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Incident Heart Failure Risk Reclassification with Race-Independent Estimated Glomerular Filtration Rate: An NHLBI Pooled Cohorts Analysis

--Manuscript Draft--

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Abstract:	Background: This study compared the predictive value of the race-independent creatinine and cystatin C-based estimated glomerular filtration rate(eGFRcr-cys) and the race-dependent creatinine-based eGFR(eGFRcr) for incident heart failure. Methods: Data from ARIC and MESA were combined for this study. Multivariable Cox models were used to assess the risk of incident heart failure over a 10-year follow-up period with the quartiles of eGFRcr-cys and eGFRcr. Risk reclassification was assessed using net reclassification improvement(NRI). Results: Among 15,615 individuals[median age:62(57,68) years; 55.0% females; 23.9% Black], the median eGFRcr-cys and eGFRcr were 91.4(79.4,102.0) ml/min/1.73m2 and 84.7(72.0,94.7) ml/min/1.73m2, respectively. Compared with the fourth quartile of eGFRcr-cys, the hazard ratio for incident heart failure was 1.02(95%CI:0.80-1.30) in the third quartile, 1.02(95%CI:0.80-1.30) in the second quartile, and 1.47(95%CI:1.16-1.86) in the first quartile. Compared with the fourth quartile of the eGFRcr, the risk of incident heart failure was similar in the third[HRadj:0.90(95%CI:0.73-1.12)], second[HRadj:0.96(95%CI:0.77-1.20)], and first[HRadj:1.15(95%CI:0.93-1.44)] quartiles. C-statistics were similar for the multivariable-adjusted Cox models for incident heart failure using eGFRcr[0.80(0.79-0.81)] and eGFRcr-cys[0.80(0.79-0.82)]. Replacing eGFRcr with eGFRcr-cys led to the correct reclassification of individuals who developed incident heart failure[NRIE:0.21(0.14-0.27)] and who did not develop incident heart failure[NRINE:0.04(0.02-0.06)]. Conclusion: The eGFRcr and eGFRcr-cys had comparable predictive values for incident heart failure.
Response to Reviewers:	Reviewer 3: In this manuscript authors aim to compare the predictive value of race-independent eGFR to race dependent eGFR. Overall the manuscript is well written, but the chosen statistical methods are not ideal for the aim. My comments:

1. NRI and IDI have been widely criticized (see references below). Please consider alternative metrics to compare the predictors.
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b. Cook, N.R. Quantifying the added value of new biomarkers: how and how not. Diagn Progn Res 2, 14 (2018). https://doi.org/10.1186/s41512-018-0037-2
c. https://www.fharrell.com/post/addvalue/

Response: We thank the Reviewer for their insightful comment and agree that net reclassification improvement (NRI) and integrated discrimination index (IDI) are not ideal measures. We highlighted the limitations of the NRI and IDI in the limitations section in the original submission. We read the references provided by the Reviewer with great interest. Based on the literature provided by the Reviewer, we agree that the NRI and IDI may not be the best measures for comparing predictors. Therefore, as per the Statistical Reviewer's suggestions, we have now removed these metrics from the revised manuscript.
Furthermore, we have added additional measures, such as the Brier score, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and the log-likelihood value for the fully adjusted models based on the Reviewers' suggestion. We have summarized these measures for the fully adjusted models for race-dependent creatinine-based eGFR and the race-independent creatinine and cystatin C-based eGFR in Reviewer Table 1. Similar to the C-statistic values, the Brier score, AIC, BIC, and log-likelihood values did not differ between the race-dependent creatinine-based eGFR and the race-independent creatinine and cystatin C equation-based models. Therefore, we can conclude that both the eGFRs are comparable in their ability to predict incident heart failure events.

Methods Page 5, Line 102
Additional metrics, including the Akaike Information Criterion, Bayesian Information Criterion, log-likelihood values (-2 log-likelihood), and the Brier score, were used to compare the performance of the fully adjusted Cox models with creatinine and cystatin C-based eGFR and cystatin C-based eGFR.

Results Page 9, Line 174
The AIC, BIC, log-likelihood values, and the Brier score were similar for the Cox models using creatinine-based eGFR and creatinine and cystatin C-based eGFR in the overall population and stratified by race. (Table 4)

Discussion Page 10, Line 184
Using the creatinine and cystatin C-based eGFR instead of the creatinine-based eGFR in the models to assess the risk of incident heart failure did not lead to a meaningful change in C-statistics or other metrics of model performance such as AIC, BIC, log-likelihood values, and the Brier score.

2. I would recommend removing or modifying the analyses that "assess the relative strength of association of the risk of incident heart failure with eGFR and other covariates…". Here the authors used the Wald test statistics to rank variables. This is ultimately equivalent to ranking the variables by p-value. The Wald test tests the hypothesis that the beta coefficient is zero (i.e. there is no association between the predictor(s) and the outcome). A large Wald statistic (and corresponding small p-value) can happen when a variable yields a precise estimate with low standard error and does not mean that the magnitude of the estimated effect is large. The resulting rankings can only be interpreted in terms of strength of evidence of non-zero association, not strength of association.

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3. In the analyses of eGFR using splines - what motivated the choice of 3 knots? How sensitive is the shape of the curve to the number and placement of knots? Please add

	the placement of the knots to the methods. Response: We appreciate the Reviewer's comment. The number of knots were chosen based on the model fit statistics (BIC). We have summarized the BIC values for the models with varying the number of knots in Reviewer Table 1. As noted in the table below, the model with 3 knots had the lowest BIC and hence 3 knots were chosen to model the splines. We have included the splines for models with 3, 5, and 7 knots to show how the shape of the spline would change with the number of knots. (Reviewer Figure 1) Knots were placed at the 10th, 50th, and 90th percentiles, as recommended by Harrell. Methods Page 5, Line 97 To assess the non-linear association of eGFR and the risk of incident heart failure in the overall population and within the subgroup of race and ethnicity, restricted cubic splines with 3 knots (10th, 50th, and 90th percentiles) were used.

UAB SCHOOL OF MEDICINE

Dr. Robert Mentz, MD
Editor-in-Chief
Journal of Cardiac Failure

May 30, 2023

Manuscript title: **Incident Heart Failure Risk Reclassification with Race-Independent Estimated Glomerular Filtration Rate: An NHLBI Pooled Cohorts Analysis**

Dear Dr. Mentz,

We are writing to you to submit our manuscript entitled, "Incident Heart Failure Risk Reclassification with Race-Independent Estimated Glomerular Filtration Rate: An NHLBI Pooled Cohorts Analysis" to the *Journal of Cardiac Failure.*

We have significantly revised our work and have incorporated the thoughtful suggestions of the Statistical Reviewer and Editor. We have now included additional metrics to compare the risk predict value of the two eGFR (estimated glomerular filtration rate) and removed the net reclassification improvement and integrated discrimination index, as suggested by the Statistical Reviewer. We believe that the comments and suggestions of the Statistical Reviewer and Editor have led to a significantly improved manuscript.

To reduce race-based health disparities, the 2021 National Kidney Foundation guidelines introduced the race-independent creatinine and cystatin C-based eGFR that approximated the measured GFR more closely compared with the other equations. However, the predictive value of the creatinine and cystatin C-based eGFR for incident heart failure and the risk reclassification for incident heart failure on replacing the creatinine-based eGFR with the creatinine and cystatin C-based eGFR is not known. We found that the creatinine and cystatin C based-eGFR but not the creatinine-based eGFR had modest predictive value for incident heart failure. Replacing the creatinine-based eGFR with the creatinine and cystatin C-based eGFR did not lead to a change in the C-statistics. Additional model performance metrics such as the Akaike Information Criterion, Bayesian Information Criterion, log-likelihood values, and the Brier Score were comparable in the Cox models using creatinine and cystatin C-based eGFR and the creatinine-based eGFR. Based on our findings, we conclude that the value of the new creatinine and cystatin C-based eGFR lies in the individual-level change in access to life-saving heart failure therapy that is based on absolute eGFR cut-offs and not the population-level risk prediction for incident heart failure. We believe our work would appeal to the broad readership of the *Journal of Cardiac Failure*.

