

# Impact of glomerular filtration rate estimation formulas on MECKI score performance and prognostic accuracy in heart failure: the MECKI-RENAL study

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## Aims

Appropriate interpretation of kidney function is essential for clinical and therapeutic management of heart failure (HF). We evaluated the prognostic accuracy of 6 glomerular filtration rate estimation (eGFR) formulas in HF patients with reduced ejection fraction (HFrEF) and their impact on the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score prognostic accuracy.

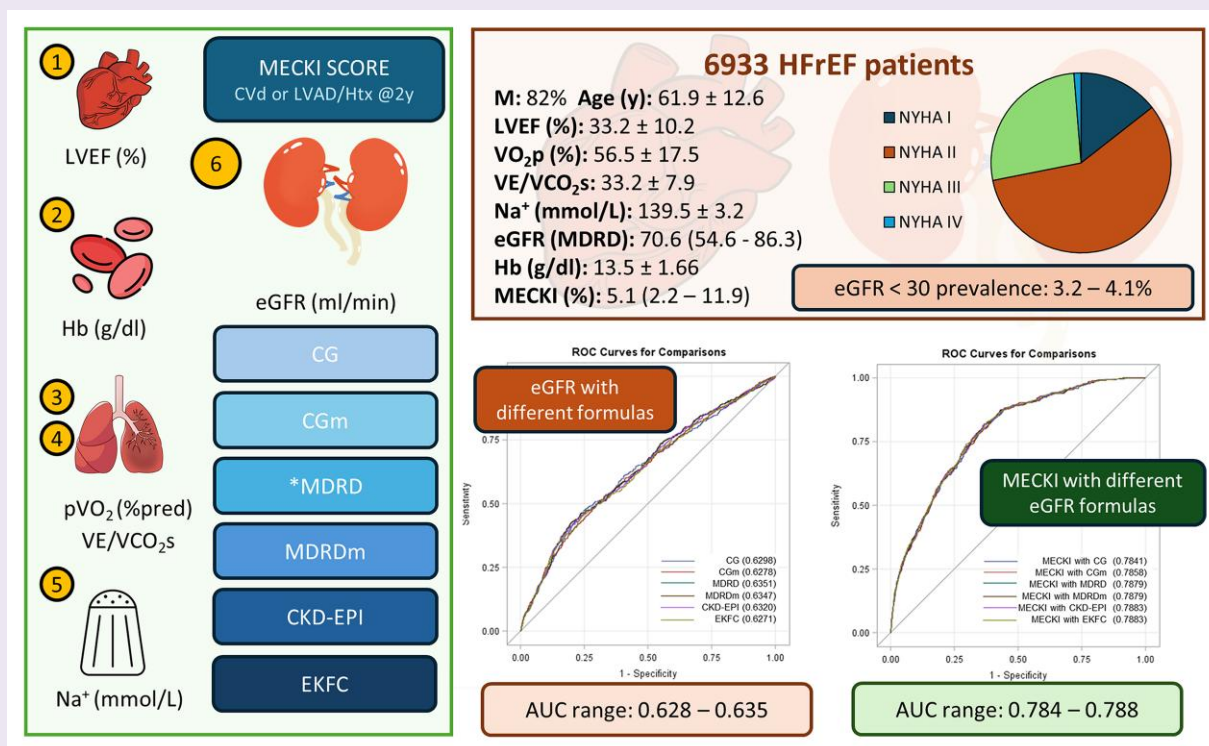
## Methods and results

We retrospectively analyzed 6933 patients enrolled in the MECKI score database. GFR was estimated using Modification of Diet in Renal Disease (MDRD); MDRD modified (MDRDm); Cockcroft-Gault (CG), CG modified (CGm); Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and the European Kidney Function Consortium (EKFC). Survival was assessed as the composite of cardiovascular death, left ventricular assist device implantation and urgent heart transplantation at 2 years. Each GFR estimation demonstrated similar but moderate prognostic capacity, with the area under the curve (AUC) for predicting survival ranging from 0.6271 (EKFC) to 0.635 (MDRD). For cardiovascular death, the AUC values ranged from 0.668 to 0.677. The prevalence of severe CKD, defined as eGFR <30 mL/min/1.73 m<sup>2</sup>, ranged from 3.2% (MDRD) to 4.5% (EKFC). When included in MECKI score, the 6 formulas showed a MECKI AUC for prognosis ranging from 0.7841 to 0.7883, with the EKFC and CKD-EPI showing the best performance.

## Conclusion

GFR estimations play a role in HFrEF prognosis without difference among the 6 most frequently used formulas. Furthermore, using eGFR calculated from the 6 different formulas in MECKI score did not significantly alter its strong prognostic power, highlighting MECKI reliability in risk stratification.

## Graphical abstract



## Keywords

Heart failure • Chronic kidney disease • Glomerular filtration rate • MECKI score • Prognosis

## Key Learning Points

What is already known:

- Kidney function assessment is crucial for risk stratification and management of heart failure with reduced ejection fraction (HFrEF).
- Several glomerular filtration rate (GFR) estimation formulas exist, but their comparative prognostic accuracy in HFrEF remains uncertain.
- The MECKI score is a well-established tool for prognostic stratification in HFrEF patients.

What this study adds:

- The prognostic capacity of six widely used GFR estimation formulas was similar but moderate in predicting survival in HFrEF patients.
- The use of different GFR formulas did not significantly alter the strong predictive power of the MECKI score.
- These findings reinforce the robustness of the MECKI score in clinical practice, regardless of the GFR estimation method used.

