ORIGINAL ARTICLE

JOURNAL OF
CARDIAC SURGERY WILEY

The predictive value of five glomerular filtration rate formulas for long-term mortality in patients undergoing coronary artery bypass grafting

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Abstract

Background and Aims: Renal function plays an important role in the management of patients referred for coronary artery bypass grafting (CABG). Current data is insufficient for precise risk stratification using the estimated glomerular filtration rate (eGFR).

Methods: This retrospective study includes 3744 consecutive patients who underwent CABG between 2004 and 2020. We assessed five different eGFR formulas: Cockcroft–Gault (CG), modification of diet in renal disease (MDRD), chronic kidney disease Epidemiology Collaboration (CKD-EPI), Mayo, and inulin clearance-based (IB).

Results: The Mayo formula yielded the highest mean eGFR (90 ± 24 ml/min per $1.73\,m^2$) and CKD-EPI the lowest (74 ± 21 ml/min per $1.73\,m^2$). As a result, more patients were classified as having a normal renal function (57%) with the Mayo formula as compared with the others. Using MDRD as the reference formula, there was a significant and stronger correlation between the values obtained from the CKD-EPI ($r = .95$, $p < .001$) and Mayo (Mayo: $r = .87$, $p < .001$) compared to the IB ($r = .8$, $p < .001$) and CG ($r = .79$, $p < .001$) formulas. Multivariable analysis demonstrated that decreased renal function is an independent predictor of 10-year mortality in all five formulas, with risk increasing by 13–17% for each 10-unit decrease in eGFR. Despite the similarities between the formulas, the ability to predict mortality was highest in the Mayo formula and lowest in the CG and IB.

Conclusions: Our data suggest that the Mayo formula may be superior to the other formulas in prognosticating mortality after CABG. We have shown that the Mayo equation classified fewer individuals as having renal dysfunction and more accurately categorized the risk for mortality than did all other formulas.

KEYWORDS
coronary artery bypass grafting, coronary artery disease, creatinine clearance, estimated glomerular filtration rate

1 | INTRODUCTION

Renal dysfunction, assessed by estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) is common in patients undergoing cardiac surgery. Approximately half of the patients undergoing coronary artery bypass grafting (CABG) have at least mild renal dysfunction and one quarter has at least moderate renal dysfunction.[1] Indeed, renal function is included in the STS and EuroSCORE risk scores for predicting CABG outcomes.[2,3] There is a graded increase in operative mortality and morbidity with worsening preoperative renal function.[1,4–11] Renal insufficiency is associated with a greater risk of both 30-day and 1-year mortality.[12] Even mild renal dysfunction is associated with increased rates of operative and long-term mortality, need for postoperative dialysis, and postoperative stroke.[13]

Patients with renal impairment have accelerated atherosclerosis and an increased risk of multivessel coronary artery disease (CAD) and, in fact, cardiovascular disease is the most common cause of death in chronic kidney disease (CKD) patients.[14] An accurate definition of CKD status and stage is thus critical for risk stratification and management of CAD patients.[15]

There are a number of equations used for GFR estimation. The Cockcroft–Gault (CG) equation has been the most commonly used method for decades. However, in the last few years, due to inherent limitations of the CG equation, several newer equations have been developed.[16–18] The Modification of Diet in Renal Disease (MDRD) and, more recently, the CKD Epidemiology Collaboration (CKD-EPI) equation, are the most extensively used formulas. The Mayo Clinic quadratic equation[19] and the inulin clearance–based (IB) eGFR equation[20] were developed in an attempt to better estimate GFR in patients with preserved kidney function.

Current literature is insufficient in measuring the ability of these five formulas to predict outcomes in patients who undergo CABG. In this study, we aim to evaluate the performance of all five eGFR formulas in predicting long-term all-cause mortality.

2 | METHODS

2.1 | Study design and population

We performed a retrospective, observational study that included prospectively-collected data from a large tertiary university hospital. Between 2004 and 2020, a total of 3744 patients underwent isolated CABG, with no prior cardiac surgery. Past medical history and current medications were all keyed into an electronic database.

