The predictive value of s-cystatin C for mortality after coronary artery bypass surgery

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ABSTRACT

Objectives: To evaluate serum creatinine (s-creatinine) and serum cystatin C (s-cystatin C) levels and estimated glomerular filtration rate (eGFR) at different time points as predictors for mortality in patients undergoing coronary artery bypass grafting (CABG).

Methods: A total of 1638 patients undergoing elective CABG were studied prospectively over a median follow-up of 3.5 years (range, 2.0-5.0 years). Renal function was assessed by a comparison of s-creatinine, s-cystatin C values measured preoperatively and at the lowest postoperative level of renal function. The eGFR was estimated by different formulas: Modification of Diet in Renal Disease, the 2009 Chronic Kidney Disease Epidemiology (CKD-EPI) for s-creatinine, the 2012 CKD-EPI formula for s-cystatin C, the 2012 CKD-EPI formula for s-cystatin C and s-creatinine in combination, and the Caucasian Asian, Pediatric, and Adult subjects formula for s-cystatin C. Cox proportional hazards model analysis and C-statistics were used to evaluate independent predictors of mortality and to assess the predictive ability of the different renal function measures.

Results: The 30-day mortality was 0.8%. Overall survival was $96.1\% \pm 0.4\%$ at 2 years and $90.0\% \pm 1.2\%$ at 5 years. Preoperative s-cystatin C showed greater predictive power than s-creatinine for overall mortality (area under the curve, 0.794 vs 0.653). Preoperative s-cystatin C (hazard ratio [HR], 1.65; 95% confidence interval [CI], 1.36-1.99) and eGFR based on s-cystatin C (HR, 0.96; 95% CI, 0.95-0.98), were both independent predictors of mortality. The unadjusted HR for mortality comparing the lowest preoperative cystatin C quintile (Q1) with Q4-Q5 were as follows: Q1 versus Q5, HR, 2.0; 95% CI, 1.6-2.5 ($P < .001$); Q1 versus Q4, HR, 1.6; 95% CI, 1.2-2.2 ($P = .005$).

Conclusions: The s-cystatin C level and s-cystatin C-based eGFR measured preoperatively are strong predictors for mortality after elective CABG. (J Thorac Cardiovasc Surg 2016;152:139-46)

Area under the curve comparison between preoperative s-cystatin C, s-creatinine, and their corresponding eGFR estimates for mortality.

Central Message

S-cystatin C levels and s-cystatin C-based eGFR measured preoperatively are strong predictors for mortality after elective CABG.

Perspective

Renal dysfunction has a major impact on mortality following cardiac surgery, however this is traditionally assessed by s-creatinine with inherent limitations. Emerging data shows the advantages of using s-cystatin C in different populations for mortality risk prediction. In cardiac surgery, however there is scarce documentation on the value of s-cystatin C compared to s-creatinine.

See Editorial Commentary page 147.

Preoperative renal insufficiency has been shown to be independently associated with acute kidney injury (AKI) and increased mortality after cardiac surgery.¹⁻⁴ Previous

studies of patients undergoing coronary artery bypass grafting (CABG) have generally relied on serum creatinine (s-creatinine) to determine preoperative renal function, and even small increments of s-creatinine have been shown to be associated with impaired survival.^{5,6} However, s-creatinine has well-known shortcomings as a measure of renal function, and its levels may not change

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Abbreviations and Acronyms

AKI	= acute kidney injury
AUC	= area under the curve
CABG	= coronary artery bypass grafting
CAPA	= Caucasian Asian, Pediatric, and Adult
CDK-EPI	= Chronic Kidney Disease Epidemiology
CI	= confidence interval
eGFR	= estimated glomerular filtration rate
HR	= hazard ratio
ICU	= intensive care unit
LVEF	= left ventricular ejection fraction
MDRD	= Modification of Diet in Renal Disease
s-creatinine	= serum creatinine
s-cystatin C	= serum cystatin C

