Introducing chronic kidney disease (CKD) as a frequent complication in patients hospitalized for acute coronary syndrome (ACS) and among the most potent predictors of adverse in-hospital outcomes and long-term mortality. The estimated glomerular filtration rate (eGFR) is the typical standard for the assessment of kidney function. The Cockcroft-Gault equation is a prevalent method for estimating GFR.

**Abstract**

**Aims:** Renal dysfunction is a powerful predictor of adverse outcomes in patients hospitalized for acute coronary syndrome. Three new glomerular filtration rate (GFR) estimating equations recently emerged, based on serum creatinine (CKD-EPI<sub>creat</sub>), serum cystatin C (CKD-EPI<sub>cyst</sub>) or a combination of both (CKD-EPI<sub>creat/cyst</sub>), and they are currently recommended to confirm the presence of renal dysfunction. Our objective was to analyze the predictive value of these new estimated GFR (eGFR) equations regarding mid-term mortality in patients with acute coronary syndrome, and compare them with the traditional Modification of Diet in Renal Disease (MDRD-4) formula.

**Methods and results:** 801 patients admitted for acute coronary syndrome (age 67.3±13.3 years, 68.5% male) and followed for 23.6±9.8 months were included. For each equation, patient risk stratification was performed based on eGFR values: high-risk group (eGFR<60ml/min per 1.73m<sup>2</sup>) and low-risk group (eGFR≥60ml/min per 1.73m<sup>2</sup>). The predictive performances of these equations were compared using area under each receiver operating characteristic curves (AUCs). Overall risk stratification improvement was assessed by the net reclassification improvement index. The incidence of the primary endpoint was 18.1%. The CKD-EPI<sub>cyst</sub> equation had the highest overall discriminate performance regarding mid-term mortality (AUC 0.782±0.20) and outperformed all other equations (ρ<0.001 in all comparisons). When compared with the MDRD-4 formula, the CKD-EPI<sub>cyst</sub> equation accurately reclassified a significant percentage of patients into more appropriate risk categories (net reclassification improvement index of 11.9% (p=0.003)). The CKD-EPI<sub>cyst</sub> equation added prognostic power to the Global Registry of Acute Coronary Events (GRACE) score in the prediction of mid-term mortality.

**Conclusion:** The CKD-EPI<sub>cyst</sub> equation provides a novel and improved method for assessing the mid-term mortality risk in patients admitted for acute coronary syndrome, outperforming the most widely used formula (MDRD-4), and improving the predictive value of the GRACE score. These results reinforce the added value of cystatin C as a risk marker in these patients.

**Keywords**

Acute coronary syndrome, glomerular filtration rate, kidney function, cystatin C, risk stratification, prognosis

**Introduction**

Chronic kidney disease (CKD) is relatively common in patients hospitalized for acute coronary syndrome (ACS) and is among the most powerful predictors of adverse in-hospital outcomes and long-term mortality. The estimated glomerular filtration rate (eGFR) is the clinical standard for the assessment of kidney function. The Cockcroft-Gault equation...
equation, based on serum creatinine concentration, has been the traditional method of estimating GFR. Later, the abbreviated Modification of Diet in Renal Disease (MDRD-4) formula proved to be more accurate in predicting risk in patients with myocardial infarction, and now is the recommended equation for use in daily clinical practice.

In recent years, cystatin C has received much attention as a potential alternative to serum creatinine for estimating kidney function. This low molecular weight basic protein exhibits favourable properties for a renal biomarker such as free filtration by the glomerulus with no reabsorption and, compared with creatinine, it is less influenced by age, gender, diet or muscle mass. In previous studies, it has consistently shown to be a better risk marker than creatinine. However, the lack of cystatin C-based equations has limited its clinical use.