Discordant eGFR was used when a patient was considered to have a normal renal function with at least one formula and abnormal renal function by at least one formula. The cohort was divided into three groups accordingly: significant renal impairment (GFR ≤ 60 ml/min per 1.73 m^2) according to all five formulas (MDRD, Mayo, CKD-EPI, CG, and IB formulas), nonsignificant renal impairment by all five formulas (GFR > 60 ml/min per 1.73 m^2), and discordant eGFR.

The study was approved by the Sheba Medical Center Institutional Ethics Committee (Protocol No 4527; February 28, 2021). The requirement for informed consent was waived because of the retrospective nature of the study.

2.2 | Assessing renal function

We assessed five different eGFR formulas, based on the initial creatinine upon admission. The formulas used were as follows: CG, MDRD, CKD-EPI, Mayo, and IB (Table S1).

Patients were categorized into five levels of renal function based on the calculated eGFR: no renal impairment (>90 ml/min per 1.73 m^2), mild renal dysfunction (60–90 ml/min per 1.73 m^2), moderate renal dysfunction (30–59 ml/min per 1.73 m^2), severe renal dysfunction (15–29 ml/min per 1.73 m^2), and kidney failure (<15 ml/min per 1.73 m^2). The US National Kidney Foundation criteria were adapted for significant renal dysfunction definition as an eGFR of <60 ml/min per 1.73 m.[2,21]

2.3 | Statistical analysis

Data are presented as mean ± standard deviation. Continuous variables were tested with the Kolmogorov–Smirnov test for normal distribution. Categorical variables are given as frequencies and percentages. A chi-square test was used for comparison of categorical variables between different renal function groups. Student's t-test was performed for comparison of normally distributed continuous variables and Mann–Whitney U test for non-normal distribution.

The correlation between CG, MDRD, Mayo, IB, and CKD-EPI formulas was tested using Pearson's correlation coefficient. We performed a Bland and Altman analysis to assess the agreement between values derived from each of the other formulas and the values obtained from the CG formula.

Survival analysis was done using the Kaplan–Meier method, and statistical differences between predefined renal dysfunction groups were tested using the log-rank test. Multivariate Cox proportional hazard modeling was used to identify factors associated with mortality risk at follow-up, with candidate factors listed in Table 1. Statistically significant variables ($p < .1$) in the univariable analysis were used in the multivariable model to identify independent predictors of mortality. In the final model, we included the following variables: age, gender, diabetes, peripheral vascular disease (PVD), atrial fibrillation, previous stroke, previous myocardial infarction, chronic obstructive pulmonary disease, hypertension, surgery after 2010, left ventricle ejection fraction (LVEF), New York Heart Association (NYHA) functional class and eGFR by the five formulas.

To evaluate the ability of the formulas to predict all-cause mortality and the benefit incurred by the addition of a GFR formula to a baseline model of mortality prediction, we estimated the net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Using binary logistic regression, we computed