until glomerular filtration rate (GFR) is reduced by approximately 50%.^{7,8}

Serum cystatin C (s-cystatin C), an alternative eGFR marker,⁹ is a low molecular weight protein that is freely filtered through the glomerular membrane and metabolized in the proximal tubules.¹⁰ In contrast to s-creatinine, s-cystatin C is produced by all nucleated cells and released continuously to the circulation. S-cystatin C has been suggested as a more sensitive marker for determining impaired eGFR,¹¹ because its levels are not significantly affected by sex, race, muscle mass, infection, liver disease, or inflammatory disease, and it is not secreted by the renal tubules.^{11,12} S-cystatin C-based equations for estimating eGFR with simpler formulas than those used for s-creatinine-based eGFR have been introduced in recent years, but have received only limited validation.¹¹ There also has been a lack of standardized calibration for analyzing cystatin C levels. An international standardized calibration method for s-cystatin C was presented in 2010.¹³ Recently, 2 equations have been presented according to the new standardized calibration method and validated in larger cohorts with either plasma inulin clearance or plasma iothexol clearance as a reference and with better performance in eGFR estimation compared with previous s-cystatin C-based GFR estimates (eGFR_{cystatin C}) the 2012 CKD-EPI eGFR_{cystatin C} presented by Inker and colleagues¹⁴ and the Caucasian and Asian Pediatric and Adult subjects (CAPA) formula presented by Grubb and colleagues.¹² Furthermore, it has been shown that the combination of s-creatinine and s-cystatin C GFR estimates (eGFR_{cystatin C + creatinine}) may provide a better eGFR estimate compared with eGFR_{cystatin C} or eGFR_{creatinine} alone in elderly patients and patients with chronic kidney disease.^{15,16} S-cystatin C and its eGFR estimates have been shown to independently predict mortality in

several patient cohorts, including patients with acute coronary syndrome,^{17,18} patients undergoing heart resynchronization therapy,¹⁹ patients with cardiovascular morbidity and mortality without cardiovascular history,²⁰ elderly patients with impaired kidney function,²¹ and patients in intensive care units (ICUs).²² However, the benefits of using s-cystatin C for predicting mortality in patients undergoing CABG has not been investigated in detail, however. Ledoux and colleagues²³ previously showed that preoperative eGFR_{cystatin C} provides a better risk assessment for 1-year mortality compared with eGFR_{creatinine} after cardiac surgery including complex procedures. Nonetheless, there are no data available on the time point at which s-cystatin C carries the greatest risk for mortality in patients undergoing cardiac surgery. Furthermore, it has not been shown whether the absolute value of s-cystatin C, eGFR_{cystatin C}, or the combination of cystatin C and creatinine eGFR (eGFR_{cystatin C + creatinine}) is independently associated with mortality in cardiac surgery. The aim of the present study was to investigate the value of preoperative s-cystatin C, independent of the occurrence of postoperative AKI, in identifying those at higher risk of postoperative mortality, in a large cohort of patients undergoing elective CABG.

METHODS**Study Design**

In this prospective study, s-cystatin C was measured in all patients undergoing cardiac surgery at the Department of Cardiothoracic Surgery at Skane University Hospital in Lund, Sweden, between January 1, 2010, and December 31, 2012. The study design and protocol were approved by the local Ethics Committee. All patients who had undergone elective CABG as a sole intervention were included in this analysis. Patients with missing preoperative s-cystatin C or preoperative s-creatinine values were excluded (n = 262), as were patients who had undergone preoperative dialysis (n = 70). The final study cohort included 1638 patients. The renal biomarkers, 1 sample per patient at each time point, were collected preoperatively and at the first, second, and fourth postoperative days. For patients remaining in the ICU because of postoperative complications, the renal biomarkers were assessed on a daily basis. The highest measured postoperative s-creatinine value was considered to correspond to the poorest renal function.