This manuscript has not been published before and is not currently under review in any other journal. Each author has contributed significantly to this work, and they all meet the full criteria and requirements for authorship. All authors have submitted their industry relationships in the disclosures. All authors have approved the manuscript and its submission to the *Journal of Cardiac Failure*.

Finally, we would like to thank you for your time in receiving this manuscript and considering it for review. Please contact me at 205-996-6630 or parora@uabmc.edu if you have any comments or questions and I will endeavor to respond to you at the earliest opportunity.

Yours sincerely,

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Response to Review

Editor and Reviewer comments:

Reviewer 3: In this manuscript authors aim to compare the predictive value of race-independent eGFR to race dependent eGFR. Overall the manuscript is well written, but the chosen statistical methods are not ideal for the aim. My comments:

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Results Page 9, Line 174
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Using the creatinine and cystatin C-based eGFR instead of the creatinine-based eGFR in the models to assess the risk of incident heart failure did not lead to a meaningful change in C-statistics *or other metrics of model performance such as AIC, BIC, log-likelihood values, and the Brier score*.

Reviewer Table 1: Model Performace Metrics for Fully Adjusted Cox Models Predicting the Risk of Incident Heart Failure Using Quartiles of Estimated Glomerular Filtration Rate in the Overall Population and Stratified by Race

	$eGFR_{Cr}$	$eGFR_{Cr\text{-}Cys}$
Overall Population		
Brier Score	0.055	0.055
AIC	14,292.88	14,277.31
BIC	14,363.39	14,347.82
Log-likelihood value	14,262.88	14,247.31
Black Individuals		
Brier Score	0.069	0.069
AIC	3,326.98	3,320.19
BIC	3,378.28	3,371.50
Log-likelihood value	3,296.98	3,290.20
Non-Black Individuals		
Brier Score	0.051	0.051
AIC	10,001.98	9,991.55
BIC	10,067.46	10,057.17
Log-likelihood value	9,971.83	9,961.55

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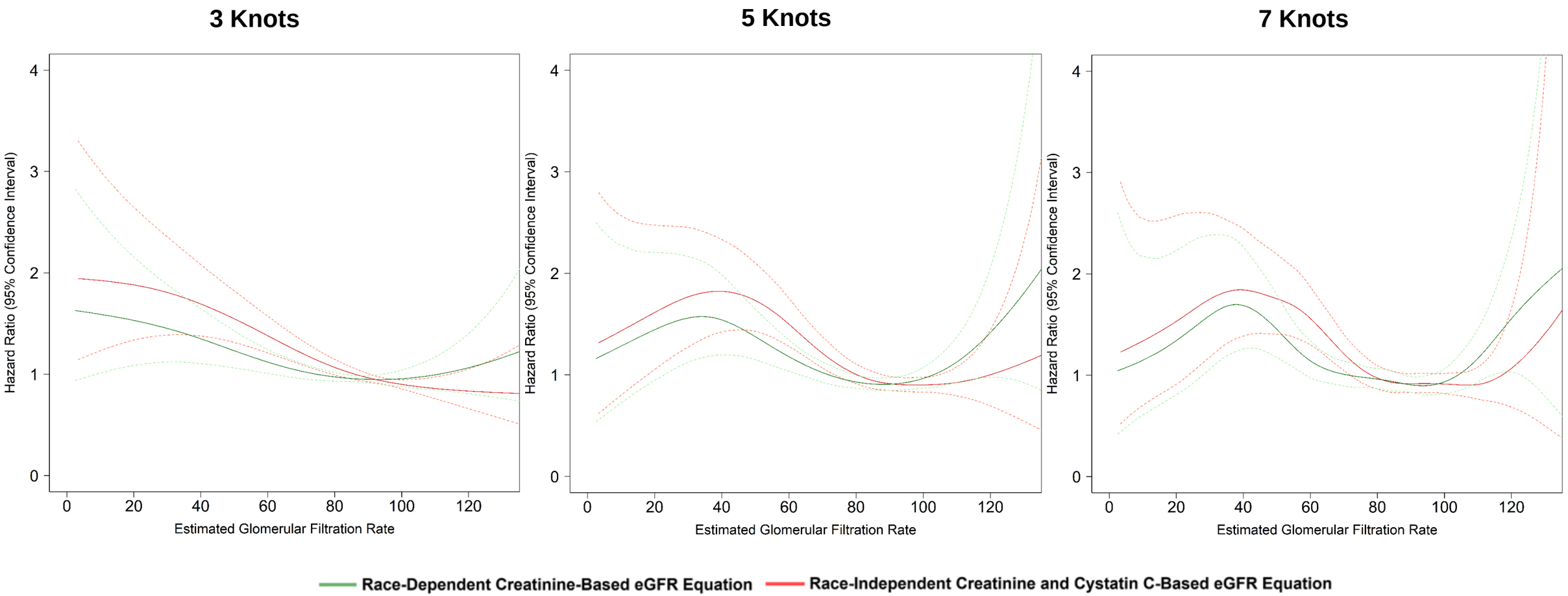
Methods Page 5, Line 97
To assess the non-linear association of eGFR and the risk of incident heart failure in the overall population and within the subgroup of race and ethnicity, restricted cubic splines with 3 knots *(10^{th}, 50^{th}, and 90^{th} percentiles)* were used.

Reviewer Table: Akaike Information Criterion and Bayesian Information Criterion for Adjusted Cox Models

Model with Creatinine-Based eGFR					
	3 Knots	**4 Knots**	**5 Knots**	**6 Knots**	**7 Knots**
Bayesian Information Criterion	14,351.7	14,352.7	14,357.2	14,362.3	14,367.9
Model with Cystatin C and Creatinine-Based eGFR					
Bayesian Information Criterion	14,334.6	14,336.3	14,341.4	14,347.2	14,353.1

Reviewer Figure 1: Restricted Cubic Splines Depicting the Non-Linear Relationship of the Risk of Incident Heart Failure According to Estimated Glomerular Filtration Rate in the Overall Population and Stratified by Race with Varying Number of Knots

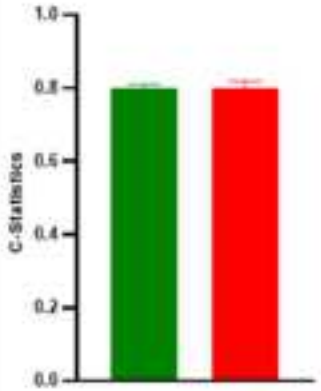


Highlights

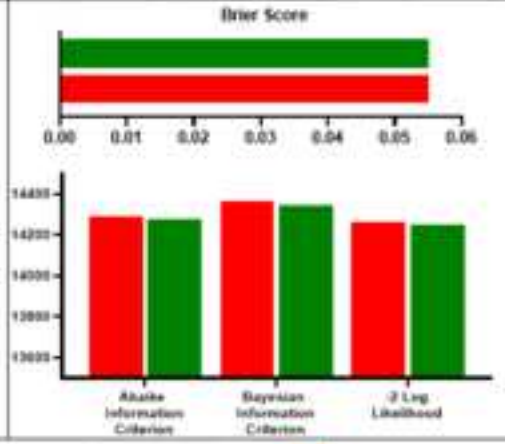
- The race-independent creatinine and cystatin C-based eGFR ($eGFR_{Cr\text{-}Cys}$) and race-dependent creatinine-based eGFR ($eGFR_{Cr}$) had comparable predictive values for incident heart failure (HF)
- $eGFR_{Cr\text{-}Cys}$ generates higher GFR estimates for Black individuals compared with the widely adopted race-independent $eGFR_{Cr}$
- Using the $eGFR_{Cr\text{-}Cys}$ instead of the race-independent $eGFR_{Cr}$ may reduce health disparities by increasing access to HF therapy