TABLE 1 Patient characteristics by the renal function categories

	eGFR ≤60 (N = 376)	Discordant eGFR (N = 742)	eGFR >60 (N = 2644)	p value
Age (years) (mean ± SD)	71.4 ± 9.1	71.1 ± 8.8	61.6 ± 9.2	<.001
Gender (male) (%)	303 (80.6)	480 (66.3)	2309 (87.3)	<.001
Obesity (%)	149 (39.6)	212 (29.3)	1175 (44.4)	<.001
Hypertension (%)	328 (89.6)	598 (83.2)	1907 (73.3)	<.001
Peripheral vascular disease (%)	89 (23.9)	95 (13.2)	246 (9.4)	<.001
Diabetes mellitus (%)	206 (55.5)	350 (48.4)	1104 (42)	<.001
Atrial Fibrillation (%)	2 (0.5)	4 (0.6)	6 (0.2)	.291
Previous myocardial infarction (%)	144 (57.6)	278 (50.5)	828 (49.5)	.058
Hyperlipidemia (%)	297 (81.4)	570 (79.4)	2027 (77.9)	.271
Smoking (%)	138 (37.2)	164 (22.7)	882 (33.5)	<.001
COPD (%)	21 (5.7)	42 (5.8)	113 (4.3)	.159
Prior CVA/TIA (%)	45 (12.7)	81 (11.7)	167 (6.7)	<.001
Neurological deficit (%)	12 (3.3)	21 (2.9)	51 (2)	.129
Carotid stenosis>70% (%)	9 (2.8)	16 (2.5)	46 (2.2)	.749
NYHA functional class (%)				<.001
I	57 (17.9)	147 (23.7)	730 (31.8)	
II	157 (49.4)	284 (45.7)	1063 (46.4)	
III	81 (25.5)	165 (26.6)	446 (19.5)	
IV	23 (7.2)	25 (4)	54 (2.4)	
NYHA functional class I–II (%)	214 (67.3)	431 (69.4)	1793 (78.2)	<.001
NYHA functional class III–IV (%)	104 (32.7)	190 (30.6)	500 (21.8)	<.001
mean NYHA (mean ± SD)	2.2 ± 0.8	2.1 ± 0.8	1.9 ± 0.8	<.001
Operative timing (%)				.849
Elective	64 (25.7)	141 (25.9)	459 (27.6)	
Same hospitalization	91 (36.5)	199 (36.5)	621 (37.4)	
Urgent (<72 h)	72 (28.9)	152 (27.9)	450 (27.1)	
Emergent (<24 h)	22 (8.8)	53 (9.7)	132 (7.9)	
Era of operation (≥ year 2010) (%)	222 (59)	380 (52.5)	1644 (62.2)	<.001
Left ventricle ejection fraction (%) (mean ± SD)	48.7 ± 12.5	50.7 ± 12.2	53.5 ± 17.4	<.001
Right ventricle dysfunction (%)				.311
None	275 (98.2)	575 (99.1)	1827 (99.2)	
Mild	3 (1.1)	5 (0.9)	7 (0.4)	
Moderate	2 (0.7)	0 (0)	7 (0.4)	
Severe	0 (0)	0 (0)	1 (0.1)	

Abbreviations: COPD, chronic obstruction pulmonary disease; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; SD, standard deviation; TIA, transient ischemic attack.

the predicted risk for 10-year mortality from a baseline model without GFR (age, sex, diabetes, PVD, atrial fibrillation, previous stroke, previous myocardial infarction, chronic obstructive pulmonary disease, hypertension, era of surgery, LVEF, and NYHA functional class) and a similar model that included GFR (for each formula separately). For calculation of the NRI, rescaled individual predicted risk from baseline model and GFR models were compared in three prespecified risk thresholds; low risk (<10%), intermediate risk

(10%–20%), and high risk (>=20%). IDI and relative IDI were computed similarly to NRI, though without prespecified risk thresholds.

Statistical significance was assumed when the null hypothesis could be rejected at $p < .05$. All p values are the results of two-sided tests. Statistical analyses were conducted using R (version 4.0.3).

3 | RESULTS

3.1 | Baseline characteristics and surgical data

Among the 3744 patients included in the study, 376 (10.1%) had significant renal impairment (GFR ≤ 60 ml/min per 1.73 m^2) according to all five formulas, 2644 (70.6%) had nonsignificant renal impairment (GFR > 60 ml/min per 1.73 m^2) according to all five formulas. In the remaining 724 patients (19.3%), the eGFR was discordant and shifted between <60 ml/min per 1.73 m^2 and >60 ml/min per 1.73 m^2 depending on the formula used.

The mean age of the cohort was 64 ± 10 years. The majority of the patients were male (83%). Patients with normal renal function tended to be younger ($p < .001$) and had fewer cardiovascular risk factors such as diabetes ($p < .001$), hypertension ($p < .001$), PVD ($p < .001$), and history of stroke ($p < .001$), however, they were more obese ($p < .001$) (Table 1). The mean LVEF of the entire cohort was 52.5 ± 16.3%, highest in the group with preserved kidney function by all formulas, and lowest in the renal impairment group by all formulas ($p < .001$) (Table 1).