Database Management

Data were collected mainly from the internal quality database, which is continuously updated with data on preoperative, perioperative, and postoperative patient care. The second source of data was collected from the blood bank and the clinical chemistry databases in the hospital. Data on survival and time of death for each patient were checked against the Swedish National Board of Health (Socialstyrelsen) database in December 2014, defining the follow-up period from a minimum of 2 years to a maximum of 5 years.

Measurements of Renal Function

The assessment of renal function was based on the following measurements and formulas: (1) absolute s-creatinine level and 2 different equations (eGFR_{creatinine} according to the Modification of Diet in Renal Disease [MDRD]²⁴ and the Chronic Kidney Disease Epidemiology

[CKD-EPI] formulas²⁵); (2) absolute s-cystatin C level and 2 different eGFR_{cystatin C} equations (the 2012 CKD-EPI as presented by Inker and colleagues¹⁴ and the CAPA equation as presented by Grubb and colleagues¹²); and (3) the combined GFR estimates of s-creatinine and s-cystatin C according to the formula presented by Inker and colleagues.¹⁴ All s-creatinine concentrations were determined using an enzymatic colorimetric method with a 1.4% to 1.7% coefficient of variation. Isotope dilution/mass spectrometry was the reference method for calibration.²⁶ S-cystatin C levels were measured by particle-enhanced turbidimetric immunoassay (Tina-quant; Roche Diagnostics, Basel, Switzerland), with a coefficient of variation of 1.0% to 4.1%.

Surgery and Postoperative Care

Surgery was performed in a standardized manner. All patients underwent on-pump surgery with either cold St. Thomas crystalloid cardioplegia or cold blood cardioplegia administered in the aortic root. Postoperatively, patient circulation was monitored invasively and urinary output was monitored during patient care in the cardiothoracic ICU. The need for diuretics, volume substitute, and transfusion therapy was evaluated in each patient by the physician in charge at the cardiothoracic ICU.

Statistical Analysis

The variables are presented as absolute numbers with percentages, mean with standard deviation or median with interquartile range (25th and 75th percentiles) when the distribution was skewed. Comparisons of means were done using the paired Student *t* test was used. The multivariate Cox proportional hazards model was used to determine independent predictors for mortality. The variables entered in the Cox proportional hazards regression model were age, sex, body mass index, preoperative s-creatinine level, preoperative hemoglobin value, leukocyte particle count, chronic obstructive pulmonary disease, diabetes, unstable angina pectoris, previous cerebrovascular lesion, peripheral vascular disease, ejection fraction, New York Heart association class, use of an intra-aortic balloon pump both preoperatively and postoperatively, perfusion time, atrial fibrillation both preoperatively and postoperatively, sepsis, logarithm of time on a ventilator, logarithm of units of plasma transfusion, postoperative bleeding, mediastinitis, erythrocyte transfusion, platelet transfusion, postoperative stroke, and renal replacement therapy. Stepwise backward elimination revealed the following risk factors as significant: age, left ventricular function (reference left ventricular ejection fraction [LVEF] <30%), logarithm of time in ICU, preoperative hemoglobin, logarithm of units of plasma transfused, and preoperative s-creatinine level. These independent predictors of mortality then formed the final model in which preoperative and postoperative estimates of glomerular function (ie, s-creatinine, s-cystatin C, and eGFR based on the different formulas) were included by substituting the preoperative s-creatinine level with each of the glomerular function estimates, one at a time. The proportional hazards assumption was tested using scaled Schoenfeld residuals. The χ^2 value, adjusted hazard ratio (HR), and 95% confidence interval (CI) were calculated for each predictor. A *P* value < .05 (2-tailed) was considered statistically significant.

The discriminatory ability of preoperative s-cystatin C, s-creatinine, and their corresponding eGFR to predict mortality was analyzed by determining the area under the receiver operating curve (c-index). The preoperative s-cystatin C values were stratified into quintiles and evaluated using Kaplan-Meier estimates of survival. The log-rank test was used to compare the statistical significance of differences between groups. Statistical analyses were performed with Statistica version 12.0 (StatSoft, Tulsa, Okla).

