

Comparative Evaluation of Creatinine- and Cystatin C–Based eGFR Equations in Patients with Ischemic Heart Disease: Implications for Renal Risk Stratification

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ABSTRACT

Background: Renal dysfunction is a common but frequently underrecognized comorbidity in patients with ischemic heart disease (IHD). Accurate estimation of glomerular filtration rate (eGFR) is essential for early identification of chronic kidney disease (CKD), cardiovascular risk stratification, and clinical management. Creatinine-based equations may underestimate renal impairment in cardiovascular patients, whereas cystatin C–based equations may provide greater sensitivity. Aim of the study: To compare creatinine- and cystatin C–based eGFR equations in patients with ischemic heart disease and evaluate their effectiveness in renal risk stratification. **Methods & Materials:** This cross-sectional comparative study was conducted in the Department of Nephrology at Sir Salimullah Medical College and Mitford Hospital from July 2020 to June 2021. A total of 234 participants were enrolled, including 194 patients with diagnosed ischemic heart disease and 40 healthy controls. Renal function was assessed using MDRD, CKD-EPIcr, CKD-EPIcys, and CKD-EPIcr-cys equations. Creatinine- and cystatin C–based equations were compared regarding CKD staging, renal dysfunction detection, and risk reclassification. Statistical analyses included chi-square test, Student's t-test, Friedman test, kappa statistics, and multivariable logistic regression. **Result:** Mean serum creatinine and cystatin C levels were significantly higher in IHD patients than controls, while all eGFR estimates were significantly lower ($p < 0.001$). Cystatin C–based equations showed significantly lower mean eGFR values than creatinine-based equations (57.1 ± 24.7 vs. 66.7 ± 29.1 mL/min/1.73m², $p = 0.001$). Renal dysfunction (eGFR < 60 mL/min/1.73m²) was detected in 52.1% of patients using cystatin C–

based equations compared with 38.1% using creatinine-based equations. CKD-EPIcys newly identified CKD in 24.7% of patients and reclassified 22.2% into higher CKD stages. The strongest agreement was observed between MDRD and CKD-EPIcr ($\kappa = 0.819$), while weak agreement existed between CKD-EPIcr and CKD-EPIcys ($\kappa = 0.199$). Age > 60 years, hypertension, diabetes mellitus, smoking, elevated serum creatinine, and elevated cystatin C were significant predictors of renal dysfunction. **Conclusion:** Cystatin C–based eGFR equations identified substantially more renal dysfunction and higher CKD stages among patients with ischemic heart disease compared with creatinine-based equations. These findings suggest that cystatin C–based assessment may improve early detection of renal impairment and enhance renal risk stratification in cardiovascular patients.

Keywords: Ischemic heart disease, estimated glomerular filtration rate, cystatin C, creatinine, chronic kidney disease

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INTRODUCTION

Estimated glomerular filtration rate (eGFR) is a widely used clinical measure that reflects kidney function by estimating how well the kidneys filter waste products from blood using serum biomarkers such as creatinine and cystatin C. It is commonly applied in cardiovascular patients to detect early renal dysfunction and improve risk stratification in chronic diseases like ischemic heart disease [1]. The global prevalence rate of 9–11% for chronic kidney disease (CKD), often assessed using eGFR-based equations, and approximately 1–2 million people died from CKD [2]. In Bangladesh, the prevalence of CKD in Bangladeshi people of 22.48%, which is higher than the global prevalence of CKD. The prevalence of CKD in females was higher with high heterogeneity in contrast to male participants (25.32% vs. 20.31%) [3]. The estimated glomerular filtration rate is

determined using validated equations based on serum creatinine or cystatin C concentrations. Creatinine is a metabolic byproduct derived mainly from muscle metabolism, whereas cystatin C is produced by all nucleated cells at a relatively constant rate [4]. Both biomarkers are freely filtered through the glomerulus, and their blood levels reflect renal filtration capacity. Equations such as the CKD-EPI formula use these biomarkers to estimate kidney function and identify early renal impairment more accurately in clinical practice [5]. Accurate eGFR estimation plays a crucial role in identifying renal dysfunction early in ischemic heart disease patients, allowing timely intervention, better cardiovascular risk prediction, and improved long-term survival outcomes. Cystatin C-based eGFR often provides stronger prognostic accuracy for cardiovascular events compared to creatinine-based methods [6]. Cystatin C–