## Introduction

Heart failure (HF) is a prevalent and debilitating cardiovascular condition affecting millions of individuals worldwide. Prognostic assessment in HF patients is crucial to guide clinical management and improve patient outcomes. Given the complex interplay between the heart and kidneys, renal function is a well-recognized factor contributing to HF prognosis.<sup>1</sup> Notably, chronic kidney disease (CKD) is not only highly prevalent among patients with HF, but it also substantially impacts their morbidity and mortality.<sup>1,2</sup> Indeed, CKD in HF is associated with an increased risk of adverse events, such as hospitalisations for acute HF, mortality, resistance to diuretic therapy, and a reduced ability to titrate guideline-directed medical therapies.<sup>1,3,4</sup>

To enhance risk stratification in HF, guidelines recommend a comprehensive assessment that account for the multifaceted nature of the disease rather than relying on individual parameters.<sup>5,6</sup> One tool is the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score, a validated risk stratification model derived from extensive multicenter data.<sup>5,7</sup> The MECKI score predicts the composite risk of cardiovascular mortality, urgent heart transplantation (HTx), or left ventricular assist device (LVAD) implantation in patients with HF and reduced ejection fraction (HFrEF).<sup>7,8</sup> It incorporates six well-established prognostic markers, including eGFR.<sup>7</sup>

While eGFR plays a role within the MECKI score, various eGFR estimation equations, including the Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas, demonstrate differing accuracies and prognostic values.<sup>9–11</sup> Moreover, modified versions of the CG (CGm) and MDRD (MDRDm) equations, as well as the European Kidney Function Consortium (EKFC) equation, have emerged, addressing limitations in specific patient populations.<sup>12–14</sup> However, the relative performance of these equations in HF patients, particularly in the context of integrated prognostic models like the MECKI score, remains unclear.

This study aims to evaluate the impact of the six most widely used eGFR equations on HF outcome as well as on the accuracy of the MECKI score in predicting outcomes prognosis for HFrEF patients. In brief, through this investigation, we aim to offer valuable insights into the optimal approach for assessing renal function when evaluating HFrEF patients, ultimately enhancing their risk stratification and clinical decision-making processes.

## Methods

We retrospectively analyzed data from a cohort of 7948 HF patients, enrolled between 1993 and January 2022 and followed up prospectively in 27 highly experienced Institutions participating in the MECKI score research group.<sup>7,8</sup> Inclusion criteria were: HF patients in New York Heart Association (NYHA) functional classes I through IV, stages B and C of American College of Cardiology/American Heart Association classification, history of HFrEF, (LVEF <40%), unchanged HF medications for at least 3 months, ability to perform cardiopulmonary exercise test (CPET), no major cardiovascular treatment or interventions planned. Exclusion criteria were a history of pulmonary embolism, moderate to severe aortic and mitral stenosis, pericardial disease, severe obstructive pulmonary disease, chronic dialytic treatment, exercise-induced angina and significant electrocardiographic alterations, or the presence of any clinical comorbidities affecting exercise capacity.<sup>7,8</sup> The MECKI score was calculated using the formula reported by Agostoni *et al.*<sup>7</sup> The primary endpoint of the study was the composite of cardiovascular death, LVAD implantation, and urgent HTx; a secondary endpoint was cardiovascular death.

Briefly, cardiac ultrasounds were used to measure LVEF (Simpson rule). CPET was performed and analyzed as previously described.<sup>7,8,15</sup> All CPETs were performed using either an electronically braked cycle-ergometer or a treadmill in <4% of the cases ( $n = 293$ ); for a proper comparison oxygen uptake ( $\text{VO}_2$ ) data measured on the treadmill were reduced by 10%.<sup>7,8,15</sup>

A ramp protocol and a modified Bruce protocol were applied in CPET with cycle-ergometer and treadmill, respectively. The exercise protocol was set to achieve peak exercise in  $\sim 10$  min.<sup>15,16</sup> If no clinical events occurred, CPET was interrupted when patients indicated that they had reached maximal effort. We performed breath-by-breath analysis of expiratory gases and ventilation.<sup>7,8,15</sup>

We estimated GFR using renal function data collected at patients enrolment in the MECKI score database using 6 different formulas: (i) the MDRD formula:  $186.3 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.75$  for women [15, 16], (ii) the MRDR modified formula (MDRDm):  $175 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$  for women, (iii) the CG formula:  $(140 - \text{age}) \times (\text{weight}) \times (0.85 \text{ for women}) / (72 \times \text{sCr})$ , (iv) the CGm, obtained by normalising the CG formula for body surface area, (v) the CKD-EPI formula:  $141 \times \min(\text{sCr}/\kappa, 1)^\alpha \times \max(\text{sCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$  [if female]  $\times 1.159$  [if black], where  $\kappa$  is 0.7 for females and 0.9 for males,  $\alpha$  is  $-0.329$  for females and  $-0.411$  for males; (vi) EKFC equation formula: if  $\text{sCr}/\text{QCr} < 1$  then  $107.3 \times (\text{sCr}/\text{QCr})^{-0.322} \times (0.99^{(\text{Age}-40)})$  [if age > 40] and if  $\text{sCr}/\text{QCr} \geq 1$  then  $107.3 \times (\text{sCr}/\text{QCr})^{-1.132} \times (0.99^{(\text{Age}-40)})$  [if age > 40], where QCr values correspond to the median sCr values for the age- and sex-specific populations.<sup>17</sup> Serum creatinine was measured with the Jaffe method.<sup>18</sup>

Patient follow-up and data management procedures were performed as previously described.<sup>7,8</sup> In brief, follow-up was performed according to the local HF program, and ended with the last clinical evaluation or with the patient's cardiovascular death, LVAD implantation, or HTx. If a patient died outside the referral hospital, the medical records of this event were asked to the family and reviewed, and the reported cause of death, if available, was considered and included in the dataset according to the study outcomes.