RESULTS

Survival

A total of 1638 patients were analyzed over a median follow-up duration of 3.5 years (range, 2.0-5.0 years).

Follow-up was 100% complete. The 30-day mortality was 0.8%. Overall survival was $96.1\% \pm 0.4\%$ at 2 years and $90.0\% \pm 1.2\%$ at 5 years. There was a significant univariate association between preoperative cystatin C level and 30-day mortality (odds ratio, 1.06; 95% CI, 1.01-1.11; *P* = .015). Overall survival was $96.1\% \pm 0.4\%$ at 2 years and $90.0\% \pm 1.2\%$ at 5 years.

Baseline and Outcome Values

The general characteristics and outcomes of the study cohort are presented in [Tables 1](#) and [2](#). The preoperative and maximum s-creatinine and s-cystatin C values registered together with the corresponding eGFR estimates are presented in [Table 3](#).

Different eGFR Estimates

The s-creatinine-based eGFR formulas resulted in statistically significant higher mean eGFR values compared with the s-cystatin C-based formulas ([Table 3](#)). The MDRD eGFR formula yielded statistically significant higher eGFR values compared with the 2009 CKD-EPI_{creatinine} formula both preoperatively (83.5 ± 22.9 for the MDRD formula vs 81.9 ± 19.0 for 2009 CKD-EPI_{creatinine} formula; *P* < .001) and when calculated at the maximum s-creatinine level postoperatively (68.7 ± 23.7 for the 2009 CKD-EPI_{creatinine} formula vs 72.3 ± 25.8 for the MDRD formula; *P* < .001) ([Table 3](#)). The 2012 CKD-EPI_{cystatin C} formula yielded slightly higher eGFR values preoperatively (66.8 ± 22.6 vs 65.4 ± 20.2 for the CAPA eGFR_{cystatin C} formula; *P* = .03). The eGFR values by these 2 formulas were similar to the postoperative eGFR values, with no statistically significant differences ([Table 3](#)).

Predictors of Mortality

Independent predictors for midterm mortality were age (HR, 1.06; 95% CI, 1.03-1.08; *P* < .001), LVEF <30% (HR, 1.78; 95% CI, 1.08-2.92; *P* < .002), time (logarithm) in ICU (HR, 1.42; 95% CI, 1.08-1.87; *P* = .013), peripheral vascular disease (HR, 1.70; 95% CI, 1.12-2.60; *P* = .013), preoperative hemoglobin (HR, 0.97; 95% CI, 0.96-0.98; *P* < .001), plasma transfusion (HR, 1.83; 95% CI, 1.42-2.36; *P* = .006), and preoperative s-creatinine level (HR, 1.00; 95% CI, 1.00-1.01; *P* = .006). These independent predictors of mortality then formed the final model in which preoperative and postoperative estimates of glomerular function (ie, s-creatinine, s-cystatin C, and eGFR based on the different formulas) were included by substituting the preoperative s-creatinine value with each of the glomerular function estimates, one at a time. The corresponding HRs for mortality for each renal function measure are presented in [Table 4](#).

S-cystatin C proved to be a more powerful predictor for overall postoperative mortality than s-creatinine ([Figure 1](#)). A preoperative cystatin C cutoff value of 0.9

TABLE 1. Preoperative characteristics of the study cohort (n = 1638)

Variable	Value
Age, y, mean $\pm$ SD	67.4 $\pm$ 9.6
Female sex, n (%)	343 (21)
Body mass index, mean $\pm$ SD	27.5 $\pm$ 3.8
Diabetes, n (%)	405 (25)
COPD, n (%)	180 (11)
Anemia, n (%)	142 (9)
Previous vascular surgery, n (%)	81 (5)
Peripheral vascular disease, n (%)	212 (13)
History of cerebrovascular injury, n (%)	150 (9)
LVEF 30%-50%, n (%)	338 (21)
LVEF <30%, n (%)	115 (7)
Previous myocardial infarction, n (%)	798 (49)
EuroScore I, additive, mean $\pm$ SD	4.3 $\pm$ 3.1
NYHA class, n (%)	
I	522 (32)
II	527 (32)
III	472 (29)
IV	117 (7)
CCS class, n (%)	
I	201 (12)
II	750 (46)
III	525 (32)
IV	162 (10)
IABP before surgery, n (%)	21 (1)
Preoperative hemoglobin, g/L, mean $\pm$ SD	136.4 $\pm$ 15.0

