ORIGINAL RESEARCH

Association Between Low Muscle Mass and Prognosis of Patients With Coronary Artery Disease Undergoing Percutaneous Coronary Intervention

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BACKGROUND: Low muscle mass has been associated with poor prognosis in certain chronic diseases, but its clinical significance in patients with coronary artery disease is unclear. We assessed the clinical significance of 2 easily measured surrogate markers of low muscle mass: the ratio of serum creatinine to serum cystatin C (Scr/Scys), and the ratio of estimated glomerular filtration rate by Scys to Scr (eGFRcys/eGFRcr).

METHODS AND RESULTS: Patients with coronary artery disease undergoing percutaneous coronary intervention were prospectively enrolled from a single tertiary center, and Scr and Scys levels were simultaneously measured at admission. Best cut-off values for Scr/Scys and eGFRcys/eGFRcr to discriminate 3-year mortality were determined; 1.0 for men and 0.8 for women in Scr/Scys, and 1.1 for men and 1.0 for women in eGFRcys/eGFRcr. The prognostic values on 3-year mortality and the additive values of 2 markers on the predictive model were compared. In 1928 patients enrolled (mean age 65.2±9.9 years, 70.8% men), the risk of 3-year mortality increased proportionally according to the decrease of the surrogate markers. Both Scr/Scys- and eGFRcys/eGFRcr-based low muscle mass groups showed significantly higher risk of death, after adjusting for possible confounders. They also increased predictive power of the mortality prediction model. Low Scr/Scys values were associated with high mortality rate in patients who were ≥65 years, nonobese, male, had renal dysfunction at baseline, and presented with acute myocardial infarction.

CONCLUSIONS: Serum surrogate markers of muscle mass, Scr/Scys, and eGFRcys/eGFRcr may have clinical significance for detecting patients with coronary artery disease at high risk for long-term mortality.

Key Words: coronary artery disease ▪ creatinine ▪ cystatin C ▪ muscle mass

Sarcopenia, an age-related decline in muscle mass and strength, is associated with metabolic disease and increases the risk of cardiovascular morbidity and mortality.[1] The presence of low muscle mass (Low-MM) is the core component of the algorithm to diagnose sarcopenia.[2] Low-MM itself has also been identified as an independent predictor of major cardiovascular events including acute myocardial infarction (MI) and mortality.[3] Therefore, body muscle mass provides important information for the risk stratification and management strategy of patients with coronary artery disease (CAD). Currently, computed tomography (CT), magnetic resonance imaging, dual energy X-ray absorptiometry, and

CLINICAL PERSPECTIVE

What Is New?

- Low muscle mass detected by the ratio of serum creatinine to cystatin C, or the ratio of estimated glomerular filtration rate by cystatin C to creatinine, was a significant predictor of 3-year mortality in patients with coronary artery disease.
- When added to classical risk factors, low muscle mass significantly increased the predictive and discriminative power of the multivariate model for the risk of 3-year mortality.
- The low muscle mass group was associated with a higher risk of mortality, especially in patients who were ≥65 years, nonobese, male, had renal dysfunction at baseline, and presented with acute myocardial infarction.

What Are the Clinical Implications?

- As an easily measurable and noninvasive biomarker of body muscle mass and mortality of patients with significant coronary artery disease, ratio of serum creatinine to cystatin C and ratio of estimated glomerular filtration rate by cystatin C to creatinine may provide important information for predicting the prognosis and establishing a secondary prevention plan for patients with coronary artery disease.
- The effects of interventions for the increase of muscle mass, such as exercise training and nutritional support, should be identified in future studies.

Nonstandard Abbreviations and Acronyms

BCV	best cut-off values
eGFR	estimated glomerular filtration rate
Low-MM	low muscle mass
Scr	serum creatinine
Scys	serum cystatin C

bioelectrical impedance analysis are used to quantitatively measure the amount of muscle mass.[4] However, these methods require specific devices and have limitations such as exposure to radiation and lack of cost-effectiveness.[5]

Recently, the ratio of 2 components, serum creatinine (Scr) and cystatin C (Scys), indices of renal function, has been proposed as a surrogate marker for muscle mass.[5] Creatinine is an endogenous product released from muscles, and its blood concentration is dependent on muscle mass.[6] Cystatin C is a small nonionic protein that is secreted by all nucleated cells;

therefore, its production and tubular secretion are uniform and not affected by muscle mass.[7] The ratio of Scr over Scys (Scr/Scys) has been reported to be a simple surrogate marker of muscle mass[5] as well as a predictor of adverse outcomes in various populations.[8,9] Furthermore, according to the hypothesis regarding lesser effect by age and sex than Scr/Scys, the ratio of estimated glomerular filtration rate (eGFR) by Scys to Scr (eGFRcys/eGFRcr) has been recently reported to be a novel biomarker of Low-MM that predicts mortality in patients with hepatocellular carcinoma.[10] However, the prognostic implication of Low-MM surrogate markers in patients with CAD has not been reported to date. In this study, we investigated the clinical significance of these 2 serum biomarkers of Low-MM, Scr/Scys, and eGFRcys/eGFRcr, as predictors of long-term mortality in patients with CAD who underwent percutaneous coronary intervention (PCI).