based equations are less influenced by age, sex, or muscle mass and therefore provide a more stable and sensitive marker for renal impairment, particularly in cardiovascular patients, where creatinine may underestimate kidney dysfunction [7]. However, cystatin C testing is more expensive, less widely available, and may be affected by inflammatory conditions, thyroid disorders, or steroid use, limiting its routine clinical application in low-resource settings [8]. Significant clinical importance exists in this study because patients with ischemic heart disease frequently exhibit subclinical renal dysfunction that may remain undetected by conventional assessment methods. Accurate estimation of eGFR, particularly through more sensitive biomarkers, may improve early identification of renal impairment, enhance cardiovascular risk stratification, and support more precise therapeutic decision-

making, ultimately contributing to better clinical outcomes and reduced disease-related morbidity and mortality [9]. Existing studies show variability in outcomes due to population differences, inconsistent use of equations, and lack of direct comparison between creatinine- and cystatin C-based eGFR in ischemic heart disease populations, limiting generalizability [10]. There is a clear need for direct comparative evaluation of both biomarkers in ischemic heart disease patients to improve accuracy in renal risk prediction and clinical decision-making, especially in developing countries. The objective of this study was to compare creatinine- and cystatin C-based eGFR equations in patients with ischemic heart disease and to evaluate their effectiveness in renal risk stratification and cardiovascular prognosis prediction.

METHODS & MATERIALS

This cross-sectional comparative study was conducted in the Department of Nephrology at Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh, from July 2020 to June 2021. A total of 234 participants were enrolled, including 194 diagnosed IHD patients and 40 healthy referents. Participants were selected using purposive non-probability sampling.

Inclusion Criteria:

- Age ≥18 years
- Both sexes
- Diagnosed ischemic heart disease including stable angina, old myocardial infarction (MI), post-percutaneous coronary intervention (PCI), post-coronary artery bypass grafting (CABG).

Exclusion Criteria:

- Acute coronary syndrome
- Acute kidney injury
- Malignancy
- Pregnancy
- Cognitive impairment
- Severe systemic illness

Ethical Considerations

Written informed consent was obtained from all participants. Each participant was thoroughly informed about the objectives, procedures, and significance of the study. Participation was completely voluntary, and participants were assured of their right to decline participation or withdraw from the study at any time without facing any disadvantage or obligation. Strict confidentiality of all personal and clinical information was maintained throughout the study period.

Data Collection

Data were collected using a structured predesigned data sheet. Demographic variables including age, sex, body mass index (BMI), body surface area (BSA), blood pressure, cardiovascular risk factors, smoking history, and previous cardiac history were recorded. Venous blood samples were collected in the morning following overnight fasting under aseptic precautions. Serum creatinine was measured using an enzymatic method, while serum cystatin C was measured by latex immunoturbidimetric assay. Serum albumin and other biochemical parameters were measured using standard laboratory techniques.

Renal function was assessed using four eGFR equations:

- Modification of Diet in Renal Disease (MDRD)
- CKD Epidemiology Collaboration creatinine equation (CKD-EPIcr)
- CKD Epidemiology Collaboration cystatin C equation (CKD-EPIcys)
- Combined creatinine–cystatin C equation (CKD-EPIcr-cys)

For comparative evaluation, MDRD and CKD-EPIcr were categorized as creatinine-based equations, while CKD-EPIcys and CKD-EPIcr-cys were categorized as cystatin C-based equations.