Graphical Abstract: Summary of Study Findings and Implications of Using the Race-Independent Creatinine and Cystatin C-Based Estimated Glomerular Filtration Rate Equation

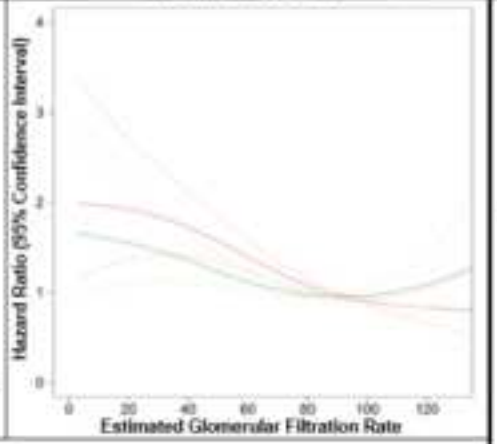
C-Statistics for Multivariable Adjusted Cox Models Predicting the Risk of Incident Heart Failure



Model Performance Metrics for Multivariable Adjusted Cox Models Predicting the Risk of Incident Heart Failure



Multivariable Adjusted Association of Estimated Glomerular Filtration Rate with Incident Heart Failure



Race-Dependent Creatinine-Based eGFR Race-Independent Creatinine and Cystatin C-Based eGFR

Implication on Population Level Risk Prediction of Incident Heart Failure

- **No Differences in Population Level Risk Prediction of Incident Heart Failure**
  - $C\text{-statistic}_{eGFR\ Cr\text{-}Cys} - C\text{-statistic}_{eGFR\ Cr}$
- Comparable Akaike Information Criterion, Bayesian Information Criterion, -2 Log-Likelihood, and Brier Score Using $eGFR_{Cr\text{-}Cys}$ and $eGFR_{Cr}$
- Similar Effect Estimates for the Association of Incident Heart Failure with per Unit Decrease in eGFR

Median Estimated Glomerular Filtration Rate

	Overall	Non-Black Individuals	Black Individuals
Race-Dependent $eGFR_{Cr}$	84.7 (72.0, 94.7)	83.9 (71.8, 93.6)	86.8 (72.9, 102.6)
Race-Independent $eGFR_{Cr}$	87.0 (74.2, 97.9)	90.0 (77.0, 98.5)	80.5 (67.7, 94.7)
Race-Independent $eGFR_{Cr\text{-}Cys}$	91.4 (79.4, 102.0)	91.6 (79.9, 102.0)	90.6 (77.5, 102.1)

Implication on Individual Level Heart Failure Treatment Allocation

Reduction in Racial Disparities by Increasing Eligibility for Heart Failure Diagnostics And Therapeutics (SGLT2i and ARNi) Among Black Individuals

Incident Heart Failure Risk Reclassification with Race-Independent Estimated Glomerular Filtration Rate: An NHLBI Pooled Cohorts Analysis

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7. Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA.

Short Title: HF Risk Reclassification with Race-Independent eGFR

Word Count: 3,568

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Disclosures: None of the other authors had any conflicts of interest or financial disclosures to declare.

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Incident Heart Failure Risk Reclassification with Race-Independent Estimated Glomerular Filtration Rate: An NHLBI Pooled Cohorts Analysis

Abstract

Background: This study compared the predictive value of the race-independent creatinine and cystatin C-based estimated glomerular filtration rate ($eGFR_{cr\text{-}cys}$) and the race-dependent creatinine-based eGFR ($eGFR_{cr}$) for incident heart failure.

Methods: This study combined the participant-level data from ARIC (visit 4) and MESA (visit 1) to calculate $eGFR_{cr\text{-}cys}$ and $eGFR_{cr}$. The primary outcome of the study was adjudicated incident heart failure over a follow-up period of 10 years. Multivariable Cox models were used to assess the risk of incident heart failure with the quartiles of $eGFR_{cr\text{-}cys}$ and $eGFR_{cr}$.

Results: Among 15,615 individuals [median age:62(57,68) years; 55.0% females; 23.9% Black], the median $eGFR_{cr\text{-}cys}$ and $eGFR_{cr}$ were 91.4(79.4,102.0) ml/min/1.73m^2 and 84.7(72.0,94.7) ml/min/1.73m^2, respectively. Compared with the fourth quartile of $eGFR_{cr\text{-}cys}$, the hazard ratio for incident heart failure was 1.02(95%CI:0.80-1.30) in the third quartile, 1.02(95%CI:0.80-1.30) in the second quartile, and 1.47(95%CI:1.16-1.86) in the first quartile. Compared with the fourth quartile of the $eGFR_{cr,}$ the risk of incident heart failure was similar in the third [HR_{adj}:0.90(95%CI:0.73-1.12)], second [HR_{adj}:0.96(95%CI:0.77-1.20)], and first [HR_{adj}:1.15(95%CI:0.93-1.44)] quartiles. C-statistics were similar for the multivariable-adjusted Cox models for incident heart failure using $eGFR_{cr}$ [0.80(0.79-0.81)] and $eGFR_{cr\text{-}cys}$ [0.80(0.79-0.82)].

Conclusion: The $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ had comparable predictive values for incident heart failure.

Keywords: Cystatin C; Heart Failure; Creatinine; Reclassification

Introduction

Chronic kidney disease (CKD) affects about 15% of US adults and is associated with a high risk of heart failure.[1-5] An increasing risk of incident heart failure has been demonstrated with decreasing creatinine-based race-dependent estimated glomerular filtration rate (eGFR).[3, 6-8] Based on the eGFR equation used, varying estimates of GFR may be generated for the same individual.[9] This may, in turn, lead to differences in the predictive value of eGFR for the estimation of heart failure risk based on the type of eGFR equation used.

The most widely used creatinine-based eGFR equation includes a race coefficient to account for the differences in the serum creatinine levels in Black and non-Black individuals.[9, 10] However, the race-dependent creatinine-based eGFR may overestimate the GFR in Black individuals. This may affect the predictive value of creatinine-based eGFR for incident heart failure in Black individuals.[9, 10] Furthermore, the inclusion of race in the creatinine-based eGFR equation may propagate existing race-based health disparities.[11, 12] To reduce race-based health disparities, the National Kidney Foundation (NKF) introduced the new race-independent eGFR based on creatinine and cystatin C that approximated the measured GFR more closely compared with the other equations.[9, 13] However, the predictive value of race-independent creatinine and cystatin C-based eGFR for incident heart failure in the overall population and within each race group is unknown.

In this study, a pooled cohort analysis was conducted to compare the risk of incident heart failure estimated by the new race-independent creatinine and cystatin C-based eGFR and the existing race-based creatinine-based eGFR equations in the overall population and stratified by race.