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

The study population was enrolled from a single-center, all-comers registry that recruited patients with CAD who underwent PCI with second-generation drug-eluting stents at Seoul National University Hospital, a tertiary referral center in South Korea. From 2007 to 2014, 3365 consecutive patients with significant CAD who underwent PCI with second-generation drug-eluting stents were prospectively enrolled without any exclusion criteria. Of these patients, a total of 1928 agreed to undergo additional blood tests including Scys and underwent follow-up for 3 years. The rate of follow-up loss was 1.6% (3 patients) (Figure 1). All patients underwent PCI according to current standard techniques. Unless there was an undisputed reason for discontinuing dual antiplatelet therapy, all patients were advised to take aspirin indefinitely and clopidogrel for at least 6 months after the index procedure. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (C-1404-052-571) and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data Collection, Follow-Up, and Study End Point

We recorded demographic data, presence of underlying diseases, clinical presentation, treatment details,
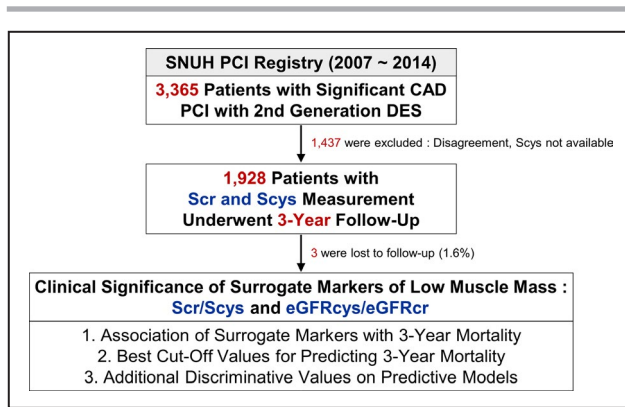
Figure 1. Study flow.
The design of study and the establishment of study population are described. CAD indicates coronary artery disease; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; Scr, serum creatinine; Scys, serum cystatin C; and SNUH, Seoul National University Hospital.

and laboratory test results before the PCI. Scr and Scys levels were measured on admission before coronary angiography, and blood tests were conducted as routine practice by a laboratory center certified by The Korean Association of Quality Assurance for Clinical Laboratory. The eGFR value was calculated based on each Scr and Scys level using the Chronic Kidney Disease Epidemiology Collaboration formulas. The details about measurement and calibration of Scr and Scys, and calculation of the Scr- and Scys-based eGFR are described in Data S1. After the index PCI, follow-up examinations were performed at 1, 3, 9, and 12 months and annually thereafter for up to 3 years. Dedicated research personnel collected clinical outcome at each outpatient visit of each patient; other data were collected through telephone interviews. All clinical data were collected using a centralized Web-based database. All relevant clinical events were reviewed by a separate adjudicating committee.

The primary outcome was all-cause mortality up to 3 years after PCI. Using the unique individual identification numbers of the Korean nationwide healthcare system, the vital status of all participants was cross-checked. The median follow-up duration of the study population was 1195.0 days (Q1–Q3, 1168.0–1209.0 days).

Statistical Analysis

Data are presented as numbers and frequencies for categorical variables, and as mean±SD for continuous variables. For comparisons between groups, the χ^2 test or Fisher's exact test was used for categorical variables, and an unpaired Student t test was used for continuous variables, as appropriate. The relationships between Scr/Scys or eGFRcys/

eGFRcr and 3-year mortality were plotted using the estimated hazard values from Cox proportional hazards model. The best cut-off values (BCV) of surrogate markers were determined by Mann–Whitney U statistics to estimate the maximal area under the time-dependent receiver operating characteristic curve. Using the BCVs for Scr/Scys and eGFRcys/eGFRcr, we separated the study population into Low-MM and Normal-MM groups. The chronological trend of outcomes was expressed as Kaplan-Meier estimates, and these were compared by Scr/Scys- and eGFRcys/eGFRcr-based Low-MM groups. The log-rank test was used to compare differences in clinical outcomes between the groups. A multivariate Cox proportional hazards model was used to adjust for baseline differences and to identify statistically significant predictors of 3-year all-cause death. The assumption of proportionality was examined using log-minus-log plot for each surrogate marker. The covariates included in the multivariate analysis were selected if they were associated with mortality with a P value <0.1 in univariate analysis, or if they were assumed to have predictive value, which are as follows: age, sex, body mass index (BMI), left ventricular ejection fraction, presentation with acute MI, presence of left main CAD, and baseline renal dysfunction (eGFR<60 mL/min per 1.73 m^2) by Scr-based Chronic Kidney Disease Epidemiology Collaboration equation. The unadjusted and adjusted hazard ratios with 95% CI are presented as summary measures. We calculated the Harrell's C-index, category-free net reclassification improvement, risk category-based net reclassification improvement, and integrated discrimination improvement to evaluate and compare the predictive value of predictive models before and after adding Low-MM. Subgroup analysis according to various demographic features and clinical risk factors was performed. Two-sided P values <0.05 were considered statistically significant. Statistical tests were performed using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY) and STATA software, version 16 (StataCorp., College Station, TX).

RESULTS

Baseline Characteristics of Study Population

Of 3365 eligible patients, a total of 1928 patients with significant CAD who underwent PCI were analyzed. The comparison of baseline characteristics between study participants versus nonparticipants are presented in Table S1. Mean age was 65.2±9.9 years, and 70.8% were men. The proportion of patients with diabetes mellitus and hypertension was 40.1% and 68.5%, respectively, and 8.3% of patients

underwent PCI for acute MI. All patients received PCI with second-generation drug-eluting stents and the procedural success rate was 99.7%. Patients with baseline renal dysfunction determined by Scr- and Scys-based Chronic Kidney Disease Epidemiology Collaboration equations were 18.0% and 13.4%, respectively (Table 1).

The 3-year follow-up showed 102 (5.3%) deaths, which was associated with risk factors such as advanced age, diabetes mellitus, history of stroke, acute MI presentation, 3-vessel disease, and in-stent restenosis. The death group also showed significantly lower body weight, BMI, and poor renal function than the survival group (Table S2).

Prognostic Significance of Scr/Scys and eGFRcys/eGFRcr

Figure S1 illustrates the association between Scr/Scys, eGFRcys/eGFRcr, and the 3-year mortality rate. As the surrogate markers of muscle mass decreased, mortality risk increased proportionally. We calculated the BCVs of the surrogate markers stratified by sex, considering the different distribution of surrogate markers between men and women (Figure S2). The BCVs for discriminating 3-year mortality by the time-dependent receiver operating characteristic method was 1.0 for men and 0.8 for women in Scr/Scys, and 1.1 for men and 1.0 for women in eGFRcys/eGFRcr (Figure S3 and S4).