Definition of Renal Dysfunction and Risk Stratification

Renal dysfunction was defined as eGFR <60 mL/min/1.73m² according to Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. Chronic kidney disease stages were categorized as:

- ≥90 mL/min/1.73m²
- 60–89 mL/min/1.73m²
- 30–59 mL/min/1.73m²
- <30 mL/min/1.73m²

Renal risk reclassification was evaluated by comparing the number of patients identified with renal dysfunction using creatinine-based versus cystatin C-based equations.

Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 and MedCalc version 13.0. Quantitative variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequency and percentage. Association between categorical variables was determined by using chi square test, and the difference between continuous variables was determined by student t test and Friedman test. Agreement between categorical variables was determined by using kappa test. Multivariable logistic regression analysis was performed to identify predictors of renal dysfunction detected by cystatin C-based equations. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant.

RESULT

The majority of IHD patients were in the 41–50 and 51–60 years age groups (31.4% each), with a higher mean age than controls (53.07±10.49 years). Male participants constituted 67% of cases and 55% of controls. Although BMI and BSA were comparable between groups, both SBP and DBP were higher among IHD patients, with DBP showing significant elevation (p=0.001) (Table I).

Table I
Baseline demographic and clinical characteristics of study population (n=234).

Variables	Healthy referants (n=40)		Case (n=194)		p-value
	n	%	n	%	
Age (years)					
21 - 30	3	7.5	5	2.6	0.081
31 - 40	5	12.5	22	11.3	
41 - 50	12	30	61	31.4	
51 - 60	13	32.5	61	31.4	
>60	7	17.5	45	23.2	
Mean ± SD	49.83 ± 11.49		53.07 ± 10.49		
Gender					
Male	22	55	130	67	0.23
Female	18	45	64	33	
BMI (kg/m ²)					
Mean ± SD	23.07 ± 3.60		23.84 ± 3.68		0.376

BSA (m2)			
Mean ± SD	1.62 ± 0.16	1.59 ± 0.18	0.321
SBP (mmHg)			
Mean ± SD	124.00 ± 9.07	131.98 ± 19.84	0.05
DBP (mmHg)			
Mean ± SD	74.00 ± 7.61	84.07 ± 10.79	0.001

HTN was the leading cardiovascular risk factor among IHD patients (85.1%), followed by diabetes mellitus (59.3%), smoking (48.5%), family history of IHD (44.3%), dyslipidemia (39.2%), and obesity (9.8%) (Figure 1).

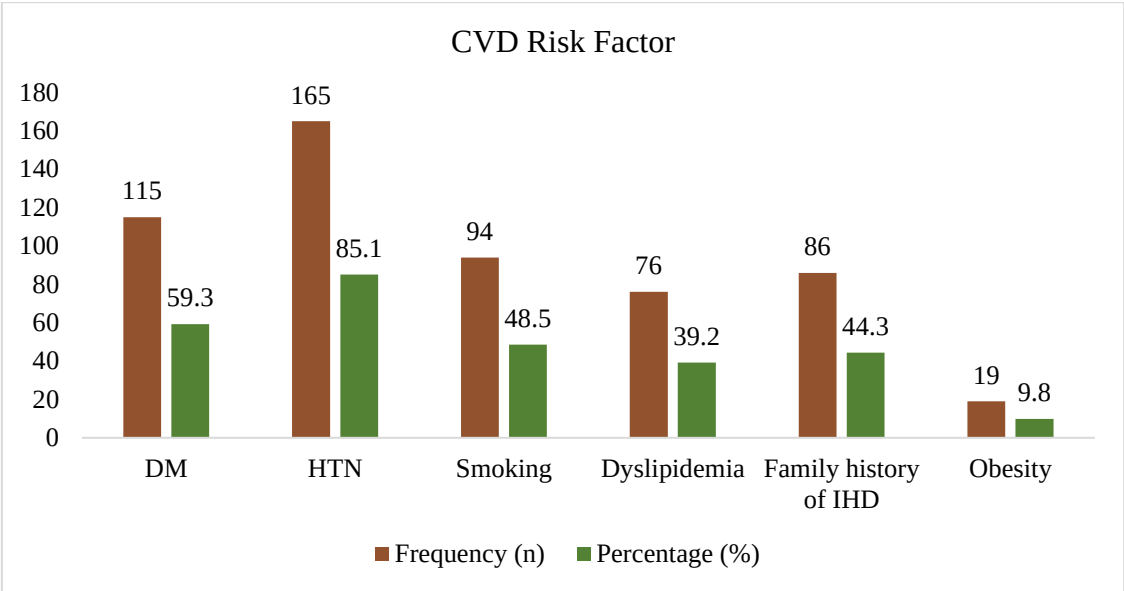


Figure 1 CVD risk factors among participants with IHD (n=194)