The mean cardiopulmonary bypass and cross-clamp times were 83.4 ± 44.5 and 54.4 ± 21.1 min in the significant renal impairment group, 80.4 ± 27.3 and 54.3 ± 19.3 min in the discordant group, and 80.9 ± 35 and 56 ± 26.4 min in the nonsignificant renal impairment group ($p = .521$ and $p = .323$, respectively).

3.2 | Estimated glomerular filtration rate

With all five formulas, only a minority of the patients had severe renal impairment or kidney failure (Figure 1). The prevalence of patients with renal failure (eGFR < 60 ml/min/1.73 m^2) at baseline was 11.1% by the Mayo equation, 20.8% by the MDRD equation, 22.6% by the CG equation, 23.2% by the IB equation, and 23.9% by the CKD-EPI equation.

The mean eGFR values on admission were in the mild renal dysfunction range by all formulas used except for the Mayo formula which was within the norm range of renal function. Specifically, the Mayo formula yielded the highest mean value (90.1 ± 24.2 ml/min per 1.73 m^2) and CKD-EPI the lowest (74.4 ± 21.1 ml/min per 1.73 m^2) (Table 2). Notably, the Mayo had more patients with normal renal function (N = 2123, 56.7%) and thus fewer patients categorized as mild renal dysfunction (N = 1206, 32.2%) and moderate renal dysfunction (N = 313, 8.4%) (Figure 1, Table 2).
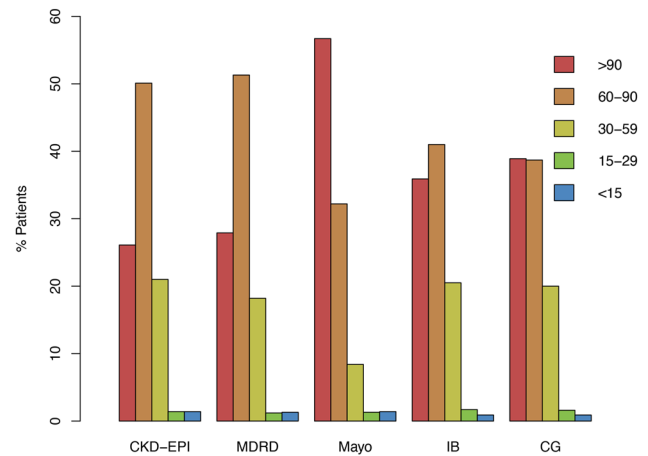

FIGURE 1 Distribution of CKD stages determined by eGFR according to the five different formulas among patients who underwent CABG. CG, Cockcroft–Gault; CKD, chronic kidney disease; CABG, coronary artery bypass grafting; CKD-EPI, chronic Kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; IB, inulin clearance–based equation; MDRD, Modification of Diet in Renal Disease.

To determine whether the MDRD method, as the reference formula, and the CKD-EPI, Mayo, IB, and CG formulas yield the same results, we calculated the correlation coefficient, and demonstrated a strong correlation between the MDRD formula and each of the other four formulas (CKD-EPI: $r = .95$, $p < .001$; Mayo: $r = .87$, $p < .001$; IB: $r = .80$, $p < .001$; CG: $r = .79$, $p < .001$). Furthermore, to assess the agreement between the values obtained from the MDRD formula and the values derived from each of the other formulas, we used the Bland and Altman analyses which showed good agreement with all formulas used. The mean ± SD of the eGFR difference between the MDRD formula (reference) and the CKD-EPI, Mayo, IB, and CG formulas were 3.4 ± 7.8, 12.2 ± 12.4, 4 ± 17.5, and 6.1 ± 19 ml/min per 1.73 m^2, respectively.