We compared the baseline characteristics and 3-year mortality between the Low-MM and Normal-MM group divided by each BCV. Patients in the Low-MM group were older, nonobese, and had a higher proportion of risk factors including diabetes mellitus, intervention for in-stent restenosis, and lower left ventricular ejection fraction (Table 1 and Table S3). The rate of 3-year mortality was significantly higher in both the Scr/Scys- and eGFRcys/eGFRcr-based Low-MM groups than in the Normal-MM groups (Figure 2A and 2B). The assumption of proportionality was satisfied for both markers (Figure S5). This difference remained significant even in multivariate analysis adjusting for possible confounding factors (Table 2).

Additive Predictive and Discriminative Value of Surrogate Markers of Muscle Mass

We developed a multivariate Cox proportional hazards model from this study cohort that estimates 3-year mortality of patients with significant CAD. The reference model included age, sex, BMI, left ventricular ejection fraction, acute MI, presence of left main CAD, and baseline renal dysfunction. We analyzed additional predictive and discriminative power of this model according to the presence of Low-MM. The Harrell's C-index increased to 0.803 (95% CI,

0.757–0.848) and 0.804 (95% CI, 0.758–0.851) when Scr/Scys- and eGFRcys/eGFRcr-based Low-MM was added to the model, respectively (Table 3). Based on the category-free net reclassification improvement and integrated discrimination improvement, both surrogate markers significantly increased the discriminative power. After stratifying the study population into 6 risk categories (<5%, 5% to <10%, 10% to <15%, 15% to <20%, 20% to <25%, and ≥25% of predicted 3-year mortality risk), the addition of Scr/Scys- and eGFRcys/eGFRcr-based Low-MM on the reference model significantly improved the reclassification performance of the model with estimated category-based net reclassification improvement of 21.3% (95% CI, 1.7–35.4) and 33.9% (95% CI, 12.5–50.1), respectively. (Table 4).

Subgroup Analysis

Exploratory subgroup analysis was performed according to the demographic features and risk factors (Figure 3). The increased risk of 3-year mortality in the Scr/Scys-based Low-MM group was consistent across all subgroups without any significant interaction. The cumulative incidence rate of 3-year mortality was particularly high when Low-MM was associated with old age, nonobesity, male, baseline renal dysfunction, or acute MI presentation.

DISCUSSION

Importance of Detecting Low-MM in Patients With CAD

Sarcopenia is defined as decreased mass and function of the skeletal muscle. It is an important factor that increases the risk of cardiovascular morbidity and mortality.[1] The presence of Low-MM constitutes the most critical step in the diagnostic algorithm of sarcopenia[2] and is a strong predictor of major adverse cardiovascular events and mortality in patients with CAD.[11] Recently, Low-MM has been reported to be a cardiovascular risk factor that operates independently of BMI and other traditional risk factors.[12] Further, having Low-MM in the same BMI level suggests a relatively large proportion of adipose tissue.[13] Therefore, Low-MM not only implies a deficiency of nutrition and cardiorespiratory fitness, but may reflect an increased metabolic risk, such that it can independently contribute to the occurrence of future cardiovascular adverse events in patients with CAD.

Notably, having low gluteal muscle mass estimated through anthropometric measures was reported to be closely linked to risk of acute MI.[3] A recent single-center all-comer cohort study also reported that low skeletal muscle mass by CT was a strong predictor of mortality

Table 1. Baseline Characteristics of Study Population According to Muscle Mass Estimated by Ratio of Serum Creatinine to Cystatin C

	Total Population (n = 1928)	Low-MM (n = 428, 22.2%)	Normal-MM (n = 1500, 77.8%)	P Value
Demographics and risk factors				
Men	1365 (70.8%)	282 (65.9%)	1083 (72.2%)	0.011
Age (y)	65.2±9.9	68.2±9.6	64.4±9.9	<0.001
Age ≥65	1086 (56.3%)	287 (67.1%)	799 (53.3%)	<0.001
Hypertension	1321 (68.5%)	301 (70.3%)	1020 (68.0%)	0.361
Diabetes mellitus	774 (40.1%)	195 (45.6%)	579 (38.6%)	0.010
History of MI	168 (8.7%)	47 (11.0%)	121 (8.1%)	0.059
Previous revascularization	395 (20.5%)	88 (20.6%)	307 (20.5%)	0.966
History of cerebrovascular accident	189 (9.8%)	46 (10.7%)	143 (9.5%)	0.456
Dyslipidemia or statin user	1431 (74.2%)	305 (71.3%)	1126 (75.1%)	0.112
Current smoker	419 (21.7%)	107 (25.0%)	312 (20.8%)	0.063
Presented as acute MI	160 (8.3%)	36 (8.4%)	124 (8.3%)	0.924
Left ventricular ejection fraction (%)	59.3±9.3	58.3±11.1	59.7±8.7	0.029
Angiographic and procedural characteristics				
Extent of coronary artery disease				0.479
1-VD	600 (31.1%)	123 (28.7%)	477 (31.8%)	…
2-VD	671 (34.8%)	155 (36.2%)	516 (34.4%)	…
3-VD	657 (34.1%)	150 (35.0%)	507 (33.8%)	…
LM disease	201 (10.4%)	38 (8.9%)	163 (10.9%)	0.235
Multiple target lesions	561 (29.1%)	140 (32.7%)	421 (28.7%)	0.062
Intervention for type B2/C lesion	1647 (85.4%)	357 (83.4%)	1290 (86.0%)	0.181
Intervention for in-stent restenosis	105 (5.4%)	34 (7.9%)	71 (4.7%)	0.010
Intervention for bifurcation lesion	1180 (61.2%)	273 (63.8%)	907 (60.5%)	0.214
Side branch treatment	261 (13.5%)	57 (13.3%)	204 (13.6%)	0.880
Procedural success	1922 (99.7%)	425 (99.3%)	1497 (99.8%)	0.101
Medications at discharge				
Aspirin	1916 (99.4%)	422 (98.6%)	1494 (99.6%)	0.020
Clopidogrel	1906 (98.9%)	423 (98.8%)	1483 (98.9%)	0.952
DAPT	1899 (98.5%)	420 (98.1%)	1479 (98.6%)	0.482
β-blockers	1019 (52.9%)	224 (52.3%)	795 (53.0%)	0.808
ACE inhibitors	246 (12.8%)	63 (14.7%)	183 (12.2%)	0.168
ARBs	743 (38.5%)	152 (35.5%)	591 (39.4%)	0.145
Statins	1716 (89.0%)	364 (85.0%)	1352 (90.1%)	0.003
CCBs	669 (34.7%)	142 (33.2%)	527 (35.1%)	0.453
Body habitus, Scr, Scys, and eGFR				
Body weight, kg	66.0±10.3	63.8±9.7	66.7±10.4	<0.001
BMI, kg/m^2	24.9±2.9	24.6±3.1	25.0±2.9	0.010
Scr, mg/dL	1.11±1.11	0.88±0.64	1.18±1.20	<0.001
Scys, mg/dL	1.00±0.81	1.10±0.81	0.98±0.81	0.004
eGFR, mL/min per 1.73 m^2				
by Scr-based CKD-EPI equation	78.7±23.0	86.7±21.1	76.4±23.0	<0.001
by Scys-based CKD-EPI equation	89.8±26.7	79.3±25.3	92.8±26.3	<0.001
Baseline renal dysfunction				
eGFR <60 by Scr-based CKD-EPI equation	347 (18.0%)	42 (9.8%)	305 (20.3%)	<0.001
eGFR <60 by Scys-based CKD-EPI equation	259 (13.4%)	87 (20.3%)	172 (11.5%)	<0.001

