGFR tended to be lower (92.8 ± 22.4 mL/min/1.73 m^2). The 2 purely creatinine-based eGFR equations correlated strongly,

Figure 2



Difference between CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$ eGFR by congenital heart disease diagnosis.A box plot showing the difference between CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$, eGFR, overall and by underlying congenital heart disease diagnosis. Boxes indicate the median difference (CKD-EPI$_{Cr}$ minus CKD-EPI$_{CysC}$), filled diamonds the mean, and error bars the 25th-75th percentile values. Values above 0 indicate a higher estimate by CKD-EPI$_{Cr}$, whereas those below 0 indicate a higher estimate by CKD-EPI$_{CysC}$.

Figure 3



Bland-Altman plots of the difference between CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$ against the average of the values.**A**, All patients (n = 911). **B**, Those with a biventricular circulation (n = 780). **C**, Only those with a single-ventricle Fontan circulation (n = 131). In the overall cohort (and biventricular subset), there is little systemic difference between the 2 estimates, although CKD-EPI$_{Cr}$ tended to provide higher estimates than CKD-EPI$_{CysC}$ at lower levels of eGFR, and the converse tended to be true at higher levels. Among the Fontan patients, CKD-EPI$_{Cr}$ tended to provide higher estimates than CKD-EPI$_{CysC}$ at all levels of eGFR, although this was slightly accentuated at lower eGFR. For all subsets, the 95% limits of agreement between CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$ were wide (±35-40 mL/min/1.73 m^2).

whereas the correlation between the creatinine-based methods and CKD-EPI$_{CysC}$ was only moderate (Online Figure 1).

The proportion of patients with eGFR <90 mL/min/1.73 m^2 was similar for the creatinine-based and cystatin C–based CKD-EPI equations (27.0% vs 29.0%, for CKD-EPI$_{Cr\ and}$ CKD-EPI$_{CysC}$, respectively; McNemar test P = .20), although the CKD-EPI$_{Cr}$ categorized a smaller proportion with eGFR <60 mL/min/1.73 m^2 (4.3 vs 6.4%, P = .001) (Figure 1; Online Figure 2). The MDRD equation classified a substantially higher proportion of patients as having eGFR <90 mL/min/1.73 m^2 (46.3%, P < .0001 compared with all CKD-EPI equations) because a higher proportion were classified with mildly impaired eGFR (60-89 mL/min/1.73 m^2).

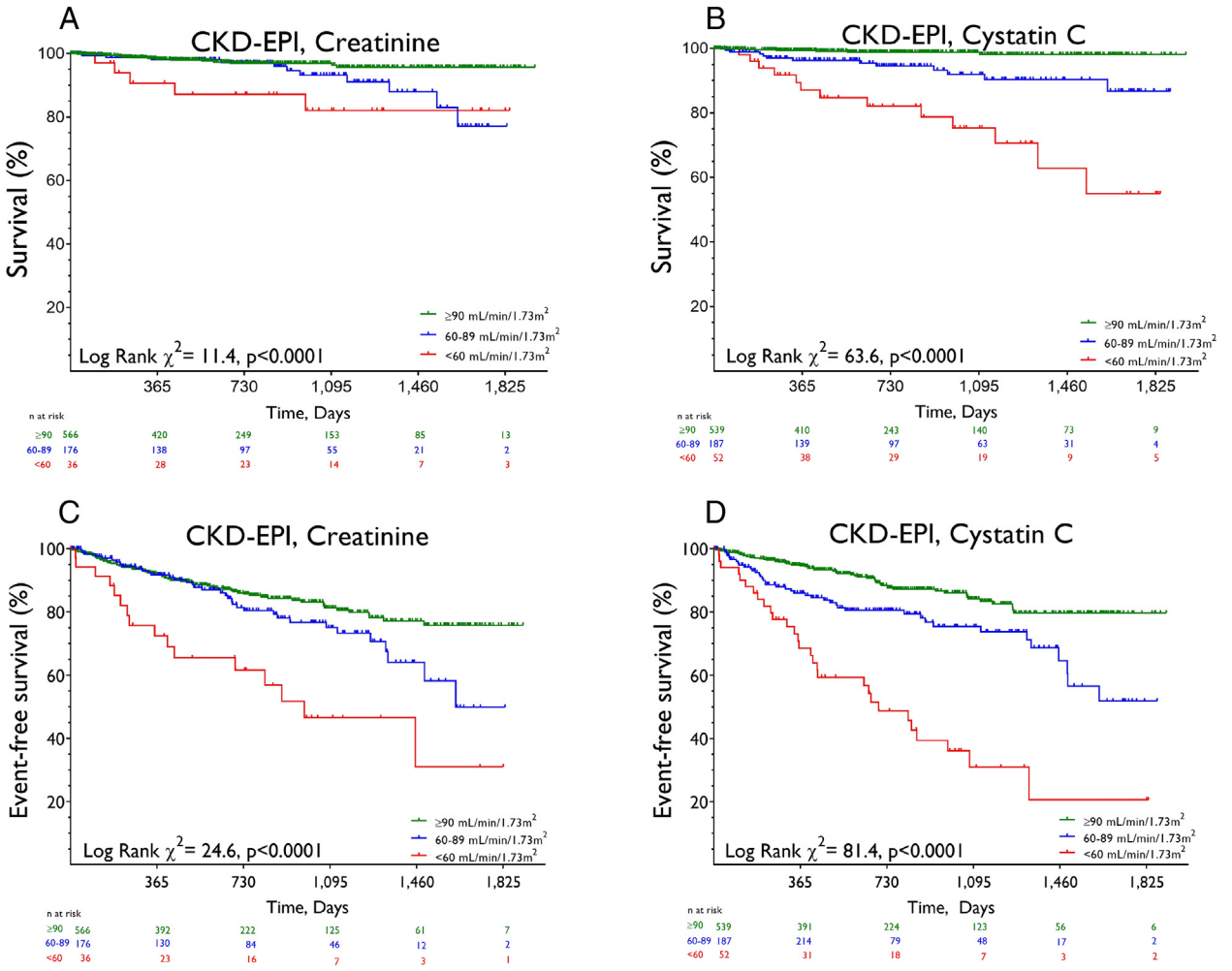
For both equations, older age and higher BMI were associated with lower eGFR, as were hypertension, diabetes, atrial arrhythmias, pulmonary hypertension, cyanosis, and functional class. Those prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were much more likely to have lower CKD-EPI$_{CysC}$, but this relationship was less prominent for CKD-EPI$_{Cr}$ (Table I, data for other equations in Online Table I).