3.3 | Mortality by renal function

Patients with eGFR ≤60 ml/min per 1.73 m^2 by all five methods had significantly higher 30-day mortality and 10-year mortality compared with patients with discordant eGFR and compared to patients with eGFR >60 mL/min per 1.73 m^2 by all five methods (8.2% vs. 1.7% vs. 0.6%, $p < .001$% and 42% vs. 23.6% vs. 9.2%, log-rank $p < .001$, respectively) (Figure 2). Furthermore, the severity of renal impairment correlated with increased mortality (Figure 3). All five formulas produced similar mortality trends, which plateaued at eGFR <30 ml/min per 1.73 m^2 (Figure 3). Multivariable analysis demonstrated that worse renal function is an independent predictor of 10-year mortality for all five formulas (Table 3). The risk of mortality increased by 13%–17% for each 10-unit decrease in eGFR, using all five formulas. Other independent predictors of 10-year mortality were older age

TABLE 2 Distribution of eGFR according to the five different formulas

	CKD-EPI	MDRD	Mayo	IB	CG
Mean eGFR (mean ± SD)	74.4 ± 21.1	77.9 ± 24.4	90.1 ± 24.2	81.9 ± 29.5	84 ± 31.2
eGFR >90	976 (26%)	1045 (28%)	2123 (57%)	1343 (36%)	1453 (39%)
eGFR 60–90	1872 (50%)	1919 (51%)	1206 (32%)	1533 (41%)	1444 (39%)
eGFR 30–59	784 (21%)	681 (18%)	313 (8%)	766 (20%)	745 (20%)
eGFR 15–29	52 (1.4%)	46 (1%)	48 (1%)	63 (2%)	60 (2%)
eGFR <15	51 (1.4%)	48 (1%)	53 (1%)	33 (1%)	32 (1%)

Abbreviations: CG, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, chronic Kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; IB, inulin clearance–based equation; MDRD, Modification of Diet in Renal Disease.
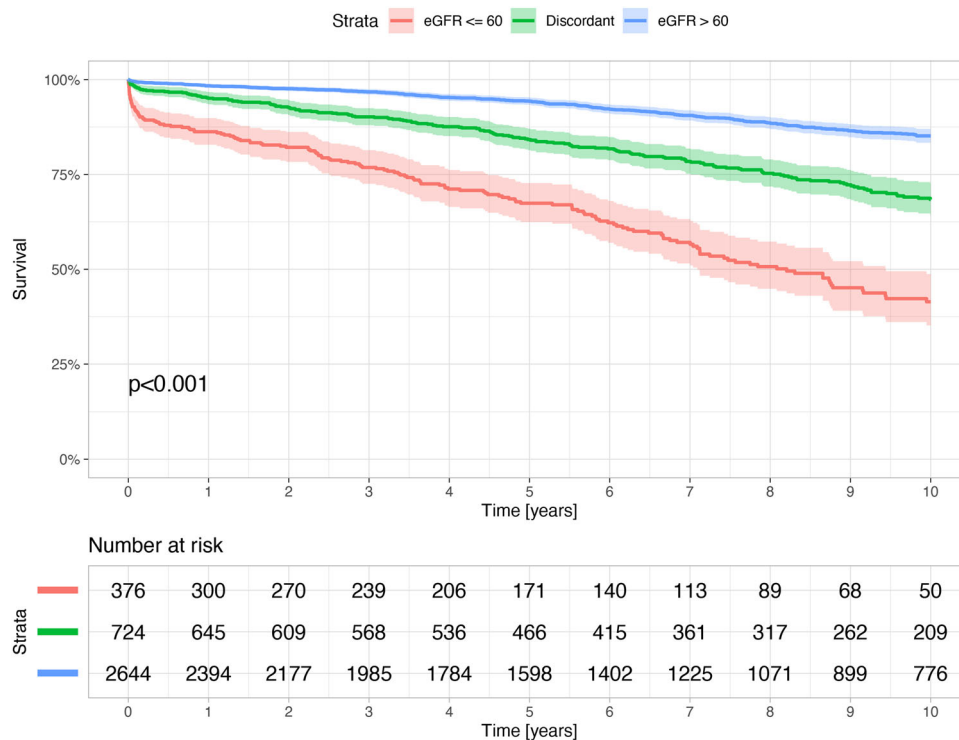
FIGURE 2 Kaplan–Mayer analysis for survival by the renal function categories. eGFR, estimated glomerular filtration rate.

(hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.04–1.09, $p < .001$), PVD (HR 2.02, 95% CI 1.28–3.18, $p = .003$), history of atrial fibrillation (HR 2.73, 95% CI 1.08–6.89, $p = .034$), lower LVEF (HR 0.98, 95% CI 0.96–0.99, $p = .009$) and NYHA functional class III–IV versus I–II (HR 1.51, 95%CI 1.01–2.27, $p = .045$).