Methods

Study Population

This study combined the participant-level data from the Atherosclerosis Risk in Communities (ARIC), and the Multi-Ethnic Study of Atherosclerosis (MESA) cohorts. Details of the study design for each of the cohorts have been previously described.[14, 15] A brief description of the cohorts has been provided in the **Supplementary Methods**. Participants free from any cardiovascular disease and with cystatin C and creatinine data were included in the study. The first visit of MESA and the fourth visit of ARIC were considered as the baseline visit for this study. Self-identified race was used to stratify the study population into Black and non-Black individuals. Written informed consent was taken at the respective study centers. Ethical oversight was provided by the University of Alabama Institutional Review Board.

Study Exposure and Variables

The eGFR equations recommended by the 2021 NKF guidelines were used in this study.[9, 13] For the primary analysis, the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) race-independent creatinine and cystatin C-based eGFR and 2009 CKD-EPI race dependent creatinine-based eGFR were used. A secondary analysis using the 2009 race-dependent creatinine-based eGFR and the 2021 CKD-EPI race-independent creatinine-based eGFR has been described in the **Supplementary Results**. Based on eGFR values, 2 strata of low (<60 ml/min/1.73 m^2) and normal (≥60 ml/min/1.73 m^2) eGFR were created. Due to skewed distribution, eGFR was divided into quartiles for analysis. Creatinine levels were measured using the modified Jaffe method in all the cohorts. Cystatin C levels were measured using the immunonephelometric method.

Age, sex, diabetes mellitus, anti-hypertensive medication use, smoking history, and statin use were self-reported. Body mass index, blood pressure, and total cholesterol were measured. NT-proBNP (N-terminal proB-type natriuretic peptide) was log-transformed to account for its skewed distribution.

Study Outcomes

The primary outcome of the study was adjudicated incident heart failure over a 10-year follow-up period. Heart failure included both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. The diagnostic criteria for heart failure varied with each cohort.

In the ARIC cohort, adjudication of heart failure began in 2005. Prior to 2005, heart failure hospitalizations or deaths associated with International Classification of Diseases 9 (ICD-9) codes beginning with 428 and the International Classification of Diseases 10 (ICD-10) code of I50 were defined as incident heart failure. From 2005, heart failure events were adjudicated by trained staff based on clinical signs and investigations.[3, 16]

The MESA cohort categorized heart failure as definite, probable, and absent. Probable heart failure was defined as physician-diagnosed heart failure with treatment for heart failure. Definite heart failure required an objective diagnostic criterion such as pulmonary edema on chest X-ray, dilated ventricles, poor left ventricular function, or diastolic dysfunction on imaging studies.[16, 17]

Statistical Analysis

All analyses were performed on SAS 9.4 (Cary, NC). Continuous and categorical variables were summarized using median (interquartile range) and frequency (percentage). The

Chi-square test and the Wilcoxon rank-sum test were used to compare categorical and continuous data, respectively. Poisson regression was used to calculate the incidence rate of heart failure in the overall population and in Black and non-Black individuals. The proportionality assumption of hazards was assessed using Schoenfeld's residuals. Multivariable adjusted Cox regression models were used to assess the 10-year risk of incident heart failure with eGFR in the overall population and stratified by race groups. The models were adjusted for age, sex, body mass index, cohort, diabetes mellitus, systolic blood pressure, total cholesterol, statin use, smoking history, anti-hypertensive use, and log-transformed NT-proBNP. To assess the non-linear association of eGFR and the risk of incident heart failure in the overall population and within the subgroup of race and ethnicity, restricted cubic splines with 3 knots (10^{th}, 50^{th}, and 90^{th} percentiles) were used.[18, 19] The change in risk estimation for incident heart failure using the creatinine and cystatin C-based eGFR instead of creatinine-based eGFR was assessed by comparing Harrell's C-statistics values of the respective Cox models. Additional metrics, including the Akaike Information Criterion, Bayesian Information Criterion, log-likelihood values (-2 log-likelihood), and the Brier score, were used to compare the performance of the fully adjusted Cox models with creatinine and cystatin C-based eGFR and cystatin C-based eGFR.

Results

Among the 15,615 individuals without prevalent cardiovascular risk included in this study, 7,029 (45.0%) were males and 3,726 (23.9%) were Black individuals. The median age of the cohort was 62 (57, 68) years. The median creatinine and cystatin C-based eGFR and creatinine-based eGFR was 91.4 (79.4, 102.0) ml/min/1.73 m^2 and 84.7 (72.0, 94.7) ml/min/1.73 m^2, respectively. The median creatinine and cystatin C-based eGFR was 91.6 (79.9, 102.0) ml/min/1.73 m^2 in non-Black individuals and 90.6 (77.5, 102.1) ml/min/1.73 m^2 in Black individuals. The median creatinine-based eGFR was 83.9 (71.8, 93.6) ml/min/1.73 m^2 in non-Black individuals and 86.8 (72.9, 102.6) ml/min/1.73 m^2 in Black individuals. The first, second, third, and fourth quartiles of the creatinine and cystatin C-based eGFR ranged from <79.4 ml/min/1.73 m^2, 79.4-91.4 ml/min/1.73 m^2, 91.4-102.0 ml/min/1.73 m^2, and >102.0 ml/min/1.73 m^2. For the creatinine-based eGFR, the first, second, third, and fourth quartiles ranged from <72 ml/min/1.73 m^2, 72-84.6 ml/min/1.73 m^2, 84.6-94.7 ml/min/1.73 m^2, >94.7 ml/min/1.73 m^2. The baseline characteristics of the overall population and stratified by race are described in **Table 1**.

Risk of Incident Heart Failure

There were 879 events of incident heart failure in the overall population. The incidence rate of heart failure was 6.1 (95% CI: 5.8-6.6) events per 1,000 person-years. A non-linear increase in the risk of incident heart failure with decreasing eGFR was noted with both eGFR equations. The estimated risk of incident heart failure was higher using the creatinine and cystatin C-based eGFR compared with the creatinine-based eGFR below 90 mL/min/1.73 m^2. With the highest quartile of creatinine and cystatin C-based eGFR as the reference group, the multivariable-adjusted risk of incident heart failure was 1.02 (95% CI: 0.80-1.30) in the third quartile, 1.02 (95% CI: 0.80-1.30) in the second quartile, and 1.47 (95% CI: 1.16-1.86) in the

first quartile. With the highest quartile of creatinine-based eGFR as the reference group, the adjusted hazard ratio for incident heart failure was 0.90 (95% CI: 0.73-1.12) in the third quartile, 0.96 (95% CI: 0.77-1.20) in the second quartile, and 1.15 (95% CI: 0.93-1.44) in the first quartile.

Among non-Black individuals, there were 617 events of incident heart failure during the study period. The incidence rate of heart failure was 5.6 (95% CI: 5.2-6.1) events per 1,000 person-years. The risk of incident heart failure increased non-linearly with decreasing eGFR below 90 mL/min/1.73 m^2 but the increase in risk was lower with the creatinine-based eGFR compared with the creatinine and cystatin C-based eGFR. With the highest quartile of creatinine and cystatin C-based eGFR as the reference group, the multivariable-adjusted hazard ratio for incident heart failure was 1.19 (95% CI: 0.88-1.62) in the third quartile, 1.11 (95% CI: 0.82-1.51) in the second quartile, and 1.58 (95% CI: 1.17-2.12) in the first quartile. With the highest quartile of creatinine-based eGFR as the reference group, the adjusted hazard ratio for incident heart failure was 1.08 (95% CI: 0.83-1.40) in the third quartile, 1.04 (95% CI: 0.79-1.38) in the second quartile, and 1.30 (95% CI: 0.98-1.70) in the first quartile.