Average eGFR was similar by both methods (mean difference CKD-EPI$_{Cr}$ minus CKD-EPI$_{CysC}$ = +0.9 ± 19.3, 95% limits of agreement −33.8 to +35.6 mL/min/1.73 m^2), but there was heterogeneity between types of CHD (Figure 2). Among the 131 patients with a single-ventricle Fontan circulation, the creatinine-based eGFR was, on average, 10.3 ± 19.3 higher with 95% limits of agreement −28.2 to +48.8 mL/min/1.73 m^2. This compared with a mean difference of −0.7 ± 16.5, with 95% limits of agreement −33.7 to +32.3 mL/min/1.73 m^2, for the 780 patients with a biventricular circulation, P < .0001 (Figure 3). Agreement also varied depending on underlying eGFR values. Compared with CKD-EPI$_{CysC}$, CKD-EPI$_{Cr}$ tended to overestimate eGFR in the low to mid range and underestimate eGFR at the higher end of the range (Figure 3; Online Figure 3). This pattern held true for both single-ventricle Fontan and biventricular circulations.

Survival analysis, overall

Of the 911 patients, 778 (85.4%) had available follow-up data. After a mean follow-up of 659 ± 547 days (median 552 [204-1064]), 31 (3.4%) patients died, whereas 128 (14.1%) experienced the primary composite outcome. In univariate analysis, there was a higher risk for both all-cause mortality and the composite outcome for patients categorized in the lowest eGFR category for all equations (Table II and Figure 4; data for other equations in Online Table III and Online Figure 4). There was a clear and statistically significant stepwise increase in risk for adverse outcomes across the 3 eGFR categories for CKD-EPI$_{CysC}$. Conversely, the risk of adverse outcomes was not significantly higher for those classified as having mildly impaired eGFR (60-89 mL/min/1.73 m^2) compared with normal eGFR based on the 3 creatinine-based equations. The superior prognostic value of CKD-EPI$_{CysC}$ was corroborated by the substantially higher C statistic for continuous CKD-EPI$_{CysC}$ eGFR, as a predictor of both all-cause mortality and the composite outcome, compared with the other equations. After multivariable adjustment, only the CKD-EPI$_{CysC}$ eGFR category remained significantly predictive of the composite outcome (Table II). Multivariable adjustment was not performed for all-

Figure 4



Kaplan-Meier plots of event-free survival for all-cause mortality and the composite outcome, by estimated glomerular filtration rate category (<60, 60-89, ≥90 mL/min/1.73 m^2) as calculated by CKD-EPI_{Cr} or CKD-EPI_{CysC}.Kaplan-Meier cumulative incidence plots for all-cause mortality for adults with congenital heart disease by eGFR category calculated by the CKD-EPI_{Cr} (**A**) and CKD-EPI_{CysC} (**B**) equations. The lower 2 panels (**C**/**D**) show the equivalent data for the composite outcome (death or nonelective cardiovascular hospitalization). The number at risk for the relevant outcome at 365-day intervals is presented below the x-axis.

cause mortality because of the relatively low number of events.

Lower CKD-EPI_{CysC} eGFR was associated with increasing risk of both all-cause mortality and the composite outcome in a largely linear relationship across the spectrum of eGFR values, as shown in Figure 5. Conversely, CKD-EPI_{Cr} eGFR was only associated with increased risk for values below ~60-80 mL/min/1.73 m^2 (Figure 5; data for other equations in Online Figure 5). At any level of eGFR, CKD-EPI_{CysC} was substantially more strongly associated with the risk for either outcome than were the creatinine-based equations.

As compared with CKD-EPI_{Cr}, CKD-EPI_{CysC} was also more strongly associated with more granular outcomes, including worsening heart failure or arrhythmia (Online Figure 6).