The ability of the five formulas to predict the 10-year mortality risk was highest with the Mayo formula (rIDI = 13.4%, $p < .001$) and lowest with the IB and CG formulas (rIDI = 7.8%, $p < .001$ and rIDI = 7.9%, $p < .001$; respectively) (Table 4). Aldo among the subgroup of male and female patients, the Mayo formula had the highest ability to predict the 10-year mortality (rIDI = 14.1%, $p < .001$; and rIDI = 12.3%, $p < .001$, respectively) (Tables S2 and S3).

4 | DISCUSSION

This study describes several findings regarding renal function and evaluation of renal function in patients who undergo CABG. We have shown that[1]: despite the significant and strong correlation between eGFR values using all five formulas, the proportion of patients categorized into the different renal function groups varied considerably in our cohort, suggesting a significant clinical impact of the GFR formula used[2]; mortality increased as renal function worsened in all renal function categories, with a plateau at eGFR <30 ml/min per 1.73 m^{2,3}; patients whose renal dysfunction status shifted from significant to nonsignificant or vice versa using the different formulas had mortality rates that were intermediate between those with and
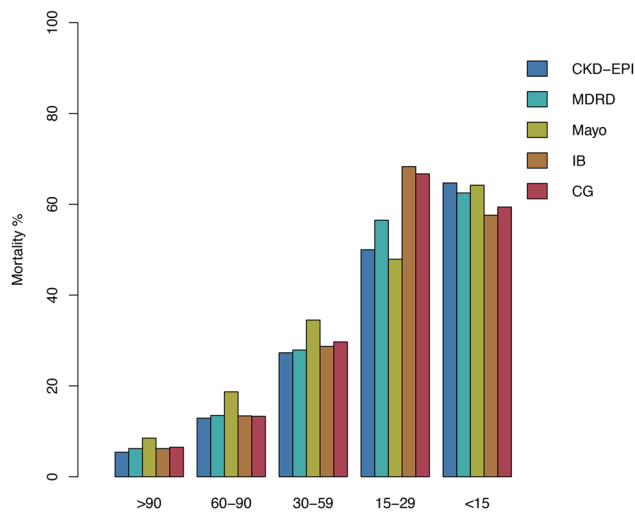
FIGURE 3 Ten-year mortality rates based on renal function status according to the five different formulas. CG, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, chronic Kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; IB, inulin clearance–based equation; MDRD, Modification of Diet in Renal Disease.

TABLE 3 Predictors for 10-year mortality[a]

Formula	Univariable analysis			Multivariable analysis[b]		
	HR	95% CI	p-value	HR	95% CI	p-value
CKD_EPI	1.42	1.36–1.47	<.001	1.18	1.06-1.28	.002
MDRD	1.36	1.31–1.41	<.001	1.14	1.04-1.25	.005
Mayo	1.33	1.29–1.37	<.001	1.14	1.05-1.22	.001
IB	1.34	1.30–1.39	<.001	1.18	1.06-1.30	.002
CG	1.33	1.29–1.38	<.001	1.18	1.06-1.28	.002

Note: A univariable and multivariable analysis.

Abbreviations: CG, Cockcroft–Gault; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, chronic Kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IB, inulin clearance–based equation; MDRD, Modification of Diet in Renal Disease.

[a]Hazard ratios with 95% CI's for 10-year mortality (for 10-unit decrements in eGFR).

[b]The covariates included in the model were: age, gender, diabetes, peripheral vascular disease, atrial fibrillation, previous stroke, previous myocardial infarction, chronic obstructive pulmonary disease, hypertension, surgery after 2010, left ventricle ejection fraction, New York Heart Association functional class and eGFR by the five formulas.

without significant renal dysfunction; and[4] although the MDRD formula is extensively used in clinical practice, it was less accurate in predicting mortality relative to other formulas such as the Mayo or CKD-EPI formulas, in patients who undergo CABG.