SD, Standard deviation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; IABP, intra-aortic balloon pump.

demonstrated 96.4% sensitivity and 79% specificity in discriminatory accuracy for mortality. Both eGFR values estimated based on s-cystatin C and s-creatinine levels were associated with increased area under the curve (AUC) values compared with crude s-cystatin and s-creatinine levels, and of these 2 values, s-cystatin C based eGFR showed the highest AUC value (AUC, 0.805; 95% CI, 0.763-0.846). The combination s-creatinine and s-cystatin C eGFR formula (eGFR_{cystatin C + creatinine}) showed a good AUC value (AUC, 0.777; 95% CI, 0.714-0.821), but was not superior to s-cystatin C eGFR or s-cystatin C level alone in terms of predictive accuracy.

The associations between preoperative s-cystatin C level stratified by quintile with overall mortality are presented in Figure 2. Patients with a preoperative s-cystatin C level in Q5 had significantly higher mortality compared with those with a level in Q1 to Q4 (Q4 vs Q1 or 2, log-rank $P = .01$; Q5 vs Q1-Q4, log-rank $P < .01$; Q4 vs Q3, log-rank $P = .08$). The unadjusted HRs for mortality comparing the lowest preoperative cystatin C quintile (Q1) to Q4-Q5 were as follows: Q1 versus Q5: HR, 2.0; 95% CI, 1.6 to 2.5 ($P < .001$); Q1 vs Q4: HR, 1.6; 95% CI, 1.2 to 2.2 ($P = .005$).

TABLE 2. Intraoperative and postoperative characteristics of the study cohort (n = 1638)

Outcomes	Value
Use of CBP, n (%)	1638 (100)
Perfusion time, min, mean $\pm$ SD	77.2 $\pm$ 26.2
Cross-clamp time, min, mean $\pm$ SD	46.1 $\pm$ 17.8
IABP after surgery, n (%)	23 (0.014)
Time in the ICU, h, median (IQR)	23 (20-27)
Sepsis, n (%)	10 (0.6)
Myocardial infarction, n (%)	8 (0.5)
Permanent stroke, n (%)	4 (0.2)
Pneumonia, n (%)	18 (1.1)
RRT, n (%)	10 (0.6)
Atrial fibrillation, n (%)	321 (19.6)
Time in ventilator, min, median (IQR)	300 (210-430)
Reoperation for bleeding, n (%)	33 (2.0)
Reoperation for mediastinitis, n (%)	14 (0.9)
RBC transfusion, n (%)	509 (31)
Units of RBC transfused, mean $\pm$ SD	1.2 $\pm$ 2.6
FFP transfusion, n (%)	203 (12.4)
Units of FFP transfused, mean $\pm$ SD	0.51 $\pm$ 2.4
PLT transfusion, n (%)	144 (9.7)
Units of PLT transfused, mean $\pm$ SD	0.22 $\pm$ 0.84

CBP, Cardiopulmonary bypass; SD, standard deviation; IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy; RBC, red blood cell; FFP, fresh-frozen plasma; PLT, platelets.

DISCUSSION

In this single-center prospective analysis of 1638 patients undergoing CABG, we aimed to investigate the value of preoperative s-cystatin C level, independent of the occurrence of postoperative AKI, in identifying those at greater risk for late postoperative mortality. The main finding is that eGFR_{cystatin C} level measured preoperatively is a strong predictor of mortality at 2 to 5 years after cardiac surgery (Figures 1 and 3 and Table 4).