New equations for estimating GFR have been recently published by the Chronic Kidney Disease Epidemiology Collaboration. In 2009, a formula based on serum creatinine (CKD-EPIcreatinine) has emerged but its use in laboratories is very limited. In 2012, an equation based on serum cystatin C (CKD-EPIcystatin) and another combining serum creatinine and cystatin C (CKD-EPIcreatinine and cystatin C) were presented. These equations are currently recommended to confirm the presence of renal dysfunction. However, studies in the area of ACS are still scarce.

The aim of the present study was to analyse the value of these three new eGFR equations in the prediction of midterm all-cause mortality in patients admitted for ACS, and to compare them with the traditional MDRD-4 formula.

**Methods**

**Study population**

One thousand and forty patients were consecutively admitted to the Acute Cardiac Care Unit of a tertiary referral hospital with a diagnosis of ACS between June 2009 and May 2012. Patients in whom baseline blood samples with creatinine and cystatin C were not available (n = 171), those who died during hospitalization (n = 61) or those lost to follow-up (n = 7) were excluded. Overall, 801 patients were included in our analysis.

**Study design**

Using collected baseline data at the time of ACS diagnosis, we retrospectively assessed the eGFR using the 4-variable MDRD formula and three new equations published by Chronic Kidney Disease Epidemiology Collaboration: CKD-EPIcreatinine, CKD-EPIcystatin, and CKD-EPIcreatinine and cystatin C. All the equations incorporate kidney-filtration markers (serum creatinine, cystatin C or both), as well as age, sex, race (Black versus nonBlack), except for the CKD-EPIcystatin equation, for which the data on race are not required.

Serum creatinine was measured by a single laboratory using a method standardized to isotope-dilution mass spectrometry (IDMS), and serum cystatin C was determined by an assay traceable to the International Federation of Clinical Chemistry.

For each equation, patient risk stratification was performed based on the eGFR, and according to the established cut-off that defines CKD. Patients with an eGFR below 60 ml/min per 1.73 m² were included in the high-risk group; an eGFR equal to or greater than 60 ml/min per 1.73 m² classified the patient as low risk.

All equations were evaluated for their overall discriminative performance and a comparison between the best of these three equations and the traditional MDRD-4 formula was performed. The characteristics and outcome of patients reclassified by the new equation into different risk groups were analysed, and the overall risk stratification improvement was estimated.

The predictive power of this new equation was compared with the Global Registry of Acute Coronary Events (GRACE) score and other common risk markers of worse prognosis.

**Study outcome and follow-up**

The primary endpoint was post-discharge all-cause mortality. Patients assigned to this study were followed for 23.6 ± 9.8 months following their hospital discharge. Follow-up data were obtained from clinical records from outpatient clinic, hospital ward and emergency department admission, and through phone calls for patients not followed at our hospital.

**Statistical analysis**

Statistical analysis was done using SPSS, v. 17.0.

We assessed the discriminative performance of each equation by calculating the area under each receiver operating characteristic curve (AUC) by the DeLong method. This parameter quantifies the ability of a specific formula to classify those having an event as high-risk patients and those not having an event as low-risk.

Then, to test the usefulness of the new equations in improving risk stratification compared with the MDRD-4 formula, we analysed the characteristics and outcome of patients who were reclassified to a different risk group (from high-risk to low-risk group and vice versa) by the equation with the highest AUC. To assess the overall improvement in reclassification, we obtained the net reclassification improvement index (NRI), calculated according to the method described by Pencina et al. A positive and significant NRI translates a net overall successful reclassification of subjects into more appropriate risk categories, for example, a patient who reaches the primary endpoint who is reclassified into higher risk group with the new
equation or a subject who does not reach the primary endpoint who is reclassified into a lower risk category with the new equation. The amount of overall reclassification is translated by the extent of the NRI.

Multivariate logistic regression analysis was performed to evaluate whether the highest-performing GFR formula could add prognostic power to the GRACE score.

**Results**

**Baseline characteristics**

Clinical characteristics of the patients are shown in Table 1.