Old myocardial infarction represented the predominant IHD subtype (72.7%), whereas stable angina accounted for 27.3% (Figure 2).

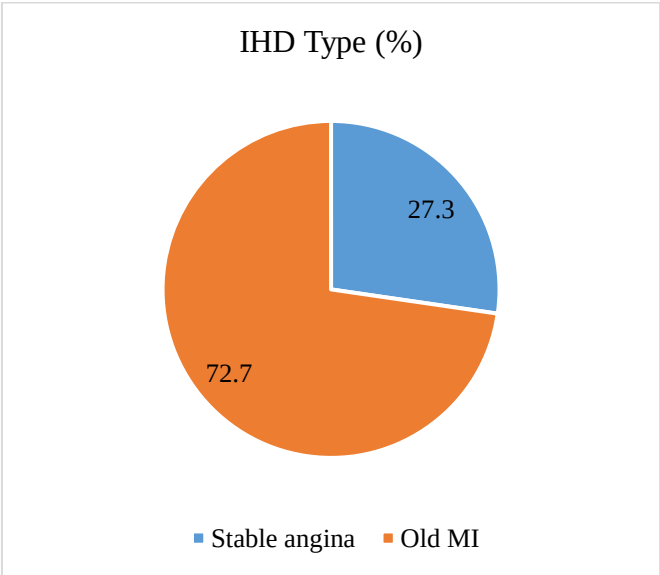


Figure 2 Type of IHD among patients (n=194)

Mean serum creatinine and cystatin C were significantly elevated in IHD patients (1.47±1.20 mg/dL and 1.63±0.80 mg/L) compared with controls. Serum albumin levels were slightly lower in IHD patients,

although the difference was not statistically significant (p=0.068). In contrast, all eGFR estimates were substantially reduced among the IHD group, particularly the CKD-EPIcys (53.0±23.7 mL/min/1.73 m²),

including eGFR-MDRD, with all comparisons showing high statistical significance (p=0.001) (Table II).

Table II

Comparison of renal biomarkers and eGFR estimates among healthy controls and IHD patients.

Variables	Healthy Controls (n=40),	IHD Patients (n=194), Mean	p-value
	Mean $\pm$ SD	$\pm$ SD	
Serum creatinine (mg/dL)	0.84 $\pm$ 0.15	1.47 $\pm$ 1.20	0.01
Serum cystatin C (mg/L)	0.83 $\pm$ 0.11	1.63 $\pm$ 0.80	0.001
Serum albumin (g/dL)	4.41 $\pm$ 0.28	4.23 $\pm$ 0.61	0.068
eGFR-MDRD (mL/min/1.73m ²)	96.2 $\pm$ 16.1	64.4 $\pm$ 28.1	0.001
eGFR-CKD-EPIcr (mL/min/1.73m ²)	107.3 $\pm$ 15.0	68.9 $\pm$ 30.0	0.001
eGFR-CKD-EPIcys (mL/min/1.73m ²)	103.3 $\pm$ 21.3	53.0 $\pm$ 23.7	0.001
eGFR-CKD-EPIcr-cys (mL/min/1.73m ²)	109.4 $\pm$ 12.0	61.1 $\pm$ 25.7	0.001

Significantly lower mean eGFR values using cystatin C-based equations than creatinine-based equations (57.1 $\pm$ 24.7 and 66.7 $\pm$ 29.1). In contrast, cystatin C-based

equations identified more patients within the eGFR 30-59 category (40.2%) and severe in the eGFR 60-89 category (38.1%). Renal dysfunction was detected in 52.1% by

cystatin C equations and 38.1% by creatinine equations (*Table III*).