S-Creatinine–Based Measures

Preoperative absolute s-creatinine level failed to independently predict postoperative midterm mortality. The eGFR_{creatinine} values based on the MDRD formula and on the 2009 CKD-EPI formula performed similarly in predicting mortality when s-creatinine was measured at its maximum level (Table 4). To further study the predictive value of s-creatinine and s-creatinine–based eGFR values for mortality, we performed a post hoc analysis in which we calculated the HR of s-creatinine and s-creatinine–based eGFR measured at the first postoperative day. Interestingly the 2 different eGFR_{creatinine} formulas; that is, both the CKD-EPI and MDRD formulas calculated on the first postoperative day were independent predictors of mortality, with similar HRs when renal function was at its lowest measured level. Thus, it seems that the risk assessed by s-creatinine level measured after the first postoperative

TABLE 3. Renal function measures preoperatively and postoperatively by s-creatinine, s-cystatin C, and their different corresponding eGFR

	Number	Mean	Median	Minimum	Maximum	LQ	UQ	SD
A								
S-cystatin C, mg/mL								
Preoperative	1638	1.17	1.07	0.64	7.16	0.94	1.27	0.42
Maximum measured value	1633	1.48	1.28	0.61	6.3	1.08	1.64	0.66
B								
S-creatinine, $\mu\text{mol/L}$								
Preoperative	1638	87.2	81.0	34.0	759.0	70.0	94.0	34.8
Maximum measured value	1637	106.1	91.0	34.0	806.0	76.0	116.0	56.8
C								
MDRD eGFR, mL/min/1.73 m ²								
Preoperative	1638	79	79	6	161	65	93	22
Poorest measured value	1637	68	68	6	172	51	84	24
D								
CKD-EPI _{creatinine} , mL/min/1.73 m ²								
Preoperative	1638	78.2	82	6	121	67	92	19
Poorest measured value	1638	68.7	70	5	123	51	88	25
E								
CKD-EPI _{cystatin C creatinine} , mL/min/1.73 m ²								
Preoperative	1638	73	75	5	124	60	87	21
Poorest measured value	1633	60	61	6	123	44	77	23
F								
CKD-EPI _{cystatin C} , mL/min/1.73 m ²								
Preoperative	1638	67	67	6	124	52	83	23
Poorest measured value	1633	54	53	7	126	37	68	22
G								
CAPA _{cystatin C} , mL/min/1.73 m ²								
Preoperative	1638	68.1	69.3	5	118	57	78	17
Poorest measured value	1633	57.5	59.3	5	113	45	72	20

All eGFR values are standardized to mL/min/1.73 m² of body surface area. LQ, Lower quartile; UQ, upper quartile; SD, standard deviation; MDRD, Modification of Diet in Renal Disease formula; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology; CAPA, Caucasian and Asian Pediatric and Adult.

day is substantial for mortality. This finding is supported by data reported by Lassnigg and colleagues,²⁷ which demonstrated that minimal changes in s-creatinine level early after surgery were associated with an increased risk of mortality. Our findings regarding creatinine-based renal function confirm the results of previous studies that focused on renal function and mortality based on s-creatinine and s-creatinine-based eGFR values that evaluated the peak s-creatinine level or the effect of recovery at discharge.^{1,28-30}

S-Cystatin C–Based Measures

In contrast to preoperative s-creatinine level, preoperative s-cystatin C level was a strong predictor of mortality, in agreement with data reported by Ledoux and colleagues.²³ Those authors showed that preoperative eGFR estimation based on s-cystatin C level may provide a better risk assessment than preoperative eGFR estimation based on s-creatinine level in patients undergoing elective cardiac surgery. In our study, the strongest predictor for mortality was found when the eGFR estimates based on s-cystatin C level were entered into the Cox proportional hazards model rather than on crude levels at all time points

measured. The 2012 CKD-EPI and the CAPA formulas performed similarly at all timepoints, with the only exception that the CAPA formula resulted in slightly lower eGFR estimates.