Survival analysis, the composite outcome in biventricular versus Fontan circulation

For both equations, higher eGFR was associated with a lower risk for the composite outcome among patients with a biventricular circulation (87 events in 780 patients). CKD-EPI_{CysC} eGFR was more strongly associated with the composite outcome than was CKD-EPI_{Cr} (HR per +10 mL/min/1.73 m^2 [95% CI] = 0.77 [0.71-0.82] vs 0.80 [0.73-0.89],

Table II. Prediction of incident clinical events by eGFR by CKD-EPI creatinine and CKD-EPI cystatin C equations

				Combined outcome									All-cause mortality					
	eGFR, mL/min/1.73 m^2	n	% of total	Events, n	1-y K-M estimate, %	*C*-statistic	HR, univariate	95% CI	*P* value	*C*-statistic, adjusted	HR, adj	95% CI	*P* value	Events, n	1-y K-M Estimate, %	*C*-statistic	HR, univariate	95% CI	*P* value
CKD-EPI$_{Cr}$	≥90	665	73.0	76	7.8	0.571	1.0	Ref	Ref	0.762	1.0	Ref	Ref	15	1.8	0.620	1.0	Ref	Ref
	60-89	207	22.7	36	8.3	–	1.4	0.96-2.1	.08	–	1.3	0.8-2.0	.28	11	1.9	–	2.2	1.03-4.9	.04
	<60	39	4.3	16	27.6	–	3.6	2.1-6.2	<.0001	–	1.5	0.8-3.1	.22	5	2.9	–	4.6	1.7-12.7	.003
CKD-EPI$_{CysC}$ .0008	≥90	647	71.0	58	5.4	0.692	1.0	Ref	Ref	0.78	1.0	Ref	Ref	6	0.2	0.797	1.0	Ref	Ref
	60-89	206	22.6	41	14.0	–	–	2.1	1.4-3.1	.0003	–	1.8	1.1-2.9	.01	12	3.7	–	5.4	2.0-14.3
	<60	58	6.4	29	26.9	–	6.3	4.0-9.9	<.0001	–	3.0	1.7-5.3	.0003	16	10.6	–	20.2	7.6-53.1	<.0001

An analysis of eGFR category (<60, 60-89, and ≥90 mL/min/1.73 m^2) as calculated by creatinine and cystatin C–based CKD-EPI equations, as a predictor of outcomes: the composite outcome of death or nonelective cardiovascular hospitalization on the left and all-cause mortality on the right. *C*-statistics are presented for continuous eGFR estimates rather than categorical group. The multivariable model adjusted for history of atrial arrhythmia, NYHA functional class, cyanosis, and qualitative systolic systemic ventricular function. The multivariable model *C*-statistic without eGFR for the composite outcome was 0.759. *Multivariable adjustment is not presented for mortality given the number of events.
adj, adjusted.

both $P < .0001$). The model *C*-statistic for CKD-EPI$_{CysC}$ was 0.700 compared with only 0.598 for CKD-EPI$_{Cr}$. Both CKD-EPI$_{CysC}$ and CKD-EPI$_{Cr}$ eGFR remained significantly associated with the composite outcome after multivariable adjustment (HR = 0.82 [0.75-0.90], $P < .0001$ vs 0.86 [0.78-0.95], $P = .002$).

In the subset of patients with a single-ventricle Fontan circulation, higher CKD-EPI$_{CysC}$ eGFR was associated with lower risk of the composite outcome (41 events in 131 patients; HR = 0.85 [0.76-0.95], $P = .005$, *C*-statistic 0.652). However, neither of the purely creatinine-based eGFR methods was significantly associated with the risk of the composite outcome in the single-ventricle Fontan group (CKD-EPI$_{Cr}$, HR = 0.96 [0.84-1.10], $P = .55$, *C*-statistic 0.515). Given the smaller number of events in each subgroup, these analyses were not performed on the outcome of all-cause mortality.

Reclassification analysis

GFR category was classified differently in 228 of the 911 patients by the CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$ equations (Table III). There were 655 patients with normal CKD-EPI$_{Cr}$ eGFR ≥90 mL/min/1.73 m^2. Most of these patients also had normal CKD-EPI$_{CysC}$, and this group had an 8.8% event rate (n = 49/556). The composite outcome was much more common among those with normal CKD-EPI$_{Cr}$ reclassified by CKD-EPI$_{CysC}$ to eGFR 60-89 (21.6%, n = 22/102) or <60 (71.4%, n = 5/7). Improved risk prediction was also seen among patients with either mildly or moderately to severely reduced CKD-EPI$_{Cr}$ eGFR who were reclassified to a different CKD-EPI$_{CysC}$ eGFR category (Table III). After accounting for baseline CKD-EPI$_{Cr}$ eGFR category, those reclassified to a lower/worse eGFR category by the CKD-EPI$_{CysC}$ model had higher risk for the composite outcome (HR =2.9 [2.0-4.3], $P < .0001$), whereas those reclassified to higher/better eGFR had lower risk (HR = 0.48 [0.25-0.93], $P = .03$).