Among Black individuals, there were 262 incident heart failure events over the 10-year follow-up period. The incidence rate of heart failure was 7.9 (95% CI: 7.0-8.9) per 1,000 person-years. On assessing the non-linear association of the risk of incident heart failure with eGFR, the creatinine and cystatin C-based eGFR showed a steeper increase in risk below 90 mL/min/1.73 m^2 compared with the creatinine-based equation. With the highest quartile of creatinine and cystatin C-based eGFR as the reference group, the adjusted risk for incident heart failure was 0.84 (95% CI: 0.54-1.31) in the third quartile, 0.89 (0.58-1.36) in the second quartile, and 1.34 (95% CI: 0.90-1.99) in the first quartile. With the highest quartile of creatinine-based

eGFR as the reference group, the adjusted hazard ratio for incident heart failure was 1.06 (95% CI: 0.72-1.58) in the third quartile, 1.09 (95% CI: 0.73-1.64) in the second quartile, and 1.19 (95% CI: 0.80-1.77) in the first quartile.

Table 2 summarizes the frequency, incidence rate, and hazard ratio of incident heart failure stratified by the quartiles of eGFR.

Table 3 summarizes the hazard ratio for incident heart failure according to eGFR (categorized using 60 mL/min/1.73 m^2 as a threshold) in the overall population and stratified by race.

The non-linear association of the risk of incident heart failure with the creatinine and cystatin C-based eGFR and creatinine-based eGFR stratified by race has been depicted in **Figure 1**.

Incident Heart Failure Risk Reclassification

In the Cox models for incident heart failure, the C-index was 0.8029 (0.7886-0.8172) using creatinine-based eGFR and 0.8046 (0.7903-0.8189) using the creatinine and cystatin C-based eGFR.

Among non-Black individuals, the C-index for Cox models predicting the risk of incident heart failure was 0.8077 (0.7908-0.8246) using creatinine-based eGFR and 0.8090 (0.7921-0.8259) using the creatinine and cystatin C-based eGFR.

Among Black individuals, the C-index for Cox models predicting the risk of incident heart failure was 0.7944 (0.7674-0.8214) using the creatinine-based eGFR and 0.7976 (0.7709-0.8243) using the creatinine and cystatin C-based eGFR.

The AIC, BIC, log-likelihood values, and the Brier score were similar for the Cox models using creatinine-based eGFR and creatinine and cystatin C-based eGFR in the overall population and stratified by race. (**Table 4**)

Discussion

In this pooled cohort study of ~16,000 individuals, the creatinine and cystatin C-based eGFR but not the creatinine-based eGFR had modest risk prediction value for the incident heart even after accounting for NT-proBNP in the Cox models. Though the creatinine and cystatin C-based eGFR predicted the risk of incident heart failure at a higher eGFR compared with the creatinine-based eGFR on assessing the non-linear association of the risk of incident heart failure with eGFR, the effect estimates for the association of incident heart failure with per unit decrease in eGFR were similar using both equations. Using the creatinine and cystatin C-based eGFR instead of the creatinine-based eGFR in the models to assess the risk of incident heart failure did not lead to a meaningful change in C-statistics or other metrics of model performance such as AIC, BIC, log-likelihood values, and the Brier score. To summarize, the new creatinine and cystatin C-based eGFR did not improve risk prediction for incident heart failure compared with the creatinine-based eGFR in the overall population and across racial groups.

Although both creatinine and cystatin C-based eGFR and creatinine-based eGFR have no differences in the population-level risk prediction for incident heart failure but using the creatinine and cystatin C-based eGFR instead of the creatinine-based eGFR may have implications in individual-level treatment allocation for heart failure medications such as SGLT-2i and ARNIs. As noted in this study, the creatinine and cystatin C-based eGFR generates higher estimates compared with the creatinine-based eGFR. The higher GFR estimates of the creatinine and cystatin C-based eGFR may increase the eligibility for life-saving heart failure medications because the initiation of these medications is based on the absolute cut-off of the eGFR values. Drugs with a mortality benefit in heart failure such as SGLT-2i are contraindicated in individuals with an eGFR <25 mL/min/1.73 m^2.[20] Additionally, these patients may also become eligible for

dye-based imaging modalities using the creatinine and cystatin C-based equation. However, healthcare systems across the US have adopted the race-independent creatinine-based eGFR equation which underestimates the GFR in Black individuals. This widely adopted change may limit access to heart failure therapy in Black individuals which may lead to the widening of healthcare disparities. Therefore, widespread use of creatinine and cystatin C-based eGFR should be encouraged to improve access to heart failure therapy.

Though there is uncertainty about the direction of causality between heart failure and CKD, several pathophysiological pathways have been elucidated to explain the risk of heart failure in CKD patients. CKD is associated with a high prevalence of heart failure precursors such as left ventricular hypertrophy (LVH) and atherosclerosis.[2, 21] LVH in CKD patients may be explained by hypertension, anemia, and increased systemic vascular resistance.[1, 2] Hypertension may be attributed to sympathetic overactivation due to over-activation of the renin-angiotensin-aldosterone-system (RAAS) and reduced activity of renalase (an inhibitor of catecholamines).[1, 22, 23] RAAS over-activation and dyslipidemia may lead to endothelial dysfunction by increasing oxidative stress.[1, 23] CKD is associated with pro-atherogenic lipid abnormalities such as reduction in HDL cholesterol levels, hypertriglyceridemia, and increased levels of oxidized LDL cholesterol levels.[1, 22] Reduction of GFR is associated with an increase in asymmetric dimethylarginine levels. Increased asymmetric dimethylarginine levels are associated with reduced nitric oxide production which may lead to increased systemic vascular resistance and endothelial dysfunction.[1, 22, 23] Accelerated vascular calcification secondary to hypercalcemia, hyperphosphatemia, and calcification inhibitor deficiency in CKD has been noted.[1, 2, 22] The increased oxidative stress, reduced nitric oxide production, and increased

vascular calcification coupled with low-grade inflammation seen in CKD promote atherosclerosis.[1]

Cystatin C, a ubiquitous protein, has been shown to be a more accurate filtration marker compared with creatinine.[9] Unlike creatinine, cystatin C levels are less affected by age, sex, weight, race, muscle mass, physical activity, and nutrition.[24-26] The GFR equations using cystatin C and creatinine were found to have an agreement of about 90% with the measured GFR.[9] The bias between the measured GFR was lower using the creatinine and cystatin C-based eGFR compared with creatinine-based eGFR in Black and non-Blacks.[9] Furthermore, the biases were similar in Black and non-Black individuals using the creatinine and cystatin C-based eGFR.[9] The improvement in agreement with the measured GFR and reduced bias of the creatinine and cystatin C-based eGFR may be attributed to the reduced confounding effect of non-GFR determinants while using cystatin C and creatinine together.[27] Hence, the creatinine and cystatin C-based eGFR best approximates the renal function compared with the other eGFR equations. Even though the creatinine and cystatin C-based eGFR provides more accurate estimates of eGFR compared with the creatinine-based eGFR, the is no change in the risk prediction value of eGFR in incident heart failure as evidenced by the stable C-statistic values and model performance metrics on replacing the creatinine-based eGFR with the creatinine and cystatin C-based eGFR in the Cox models.