The relationship between the time point of s-cystatin C measurement and mortality differed from that between s-creatinine measurement and mortality. We found a similar HR for preoperative eGFR_{cystatin C} and postoperative maximum eGFR_{cystatin C}. Bell and colleagues,²² in a study of general ICU patients, identified s-cystatin C level as a predictor of mortality independent of renal function evaluated by s-creatinine measurement. The authors suggested that this finding could be related to the inability of s-creatinine measurement to detect subclinical renal impairment. This explanation may be applicable to our findings as well. We find support for this possibility in a study reported by Lassus and colleagues³¹ of patients with acute heart failure, in which s-cystatin C level was identified as an independent predictor of mortality even in patients with a normal s-creatinine level.³¹ This could indicate that s-cystatin C level predicts the risk of AKI better than s-creatinine level. This is difficult to assess, however, given that the use of AKI as an endpoint is challenging owing to

TABLE 4. Methods of renal measurements preoperatively and postoperatively as predictors for mortality

Variable	P value	HR	95% CI	χ^2
Preoperative measures				
S-creatinine ($\mu\text{mol/L}$)	.0060	1.003	1.001-1.005	7.56
S-cystatin C (mg/L)	.0000	1.646	1.360-1.992	26.11
MDRD eGFR	.0029	0.987	0.979-0.996	8.89
CKD-EPI _{creatinine} eGFR	.0009	0.984	0.975-0.993	11.02
CKD-EPI _{cystatin C} eGFR	.0000	0.965	0.954-0.976	37.87
CKD-EPI _{cystatin C + creatinine} eGFR	.0000	0.973	0.963-0.983	27.29
CAPA _{cystatin C} eGFR	.0000	0.964	0.953-0.976	37.97
Postoperative poorest renal function measures				
s-creatinine ($\mu\text{mol/L}$)	.0002	1.003	1.001-1.005	20.09
s-cystatin C (mg/L)	.0000	1.747	1.461-2.089	37.31
MDRD eGFR	.0005	0.985	0.977-0.993	12.08
CKD-EPI _{creatinine} eGFR	.0001	0.982	0.973-0.993	15.88
CKD-EPI _{cystatin C} eGFR	.0000	0.963	0.951-0.976	30.93
CKD-EPI _{cystatin C + creatinine} eGFR	.0000	0.973	0.962-0.983	24.68
CAPA _{cystatin C} eGFR	.0000	0.963	0.951-0.976	32.15

HR values <1 are due to the indirect relation of eGFR and postoperative mortality, with lower eGFR related to higher mortality. HR, Hazard ratio; CI, confidence interval; MDRD, Modification of Diet in Renal Disease formula; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology; CAPA, Caucasian and Asian Pediatric and Adult.

varying definitions and the dichotomous nature of the variable. Nonetheless, a study by Shlipak and colleagues³² found a strong association between preoperative s-cystatin C level and postoperative AKI as defined by the Acute Kidney Injury Network criteria. Whether s-cystatin C is a

	AUC	95% CI
Cystatin C	0.794	0.751-0.838
CKD-EPI CyC eGFR	0.805	0.763-0.846
Creatinine	0.653	0.593-0.713
CKD-EPI Creat eGFR	0.702	0.649-0.755
CKD-EPI CyC+Creat eGFR	0.777	0.734-0.821

FIGURE 1. Area under the curve (AUC) comparison between preoperative s-cystatin C, s-creatinine, their corresponding GFR estimates, and the combined GFR estimate of s-creatinine and s-cystatin C for overall mortality. CKD-EPI, Chronic Kidney Disease-Epidemiology; CyC, cystatin C; eGFR, estimated glomerular filtration rate; creat, creatinine; CI, confidence interval.