Study data were collected and managed using REDCap<sup>19</sup> electronic data capture tools hosted at Centro Cardiologico Monzino IRCCS.

## Statistical analysis

Continuous variables were expressed as mean and standard deviation if normally distributed, otherwise as median and interquartile range (IQR); categorical variables were reported as frequencies and percentages. Receiver operating characteristic (ROC) curves were used to evaluate the performance of eGFR assessed using 6 different formulas (CG, CGm, MDRD, MDRDm, CKD-EPI and EKFC) to predict the primary endpoint. Moreover, a second ROC analysis was carried out to evaluate the performance of the 6 eGFR formulas when included in the MECKI score calculation. Comparisons among AUCs were made using DeLong's test.<sup>20</sup> Results were presented as area under the ROC curve (AUC).<sup>21,22</sup>

Subgroup analysis were performed stratifying the population according to cut-off values based on clinical recognized values or median ( $\theta$ ): gender, age (< 75 and  $\geq 75$  years), body mass index (BMI < 30 and  $\geq 30$  kg/m<sup>2</sup>), serum creatinine levels ( $\leq 1.09$  and  $> 1.09$  mg/dL,  $\theta$ ), HF medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor/neprilysin inhibitors, mineralocorticoid receptor antagonists, or diuretics), peak oxygen consumption (peak  $\text{VO}_2\%$  < 55 and  $\geq 55$ ,  $\theta$ ), ventilation/carbon dioxide production ( $\text{VE}/\text{VCO}_2$ ) slope (< 32 and  $\geq 32$ ,  $\theta$ ), LVEF % ( $\leq 40$  and  $> 40$ ), diabetes mellitus, ischaemic HF aetiology, haemoglobin (Hb < 13.6 and  $\geq 13.6$  m/dL,  $\theta$ ), NYHA class. All tests were two-sided, and a  $P$ -value < 0.05 was considered statistically significant. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

## Results

Among the 7948 patients enrolled in the MECKI score database, only the 6933 with all the information needed to calculate the 6 different GFR formulas have been included in the present analysis.

The study population characteristics are reported in Table 1. On average, patients had a moderate HF as shown by NYHA class, peak  $\text{VO}_2$ , BNP and Hb value, renal function, and had a relatively favourable prognosis as indicated by the calculated MECKI score values. The median follow-up was 4.2 years (IQR 1.8–7.6) but, as in the original MECKI score, all analyses were truncated at 2 years. At 2 years the endpoint was reached in 433 cases (cardiovascular death  $n = 335$ , LVAD  $n = 20$ , HTx  $n = 78$ ). Non-cardiovascular deaths were 60, which were not

**Table 1** Baseline characteristics of the study population (N = 6933)

Characteristics	N
<b>Males</b> , No. (%)	5659 (81.62%)
<b>Age</b> , mean (SD), years	61.95 ± 12.58
<b>BMI</b> , mean (SD), kg/m <sup>2</sup>	26.77 ± 4.38
<b>Aetiology</b> , No. (%)	
Idiopathic	2599 (40.34%)
Ischaemic	2958 (45.91%)
Other	886 (13.75%)
<b>NYHA</b> , No. (%)	
I	996 (14.43%)
II	3966 (57.44%)
III	1853 (26.84%)
IV	89 (1.29%)
<b>LVEF</b> , mean (SD), %	33.2 ± 10.2
<b>Systolic BP</b> , mean (SD), mmHg	117 ± 18
<b>HR</b> , mean (SD), b/min	70 ± 12
<b>BNP</b> , median (IQR), pg/mL	248 (98–647)
<b>Creatinine</b> , mean (SD), mg/dL	1.2 ± 0.58
<b>VO<sub>2</sub> peak</b> , mean (SD), mL/min	1155 ± 435
<b>VO<sub>2</sub> peak</b> , mean (SD), % pred	56.5 ± 17.5
<b>VO<sub>2</sub> peak</b> , mean (SD), mL/min/kg	14.89 ± 4.89
<b>VE/VCO<sub>2</sub> slope</b> , mean (SD)	33.2 ± 7.9
<b>VE/VCO<sub>2</sub></b> , mean (SD), % pred	126 ± 29
<b>HR peak</b> , mean (SD), b/min	118 ± 25
<b>Haemoglobin</b> , mean (SD), m/dL	13.5 ± 1.7
<b>Na<sup>+</sup></b> , mean (SD), mmol/L	139 ± 3
<b>K<sup>+</sup></b> , mean (SD), mmol/L	4.3 ± 0.5
<b>eGFR</b> mL/min/1.73 m <sup>2</sup>	
<b>MDRD</b> , median (IQR)	70.58 (54.63–86.35)
<b>CKD-EPI</b> , median (IQR)	69.6 (52.35–87.06)
<b>CG</b> , median (IQR)	72.87 (53.48–95.65)
<b>CGm</b> , median (IQR)	68.23 (50.97–88.25)
<b>MDRDm</b> , median (IQR)	66.12 (51.18–80.96)
<b>EKFC</b> , median (IQR)	66.49 (50.14–82.39)
<b>MECKI score</b>	
<b>With MDRD</b> , median (IQR)	5.1 (2.2–11.9)
<b>With CG</b> , median (IQR)	4.8 (1.9–11.6)
<b>With CGm</b> , median (IQR)	5.2 (2.1–12.2)
<b>With MDRDm</b> , median (IQR)	5.5 (2.3–12.5)
<b>With CKD-EPI</b> , median (IQR)	5.2 (2.2–12.1)
<b>With EKFC</b> , median (IQR)	5.4 (2.3–12.5)
<b>Diabetes</b> , No. (%)	1082 (21.47%)
<b>AF</b> , No. (%)	1214 (17.54%)
<b>ICD</b> , No. (%)	2408 (34.76%)
<b>CRT</b> , No. (%)	1015 (14.77%)
<b>ARBs</b> , No. (%)	1369 (20.74%)
<b>ACEi</b> , No. (%)	4804 (70.13%)
<b>Diuretics</b> , No. (%)	5473 (80.26%)