**Risk stratification of patients based on different eGFR equations**

The mean values of eGFR as measured by the MDRD-4 formula, CKD-EPIcreat, CKD-EPIcyst and CKD-EPIcreat/cyst equations were 77.4 ± 31.6, 73.9 ± 27.7, 83.7 ± 34.4 and 79.6 ± 31.7 ml/min per 1.73m² respectively.

The prevalence of patients classified as high-risk (e.g. eGFR < 60ml/min per 1.73m²) ranged between 27.3% (by the CKD-EPIcyst equation) and 30.6% (by the CKD-EPIcreat equation), as illustrated in Table 2.

**Predictive value of each eGFR equation and comparison between them**

During a mean follow-up of 23.6 ± 9.8 months, 18.1% of patients died (n = 145).

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Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67.3 ± 13.3</td>
</tr>
<tr>
<td>Male gender</td>
<td>68.5% (n = 549)</td>
</tr>
<tr>
<td>NonBlack race</td>
<td>100% (n = 801)</td>
</tr>
<tr>
<td>Type of myocardial infarction</td>
<td>NSTE-ACS 55.2% (n=442); STEMI 40.8% (n=327); other 4.0% (n=32)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>74.8% (n = 599)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31.0% (n = 248)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>63.9% (n = 512)</td>
</tr>
<tr>
<td>Smoking habits</td>
<td>34.5% (n = 276)</td>
</tr>
<tr>
<td>Previously known coronary disease</td>
<td>25.3% (n = 203)</td>
</tr>
<tr>
<td>Mean serum creatinine, µmol/l</td>
<td>109.0 ± 109.2 (IQR 68.8–105.3)</td>
</tr>
<tr>
<td>Mean serum cystatin, mg/l</td>
<td>1.10 ± 0.80 (IQR 0.69–1.18)</td>
</tr>
<tr>
<td>Admission Killip–Kimball class &gt; 1</td>
<td>20.0% (n = 160)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>94.9% (n = 760)</td>
</tr>
<tr>
<td>Number of vessels with significant lesions*</td>
<td>1.54 ± 0.96</td>
</tr>
<tr>
<td>Revascularization procedures</td>
<td>81.6% (n = 556)</td>
</tr>
<tr>
<td>GRACE score for in-hospital mortality</td>
<td>134.9 ± 50.6</td>
</tr>
<tr>
<td>GRACE score for six-month mortality</td>
<td>111.1 ± 41.2</td>
</tr>
</tbody>
</table>

*Significant coronary lesion was defined as ≥ 50% stenosis of a major epicardial coronary artery.

NSTE-ACS: non-ST elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; other: patients with previously known left bundle branch block or ventricular pacemaker rhythm; IQR: interquartile range; GRACE: Global Registry of Acute Coronary Events

Table 2. Categorization of patients in high- and low-risk groups according to each eGFR equation.

<table>
<thead>
<tr>
<th>eGFR equation</th>
<th>High-risk group (eGFR &lt; 60ml/min per 1.73m²)</th>
<th>Low-risk group (eGFR ≥ 60ml/min per 1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD formula</td>
<td>29.5% (n = 236)</td>
<td>70.5% (n = 565)</td>
</tr>
<tr>
<td>CKD-EPIcreat</td>
<td>30.6% (n = 245)</td>
<td>69.4% (n = 556)</td>
</tr>
<tr>
<td>CKD-EPIcyst</td>
<td>27.3% (n = 219)</td>
<td>72.7% (n = 582)</td>
</tr>
<tr>
<td>CKD-EPIcreat/cyst</td>
<td>28.3% (n = 227)</td>
<td>71.7% (n = 574)</td>
</tr>
</tbody>
</table>

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; CKD-EPIcreat: Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine; CKD-EPIcyst: CKD-EPI equation based on cystatin C; CKD-EPIcreat/cyst: CKD-EPI equation based on combined creatinine and cystatin C

The rates of the primary endpoint per risk group determined by each equation are reported in Table 3. As expected, the risk of death from any cause was consistently higher in patients included in the high-risk group, regardless of the equation used. All equations predicted this endpoint (p < 0.001). Despite a similar prevalence of patients classified as high-risk between equations, high-risk patients according to the CKD-EPIcyst equation had slightly higher mortality rates compared with high-risk patients according to any of the other formulae.