Table III

Comparative evaluation of creatinine- and cystatin C-based equations in IHD patients (n=194).

Variables	Creatinine-based Equations		Cystatin C-based Equations		p-value
	n	%	n	%	
Mean eGFR (mL/min/1.73m ²)	66.7 $\pm$ 29.1		57.1 $\pm$ 24.7		0.001
eGFR $\geq$ 90	46	23.7	18	9.3	0.001
eGFR 60-89	74	38.1	75	38.7	0.892
eGFR 30-59	58	29.9	78	40.2	0.024
eGFR <30	16	8.2	23	11.9	0.041
Renal dysfunction (<60 mL/min/1.73m ²)	74	38.1	101	52.1	0.002

CKD-EPIcys classified more patients within the 30-59 (45.9%) and <30 category (14.4%) than other equations, whereas

CKD-EPIcr classified more patients in $\geq$ 90 (26.8%) category. But, MDRD shows the highest in 60-89 (39.2%) (*Table IV*).

Table IV

Distribution of chronic kidney disease stages according to different eGFR equations among IHD patients (n=194).

CKD Stage (mL/min/1.73m ²)	MDRD, n (%)	CKD-EPIcr, n (%)	CKD-EPIcys, n (%)	CKD-EPIcr-cys, n (%)
$\geq$ 90	39 (20.1)	52 (26.8)	13 (6.7)	23 (11.9)
60-89	76 (39.2)	73 (37.6)	64 (33.0)	85 (43.8)
30-59	61 (31.4)	55 (28.4)	89 (45.9)	69 (35.6)
<30	18 (9.3)	14 (7.2)	28 (14.4)	17 (8.8)

CKD-EPIcys newly identified CKD in 24.7% of patients and reclassified 22.2% into higher CKD stages. Additionally, 17%

of patients were shifted from eGFR $\geq$ 60 to <60 group. Severe renal dysfunction was newly detected in 4.6% of cases (*Table V*).

Table V

Renal risk reclassification by cystatin C-based equations among IHD patients (n=194).

Variables	Frequency (n)	Percentage (%)
Newly identified CKD cases by CKD-EPIcys	48	24.7
Reclassified to higher CKD stage	43	22.2
Patients shifted from eGFR $\geq$ 60 to <60	33	17
Severe renal dysfunction newly detected (<30)	9	4.6

The highest detection was seen in diabetes mellitus (68.7% and 46.1%). Similar findings were observed in patients with

hypertension (61.2% and 40%), smoking (58.5% and 37.2%), dyslipidemia (57.9%

and 36.8%), and old myocardial infarction (63.1% and 41.8%) (*Table VI*).

Table VI

Comparison of renal dysfunction detection according to cardiovascular risk factors among IHD patients (n=194).

Variables	Creatinine-based Equations		Cystatin C-based Equations		p-value
	n	%	n	%	
Hypertension	66	40	101	61.2	0.002
Diabetes mellitus	53	46.1	79	68.7	0.001
Smoking	35	37.2	55	58.5	0.004
Dyslipidemia	28	36.8	44	57.9	0.012
Old myocardial infarction	59	41.8	89	63.1	0.001

The strongest agreement was observed between MDRD and CKD-EPIcr equations ($\kappa=0.819$). Moderate agreement was found between MDRD and CKD-EPIcr-cys ($\kappa=0.637$) and between CKD-EPIcr and CKD-EPIcr-cys ($\kappa=0.529$). In contrast, the lowest between CKD-EPIcr and CKD-EPIcys ($\kappa=0.199$), despite all comparisons being statistically significant ($p<0.001$) (*Table VII*).

Table VII
Agreement analysis between creatinine- and cystatin C–based eGFR equations in IHD patients.