Prior studies have shown that reduced eGFR, regardless of the renal marker used to predict GFR, is a predictor of incident heart failure.[2, 3, 6] Considering the varying estimates of eGFR using different renal markers, a study assessing the association of the difference between the 2012 CKD-EPI cystatin C-based eGFR and 2021 race-free creatinine-based eGFR with incident heart failure showed that individuals with a lower cystatin C-based eGFR compared with

creatinine-based eGFR had a higher risk of incident heart failure compared with other permutations.[24] A UK Biobank-based study assessing the risk reclassification by adding renal markers to the ARIC model for heart failure risk (without natriuretic peptides) showed that the addition of 2012 CKD-EPI cystatin C-based eGFR to the model led to a greater improvement in the C-statistic compared with the addition of 2009 creatinine-based eGFR to the model.[28] The current study differs from the prior literature by assessing, 1) the impact of removing race from the eGFR equations through a direct comparison of the predictive values of the new race-independent creatinine and cystatin C-based eGFR and the most widely used race-dependent creatinine-based eGFR in a racially diverse population, and 2) using natriuretic peptides in the risk prediction models for incident heart failure.

Though race is a social construct, racial differences in serum creatinine levels have been noted. These differences led to the inclusion of a race coefficient in the previous eGFR equations. However, the race-based creatinine eGFR equation led to the overestimation of eGFR in Black individuals which limits their access to CKD therapy.[9] The introduction of the new eGFR equations attempts to mitigate this disparity by excluding the race coefficient and providing more accurate estimates of GFR.[9]

Limitations

There are several limitations to this study. This study combined cohorts that are demographically and clinically different from each other. These differences were accounted for by including the cohort as a covariate in the multivariate-adjusted Cox models. The eGFR equations may not provide reliable estimates for non-White and non-Black individuals and less precise estimates for Black individuals as the validation cohorts had limited Black individuals

and insufficient representation of individuals who were not White or Black.[9] Though cystatin C levels are less affected by the non-eGFR determinants, factors such as hypothyroidism, glucocorticoid use, inflammation, adiposity, and smoking are known to affect cystatin C levels.[29] The current study did not stratify heart failure based on ejection fraction due to limited data. eGFR has been shown to be a stronger predictor of systolic heart failure compared with diastolic heart failure.[30] While the analysis controlled for key clinical factors, there may be unaccounted and unmeasured residual confounding contributing to the incident heart failure risk prediction value of eGFR.

Conclusion

The risk prediction value of new race-independent creatinine and cystatin C-based eGFR and the race-dependent creatinine-based eGFR for incident heart failure were comparable. Widespread use of race-independent creatinine and cystatin C-based eGFR may help mitigate health disparities by improving access to heart failure therapy in previously ineligible individuals.

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Figure legends:

Figure 1: Restricted Cubic Splines Depicting the Non-Linear Relationship of the Risk of Incident Heart Failure According to Estimated Glomerular Filtration Rate in the Overall Population and Stratified by Race

This figure depicts the non-linear association of the risk of incident heart failure according to the estimated glomerular filtration rate (eGFR) (calculated using the race-independent creatinine and cystatin C-based equation and the race-dependent creatinine-based equation) in the overall population and stratified by race. In each panel, the race-dependent creatinine-based eGFR and race-independent creatinine and cystatin C-based eGFR have been depicted in green and red, respectively.

Table 1: Baseline Characteristics in the Overall Population and Stratified by Race

	Overall (n=15,615)	Non-Black (n=11,889)	Black (n=3,726)
Age (years)	62.0 (57.0, 68.0)	62.0 (57.0, 68.0)	61.0 (56.0, 68.0)
Sex (n)			
Female	8,586 (55.0%)	6,368 (53.6%)	2,218 (59.5%)
Male	7,029 (45.0%)	5,521 (46.4%)	1,508 (40.5%)
Body Mass Index (Kg/m^2)	27.7 (24.7, 31.3)	27.2 (24.4, 30.6)	29.4 (26.2, 33.5)
Systolic Blood Pressure (mmHg)	125 (113, 139)	123 (111, 137)	131 (118, 145)
Diastolic Blood Pressure (mmHg)	71 (65, 78)	70 (64, 77)	75 (68, 81)
Total Cholesterol (mg/dL)	196.0 (174.0, 220.0)	197.0 (176.0, 221.0)	192.0 (169.0, 218.0)
LDL Cholesterol (mg/dL)	119.0 (98.8, 140.8)	119.0 (99.2, 140.8)	118.0 (96.8, 140.8)
NT-proBNP (ng/L)	60.2 (28.8, 119.1)	65.4 (32.5, 125.2)	42.9 (18.0, 90.4)
Diabetes (n)	1,990 (12.7%)	1,256 (10.6%)	734 (19.7%)
Estimated Glomerular Filtration Rate			
eGFR$_{Cr}$ (ASR)	84.7 (72.0, 94.7)	83.9 (71.8, 93.6)	86.8 (72.9, 102.6)
eGFR$_{Cr}$ (AS)	87.0 (74.2, 97.9)	90.0 (77.0, 98.5)	80.5 (67.7, 94.7)
eGFR$_{Cr\text{-}Cys}$ (AS)	91.4 (79.4, 102.0)	91.6 (79.9, 102.0)	90.6 (77.5, 102.1)
Smoking (n)			
Never	7,150 (45.8%)	5,439 (45.7%)	1,711 (45.9%)
Past	6,218 (39.8%)	4,903 (41.2%)	1,315 (35.3%)
Current	2,182 (14.0%)	1,528 (12.9%)	654 (17.6%)
Cohort (n)			
ARIC	8,895 (57.0%)	7,023 (59.1%)	1,872 (50.2%)
MESA	6,720 (43.0%)	4,866 (40.9%)	1,854 (49.8%)
Heart Failure Events (n)	879 (5.6%)	617 (5.2%)	262 (7.0%)

Categorical and continuous data are depicted as frequency (percentage) and median (interquartile range)

Abbreviations: LDL: low-density lipoproteins; eGFR$_{Cr}$ (ASR): glomerular filtration rate estimated using creatinine adjusted for age, sex, and race; eGFR$_{Cr}$ (AS): glomerular filtration rate estimated using creatinine adjusted for age and sex; eGFR$_{Cr\text{-}Cys}$ (AS): glomerular filtration rate estimated using creatinine and cystatin C adjusted for age and sex; ARIC: Atherosclerosis Risk in Communities; MESA: Multi-Ethnic Study of Atherosclerosis

Table 2: Adjusted and Unadjusted Hazard Ratios for Incident Heart Failure Using Quartiles of Estimated Glomerular Filtration Rate in the Overall Population and Stratified by Race