The discriminatory power of each formula was assessed by calculating the AUC for the primary endpoint (Figure 1, Table 4). The CKD-EPIcyst equation showed the highest predictive value in regard to post-discharge mortality (AUC 0.782 ± 0.20, 95% confidence interval (CI)
Table 3. Post-discharge mortality rate (primary endpoint) according to eGFR equation risk-group stratification.

<table>
<thead>
<tr>
<th>eGFR equation</th>
<th>High-risk group</th>
<th>Low-risk group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(eGFR &lt; 60ml/min per 1.73m²)</td>
<td>(eGFR ≥ 60ml/min per 1.73m²)</td>
<td></td>
</tr>
<tr>
<td>MDRD formula</td>
<td>32.2% (n = 76)</td>
<td>12.2% (n = 69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-EPIcreat</td>
<td>32.7% (n = 80)</td>
<td>11.7% (n = 65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-EPIcyst</td>
<td>39.7% (n= 87)</td>
<td>10.0% (n = 58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-EPIcreat/cyst</td>
<td>37.0% (n = 84)</td>
<td>10.6% (n = 61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; CKD-EPIcreat: Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine; CKD-EPIcyst: CKD-EPI equation based on cystatin C; CKD-EPIcreat/cyst: CKD-EPI equation based on combined creatinine and cystatin C

Figure 1. Receiver operating characteristic (ROC) curves for post-discharge mortality prediction by different glomerular filtration rate estimation equations.

Table 4. Discriminatory power of each formula assessed by the area under each receiver operating characteristic curve for the primary endpoint.

<table>
<thead>
<tr>
<th>Equation</th>
<th>AUC</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD-4 formula</td>
<td>0.679</td>
<td>0.628 – 0.730</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-EPIcreat</td>
<td>0.707</td>
<td>0.660 – 0.754</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-EPIcyst</td>
<td>0.782</td>
<td>0.743 – 0.821</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD-EPIcreat/cyst</td>
<td>0.759</td>
<td>0.718 – 0.801</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AUC: area under each receiver operating characteristic curve; CI: confidence interval; MDRD: Modification of Diet in Renal Disease; CKD-EPIcreat: Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine; CKD-EPIcyst: CKD-EPI equation based on cystatin C; CKD-EPIcreat/cyst: CKD-EPI equation based on combined creatinine and cystatin C

0.743–0.821) and outperformed all other equations (p < 0.001 in all comparisons).

Risk reclassification with the CKD-EPIcyst equation

When compared with the MDRD-4 formula, the CKD-EPIcyst equation reclassified 13.1% of the patients: 5.5% to a higher-risk group and 7.6% to a lower-risk group.

Patients who were reclassified to a higher-risk group by the CKD-EPIcyst equation were more likely to be older (79.5 ± 7.7 vs. 62.5 ± 12.6 years, p < 0.001) and female (45.4% vs. 25.0%, p = 0.003) compared with patients who remained in the low-risk group. In contrast, the patients
reclassified to a lower-risk group by the CKD-EPI\textsubscript{cyst} equation were much younger (70.3 ± 10.5 vs. 77.5 ± 8.8 years, \(p < 0.001\)) and more frequently male (54.1\% vs. 39.4\%, \(p = 0.05\)) than those who were not reclassified.