Continued

**Table 1** Continued

Characteristics	N
<b>MRA</b> , No. (%)	3650 (53.95%)
<b>Sacubitril/Valsartan</b> , No. (%)	196 (11.67%)
<b>Betablockers</b> , No. (%)	6019 (87.49%)
<b>Statin</b> , No. (%)	3289 (49.16%)
<b>Allopurinol</b> , No. (%)	1967 (29.08%)
<b>Antiplatelet</b> , No. (%)	3745 (55.08%)
<b>OAT</b> , No. (%)	2148 (31.58%)
<b>Digitalis</b> , No. (%)	1115 (17.18%)
<b>Amiodarone</b> , No. (%)	1619 (24.93%)

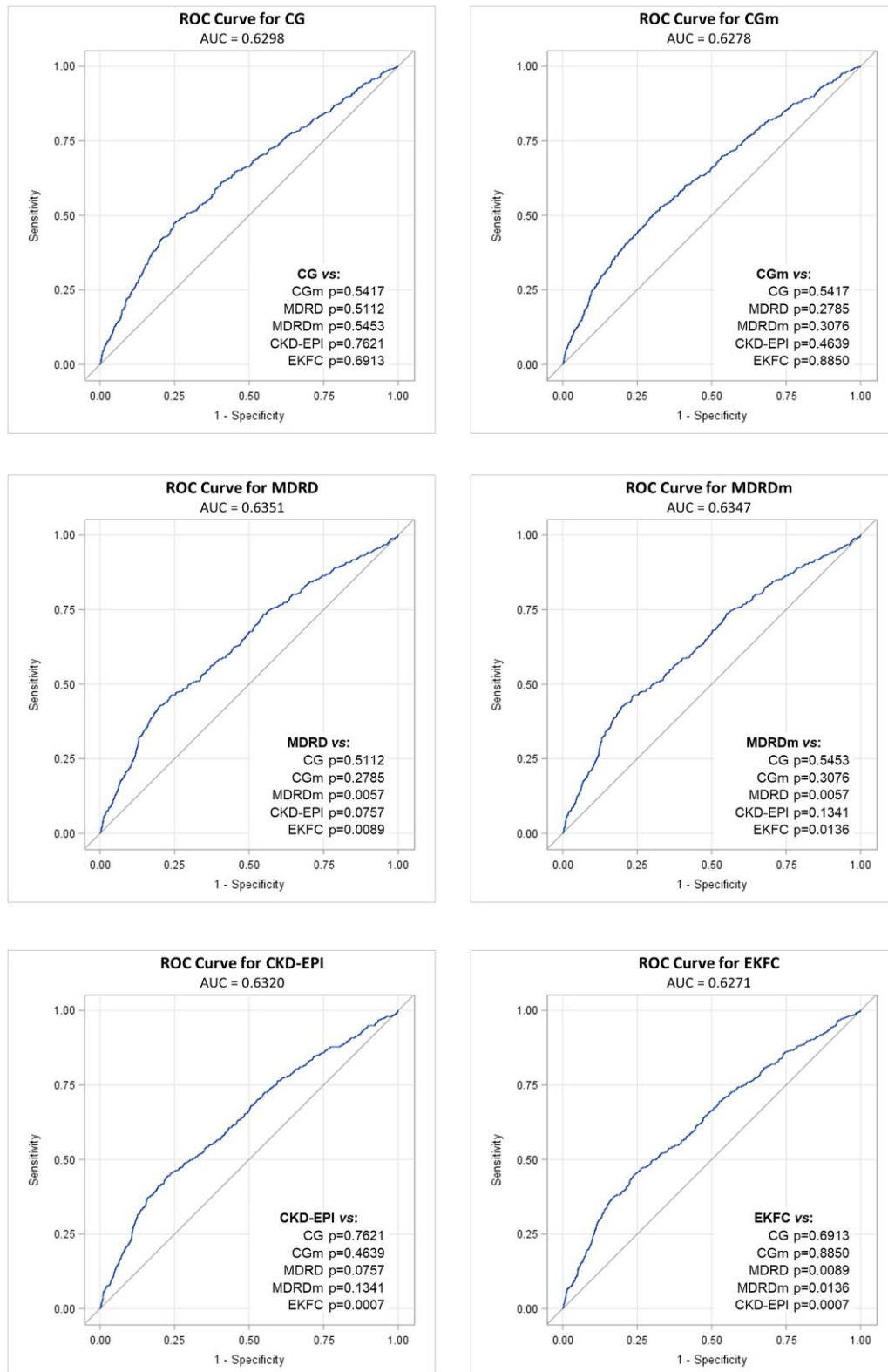
Continuous data were reported as Mean ± SD or Median (IQR).