	First Quartile	Second Quartile	Third Quartile	Fourth Quartile	
Overall					
Number of Events (%)					
eGFR$_{Cr}$	311 (8.0%)	185 (4.8%)	205 (5.2%)	178 (4.6%)	
eGFR$_{Cr-Cys}$	397 (10.2%)	195 (5.0%)	167 (4.3%)	120 (3.1%)	
Incidence Rate (events/1000 person-years)					
eGFR$_{Cr}$	9.0 (8.0-10.0)	5.2 (4.5-5.9)	5.7 (4.9-6.5)	4.9 (4.2-5.7)	
eGFR$_{Cr-Cys}$	11.7 (10.6-12.9)	5.4 (4.7-6.2)	4.6 (3.9-5.3)	3.3 (2.7-3.9)	
Hazard Ratio					**C-Statistic**
Unadjusted					
eGFR$_{Cr}$	1.84 (1.53-2.21)	1.05 (0.86-1.29)	1.15 (0.94-1.41)	Ref.	0.5635 (0.5445-0.5825)
eGFR$_{Cr-Cys}$	3.62 (2.95-4.44)	1.67 (1.33-2.09)	1.40 (1.11-1.77)	Ref.	0.6313 (0.6133-0.6493)
Model 1					
eGFR$_{Cr}$	1.38 (1.12-1.69)	0.91 (0.74-1.13)	0.88 (0.71-1.08)	Ref.	0.7220 (0.7061-0.7379)
eGFR$_{Cr-Cys}$	1.95 (1.56-2.43)	1.07 (0.85-1.35)	1.06 (0.83-1.34)	Ref.	0.7295 (0.7138-0.7452)
Model 2*					
eGFR$_{Cr}$	1.59 (1.29-1.96)	1.11 (0.90-1.38)	1.04 (0.84-1.28)	Ref.	0.7744 (0.7599-0.7889)
eGFR$_{Cr-Cys}$	2.03 (1.63-2.55)	1.21 (0.96-1.54)	1.14 (0.89-1.45)	Ref.	0.7793 (0.7650-0.7936)
Model 3#					
eGFR$_{Cr}$	1.15 (0.93-1.44)	0.96 (0.77-1.20)	0.90 (0.73-1.12)	Ref.	0.8029 (0.7886-0.8172)
eGFR$_{Cr-Cys}$	1.47 (1.16-1.86)	1.02 (0.80-1.30)	1.02 (0.80-1.30)	Ref.	0.8046 (0.7903-0.8189)
Non-Black Individuals					
Number of Events (%)					
eGFR$_{Cr}$	223 (7.5%)	126 (4.2%)	166 (5.6%)	102 (3.4%)	
eGFR$_{Cr-Cys}$	286 (9.6%)	137 (4.6%)	125 (4.2%)	69 (2.3%)	
Incidence Rate (events/1000 person-years)					
eGFR$_{Cr}$	8.4 (7.4-9.6)	4.5 (3.8-5.4)	6.1 (5.2-7.0)	3.7 (3.0-4.4)	
eGFR$_{Cr-Cys}$	10.9 (9.7-12.2)	5.0 (4.2-5.9)	4.5 (3.8-5.3)	2.5 (1.9-3.1)	
Hazard Ratio					**C-Statistic**
Unadjusted					
eGFR$_{Cr}$	2.32 (1.84-2.93)	1.24 (0.96-1.64)	1.66 (1.30-2.13)	Ref.	0.5873 (0.5655-0.6091)
eGFR$_{Cr-Cys}$	4.51 (3.46-5.86)	2.04 (1.53-2.73)	1.83 (1.36-2.46)	Ref.	0.6429 (0.6221-0.6637)
Model 1					
eGFR$_{Cr}$	1.48 (1.14-1.93)	0.97 (0.74-1.27)	1.02 (0.79-1.32)	Ref.	0.7346 (0.7162-0.7530)
eGFR$_{Cr-Cys}$	2.13 (1.60-2.82)	1.21 (0.90-1.62)	1.29 (0.96-1.73)	Ref.	0.7411 (0.7227-0.7595)

Model 2*					
eGFR$_{Cr}$	1.60 (1.23-2.10)	1.11 (0.84-1.46)	1.12 (0.86-1.45)	Ref.	0.7790 (0.7621-0.7959)
eGFR$_{Cr-Cys}$	2.13 (1.60-2.83)	1.28 (0.95-1.73)	1.33 (0.99-1.79)	Ref.	0.7830 (0.7661-0.7999)
Model 3$^{\#}$					
eGFR$_{Cr}$	1.30 (0.98-1.70)	1.04 (0.79-1.38)	1.08 (0.83-1.40)	Ref.	0.8077 (0.7908-0.8246)
eGFR$_{Cr-Cys}$	1.58 (1.17-2.12)	1.11 (0.82-1.51)	1.19 (0.88-1.62)	Ref.	0.8090 (0.7921-0.8259)
Black Individuals					
Number of Events (%)					
eGFR$_{Cr}$	88 (9.5%)	56 (6.0%)	56 (6.0%)	62 (6.7%)	
eGFR$_{Cr-Cys}$	112 (12.0%)	54 (5.8%)	45 (4.8%)	51 (5.5%)	
Incidence Rate (events/1000 person-years)					
eGFR$_{Cr}$	11.0 (8.9-13.5)	6.7 (5.2-8.7)	6.6 (5.1-8.6)	7.3 (5.7-9.3)	
eGFR$_{Cr-Cys}$	14.4 (12.0-17.3)	6.4 (4.9-8.4)	5.2 (3.9-7.0)	5.9 (4.5-7.8)	
Hazard Ratio					**C-Statistic**
Unadjusted					
eGFR$_{Cr}$	1.53 (1.11-2.12)	0.93 (0.64-1.33)	0.91 (0.64-1.31)	Ref.	0.5530 (0.5181-0.5879)
eGFR$_{Cr-Cys}$	2.46 (1.76-3.42)	1.08 (0.74-1.58)	0.88 (0.59-1.32)	Ref.	0.6071 (0.5724-0.6418)
Model 1					
eGFR$_{Cr}$	1.58 (1.10-2.29)	1.09 (0.74-1.58)	1.02 (0.70-1.47)	Ref.	0.6981 (0.6679-0.7283)
eGFR$_{Cr-Cys}$	1.87 (1.30-2.68)	0.89 (0.60-1.32)	0.80 (0.54-1.21)	Ref.	0.7128 (0.6834-0.7422)
Model 2*					
eGFR$_{Cr}$	1.70 (1.17-2.48)	1.20 (0.81-1.77)	1.10 (0.75-1.60)	Ref.	0.7570 (0.7286-0.7854)
eGFR$_{Cr-Cys}$	1.99 (1.37-2.89)	1.06 (0.71-1.60)	0.89 (0.59-1.36)	Ref.	0.7681 (0.7405-0.7957)
Model 3$^{\#}$					
eGFR$_{Cr}$	1.19 (0.80-1.77)	1.09 (0.73-1.64)	1.06 (0.72-1.58)	Ref.	0.7944 (0.7674-0.8214)
eGFR$_{Cr-Cys}$	1.34 (0.90-1.99)	0.89 (0.58-1.36)	0.84 (0.54-1.31)	Ref.	0.7976 (0.7709-0.8243)

Adjusted Model 1: Adjusted for age, sex, body mass index, and cohort.

Adjusted Model 2: Adjusted for age, sex, body mass index, cohort, anti-hypertensive use, statin use, systolic blood pressure, total cholesterol, smoking history, and diabetes mellitus.

Adjusted Model 3: Adjusted for age, sex, body mass index, cohort, anti-hypertensive use, statin use, systolic blood pressure, total cholesterol, smoking history, diabetes mellitus, and log NT-proBNP.

eGFR$_{Cr}$: estimated glomerular filtration rate based on race-dependent creatinine-based equation; eGFR$_{Cr-Cys}$: estimated glomerular filtration rate based on race-independent creatinine and cystatin C-based equation;

*****Analysis was conducted in 15,512, 11,861, and 3,651 individuals in the overall population, non-Black group, and Black group.

$^{\#}$ Analysis was conducted in 14,269, 11,143, and 3,126 individuals in the overall population, non-Black group, and Black group.