Reclassification of patients from low-risk to high-risk group by the CKD-EPI\textsubscript{cyst} equation predicted a significantly higher risk of events. The mortality rate of these reclassified patients was similar to the mortality rate of the CKD-EPI\textsubscript{cyst} high-risk group (45.5\% vs. 38.3\%, \(p = 0.386\)), and much higher than the mortality of non-reclassified low-risk patients (45.5\% vs. 9.4\%, \(p < 0.001\)). Conversely, reclassification of patients from high-risk to low-risk group predicted a lower risk of events. The mortality risk of these patients was similar to the CKD-EPI\textsubscript{cyst} low-risk group (14.8\% vs. 9.4\%, \(p = 0.187\)) and much lower than that of non-reclassified high-risk patients (14.8\% vs. 38.3\%, \(p < 0.001\)).

**Overall improvement in reclassification**

Overall, the CKD-EPI\textsubscript{cyst} equation correctly reclassified 11.9\% of cases into risk strata that were more accurate representations of observed mortality risks.

The net improvement estimate for those not reaching the primary endpoint – the difference between patients correctly reclassified as a low risk (\(n = 52\)) and patients incorrectly reclassified as high risk (\(n = 24\)) divided by the total number of patients who did not reach the primary endpoint (\(n = 656\)) – was 4.27\%.

The net estimate for those reaching the primary endpoint – the difference between patients correctly reclassified as high risk (\(n = 20\)) and patients incorrectly reclassified as low risk (\(n = 9\)) divided by the total number of events (\(n = 145\)) – was 7.59\%.

The NRI index was then the sum of these two net estimates: 11.9\% (95\% CI 4.1–19.6\%, \(p\ (2\text{-sided}) = 0.003\)). Cross tabulation between the MDRD-4 formula and CKD-EPI\textsubscript{cyst} equation (according to the level of risk estimated by both), with respective NRI, is described in Table 5.

**Comparison of the predictive value of the CKD-EPI\textsubscript{cyst} equation with that of other common risk markers used in clinical practice**

Multivariate logistic regression analysis showed that the CKD-EPI\textsubscript{cyst} equation (odds ratio (OR) 0.977, 95\% CI 0.970–0.983, \(p < 0.001\)) added prognostic power to the GRACE score (OR 1.015, 95\% CI 1.009–1.022, \(p < 0.001\)) in the prediction of mid-term all-cause mortality in patients admitted for ACS. Comparison of a combined model including CKD-EPI\textsubscript{cyst} equation/GRACE score with the GRACE score alone, through receiver operating characteristic (ROC) curve analysis, revealed that the discriminative value of the former (AUC 0.803 ± 0.19, 95\% CI 0.766–0.841) was greater than that of the GRACE score alone (AUC 0.757 ± 0.21, 95\% CI 0.716–0.798), confirming the additive prognostic utility of the CKD-EPI\textsubscript{cyst} equation.

A Cox regression analysis showed the following variables as independent predictors of mid-term all-cause mortality in these patients: CKD-EPI\textsubscript{cyst} equation (hazard ratio (HR) 0.973, 95\% CI 0.968–0.979, \(p < 0.001\)), age (HR 1.035, 95\% CI 1.014–1.056, \(p = 0.001\)) and left ventricular systolic function (HR 1.342, 95\% CI 1.179–1.528, \(p < 0.001\)), while gender, Killip class, maximum troponin I, haemoglobin level at discharge and number of diseased coronary arteries were not associated with the endpoint.

**Discussion**

In the present study, all new equations for GFR estimation showed good discriminative power in the prediction of post-discharge all-cause mortality in patients with ACS. However, the CKD-EPI\textsubscript{cyst} equation revealed the highest overall discriminative performance and outperformed the most widely used eGFR equation – the MDRD-4 formula. Compared with the MDRD-4 formula, the CKD-EPI\textsubscript{cyst} equation accurately reclassified a significant percentage of patients into more appropriate risk categories. Furthermore, the utility of the CKD-EPI\textsubscript{cyst} equation was revealed by the
fact that it could add predictive value to the mostly widely used prognostic score in these patients – the GRACE score. The use of the CKD-EPI<sub>cyst</sub> equation in daily routine in an Intensive Cardiac Care Unit requires the additional measurement of cystatin C in blood tests and increases laboratory costs only slightly. It is readily obtained, even in smaller community hospitals, and easily calculated through computerized algorithms. Our study suggests that the routine implementation of this equation could improve risk stratification of patients with ACS and potentially lead to more appropriate treatment decisions.