(Continued)

Table 1. Continued

	Total Population (n = 1928)	Low-MM (n = 428, 22.2%)	Normal-MM (n = 1500, 77.8%)	P Value
Scr/Scys	1.10±0.26	0.81±0.14	1.19±0.22	<0.001
eGFRcys/eGFRcr	1.16±0.23	0.90±0.15	1.23±0.19	<0.001

Values are described as numbers (%) or mean±SD.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CCBs, calcium channel blockers; CKD, chronic kidney disease; EPI, Epidemiology Collaboration; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LM, left main; Low-MM, low muscle mass; MI, myocardial infarction; Scr, serum creatinine; Scys, serum cystatin C; and VD, vessel disease.

and major adverse cardiovascular events in 475 patients who underwent PCI.[11] Similarly, a cohort study of >9000 elderly patients who underwent PCI showed poor angiographic features and high long-term cardiovascular mortality in the Low-MM group, which was defined by normal BMI and low Scr.[14] Therefore, the identification of Low-MM in patients with significant CAD requiring PCI has become important in terms of risk stratification and in planning primary or secondary prevention.

There are several methods to quantitatively assess the body muscle mass. One of the traditional and most feasible methods in the clinical setting is to measure 24-hour urinary creatinine excretion.[15] However, the major limitation is the time required for testing and the dependence on patient compliance, which makes this method inconvenient. Currently, direct measurement of skeletal muscle area through CT or magnetic resonance imaging have been established as a standard method for Low-MM detection, while other tests that estimate muscle mass through body composition analysis such as dual energy X-ray absorptiometry or bioelectrical impedance analysis have also been

used.[2,4] However, these tests are expensive, raising the issue of cost-effectiveness, come with radiation hazards, and have limited accessibility prohibiting its widespread use in daily clinical practice and limiting its use for only research purposes.[5] Serum biomarkers have been recently introduced to easily estimate body muscle mass using Scr and Scys, which are indicators of renal function,[5,8] yet the clinical implications of these markers in patient populations with CAD have not been established. Therefore, the evaluation of convenient, easy-to-measure surrogate markers of muscle mass such as Scr/Scys and eGFRcys/eGFRcr to study whether they have added value to predictive models and can stratify the risk of patients with significant CAD who require PCI has profound implications to the clinician.

Clinical Significance of Scr/Scys and eGFRcys/eGFRcr as Biomarkers Detecting Low-MM

Creatinine is a derivative of creatine phosphate, a skeletal muscle protein, which is significantly affected
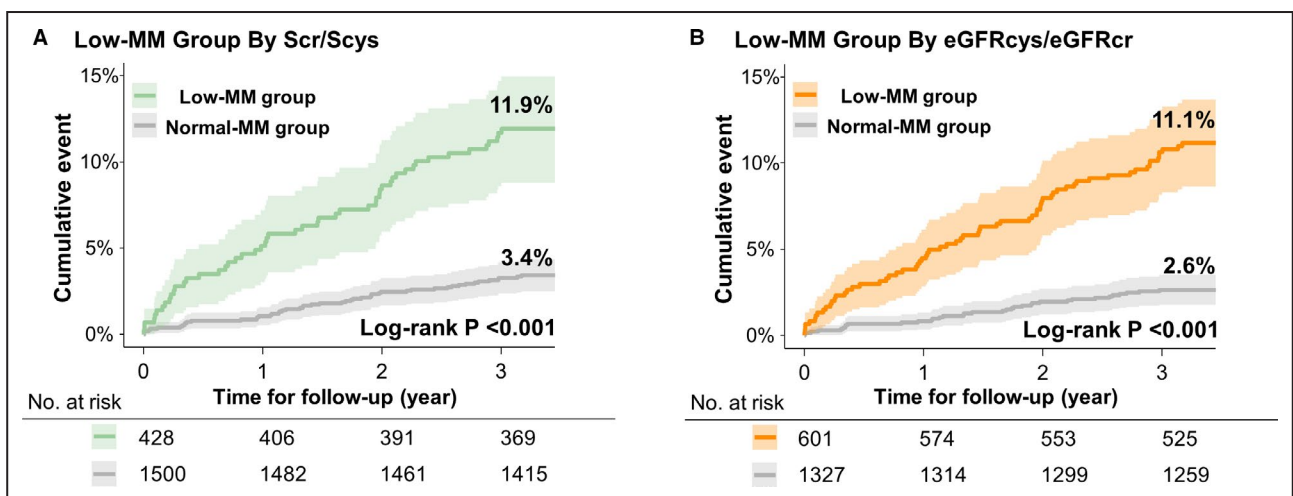
Figure 2. Association of low muscle mass with 3-year risk of all-cause death.
The association of surrogate markers of muscle mass with estimated 3-year mortality risk is presented. The comparison of 3-year mortality between Low-MM and Normal-MM groups defined by the best cut-off values of **(A)** Scr/Scys and **(B)** eGFRcys/eGFRcr is shown. eGFR indicates estimated glomerular filtration rate; Low-MM, low muscle mass; Scr, serum creatinine; and Scys, serum cystatin C.