Among patients with at least 1-year of follow-up (n = 465), 1-year predicted probabilities of the composite outcome were calculated using a multivariable logistic regression model, including either CKD-EPI$_{Cr}$ or CKD-EPI$_{CysC}$ as a covariate (Table IV). Both models had acceptable goodness of fit (Hosmer-Lemeshow $P > .50$). Mean predicted probability of the composite outcome was 10.5% for both models, but the CKD-EPI$_{CysC}$ model predicted very low risk of <2.5% for a higher proportion of patients than did the CKD-EPI$_{Cr}$ model. Of the 303 patients predicted to have a 2.5%-10% probability of the composite outcome by the CKD-EPI$_{Cr}$, 121 were predicted to have lower risk (<2.5%), 171 were assigned the same predicted risk category, and 11 were predicted to have a higher risk (10%-20%) by the CKD-EPI$_{CysC}$ model. The true

Figure 5

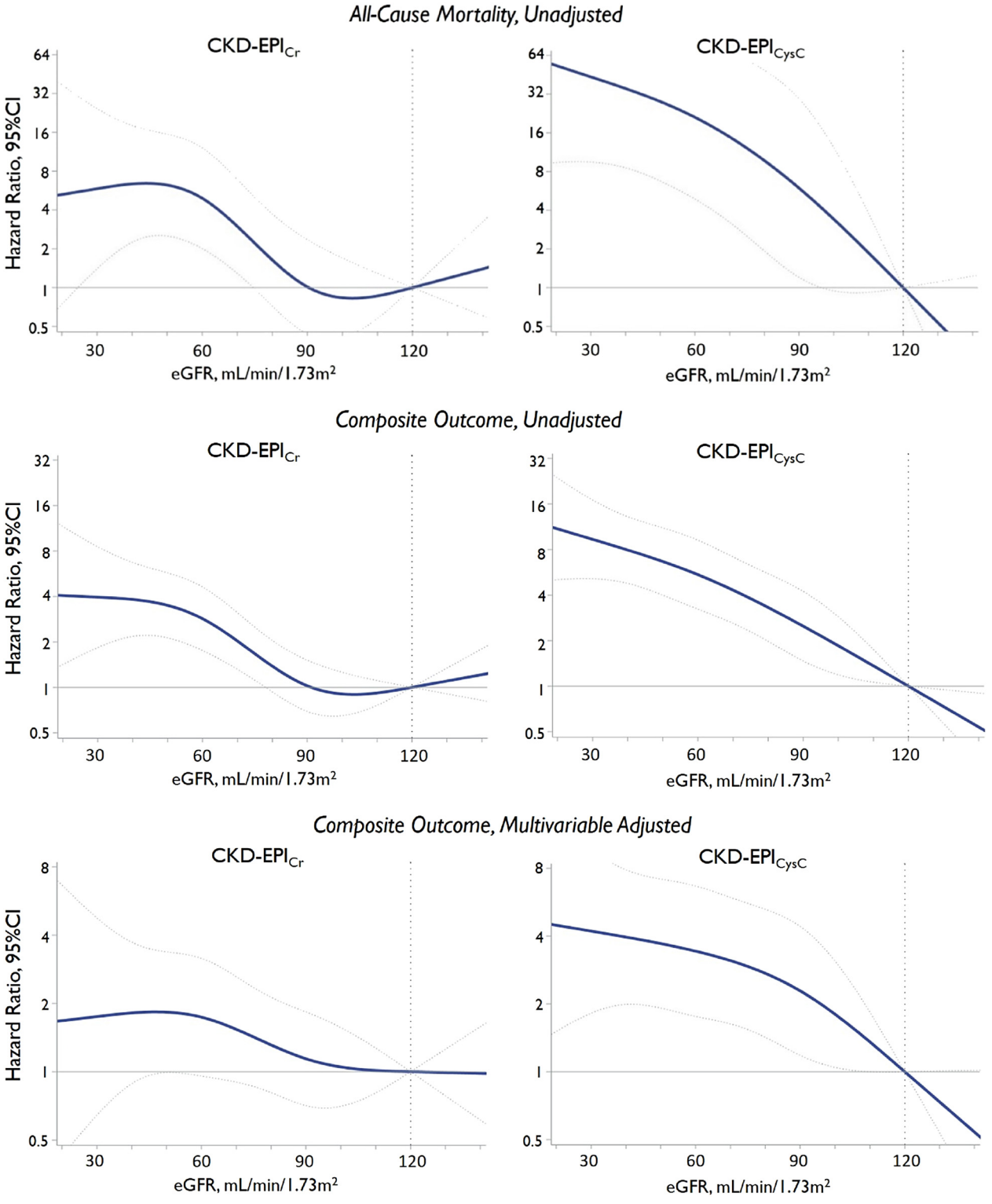

All-Cause Mortality, Unadjusted
CKD-EPI$_{Cr}$
CKD-EPI$_{CysC}$
Hazard Ratio, 95%CI
64
32
16
8
4
2
1
0.5
30
60
90
120
eGFR, mL/min/1.73m^2
Composite Outcome, Unadjusted
CKD-EPI$_{Cr}$
CKD-EPI$_{CysC}$
Hazard Ratio, 95%CI
32
16
8
4
2
1
0.5
30
60
90
120
eGFR, mL/min/1.73m^2
Composite Outcome, Multivariable Adjusted
CKD-EPI$_{Cr}$
CKD-EPI$_{CysC}$
Hazard Ratio, 95%CI
8
4
2
1
0.5
30
60
90
120
eGFR, mL/min/1.73m^2

Table III. Occurrence of death or nonelective cardiovascular hospitalization by classification of eGFR category by CKD-EPI$_{Cr}$ and CKD-EPI$_{CysC}$