The role of cystatin C as marker of renal function

The high performance of the CKD-EPI<sub>cyst</sub> equation, compared with the MDRD-4 formula and other creatinine-based equations, highlights the value of cystatin C as a biomarker.

In recent years, the interest in cystatin C has been growing. It exhibits favourable metabolic properties (as free filtration in the glomerulus, complete reabsorption and catabolism in proximal tubule and lack of tubular secretion), and so its serum concentration is mainly determined by the GFR. Also, it is little influenced by muscular mass, age, sex or race. Only few less common circumstances have been described to increase the production of cystatin C: liver disease, hyperthyroidism, and high doses of corticosteroids. Therefore, it has been proposed as a more reliable marker of renal function than serum creatinine, in particular in the detection of “preclinical” kidney dysfunction. However, the lack of cystatin C-based eGFR equations has limited its use in clinical practice.

Since the publication of the guidelines of the Chronic Kidney Disease Epidemiology Collaboration a set of studies testing these new formulas have shown that the CKD-EPI equations based on cystatin C – alone or in combination with creatinine – provide a more precise and accurate estimate of GFR than creatinine-based equations. This was also confirmed in studies involving children. Therefore, the use of cystatin C-based equations is currently recommended as a confirmatory test for CKD, namely in patients with mild kidney dysfunction, muscle wasting or chronic illness.

Given that cystatin C is considered a better marker of renal (dys)function, and renal (dys)function is a prognostic marker in patients admitted with ACS, this may help explain why the CKD-EPI<sub>cyst</sub> equation (followed by the CKD-EPI<sub>creat/cyst</sub> equation) had a better performance in risk stratification in the present study compared with other formulas.

Cystatin C: more than a renal biomarker

The role of cystatin C has not been limited to detection and stratification of CKD. In recent years, it has also emerged as a potential marker of cardiovascular risk.

Cystatin C is an endogenous inhibitor of cathepsins, which are cysteine proteases secreted by all nucleated cells. The dynamic balance between cathepsins and cystatin C modulates the catabolism of proteins and different physiological pathways, as neutrophil chemotaxis and tissue remodelling. The unbalance between these two molecules triggers a set of pathophysiological mechanisms – extracellular matrix degradation, endothelial activation, lipid accumulation in vascular wall – responsible for the genesis and the progression of diseases with a known inflammatory hub, such as atherosclerosis. Some studies have described a positive correlation between elevated cystatin C concentrations and high-sensitivity C-reactive protein and fibrinogen. In this perspective, cystatin C might be a systemic sensitive marker of ongoing inflammatory process that is the leading pathological mechanism promoting several diseases, such as cardiovascular diseases.

Some clinical studies have confirmed this relationship between cystatin C and cardiovascular disease, independently of renal function. Parikh et al. reported that high concentrations of cystatin C were independently associated with cardiovascular risk factors, such as age, body mass index, low high-density lipoprotein cholesterol, and smoking, even in individuals without CKD or microalbuminuria. In a study of Svensson-Färbom et al., including middle-age subjects without a history of cardiovascular disease, cystatin C proved to be a better risk marker for cardiovascular morbidity and mortality than creatinine-based GFR. This relationship has been also demonstrated in elderly patients.

The prognostic role of cystatin C has also been studied specifically in acute patients. Higher levels of plasma cystatin C have been associated with adverse outcomes in patients with ACS. In a study by Acuña et al., involving 203 hospitalized ACS patients, elevated cystatin C values predicted the development of cardiovascular complications (in-hospital heart failure, myocardial infarction and cardiovascular death), and this association was stronger than that of other widely used parameters for estimating renal function (creatinine or GFR) and was maintained even in the group with normal GFR. Also, in patients with heart failure, cystatin C and the two new cystatin C-based equations have shown better prognostic performance than creatinine-only based equations.