Table 2. Risk of 3-Year All-Cause Death According to Surrogate Markers of L-MM

	Low-MM Group	Normal-MM Group	Unadjusted HR (95% CI)	P Value	MV-Adjusted HR (95% CI)	P Value
By Scr/Scys			…	…	…	…
Per 0.1 decrease (Continuous variable)	…	…	1.22 (1.13–1.33)	<0.001	1.25 (1.14–1.38)	<0.001
Low-MM (Men <1.0, Women <0.8)	11.9% (51/428)	3.4% (51/1500)	3.67 (2.49–5.41)	<0.001	2.84 (1.91–4.22)	<0.001
By eGFRcys/eGFRcr			…	…	…	…
Per 0.1 decrease (Continuous variable)	…	…	1.38 (1.27–1.52)	<0.001	1.26 (1.16–1.37)	<0.001
Low-MM (Men <1.1, Women <1.0)	11.1% (67/601)	2.6% (35/1327)	4.41 (2.93–6.64)	<0.001	3.78 (2.49–5.73)	<0.001

The covariates included in the multivariate analysis were age, sex, body mass index, left ventricular ejection fraction, presentation with acute myocardial infarction, presence of left main coronary artery disease, and chronic kidney disease ≥stage 3.

eGFR indicates estimated glomerular filtration rate; HR, hazard ratio; Low-MM, low muscle mass; MV, multivariate; Scr, serum creatinine; and Scys, serum cystatin C.

by dietary protein intake and muscle mass as well as age or sex.[6] Cystatin C, on the other hand, is a nonionic protein that is less affected by these factors than creatinine because it is constantly generated from all nucleated cells and is freely permeable and reabsorbable without secretion.[16] As the clinical importance of Low-MM detection has emerged, the Scr/Scys ratio has been proposed as a quantitative surrogate marker that can measure muscle mass independently of renal function.[17] In addition, it is also reported that the Low-MM group defined by Scr and Scys is associated with adverse characteristics and poor outcomes in patients with various disease conditions.[8–10]

In a cohort study of patients in an intensive care unit setting, Scr/Scys was identified as a useful marker showing a strong correlation with the paraspinal muscle mass evaluated by CT.[5] In the same study, Scr/Scys was an independent predictor of mortality that improved the discriminative ability of the clinical model. However, Scr/Scys has been shown to be high in men and to decrease progressively with increasing age.[18] In an external validation study in community-dwelling elderly individuals, the diagnostic performance of Scr/Scys for detecting Low-MM was as low as area under the curve 0.505 to 0.558, when the bioelectrical impedance analysis method was used as a reference standard.[19] In this regard, the eGFR ratio of cystatin C to creatinine (eGFRcys/eGFRcr) has been proposed as an alternative to Scr/Scys based on the hypothesis that it may be less affected by age and sex than Scr/

Scys. In a small cohort study of patients with hepatocellular carcinoma, eGFRcys/eGFRcr was found to be a stronger independent predictor of survival than Scr/Scys.[10]

The results of this study are consistent with previous observations on the surrogate markers of Low-MM. We found that both Scr/Scys and eGFRcys/eGFRcr were significant predictors of the risk of 3-year mortality in 1928 patients with CAD who underwent PCI. Based on the BCV showing maximal discriminative power, the Scr/Scys-based Low-MM group had a mortality risk that was 2.84 times higher than that of the Normal-MM group and 3.78 times higher for the eGFRcys/eGFRcr-based Low-MM group, after adjusting for possible confounding factors. These serum biomarkers increased the predictive and discriminative power of the multivariate model derived from this cohort.

The different characteristics between creatinine and cystatin C may explain these results. Creatinine is predominantly affected by muscle mass and age, whereas cystatin C is associated with body fat mass and waist circumference.[20] Thus, low Scr/Scys and eGFRcys/eGFRcr values, though primarily determined by the reduction in muscle mass, may also reflect an increase of body fat mass. This may be the reason why these indicators have shown such strong correlation with outcome in patients with CAD.

Our results showed that the prognostic values of the 2 biomarkers were comparable, which was consistent after adjusting for confounding factors including age and sex. However, unlike Scr/Scys, there is little evidence on how

Table 3. Additive Discriminative and Predictive Value of Low-MM Group on Mortality Prediction Model

	Harrell's C-Index	Category-Free NRI	P Value	IDI	P Value
Reference model	0.776 (0.728–0.825)	Reference	…	Reference	…
+ Scr/Scys-based Low-MM group	0.803 (0.757–0.848)	0.266 (0.132–0.364)	<0.001	0.035 (0.011–0.072)	<0.001
+ eGFRcys/eGFRcr-based Low-MM group	0.804 (0.758–0.851)	0.342 (0.230–0.443)	<0.001	0.042 (0.017–0.078)	<0.001

eGFR indicates estimated glomerular filtration rate; IDI, integrated discrimination improvement; Low-MM, low muscle mass; NRI, net reclassification improvement; Scr, serum creatinine; and Scys, serum cystatin C.