ACE-I, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, Angiotensin receptor blockers; BMI, body mass index; BP, blood pressure; CG, Cockcroft-Gault; CGm, Cockcroft-Gault modified; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, Cardiac Resynchronisation Therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MDRDm, Modification of Diet in Renal Disease modified; MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; No, number; OAT, oral anticoagulant; peak VO<sub>2</sub>, peak oxygen consumption; SD, standard deviation; VE/VCO<sub>2</sub> slope, ventilation/carbon dioxide production; VO<sub>2</sub>, oxygen consumption.

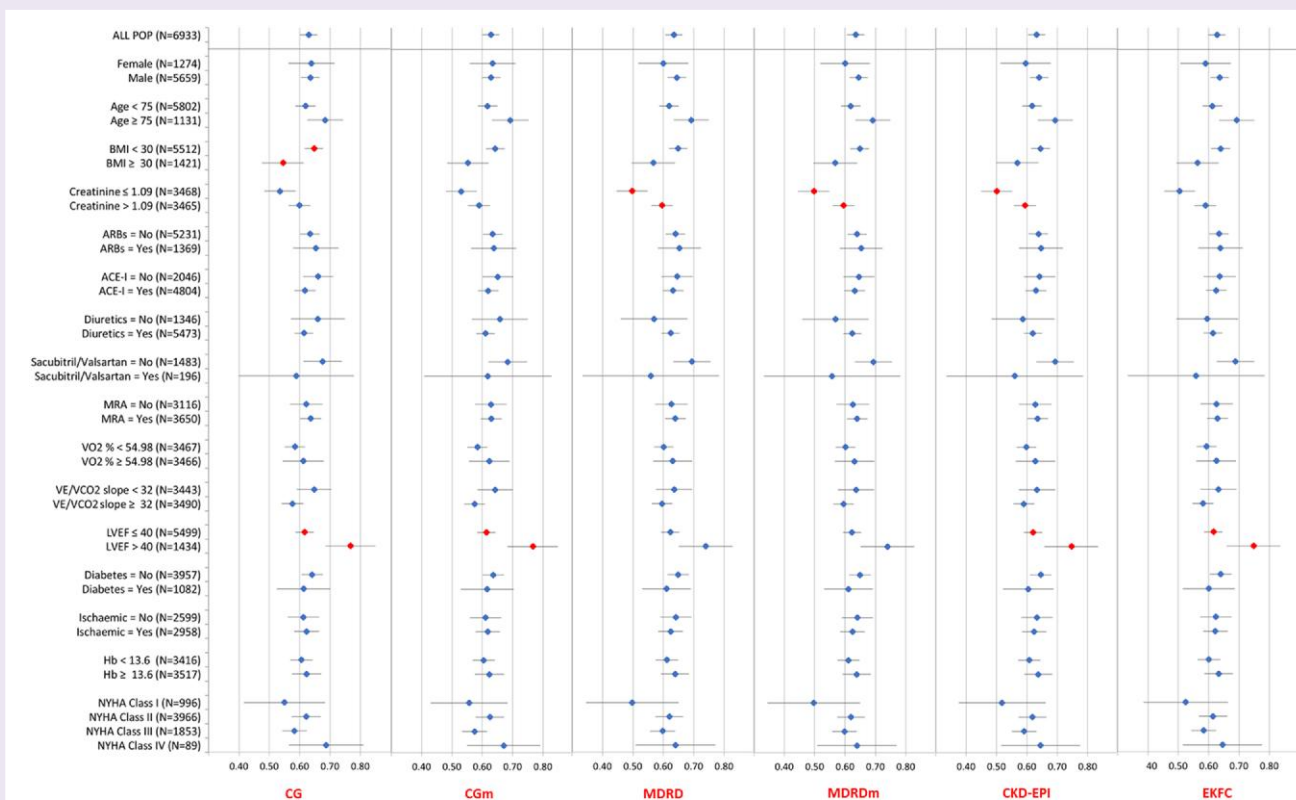
included in the present analysis. In the entire population, median eGFR was 72.87 (53.48–95.65), 68.23 (50.97–88.25), 70.58 (54.63–86.35), 66.12 (51.18–80.96), 69.6 (52.35–87.06), and 66.49 (50.14–82.39) mL/min/1.73 m<sup>2</sup> according to CG, CGm, MDRD, MDRDm, CKD-EPI equations, and EKFC equation, respectively. Each eGFR estimation was associated with only a moderate prognostic capacity with an AUC ranging between 0.6271 and 0.635; the former corresponding to the EKFC formula and the latter to MDRD equation (Figure 1). Considering only cardiovascular death, data were slightly higher with AUC ranging between 0.6677 and 0.6768. Subgroup analysis, as reported in Figure 2, revealed differences among formulas (statistically significant differences among subgroups in each GFR formula are in red). None of the examined subgroups showed a statistical difference in AUC for all the 6 formulas. Regardless, an overall tendency of a higher AUC was observed for patients with higher LVEF and serum creatinine, and lower BMI.

The prevalence of severe CKD, as identified by an eGFR of < 30 mL/min/1.73 m<sup>2</sup>, ranged from a minimum of 3.2% using the MDRD formula to a maximum of 4.5% using the EKFC formula, with the other formulas providing intermediate values (CG 3.7%, MDRDm 4%, CGm 4.1% and CKD-EPI 4.1%). The prognostic accuracy of eGFR <30 mL/min/1.73 m<sup>2</sup> did not differ among the 6 different eGFR formulas used for its estimation.