		CKD-EPI$_{CysC}$ eGFR			
CKD-EPI$_{Cr}$ eGFR		< 60	60-89	≥ 90	**Total**
< 60	n	31	8	0	*39*
	n, event	14	2	0	*16*
	% event	45.2%	25.0%	0%	*41.0%*
60-89	n	20	96	91	*207*
	n, event	10	17	9	*36*
	% event	50.0%	17.7%	9.9%	*17.4%*
≥ 90	n	7	102	556	*665*
	n, event	5	22	49	*76*
	% event	71.4%	21.6%	8.8%	*11.4%*
	Total n	*58*	*206*	*647*	*911*
	n, event	*29*	*41*	*58*	*128*
	%, event	*50.0%*	*19.9%*	*9.0%*	*14.1%*

observed event rates aligned with the CKD-EPI$_{CysC}$ model predicted probabilities: 1.7%, 4.7%, and 18.2%. There were fewer patients in the other CKD-EPI$_{Cr}$ model predicted probability bins, but the pattern was similar (Table IV). Overall net reclassification improvement was 0.416, 0.082, and 0.334 for cases and controls, respectively.

Additive value of albuminuria

Of the 911 patients in the overall cohort, 740 had valid urine albumin and creatinine measurements. Log ACR correlated weakly with both CKD-EPI$_{Cr}$ ($r = -0.18$, $P < .0001$) and CKD-EPI$_{CysC}$ ($r = -0.29$, $P < .0001$). There was a stepwise increase in the risk of the composite outcome with both decreasing eGFR and increasing albuminuria (Online Table IV). In a Cox regression model including albuminuria category and CKD-EPI$_{CysC}$ category, both remained strongly predictive of the composite outcome (for CKD-EPI$_{CysC}$ 60-89 and <60, respectively: HR = 2.1, 1.4-3.2 and HR = 3.3, 1.9-15.8, $\chi^2 = 21.4$; for ACR 30-300 and ACR >300 mg/g, respectively: HR = 2.2, 1.4-3.4 and HR = 5.2, 2.5-10.9, $\chi^2 = 25.8$). The model *C*-statistic was 0.683 compared with 0.619 for albuminuria alone and 0.648 for CKD-EPI$_{CysC}$ alone. On the other hand, CKD-EPI$_{Cr}$ category was only marginally associated with the composite outcome after adjustment for albuminuria category (*P* value .06 for CKD-EPI$_{Cr}$ category; overall model *C*-statistic 0.641).

Discussion

In this prospective cohort study of 911 ambulatory ACHD patients, we report that (1) cystatin C-based eGFR classified a larger proportion of patients as having moderately or severely reduced eGFR; (2) there was poor agreement between creatinine-based and cystatin C-based eGFR, especially in the subset of patients with single-ventricle Fontan circulation; and (3) cystatin C–based eGFR was a notably better predictor of both all-cause mortality alone and the composite of death or nonelective cardiovascular hospitalization. Given the importance of eGFR for both clinical decision making and risk prediction, these findings argue that measurement of cystatin C to estimate GFR may provide considerable benefit in ACHD practice.

Chronic kidney disease is much more common in ACHD compared to similarly aged peers.[3] Our results align with a previously published retrospective study that reported an 18-fold higher prevalence of at least moderately reduced eGFR (<60 mL/min/1.73 m^2 by MDRD) in acyanotic ACHD compared with the general population, with an even greater burden in those with cyanosis.[8] There are likely many reasons for the increased prevalence of reduced eGFR including cyanosis, heart failure, nephrotoxic medications, and procedures associated with kidney injury.

The presence of renal dysfunction is a strong predictor of survival in diverse populations, including patients with CHD. Dimopoulos and colleagues reported that, compared to patients with normal

Hazard ratio for all-cause mortality or the composite outcome in adults with congenital heart disease by continuous estimated glomerular filtration rate using CKD-EPI$_{Cr}$ versus CKD-EPI$_{CysC}$.Cubic spline plots of the relative hazard ratios for all-cause mortality (top row), and the composite outcome of death or nonelective cardiovascular hospitalization, unadjusted (middle row) and multivariable adjusted (bottom row) by CKD-EPI$_{Cr}$ (left-hand column) and CKD-EPI$_{CysC}$ (right-hand column). The multivariable model adjusted for NYHA functional class, history of atrial arrhythmia, cyanosis, and systemic ventricular function. Note that the y-axis scale differs between analyses.

eGFR, those with moderately or severely reduced eGFR (<60 mL/min/1.73 m^2 estimated by the MDRD equation) had a 3-fold increase in mortality at 6 years after creatinine measurement, but mildly reduced eGFR (60-89 mL/min/1.73 m^2) was not associated with statistically significantly increased risk.[8] Similarly, the mildly reduced creatinine-based eGFR was not associated with appreciably increased risk in the current study.

In contrast, not only was moderately to severely reduced eGFR estimated by the cystatin C–based equation, CKD-EPI_{CysC}, associated with a markedly higher relative risk of adverse outcomes than seen for the creatinine-based estimates, there was also a substantially increased risk among those with less severely reduced eGFR. CKD-EPI_{CysC} provided much improved risk prediction compared with any of the creatinine-based equations including the combine cystatin C and creatinine equation. Lower CKD-EPI_{CysC} eGFR was associated with increasing risk across the spectrum of eGFR values, whereas CKD-EPI_{Cr} eGFR was only associated with increased risk for values below ~60-80 mL/min/1.73 m^2. In the single-ventricle Fontan subset, only cystatin C–based eGFR was predictive of future events, whereas creatinine-based eGFR was not.