Table 4. Reclassification of Predicted 3-Year Mortality Risk by the Addition of Low-MM Group on Reference Model

Predicted Risk (reference model)	Reference Model + Scr/Scys-Based Low-MM Group						Reclassified as		Net % Correctly Reclassified	Category-Based NRI (95% CI)
	<5%	5% to <10%	10% to <15%	15% to <20%	20 to <25%	≥25%	Increased Risk	Decreased Risk		
3-y mortality (+)										21.3% (1.7–35.4)
<5%	19	12	0	2	0	0	41.2%	23.5%	17.6%	
5% to <10%	8	5	11	3	0	1				
10% to <15%	1	6	3	3	1	3				
15% to <20%	0	3	5	0	1	2				
20% to <25%	0	0	0	0	0	3				
≥25%	0	0	0	1	0	9				
3-y mortality (−)										
<5%	1102	148	9	1	0	0	14.5%	18.2%	3.7%	
5% to <10%	200	97	50	20	7	0				
10% to <15%	1	81	9	5	9	8				
15% to <20%	0	12	18	3	1	2				
20% to <25%	0	0	5	4	2	5				
≥25%	0	0	0	4	7	16				
Predicted Risk (Reference Model)	Reference Model + eGFRcys/eGFRcr-Based Low-MM Group						Reclassified as		Net % Correctly Reclassified	Cateogry-Based NRI (95% CI)
	<5%	5% to <10%	10% to <15%	15% to <20%	20% to <25%	≥25%	Increased Risk	Decreased Risk		
3-y mortality (+)										33.9% (12.5–50.1)
<5%	18	13	2	0	0	0	52.9%	19.6%	33.3%	
5% to <10%	9	2	14	1	2	0				
10% to <15%	0	4	0	3	6	4				
15% to <20%	0	5	0	0	1	5				
20% to <25%	0	0	0	0	0	3				
≥25%	0	0	0	1	1	8				
3-y mortality (−)										
<5%	1070	183	7	0	0	0	18.7%	19.3%	0.6%	
5% to <10%	229	47	72	24	2	0				
10% to <15%	12	58	2	15	22	4				
15% to <20%	0	21	7	0	3	5				
20% to <25%	0	5	6	1	0	4				
≥25%	0	0	2	8	3	14				

eGFR indicates estimated glomerular filtration rate; Low-MM, low muscle mass; and NRI, net reclassification improvement.

accurately eGFRcys/eGFRcr can reflect body muscle mass. Further studies are required to correlate eGFRcys/eGFRcr with muscle mass and the prognosis in patients with CAD.

Application of Low-MM Biomarkers to the Management of Patients With CAD After PCI

As a noninvasive and cost-effective biomarker of body muscle mass and a useful prognosticator for patients with CAD, Scr/Scys may be useful in various aspects of future clinical practice. Physicians will be able to obtain important information for predicting the prognosis and establishing a primary or secondary prevention plan for patients with CAD if they evaluate Scr and Scys at admission and determine whether a patient fits in the Low-MM group by Scr/Scys values. Furthermore, unlike device-based methods such as CT, magnetic resonance imaging, or dual energy X-ray absorptiometry, measuring for these serum biomarkers can be performed easily in the daily practice setting.[21] We also demonstrated through exploratory subgroup analysis that Scr/Scys
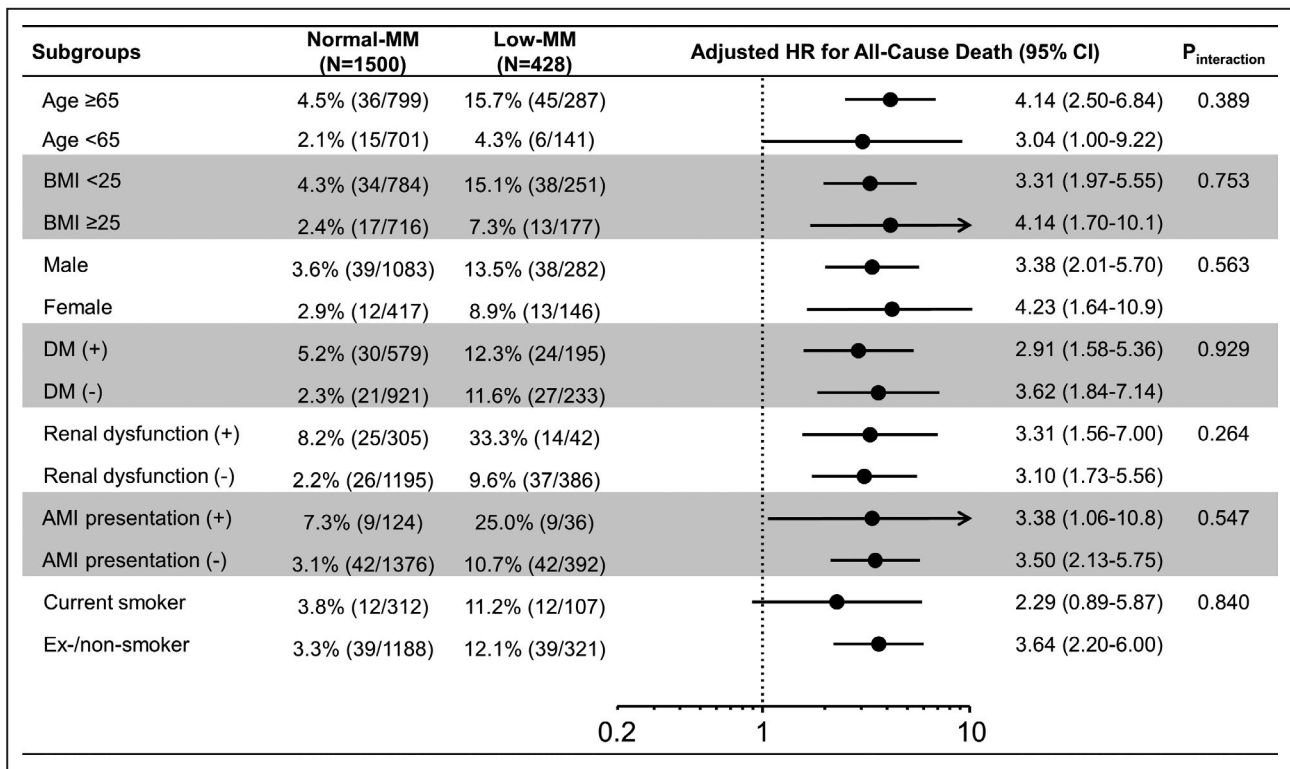
Subgroups	Normal-MM (N=1500)	Low-MM (N=428)	Adjusted HR for All-Cause Death (95% CI)	P interaction
Age ≥65	4.5% (36/799)	15.7% (45/287)	4.14 (2.50-6.84)	0.389
Age <65	2.1% (15/701)	4.3% (6/141)	3.04 (1.00-9.22)	
BMI <25	4.3% (34/784)	15.1% (38/251)	3.31 (1.97-5.55)	0.753
BMI ≥25	2.4% (17/716)	7.3% (13/177)	4.14 (1.70-10.1)	
Male	3.6% (39/1083)	13.5% (38/282)	3.38 (2.01-5.70)	0.563
Female	2.9% (12/417)	8.9% (13/146)	4.23 (1.64-10.9)	
DM (+)	5.2% (30/579)	12.3% (24/195)	2.91 (1.58-5.36)	0.929
DM (−)	2.3% (21/921)	11.6% (27/233)	3.62 (1.84-7.14)	
Renal dysfunction (+)	8.2% (25/305)	33.3% (14/42)	3.31 (1.56-7.00)	0.264
Renal dysfunction (−)	2.2% (26/1195)	9.6% (37/386)	3.10 (1.73-5.56)	
AMI presentation (+)	7.3% (9/124)	25.0% (9/36)	3.38 (1.06-10.8)	0.547
AMI presentation (−)	3.1% (42/1376)	10.7% (42/392)	3.50 (2.13-5.75)	
Current smoker	3.8% (12/312)	11.2% (12/107)	2.29 (0.89-5.87)	0.840
Ex-/non-smoker	3.3% (39/1188)	12.1% (39/321)	3.64 (2.20-6.00)	