All the 6 formulas used to estimate the eGFR value yielded a similar trend when included in the MECKI score calculation. Specifically, AUC of the MECKI score was 0.7841 (95% CI: 0.7636–0.8047), 0.7858 (95% CI: 0.7654–0.8062), 0.7879 (95% CI: 0.7675–0.8083), 0.7879 (95% CI: 0.7675–0.8083), 0.7883 (95% CI: 0.7679–0.8087), and 0.7883 (95% CI: 0.7679–0.8087) applying CG, CGm, MDRD, MDRDm, CKD-EPI, and EKFC equation formula, respectively (Figure 3), with EKFC and CKD-EPI showing the best performance. Data were superimposable if only cardiovascular death was considered. Nonetheless, AUC differences among the investigated eGFR formulas were minor with likely no clinical significance. Subgroup analysis is reported in Figure 4. An overall tendency of a higher AUC was observed for patients with no diuretic treatment.



**Figure 1** Prognostic accuracy (area under the curve) of the 6 different formulas used to estimate glomerular filtration rate in the overall population. AUC, area under the curve; CG, Cockcroft-Gault formula; CGm, Cockcroft-Gault modified formula; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; EKFC, European Kidney Function Consortium EKFC formula; MDRD, Modification of Diet in Renal Disease formula; MDRDm, Modification of Diet in Renal Disease modified formula; ROC, Receiver Operating Characteristic.



**Figure 2** Prognostic accuracy (area under the curve values) of the 6 different formulas used to estimate glomerular filtration rate stratified according to patients' subgroups. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, Body mass index; CG, Cockcroft-Gault formula; CGm, Cockcroft-Gault modified formula; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; EKFC, European Kidney Function Consortium EKFC formula; Hb, haemoglobin; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease formula; MDRDm, Modification of Diet in Renal Disease modified formula; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; ROC, Receiver Operating Characteristic; VE/VCO<sub>2</sub> slope, ventilation/carbon dioxide production slope; VO<sub>2</sub>, oxygen uptake. Red colour is used for statistically significant values ( $P < 0.05$ ).

## Discussion

This study demonstrates that all 6 creatinine-based eGFR estimation formulas evaluated have a similar but moderate impact on prognosis in patients with HFrEF or history of HFrEF, with minimal variation in the categorisation of severe CKD. Importantly, when integrated into the MECKI score, none of the 6 formulas significantly alter the score's robust predictive ability (Central illustration). The similar prognostic capacity of the evaluated eGFR equations suggests that while renal function is a key contributor to HF risk stratification, the choice of a specific eGFR formula is unlikely to meaningfully affect clinical decision-making when using the MECKI score. This highlights the robustness of the MECKI score as a prognostic model and its ability to integrate multifaceted disease markers without being overly sensitive to small variations in renal function estimation.

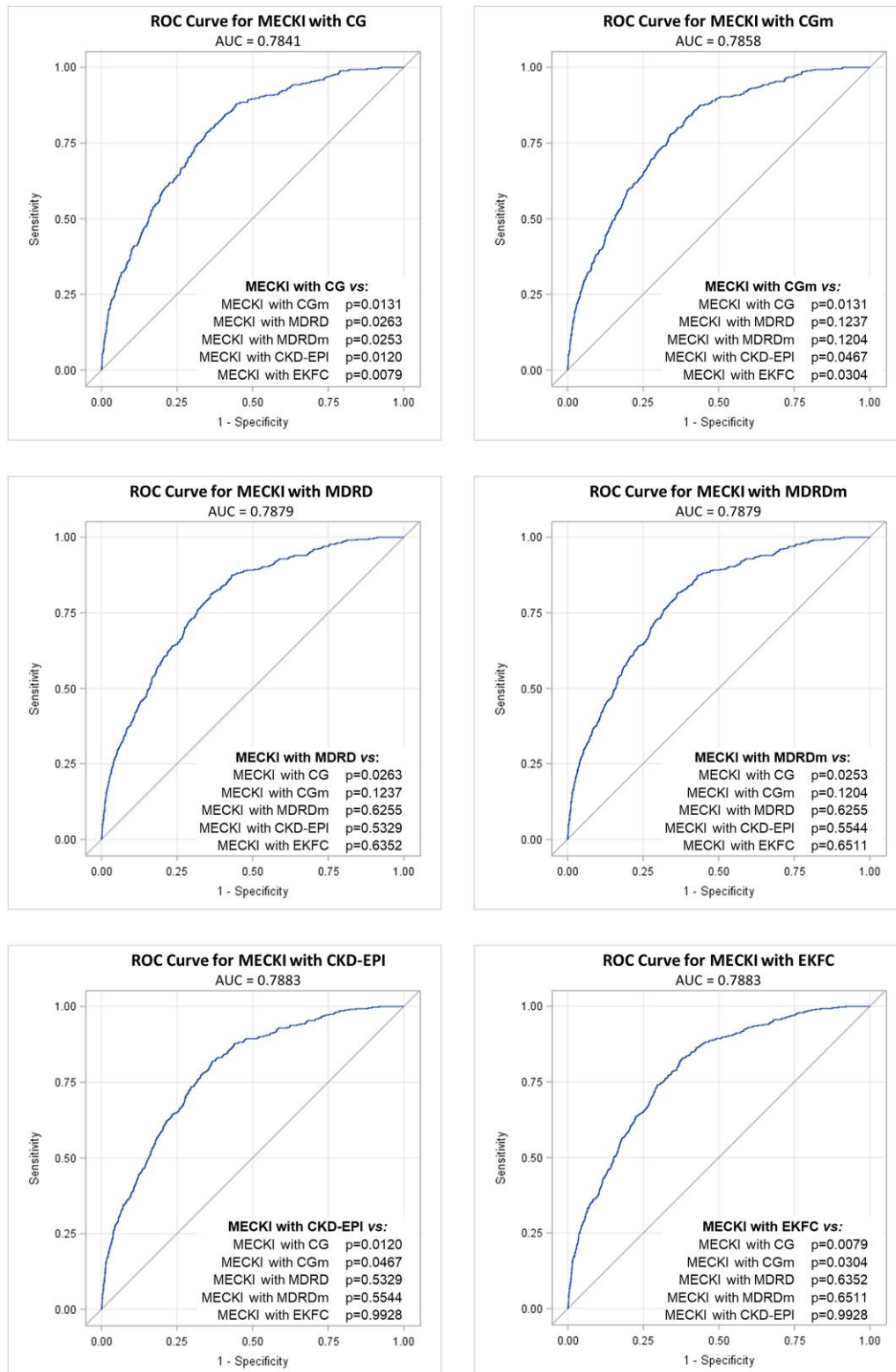
In this study, each eGFR formula demonstrated, if taken on its own, only a moderate prognostic capability, as evidenced by AUC values ranging from 0.6271 to 0.6351. These findings suggest that while renal function plays a clinically relevant role in HF prognosis, it represents just one of several contributing factors. Beyond the overall consistency in prognostic performance, our study sheds light on certain limitations and subgroup-specific nuances of eGFR formulas in specific patient subgroups, suggesting that individual characteristics such as BMI, LVEF, and serum creatinine levels may influence GFR estimation accuracy. These