Table 3: Adjusted and Unadjusted Hazard Ratios for Incident Heart Failure in the Overall Population and Stratified by Race

	$eGFR_{Cr}$		$eGFR_{Cr-Cys}$	
	≥60 mL/min/1.73m²	**<60 mL/min/1.73m²**	**≥60 mL/min/1.73m²**	**<60 mL/min/1.73m²**
Overall				
Unadjusted Model	Ref.	2.91 (2.46-3.43)	Ref.	4.36 (3.66-5.19)
Adjusted Model 1	Ref.	2.24 (1.87-2.68)	Ref.	2.85 (2.37-3.42)
Adjusted Model 2*	Ref.	2.07 (1.73-2.49)	Ref.	2.34 (1.94-2.82)
Adjusted Model 3#	Ref.	1.52 (1.25-1.84)	Ref.	1.60 (1.31-1.96)
Black Individuals				
Unadjusted Model	Ref.	2.76 (2.03-3.77)	Ref.	4.05 (2.96-5.55)
Adjusted Model 1	Ref.	2.44 (1.74-3.40)	Ref.	3.16 (2.27-4.40)
Adjusted Model 2*	Ref.	2.29 (1.64-3.20)	Ref.	2.79 (1.99-3.92)
Adjusted Model 3#	Ref.	1.44 (0.98-2.10)	Ref.	1.47 (0.99-2.18)
Non-Black Individuals				
Unadjusted Model	Ref.	2.98 (2.45-3.62)	Ref.	4.43 (3.59-5.47)
Adjusted Model 1	Ref.	2.15 (1.74-2.66)	Ref.	2.72 (2.19-3.39)
Adjusted Model 2*	Ref.	1.98 (1.59-2.45)	Ref.	2.20 (1.75-2.75)
Adjusted Model 3#	Ref.	1.53 (1.22-1.91)	Ref.	1.64 (1.30-2.07)

Adjusted Model 1: Adjusted for age, sex, body mass index, and cohort.

Adjusted Model 2: Adjusted for age, sex, body mass index, cohort, anti-hypertensive use, statin use, systolic blood pressure, total cholesterol, smoking history, and diabetes mellitus.

Adjusted Model 3: Adjusted for age, sex, body mass index, cohort, anti-hypertensive use, statin use, systolic blood pressure, total cholesterol, smoking history, diabetes mellitus, and log NT-proBNP.

$eGFR_{Cr}$: estimated glomerular filtration rate based on race-dependent creatinine-based equation; $eGFR_{Cr-Cys}$: estimated glomerular filtration rate based on race-independent creatinine and cystatin C-based equation;

*****Analysis was conducted in 15,512, 11,861, and 3,651 individuals in the overall population, non-Black group, and Black group.

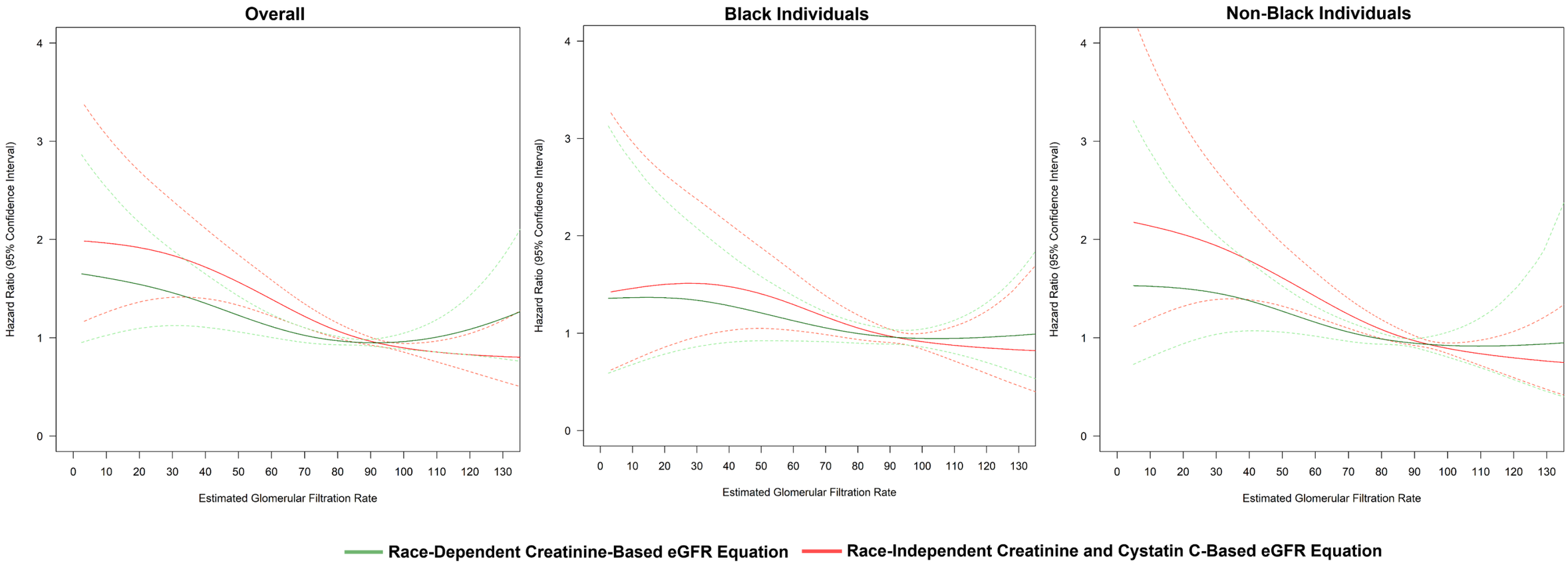
Analysis was conducted in 14,269, 11,143, and 3,126 individuals in the overall population, non-Black group, and Black group.

Table 4: Model Performace Metrics for Fully Adjusted Cox Models Predicting the Risk of Incident Heart Failure Using Quartiles of Estimated Glomerular Filtration Rate in the Overall Population and Stratified by Race

	$eGFR_{Cr}$	$eGFR_{Cr\text{-}Cys}$
Overall Population		
Brier Score	0.055	0.055
AIC	14,292.88	14,277.31
BIC	14,363.39	14,347.82
-2 LL	14,262.88	14,247.31
Black Individuals		
Brier Score	0.069	0.069
AIC	3,326.98	3,320.19
BIC	3,378.28	3,371.50
-2 LL	3,296.98	3,290.20
Non-Black Individuals		
Brier Score	0.051	0.051
AIC	10,001.98	9,991.55
BIC	10,067.46	10,057.17
-2 LL	9,971.83	9,961.55

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; -2 LL: -2 Log-Likelihood

Figure 1: Restricted Cubic Splines Depicting the Non-Linear Relationship of the Risk of Incident Heart Failure According to Estimated Glomerular Filtration Rate in the Overall Population and Stratified by Race



This figure depicts the non-linear association of the risk of incident heart failure according to the estimated glomerular filtration rate (eGFR) (calculated using the race-independent creatinine and cystatin C-based equation and the race-dependent creatinine-based equation) in the overall population and stratified by race. In each panel, the creatinine-based race-dependent eGFR and creatinine and cystatin C-based race-independent eGFR have been depicted in green and red, respectively.

Author headshot photograph

Lay Summary

In an attempt to reduce health disparities, race-independent equations to estimate kidney function were introduced recently. However, the risk prediction value of the new race-independent creatinine and cystatin-C-based equation ($eGFR_{Cr\text{-}Cys}$) compared with the old race-dependent creatinine-based equation ($eGFR_{Cr}$) for incident heart failure (HF) was unknown. This study found that $eGFR_{Cr\text{-}Cys}$ and $eGFR_{Cr}$ were comparable in predicting the risk of incident HF. However, the $eGFR_{Cr\text{-}Cys}$ generates higher estimates compared with the $eGFR_{Cr}$ in Black individuals. Therefore, widespread use of the $eGFR_{Cr\text{-}Cys}$ may reduce health disparities by increasing access to heart failure therapy among Black individuals.

Tweet

The new race-free eGFR and old race-dependent eGFR have comparable risk prediction value for incident heart failure. The new equation may reduce racial disparities by improving access to heart failure therapy among Black individuals.