0.2   1   10

Figure 3. Subgroup analysis.
The adjusted risk of 3-year mortality by Scr/Scys-based Low-MM group was calculated according to various exploratory subgroups. AMI indicates acute myocardial infarction; BMI, body mass index; DM, diabetes mellitus; HR, hazard ratio; and Low-MM, low muscle mass.

is a reliable marker that can be used regardless of demographic factors including age, sex, and the patient's status for obesity. Furthermore, the Scr/Scys-based Low-MM group exhibited an additive effect on traditional risk factors (eg, old age, male, renal dysfunction, or presentation with acute MI). Therefore, careful screening for the presence of Low-MM may be helpful in these subgroups.

The current guidelines recommend that all patients with CAD be referred to cardiac rehabilitation.[22] However, in real-world practice, the adherence to such recommendations largely varies according to the national policies or medical payment systems.[23] In this regard, the application of serum Low-MM indices to routine practice may help physicians identify select populations that may benefit the most from cardiac rehabilitation. This may also contribute to the effective allocation of medical resources. Furthermore, future studies need to investigate whether interventions to increase muscle mass in the Low-MM group will result in a prognostic benefit. In addition to exercise training and rehabilitation programs, which have been shown to be the most effective intervention to improve sarcopenia-related adverse outcomes, a thorough evaluation of nutritional status and supplementation of protein and vitamin D may be important.[24]

Study Limitations

Several limitations should be discussed. First, the study population was from a single-center registry, and the analysis was retrospective. Second, although the results were consistent after statistical adjustment, the possibility of unmeasured confounding factors, such as a measure of fitness, frailty, waist circumference, fat mass, and the blood cholesterol level, cannot be excluded. Since we used the Scr and Scys values measured at a single timepoint, the unmeasured bias may exist because of the temporal variability of test results and the effect of simultaneous acute kidney injury. Also, there is a possibility of selection bias, since patients who did not agree to have Scr and Scys levels measured at admission were excluded. In particular, the fact that the percentage of patients who presented as acute MI was low in the present analysis and was much higher in the nonparticipants suggests selection bias and is a limitation of the present study. Thus, it is difficult to apply the results of this study to the entire acute MI population. This will require further validations in future studies. Third, we did not validate Scr/Scys and eGFRcys/eGFRcr through direct comparison with muscle mass measured by CT, magnetic resonance imaging, dual energy X-ray absorptiometry, or bioelectrical impedance analysis. However, we aimed to focus

more on the prognostic value of these markers and to derive results that could be helpful in actual clinical practice. Finally, the generalizability of the study results may be limited until an appropriate validation cohort can be found. The results of this study also need to be validated in medically managed patients with CAD. Further studies are warranted to determine whether this result can be extrapolated to larger, ambulatory populations or ethnically diverse populations.

CONCLUSIONS

The Low-MM group detected by Scr/Scys and eGFRcys/eGFRcr was a statistically significant predictor for 3-year mortality in patients with significant CAD. Both Scr/Scys and eGFRcys/eGFRcr were a surrogate marker that can add significant predictive power on the previous model and may be useful for discrimination of and prevention planning for high-risk patients with CAD.