findings emphasize the importance of considering individual patient characteristics when interpreting GFR estimates.

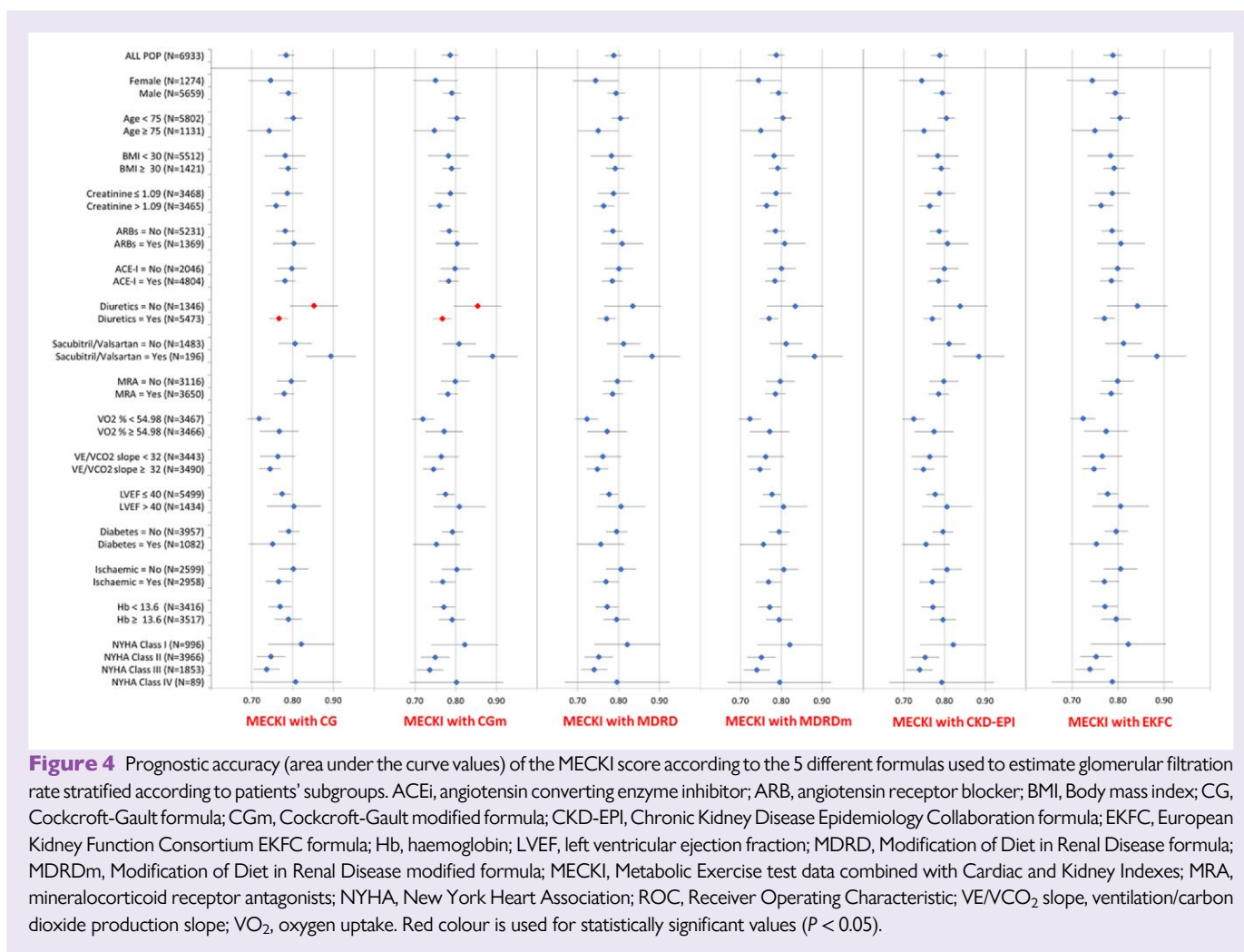
Moreover, while the differences in eGFR formulas were minor when integrated into the MECKI score, they did impact the proportion of patients categorized with severe CKD (eGFR < 30 mL/min/1.73m<sup>2</sup>). Depending on the formula used, this proportion ranged from 3.2% (MDRD) to 4.5% (CGm and CKD-EPI). This variability has practical implications, as eGFR thresholds are often used to guide treatment decisions, such as prescribing anticoagulants or renin-angiotensin-aldosterone system inhibitors. These findings suggest that clinicians should remain cautious when relying solely on eGFR thresholds for such decisions, as the choice of formula may inadvertently exclude patients from potentially beneficial therapies. It should be noticed that in 2021 a revised formula for eGFR estimation was introduced for CKD-EPI.<sup>23</sup> This formula does not consider ethnic differences. However, in the present setting results of the 2 CKD-EPI formulae were very similar.