Therefore, the prognostic role of cystatin C in ACS patients may be related not only to a more precise measurement of kidney function but also to an association with non-renal factors such as inflammation and atherogenesis, further reinforcing the importance of use of cystatin C-based equations in risk stratification of these patients.

Cystatin C-based GFR equation and risk stratification

In the present study, the new CKD-EPI<sub>cyst</sub> equation outperformed the creatinine-based formulas in risk stratification of patients with an ACS.
Recent studies have shown a better estimate of morbidity and mortality risk when using cystatin C-based equations compared with creatinine-based equations, in a variety of populations: general-population, patients with CKD or heart failure. However, information about the usefulness of these new formulas in patients with ACS is still scarce.

In a study by Abu-Assi et al., including patients with acute myocardial infarction, the CKD-EPI<sub>cyst</sub> and CKD-EPI<sub>crea/cyst</sub> equations were the most accurate for predicting in-hospital mortality, rather than the MDRD-4 and CKD-EPI<sub>crea</sub> equations. A particular finding in our study is the performance of the CKD-EPI<sub>cyst</sub> rather than creatinine-based equations in risk stratification was the confounding effect of non-GFR determinants of serum creatinine (muscle mass, diet and physical activity). Serum creatinine levels are lower than expected for the level of GFR in patients who are in poor health and who are most likely to die. Non-GFR determinants of cystatin C also exist (obesity, inflammation, diabetes), though they enhance the association between cystatin C-based eGFR and the risk of death.

GFR estimating equations based on creatinine concentration

A particular finding in our study is the performance of the two creatinine-based formulas: the CKD-EPI<sub>crea</sub> equation included a slightly higher percentage of patients in the high-risk group compared with the MDRD-4 formula (30.6% vs. 29.5%). According to previous studies, involving the general population, the CKD-EPI<sub>crea</sub> equation was less sensitive but more specific for detecting eGFR < 60 ml/min per 1.73m<sup>2</sup>, leading to a lower prevalence of CKD. This shift of distribution toward higher eGFR by this equation was more evident in younger patients (< 65 years) and females. Our study involves higher-risk patients with a higher mean age and a higher prevalence of males, which may explain the similar percentage of patients with a mean eGFR < 60 ml/min per 1.73m<sup>2</sup>. However, the CKD-EPI<sub>crea</sub> equation still had a better predictive value compared with the MDRD-4 formula, according to the AUC. These results are similar to the study conducted by Morici et al., involving elderly patients (≥ 75 years) with ACS.

Limitations of study

The moderate size of our single-centre sample should be considered the main limitation of this research. Our results should be validated in larger cohorts of patients before routine clinical implementation of the CKD-EPI<sub>cyst</sub> equation.

It is also noteworthy that this study was conducted in an entirely Caucasian population, so our results cannot be extrapolated to mixed race populations.

Patients (n = 171) in whom baseline blood samples with cystatin C were not available were excluded. However, their baseline characteristics (sex, age, cardiovascular risk factors, mean serum creatinine at admission and Killip class) were similar to those of the study patients. Mid-term mortality was also similar between groups.

Furthermore, the creatinine and cystatin C values were collected at the time of ACS diagnosis and therefore they do not reflect a steady state.

Conclusion

The CKD-EPI<sub>cyst</sub> equation provides a novel, widely applicable and apparently improved method for assessing the mid-term mortality risk in patients admitted to hospital with an ACS, compared with the creatinine-based eGFR equations. The new equation improved the predictive value of the GRACE score, reinforcing its potential value in daily clinical practice in an Intensive Cardiac Care Unite. These results further highlight the added value of cystatin C as a risk marker in these patients.

Conflict of interest

The authors declare that there is no conflict of interest.

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