Comparison	Kappa (κ) Value	p-value
MDRD vs CKD-EPIcr	0.819	<0.001
MDRD vs CKD-EPIcys	0.301	<0.001
MDRD vs CKD-EPIcr-cys	0.637	<0.001
CKD-EPIcr vs CKD-EPIcys	0.199	<0.001
CKD-EPIcr vs CKD-EPIcr-cys	0.513	<0.001
CKD-EPIcys vs CKD-EPIcr-cys	0.529	<0.001

Age >60 years, hypertension, diabetes mellitus, and smoking were significantly associated with renal dysfunction, while serum cystatin C >1.4 mg/L demonstrated the highest predictive value (AOR: 5.84). In contrast, male sex and dyslipidemia were not significantly associated (*Table VIII*).

Table VIII
Multivariable logistic regression analysis for predictors of renal dysfunction identified by cystatin C–based equations.

Variables	Adjusted OR	95% CI	p-value
Age >60 years	2.14	1.18–3.89	0.011
Male sex	1.29	0.72–2.31	0.384
Hypertension	2.87	1.34–6.12	0.006
Diabetes mellitus	2.46	1.39–4.37	0.002
Smoking	1.91	1.07–3.41	0.028
Dyslipidemia	1.63	0.89–2.99	0.113
Serum creatinine >1.2 mg/dL	3.72	1.88–7.36	<0.001
Serum cystatin C >1.4 mg/L	5.84	2.91–11.71	<0.001

DISCUSSION

Renal dysfunction is a frequent yet often underrecognized comorbidity in patients with ischemic heart disease, making accurate estimation of glomerular filtration rate essential for effective risk stratification and clinical decision-making [11]. The IHD cohort was characterized by older age and significantly higher systolic and diastolic blood pressure compared with healthy controls, while BMI and gender distribution remained comparable. This pattern is consistent with the INTERHEART study, which identified hypertension as one of the most powerful global risk factors for coronary artery disease independent of body composition or sex distribution [12]. Similarly, data from the Framingham Heart Study confirmed that blood pressure elevation is a dominant determinant of coronary risk, outweighing anthropometric differences in middle-aged populations [13]. Our demographic distribution mirrors the INTERHEART study, which identified smoking, diabetes, abdominal obesity, and hypertension as critical risk factors for MI across diverse global regions [14]. We observed significantly higher serum creatinine and cystatin C levels in IHD patients, accompanied by marked reductions in eGFR across all equations. Notably, the CKD-EPI cystatin C equation yielded the lowest mean eGFR (53.0 ± 23.7 mL/min/1.73 m²), indicating more severe renal impairment. This is consistent with the landmark CKD Prognosis Consortium meta-analysis, which

demonstrated that cystatin C-based eGFR reclassifies a substantial proportion of individuals into lower GFR categories compared with creatinine and improves prediction of mortality and end-stage renal disease (ESRD) risk [7]. Similarly, Stevens et al. reported that creatinine-based equations systematically overestimate GFR in patients with chronic illness, particularly in cardiovascular patients with altered muscle mass [4]. Our study demonstrates that cystatin C-based equations reduce mean eGFR and increase detection of renal dysfunction (<60 mL/min/1.73 m²: 52.1% and 38.1%). These findings are strongly supported by the CKD-EPI collaborative work, which showed that cystatin C improves classification accuracy and reclassifies up to 16.9% of patients initially categorized as non-CKD by creatinine-based estimates [5]. Additionally, a cardiology group analysis by Lamb et al. demonstrated systematic downward reclassification of GFR using cystatin C in over one-third of hospitalized cardiac patients, similar to our findings [15]. Ntaios et al. reported that in patients with coronary artery disease, cystatin C identified a higher prevalence of hidden CKD compared to creatinine, supporting our observation that 52.1% of patients had renal dysfunction according to cystatin C versus only 38.1% via creatinine [16]. Furthermore, CKD staging analysis shows a clear shift toward more advanced CKD categories when cystatin C is used, particularly increasing the prevalence of Stage 3-4 disease.