Patients reclassified to worse eGFR by CKD-EPI_{CysC} were at increased risk for adverse outcomes, whereas those reclassified to higher eGFR were less likely to sustain an adverse outcome, in agreement with data from other populations.[19] A meta-analysis on >90,000 patients provided evidence that cystatin C–based eGFR is more predictive of both all-cause mortality and cardiovascular mortality in the general population and in those with chronic kidney disease. Reclassification to a lower eGFR using cystatin C–based eGFR was associated with a significantly higher adjusted risk of death. Among patients with a creatinine-based eGFR of 60-89 mL/min/1.73 m^2, 14% were reclassified to a cystatin C–based eGFR of less than 60 mL/min/1.73 m^2 and had a relative increase of 57% in the risk of death.[19] In our study, 20 of the 207 patients with 60-89 mL/min/1.73 m^2 CKD-EPI_{Cr} were reclassified to a cystatin C–based eGFR <60 mL/min/1.73 m^2. These patients had almost 3 times the risk of the composite outcome (50% vs 17.4%).

The MDRD and CKD-EPI_{Cr} equations are recommended for adults by existing guidelines, and both incorporate 4 variables (serum creatinine, sex, age, and race) to estimate GFR.[6,13,20,21] MDRD, however, underestimates measured GFR at higher levels and classifies more patients as having reduced eGFR.[22] To address such shortcomings, the CKD-EPI_{Cr} equation was developed in 2009.[13] CKD-EPI_{Cr} agrees better with measured GFR, especially in the normal or mildly reduced range, and also more strongly predicts adverse outcomes in various populations.[13,22] Likewise, among 102 adults with CHD, CKD-EPI_{Cr} eGFR, as compared with original MDRD eGFR, more strongly correlated with CKD-EPI_{CysC} eGFR and with symmetrical dimethylarginine, another marker of renal function.[23] Both MDRD and CKD-EPI_{Cr} depend on a predictable relationship between serum creatinine and GFR. Creatinine is produced by muscle, whereas cystatin C is produced by all nucleated cells; creatinine-based eGFR equations are inaccurate when actual muscle mass differs from expected population-based norms, whereas cystatin C eGFR does not depend on muscle mass.[24] This has particular relevance because at least some adult CHD subsets, most notably the single-ventricle Fontan population, have lower lean muscle mass and lower muscle strength than matched healthy controls.[9,10,25,26] In such populations, creatinine-based methods would be expected to overestimate GFR. One study that included 17 adults among a total single-ventricle Fontan cohort of 68 patients reported no significant difference between creatinine-based and cystatin-based eGFR, although this was a generally healthy, young cohort seen at a primarily pediatric clinic.[27] A recent study found that about half of adult Fontan patients with creatinine-based eGFR >90 mL/min/1.73 m^2 had ^{99m}Tc-DTPA renal dynamic imaging eGFR <90 mL/min/1.73 m^2.[28] Although renal dynamic imaging is not necessarily more accurate than creatinine-based eGFR,[29-31] the consistency between our finding of overestimation of eGFR by creatinine-based methods with these data supports the argument that creatinine-based eGFR overestimates true GFR in the adult Fontan population.

Current clinical recommendations for GFR evaluation include measurement of serum creatinine and use of a GFR estimating equation for most patients, but additional confirmation with either cystatin C–based eGFR or measurement of GFR is recommended for groups in whom creatinine-based eGFR is known to be less accurate.[6] Although the overall cost-benefit balance of measuring cystatin C for all adults with CHD merits further study, we believe the currently available evidence supports using cystatin C to better estimate GFR in the adult Fontan population, especially when it is likely to influence important clinical decisions.

Existing guidelines suggest that evaluation for CKD risk should include assessment of both GFR and albuminuria to guide appropriate management.[4] Our findings support the synergistic value of these distinct dimensions of kidney dysfunction in the overall ACHD population, although the implications of albuminuria in the Fontan subset are less clear.[15,17] More accurate identification of renal dysfunction could enable earlier intervention targeted at mechanisms of kidney disease such as renin-angiotensin-aldosterone system activation as well as minimizing exposure to potential nephrotoxins.

The implications for estimating GFR using a cystatin C–based formula in ACHD, therefore, extend beyond clinical risk prediction. For example, drug dosing could

Table IV. Reclassification table comparing risk strata using a multivariable clinical risk model with creatinine-based versus cystatin C–based eGFR with observed risk of death or nonelective cardiovascular hospitalization

Predicted Risk, Model with $CKD\text{-}EPI_{Cr}$		Predicted Risk, Model with $CKD\text{-}EPI_{CysC}$					
		<2.5%	2.5-10%	10-20%	20-30%	>30%	Total
<2.5%	All	19	3	0	0	0	22
	Controls	19	3	0	0	0	22
	Cases	0	0	0	0	0	0
	Observed risk, %	0.0	0.0	0.0	0.0	0.0	0.0
2.5-10%	All	121	171	11	0	0	303
	Controls	119	163	9	0	0	291
	Cases	2	8	2	0	0	12
	Observed risk, %	1.7	4.7	18.2	0.0	0.0	4.0
10-20%	All	0	28	36	9	1	74
	Controls	0	27	31	6	1	65
	Cases	0	1	5	3	0	9
	Observed risk, %	0.0	3.6	13.9	33.3	0.0	12.2
20-30%	All	0	0	4	9	5	18
	Controls	0	0	4	7	2	13
	Cases	0	0	0	2	3	5
	Observed risk, %	0.0	0.0	0.0	22.2	60.0	27.8
>30%	All	0	0	5	6	37	48
	Controls	0	0	4	6	15	25
	Cases	0	0	1	0	22	23
	Observed risk, %	0.0	0.0	20.0	0.0	59.5	47.9
	All	140	202	56	24	43	
	Controls	138	193	48	19	18	
	Cases	2	9	8	5	25	
	Observed risk, %	1.4	4.5	14.3	20.8	58.1	