FIGURE 2. Preoperative s-cystatin C quintiles and all-cause mortality. Cutoff points for s-cystatin C quintiles are <0.91, 0.91 to 1.02, 1.02 to 1.15, 1.15 to 1.35, and >1.35 mg/L. For comparison among quintiles, there were significant differences among quintiles 1, 2, and 4 (log-rank $P < .01$) and among quintiles 1, 2, 3, 4, and 5 (log-rank $P < .001$).

strong predictor for mortality owing to isolated renal impairment, or whether other mechanisms play a role as well, is beyond the scope of this study. However, given the robust documentation of s-cystatin C measurements, it is likely that our strong findings in favor of s-cystatin C and its eGFR estimates are explained by the superiority of this method for assessing renal function and its impact on survival. In our opinion, our results indicate that eGFR_{cystatin C} is a powerful independent preoperative predictor of mortality, which can aid clinicians in risk

FIGURE 3. Forest plot for preoperative different GFR estimates and 2 to 5-year mortality with HR (95% CI). HR values <1 are due to the indirect relationship of eGFR and postoperative mortality, with lower eGFR related to higher mortality. CAPA, Caucasian and Asian Pediatric and Adult subjects; CyC, cystatin C; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology; creat, creatinine; MDRD, Modification of Diet in Renal Disease formula; HR, hazard ratio.

stratification and optimization of patients preoperatively and perioperatively.

Combination of S-Cystatin C and S-Creatinine eGFR Estimates

The $\text{eGFR}_{\text{cystatin C} + \text{creatinine}}$ values were calculated at different time points according to the CKD-EPI 2012 formula presented by Inker and colleagues.¹⁴ The discriminatory ability for mortality based on this combination was, as expected, better than that for $\text{eGFR}_{\text{creatinine}}$ (AUC, 0.777 vs 0.653), but weaker than that for $\text{eGFR}_{\text{cystatin C}}$ (AUC, 0.805). It was previously shown that the combination of s-creatinine and s-cystatin C measurements may produce a more accurate eGFR value in elderly patients, patients with chronic kidney disease, patients treated with corticosteroids, and patients with thyroid disease.^{15,16,33,34} However, other studies reporting measures of outcome have shown that eGFR values based on s-cystatin C alone is superior to the combination formula^{25,35} and a strong predictor of dialysis and impaired survival. This finding is also in line with the findings reported by Astor and colleagues,²⁵ who studied the predictive power of the eGFR estimates of s-creatinine, s-cystatin C, and s-creatinine + s-cystatin C values in a population of more than 6900 adults with a mean follow-up time of 8 years. They concluded that equations based on both s-cystatin C and s-creatinine levels did not predict all-cause and cardiovascular mortality as well as equations based on s-cystatin C level alone. Thus the predictive ability for mortality in the cardiac surgical setting seems to be stronger for eGFR based on s-cystatin C value alone compared with eGFR based on the combination of s-cystatin C and s-creatinine values.

Study Strengths and Limitations

Two major strengths of this study are the relatively large number of patients with prospectively collected data and the homogenous patient population undergoing CABG as a sole intervention. The study's single-center design should be considered an additional strength, because it contributes to limiting heterogeneity and confounding factors such as difference in patient care and sampling point methods for measuring s-creatinine and s-cystatin C levels. A limitation of this study is that, despite the large number of patients included, there were only 114 deaths during the follow-up period, which may be explained by the short follow-up period of 2 to 5 years.

CONCLUSIONS

Preoperative renal insufficiency and postoperative impairment have major impacts on morbidity and mortality after CABG. Traditionally, postoperative renal function at its poorest level has been strongly associated with impaired survival. Our findings identify preoperative evaluation of

renal function based on s-cystatin C level alone as an independent predictor of mortality which, in terms of HR, is comparable with the poorest level of renal function postoperatively. A single preoperative measurement of s-cystatin C is predictive of outcome and potentiates the ability to detect patients at greater risk for mortality before surgery. The association between preoperative s-cystatin C level and postoperative AKI remains to be studied in detail; furthermore, the clinical impact and importance of s-cystatin C level needs to be addressed by future studies.

Conflict of Interest Statement

L.A. lectures for Orion Pharma AB and Abbott Scandinavia AB. H.B. reports grant support from Novo Nordisk and Neurovive Pharmaceutical, and consultant fees from Boston Scientific. All other authors have nothing to disclose with regard to commercial support.

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