Research by Levey et al. introduced the CKD-EPIcr equation to improve accuracy over MDRD [4]. A key finding of our study is that 24.7% of patients were newly classified as CKD using cystatin C, with 22.2% reclassified into higher CKD stages and 17% crossing the clinically important threshold of eGFR <60. Similarly, Peralta et al. demonstrated that cystatin C identifies a high-risk subgroup for CKD by creatinine in only 3.23%, particularly those with intermediate renal impairment, who still carry elevated cardiovascular risk [17]. Our observation that severe renal dysfunction was newly detected in 4.6% of patients aligns with research, which found that cystatin C-based eGFR better identifies patients at risk for end-stage renal disease (ESRD) and all-cause mortality compared to creatinine-based equations [18]. Cystatin C-based equations identified significantly more renal dysfunction among patients with hypertension, diabetes, smoking history, dyslipidemia, and prior myocardial infarction. Likewise, Svensson-Färbom et al. found that cystatin C predicts incident cardiovascular events more effectively than creatinine-based eGFR in middle-aged individuals without prior CVD [19]. Our findings are consistent with the SPRINT trial analysis, which reported that cystatin C is more sensitive than creatinine for detecting early declines in kidney function among hypertensive adults [20]. In patients with old myocardial infarction, cystatin C detected dysfunction in 63.1% of cases compared to 41.8% by creatinine. This

aligns with research by Windhausen et al., which suggests cystatin C is a superior marker for the cardiorenal syndrome frequently seen post-MI [21]. We observed weak concordance between cystatin C and creatinine equations (CKD-EPIcr vs CKD-EPIcys $k=0.199$), indicating substantial disagreement in CKD classification. This is consistent with prior cardiology studies reporting frequent discordance between biomarkers, particularly in hospitalized cardiac populations where creatinine is influenced by muscle mass and acute illness states [15]. The moderate agreement found between CKD-EPIcys and the combined CKD-EPIcr-cys equation ($k=0.529$), is consistent with Inker et al., who demonstrated that the combined equation provides the most accurate GFR estimates by balancing the non-GFR determinants of both markers [5]. Our finding that MDRD vs. CKD-EPIcys had a low Kappa of 0.301 supports the conclusion by Stevens et al. that older equations like MDRD significantly underestimate the prevalence of CKD in cardiac populations when compared to more modern, standardized cystatin C assays [22]. Our findings mirror those of Stevens et al., who established that hypertension and diabetes are the primary drivers of renal decline, and that cystatin C provides a more accurate reflection of this decline across these specific subgroups [22]. The increased risk associated with age in our study is supported by Odden et al., who noted that the discrepancy between creatinine and cystatin C grows with age, primarily due to the loss of muscle mass affecting creatinine levels, a factor less likely to confound cystatin C measurements [23].

LIMITATIONS

- The cross-sectional design prevented assessment of long-term cardiovascular and renal outcomes.
- Serum cystatin C measurement is relatively expensive and less accessible in low-resource settings, which may affect broader clinical applicability.
- Potential confounding factors affecting cystatin C levels, such as inflammatory conditions or thyroid disorders, could not be completely excluded.

CONCLUSION & RECOMMENDATIONS

This study demonstrated significant variability between creatinine- and cystatin C-based eGFR equations in patients with ischemic heart disease. Cystatin C-based equations identified a substantially higher proportion of patients with renal dysfunction and advanced CKD stages compared with creatinine-based equations. A considerable number of patients were

newly classified into higher renal risk categories when cystatin C was incorporated, indicating that creatinine alone may underestimate renal impairment in cardiovascular patients. Factors such as older age, hypertension, diabetes mellitus, smoking, and elevated cystatin C levels were significantly associated with renal dysfunction. Therefore, cystatin C-based eGFR assessment may provide superior renal risk stratification and facilitate earlier detection of kidney dysfunction in patients with ischemic heart disease. Incorporation of cystatin C-based equations into clinical practice may improve cardiovascular and renal prognostic evaluation, particularly among high-risk patients.

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CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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