be more appropriately directed for the many renally cleared cardiovascular medications. Other benefits of more accurate eGFR include assessment of risk when using iodinated contrast media for computed tomography and catheterization, identification of patients at highest risk for acute kidney injury after surgery involving cardiopulmonary bypass, and more informed consideration during heart transplant evaluation.

Limitations

ACHD is comprised of a wide array of diagnoses with variable pathophysiology. The current cohort was enrolled at a major referral center and tended to have moderately or severely complex CHD. Although this high-risk population is of particular interest to providers, the findings may not be generalizable to ACHD seen in the community. The current analysis does not include multivariable adjustment for all relevant clinical variables, such as circulating biomarkers.[17,32,33] The purpose of this analysis was to compare creatinine and cystatin C estimates of GFR, and adjustment for these variables would not be anticipated to affect the conclusion that cystatin C estimates are superior. We did not measure GFR using a criterion-standard method, such as inulin clearance. Although the improved prognostic performance of cystatin C eGFR strongly suggests that it more accurately estimates GFR, other variables also influence cystatin C levels; based on the current data, we cannot reject alternative explanations such as an independent link between circulating cystatin C levels and outcome.[34,35] Finally, the current data include only a single measurement which results in a great variation between follow-up times from initial surgical corrections, particularly when smaller subgroups are examined (such as single-ventricle patients), and also do not provide insight on repeated measurements.

Conclusions

Adults with CHD are at increased risk for chronic kidney disease. Those with reduced eGFR are at higher risk for adverse clinical outcomes, including all-cause mortality and cardiovascular events. Cystatin C–based eGFR appears to be more strongly predictive of clinical

risk than is creatinine-based eGFR in the overall ACHD population. Measurement of cystatin C to better estimate eGFR may be considered, espesscially in patient subgroups where cystatin C eGFR is most clearly superior, including those with mildly reduced eGFR and patients with a single-ventricle Fontan circulation.

Disclosures

The authors have no conflicts of interest pertinent to the topic of this manuscript.

This table shows the percentage of patients who experienced the composite outcome by of eGFR category (<60, 60-89, and ≥ 90 mL/min/1.73 m^2) by CKD-EPI_{Cr} and CKD-EPI_{CysC}. The analysis includes all patients irrespective of follow-up time or event status. The *% event values* are defined as the percentage of all patients included in a given cell that experienced the composite primary outcome of death or nonelective cardiovascular hospitalization. Cells shaded gray indicate patients assigned to the same eGFR category by both equations (total n = 683). Of the remaining 228, 129 were assigned a lower eGFR category by CKD-EPI_{CysC}, whereas 99 were assigned to a higher category by CKD-EPI_{CysC}.

Comparison of observed 1-year outcomes by the assigned risk strata from a base multivariable clinical risk model plus CKD-EPI_{Cr} to this model plus CKD-EPI_{CysC}. The base multivariable logistic regression model included history of atrial arrhythmia, NYHA functional class, cyanosis, and qualitative systolic ventricular function. The dependent variable was the presence or absence of the composite outcome, death or nonelective cardiovascular hospitalization. This analysis included any patient who had experienced an event within 1-year or who had at least 1-year of event-free follow-up time (n = 465/911; n = 49 events). The *observed risk* was defined as the percentage of patients who sustained the composite outcome over 1 year. Cells shaded gray indicate patients assigned to the same risk category by both models, whereas red and green cells indicate those assigned to higher and lower risk, respectively, by CKD-EPI_{CysC} compared with CKD-EPI_{Cr}. Reclassification improvement was 8.2% among those who experienced an event ([8 − 4]/49) and 33.4% among those who did not ([160 − 21]/416) for an overall net reclassification improvement of 41.6%.

TGA, transposition of great arteries; *RV*, right ventricle; *LV*, left ventricle; *AV*, atrioventricular.

The blue dashed line designates the mean difference between CKD-EPI_{Cr} and CKD-EPI_{CysC}, whereas the gray dashed lines indicate the 95% upper and lower limits of agreement. The solid gray line and semitransparent blue area indicate a locally weighted scatterplot smoothing line of the mean difference between CKD-EPI_{Cr} and CKD-EPI_{CysC} and a 95% confidence limit for the estimate of that line.

Green triangles indicate that CKD-$EPI_{Cr\ and}$ CKD-EPI_{CysC} assigned the same eGFR category (<60, 60-89, ≥90 mL/min/1.73 m^2); purple diamonds indicate patients assigned 1 level higher/better category by CKD-EPI_{CysC}, whereas the yellow squares and blue diamonds, respectively, indicate patients assigned categories 1 and 2 levels lower by CKD-EPI_{CysC}.

The solid, thick, blue line indicates the hazard ratio, and the thin, dashed, black lines indicate 95% CIs. The reference eGFR value, where the hazard ratio = 1, was set to 120 mL/min/1.73 m^2.