Acute renal failure ensuing after CABG with cardiopulmonary bypass is an ominous event and is often associated with preoperative renal function. A previous publication by Mangano et al. showed that renal dysfunction not requiring dialysis occurred in 6.3%, and renal dysfunction requiring hemodialysis developed in 1.4%, after CABG. Mortality was directly related to postoperative renal function. Patients with no renal dysfunction had 0.9% mortality. Postoperative renal dysfunction increased mortality to 19% even if no dialysis was needed.[22,23] We reported a 30-day mortality rate of 0.2% and 0.3% in there was normal or "discordant" renal function, and 8.2% in patients with renal dysfunction (by all formulas), a lower incidence than published previously.[22–24]

The percentage of renal dysfunction in our cohort is higher than the prevalence of CKD in the general population worldwide (estimated about 15%) due to the inherent risk factor of cardiovascular disease. In fact, in the United States, data from USRDS shows that about 29% of patients with self-reported cardiovascular disease have CKD.

The impact of eGFR on mortality in CAD patients has been previously evaluated using a single eGFR formula or at most comparing three formulas.[25–31] To date, there is no literature comparing all five eGFR formulas and their ability to predict mortality in patients who undergo CABG.

The 2011 European Society of Cardiology (ESC) guidelines recommended the MDRD and GC formulas for the assessment of renal function in CAD patients.[32] However, according to the more recent ESC guidelines published in 2015, there is no recommended formula.[33] The CKD-EPI formula is considered the gold standard for eGFR by the 2012 Kidney Disease Improving Global Outcomes guidelines (KDIGO).[34] It is also the equation used by the USRDS and recently the CDC to estimate global CKD and end stage renal disease trends. Our report suggests that the most accurate formula in predicting late outcomes are the Mayo and CKD-EPI formulas, thus confirming the results of several previous studies.[29–31] However, these formulas are less widely used and have not been validated in diverse populations.

4.1 | Limitations

There are a few limitations in our study. First, despite it being retrospective in design, data were collected prospectively and recorded in a well-defined database. Second, is the lack of available data on the duration of renal dysfunction. By definition, chronic kidney disease is defined as GFR < 60 ml/min/1.73 m^2 for at least three consecutive months. Our data cannot rule out a component of acute kidney injury associated with the cardiovascular event. Moreover, GFR formulas assume a steady state situation and are less accurate in acute kidney injury. However, this limitation is common to most of the studies estimating GFR in CAD. Our results were adjusted for possible confounding variables, but residual confounding cannot be excluded, and the lack of adjustment for variables not captured in the database may represent a limitation. Data regarding other outcomes such as recurrent myocardial infarction and renal function during the follow-up period were not available.

TABLE 4 Discrimination analysis for 10-years mortality according to different GFR formulas

Formula	NRI	IDI	rIDI
MDRD	3.4% (0.1%–7%), *p* = .061	0.024 (0.017–0.032), *p* < .001	10.6%
CKD-EPI	3.2% (0.6%–7%), *p* = .103	0.029 (0.02–0.037), *p* < .001	12.3%
Mayo	4.2% (0.5%–8%), *p* = .027	0.032 (0.022–0.041), *p* < .001	13.4%
IB	3.4% (0.1%–6.9%), *p* = .059	0.017 (0.011–0.024), *p* < .001	7.8%
CG	3.3% (0.2%–6.8%), *p* = .062	0.018 (0.011–0.024), *p* < .001	7.9%

Abbreviations: CG, Cockcroft–Gault; CKD, chronic kidney disease; CKD-EPI, chronic Kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; IB, inulin clearance–based equation; IDI, integrated discrimination improvement; MDRD, modification of diet in renal disease; NRI, net reclassification improvement; rIDI, relative integrated discrimination improvement.

5 | CONCLUSIONS

In patients who undergo CABG, significant renal dysfunction upon admission is associated with mortality, regardless of the GFR estimation formula used and despite the variability in values using the different formulas. Our data suggest that the Mayo formula may be the most accurate predictor of mortality among patients who undergo CABG. These findings have important implications for everyday clinical practice in risk stratification and management of CAD patients.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.