The MECKI score is one of the most powerful prognostic tools in chronic HF. Its use is suggested by guidelines.<sup>5,24</sup> It integrates six variables with independent prognostic power—peak VO<sub>2</sub>, VE/VCO<sub>2</sub> slope, plasma sodium, haemoglobin, LVEF, and renal function into a comprehensive risk stratification model.<sup>7,8</sup>

Our study reaffirms the score's robustness, with consistent 2-year AUC values ranging from 0.7841 to 0.7883 across different GFR estimation methods. Importantly, the MECKI score's predictive accuracy



**Figure 3** Prognostic accuracy (area under the curve) of the MECKI score according to the 6 different formulas used to estimate glomerular filtration rate in the overall population. AUC, area under the curve; CG, Cockcroft-Gault formula; CGm, Cockcroft-Gault modified formula; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; EKFC, European Kidney Function Consortium EKFC formula; MDRD, Modification of Diet in Renal Disease formula; MDRDm, Modification of Diet in Renal Disease modified formula; MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes; ROC, Receiver Operating Characteristic.



was not significantly influenced by the choice of eGFR formula, underscoring its strength as a multiparametric tool that appropriately weights each variable.

Thus, our study confirmed the robust prognostic accuracy of the MECKI score in stratifying HF patients' outcomes and the usefulness of a multiparametric approach to HF patients where each variable is properly weighted to accurately estimate prognosis. Of note, the score's prognostic power tended to be higher in patients not receiving diuretic treatment, supporting the concept that diuretics, while effective for symptom relief, are not disease-modifying therapies.<sup>5,6</sup>

Prognostic stratification in HF patients is crucial for guiding personalized treatment decisions, optimising resource allocation, facilitating shared decision-making, appropriate monitoring and follow-up, and informing clinical trial design.

Our findings highlight the robustness of the MECKI score across various renal function estimation methods, while also drawing attention to the inherent limitations of eGFR formulas in specific HF subgroups. These insights provide clinicians with a clearer understanding of the nuances of renal function assessment in HF and reaffirm the MECKI score as a reliable tool for risk prediction in diverse patient populations.

## Limitations

Although our study provides valuable insights into the comparative performance of different GFR estimation methods and their impact on risk prediction in a large dataset from experienced HF centers, several

limitations should be acknowledged. First, it is an observational study with a retrospective design, which carries potential biases related to data collection and patient selection, although the study is based on an extensive database with a long follow-up period conducted by highly experienced HF centers. Second, due to the retrospective design and the era of patient enrolment, cystatin C measurements were not available for this cohort. Cystatin C has demonstrated superior performance compared with creatinine as a biomarker for estimating GFR, particularly in predicting cardiovascular outcomes and mortality. Therefore, future analyses in cohorts where cystatin C data are available should consider incorporating this biomarker to potentially improve the predictive accuracy of eGFR estimates. Third, changes in clinical, laboratory, echocardiographic, and CPET data, as well as treatment strategies during follow-up are unknown. Future prospective studies involving larger and more diverse cohorts are warranted to validate these results and further elucidate the optimal approach for renal function assessment in HF prognostication. Fourth, the MECKI score includes only patients with reduced LVEF or a history of reduced LVEF; therefore, our data do not provide information on other HF phenotypes. Additionally, a minority of the study population were female, and < 5% of patients had an eGFR below 30 mL/min/1.73 m<sup>2</sup>, limiting the generalisability of our findings to these subgroups. Similarly, non-Caucasian subjects represented < 1% of the present study population precluding independent assessments of these individuals. Fifth, cut-off values for subgroup analysis were arbitrarily chosen based on clinical conventions or as the median of the present

population, which, like all cut-off values, may be questioned. Finally, due to the prolonged recruitment period, impact of more recent HF therapies—such as ARNI and sodium-glucose cotransporter-2 inhibitors, which are known to preserve renal function—could not be fully evaluated in this analysis. Thus, future prospective studies are needed to validate these findings and determine the optimal approach for renal function assessment in HF prognostication.

## Conclusions

In conclusion, while different GFR estimation methods show moderate prognostic capacity with minimal variations in performance, the MECKI score consistently delivers reliable prognostic results in HFrEF patients, regardless of the GFR estimation method used. This underscores the robustness of the MECKI score as a valuable tool for risk prediction and individualized treatment planning in HF management. Further research and validation are warranted to refine individualized risk assessment and enhance clinical decision-making in HF care.

## Author contributions

MM, PA, ES, FP and NC contributed to the conception or design of the work. ES, AG, AB contributed to the acquisition, analysis, or interpretation of data for the work. PA, MM, NC, FP, ES drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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## Data availability

Repository of raw data will be available after acceptance at [www.zenodo.org](http://www.zenodo.org).

## Ethical approval statement

The study was approved by the local ethics committee (protocol number: CCM04\_21 PA).

## Appendix

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