Acknowledgements

We are grateful to Allison Bradley, Keith Taillie, Prince Owusu, and Justin Owumi for their diligent work on this project.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.04.018.

References

1. Gilboa SM, Devine OJ, Kucik JE, et al. Congenital heart defects in the united states: estimating the magnitude of the affected population in 2010. Circulation 2016;134(2):101-9.
2. Norozi K, Oechslin E. Renal dysfunction in adults with congenital heart defects. Prog Pediatr Cardiol 2016;41(IN PRESS):51-7.
3. Morgan C, Al-Aklabi M, Garcia Guerra G. Chronic kidney disease in congenital heart disease patients: a narrative review of evidence. Can J Kidney Health Dis 2015;2:27.
4. Levin A, Stevens P, Bilous R, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3(1):e150.
5. Damman K, Valente MA, Voors AA, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J 2014;35(7):455-69.
6. Levey AS, Inker LA. Assessment of glomerular filtration rate in health and disease: a state of the art review. Clin Pharmacol Ther 2017;102(3):405-19.
7. Hart LA, Anderson GD. Methods of estimating kidney function for drug dosing in special populations. Clin Pharmacokinet 2018;57(8):943-76, https://doi.org/10.1007/s40262-018-0628-7. Epub 2018/01/23. PubMed PMID: 29357102.
8. Dimopoulos K, Diller GP, Koltsida E, et al. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation 2008;117(18):2320-8.
9. Cordina R, O'Meagher S, Gould H, et al. Skeletal muscle abnormalities and exercise capacity in adults with a Fontan circulation. Heart 2013;99(20):1530-4.
10. Avitabile CM, Leonard MB, Zemel BS, et al. Lean mass deficits, vitamin D status and exercise capacity in children and young adults after Fontan palliation. Heart 2014;100(21):1702-7.
11. Opotowsky AR, Loukas B, Ellervik C, et al. Design and implementation of a prospective adult congenital heart disease biobank. World J for Pediatr and Congenital Heart Surg 2016;7(6):734-43.

12. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-70.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12.
14. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367(1):20-9.
15. Opotowsky AR, Baraona FR, Mc Causland FR, et al. Estimated glomerular filtration rate and urine biomarkers in patients with single-ventricle Fontan circulation. Heart 2017;103(6):434-42.
16. Harrell Jr FE, Lee KL, Califf RM, et al. Regression modelling strategies for improved prognostic prediction. Stat Med 1984;3 (2):143-52.
17. Rajpal S, Alshawabkeh L, Almaddah N, et al. Association of albuminuria with major adverse outcomes in adults with congenital heart disease: results from the Boston Adult Congenital Heart Biobank. JAMA Cardiol 2018;3(4):308-16.
18. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013;369(10):932-43.
19. Lamb EJ, Levey AS, Stevens PE. The Kidney Disease Improving Global Outcomes (KDIGO) guideline update for chronic kidney disease: evolution not revolution. Clin Chem 2013;59(3):462-5.
20. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007;53(4):766-72.
21. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA 2012;307 (18):1941-51.
22. Tutarel O, Denecke A, Bode-Boger SM, et al. Symmetrical dimethylarginine outperforms CKD-EPI and MDRD-derived eGFR for the assessment of renal function in patients with adult congenital heart disease. Kidney Blood Press Res 2011;34 (1):41-5.
23. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clinical J of the Amer Soc of Nephrology : CJASN 2008;3(2):348–54.
24. Greutmann M, Le TL, Tobler D, et al. Generalised muscle weakness in young adults with congenital heart disease. Heart 2011;97(14):1164-8.
25. Kroonstrom LA, Johansson L, Zetterstrom AK, et al. Muscle function in adults with congenital heart disease. Int J Cardiol 2014;170(3):358-63.
26. Sharma S, Ruebner RL, Furth SL, et al. Assessment of kidney function in survivors following Fontan palliation. Congenit Heart Dis 2016;11(6):630-6.
27. Lee D, Levin A, Kiess M, et al. Chronic kidney damage in the adult Fontan population. Int J Cardiol 2018;257:62-6.
28. Xie P, Huang JM, Liu XM, et al. (99m)Tc-DTPA renal dynamic imaging method may be unsuitable to be used as the reference method in investigating the validity of CDK-EPI equation for determining glomerular filtration rate. PLoS One 2013;8(5), e62328.
29. Assadi M, Eftekhari M, Hozhabrosadati M, et al. Comparison of methods for determination of glomerular filtration rate: low and high-dose Tc-99m-DTPA renography, predicted creatinine clearance method, and plasma sample method. Int Urol Nephrol 2008;40(4):1059-65.
30. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol 2009;20(11):2305-13.
31. Baggen VJ, van den Bosch AE, Eindhoven JA, et al. Prognostic value of N-terminal pro–B-type natriuretic peptide, troponin-t, and growth-differentiation factor 15 in adult congenital heart disease. Circulation 2017;135(3):264-79.
32. Opotowsky AR, Valente AM, Alshawabkeh L, et al. Prospective cohort study of C-reactive protein as a predictor of clinical events in adults with congenital heart disease: results of the Boston adult congenital heart disease biobank. Eur Heart J 2018;39(34):3253-61.
33. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int 2004;65(4):1416-21.
34. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009;75(6):652-60.