ARTICLE INFORMATION

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Supplementary Material

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REFERENCES

1. Srikanthan P, Karlamangla AS. Muscle mass index as a predictor of longevity in older adults. *Am J Med*. 2014;127:547–553. DOI: 10.1016/j.amjmed.2014.02.007.
2. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc*. 2014;15:95–101. DOI: 10.1016/j.jamda.2013.11.025.
3. Nilsson G, Hedberg P, Leppert J, Ohrvik J. Basic anthropometric measures in acute myocardial infarction patients and individually sex- and age-matched controls from the general population. *J Obes*. 2018;2018:3839482.
4. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39:412–423. DOI: 10.1093/ageing/afq034.
5. Kashani KB, Frazee EN, Kukralova L, Sarvottam K, Herasevich V, Young PM, Kashyap R, Lieske JC. Evaluating muscle mass by using markers of kidney function: development of the sarcopenia index. *Crit Care Med*. 2017;45:e23–e29. DOI: 10.1097/CCM.0000000000002013.
6. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol*. 2008;3:348–354. DOI: 10.2215/CJN.02870707.
7. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29. DOI: 10.1056/NEJMoa1114248.
8. Suzuki K, Furuse H, Tsuda T, Masaki Y, Okazawa S, Kambara K, Inomata M, Miwa T, Matsui S, Kashii T, et al. Utility of creatinine/cystatin C ratio as a predictive marker for adverse effects of chemotherapy in lung cancer: a retrospective study. *J Int Med Res*. 2015;43:573–582. DOI: 10.1177/0300060515579116.
9. Amado CA, Garcia-Unzueta MT, Lavin BA, Guerra AR, Aguero J, Ramos L, Munoz P. The ratio serum creatinine/serum cystatin C (a surrogate marker of muscle mass) as a predictor of hospitalization in chronic obstructive pulmonary disease outpatients. *Respiration*. 2019;97:302–309. DOI: 10.1159/000494296.
10. Tamai Y, Iwasa M, Kawasaki Y, Yoshizawa N, Ogura S, Sugimoto R, Eguchi A, Yamamoto N, Sugimoto K, Hasegawa H, et al. Ratio between estimated glomerular filtration rates of creatinine and cystatin C predicts overall survival in patients with hepatocellular carcinoma. *Hepatol Res*. 2019;49:153–163. DOI: 10.1111/hepr.13230.
11. Kang DO, Park SY, Choi BG, Na JO, Choi CU, Kim EJ, Rha SW, Park CG, Hong SJ, Seo HS. Prognostic impact of low skeletal muscle mass on major adverse cardiovascular events in coronary artery disease: a propensity score-matched analysis of a single center all-comer cohort. *J Clin Med*. 2019;8:712. DOI: 10.3390/jcm8050712.
12. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. *J Am Geriatr Soc*. 2014;62:253–260. DOI: 10.1111/jgs.12652.
13. Park S, Ham JO, Lee BK. A positive association between stroke risk and sarcopenia in men aged >/= 50 years, but not women: results from the Korean National Health and Nutrition Examination Survey 2008–2010. *J Nutr Health Aging*. 2014;18:806–812.
14. Goel K, Gulati R, Reeder GS, Lennon RJ, Lewis BR, Behfar A, Sandhu GS, Rihal CS, Singh M. Low body mass index, serum creatinine, and cause of death in patients undergoing percutaneous coronary intervention. *J Am Heart Assoc*. 2016;5:e003633. DOI: 10.1161/JAHA.116.003633.
15. ter Maaten JM, Damman K, Hillege HL, Bakker SJ, Anker SD, Navis G, Voors AA. Creatinine excretion rate, a marker of muscle mass, is related to clinical outcome in patients with chronic systolic heart failure. *Clin Res Cardiol*. 2014;103:976–983. DOI: 10.1007/s00392-014-0738-7.
16. Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C among different clinical presentations. *Kidney Int*. 2006;69:399–405. DOI: 10.1038/sj.ki.5000073.
17. Tetsuka S, Morita M, Ikeguchi K, Nakano I. Creatinine/cystatin C ratio as a surrogate marker of residual muscle mass in amyotrophic lateral sclerosis. *Neurol Clin Neurosci*. 2013;1:32–37. DOI: 10.1002/ncn3.11.
18. Purde MT, Nock S, Risch L, Medina Escobar P, Grebhardt C, Nydegger UE, Stanga Z, Risch M. The cystatin C/creatinine ratio, a marker of glomerular filtration quality: associated factors, reference intervals, and prediction of morbidity and mortality in healthy seniors. *Transl Res*. 2016;169:80–90.e2. DOI: 10.1016/j.trsl.2015.11.001.
19. He Q, Jiang J, Xie L, Zhang L, Yang M. A sarcopenia index based on serum creatinine and cystatin C cannot accurately detect either low muscle mass or sarcopenia in urban community-dwelling older people. *Sci Rep*. 2018;8:11534. DOI: 10.1038/s41598-018-29808-6.

20. Chew-Harris JS, Florkowski CM, George PM, Elmslie JL, Endre ZH. The relative effects of fat versus muscle mass on cystatin C and estimates of renal function in healthy young men. *Ann Clin Biochem*. 2013;50:39–46. DOI: 10.1258/acb.2012.011241.

21. Kim SW, Jung HW, Kim CH, Kim KI, Chin HJ, Lee H. A new equation to estimate muscle mass from creatinine and cystatin C. *PLoS One*. 2016;11:e0148495. DOI: 10.1371/journal.pone.0148495.

22. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381. DOI: 10.1093/eurheartj/ehw106.

23. Bjarnason-Wehrens B, McGee H, Zwisler AD, Piepoli MF, Benzer W, Schmid JP, Dendale P, Pogosova NG, Zdrenghea D, Niebauer J, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil*. 2010;17:410–418. DOI: 10.1097/HJR.0b013e328334f42d.

24. Liguori I, Russo G, Aran L, Bulli G, Curcio F, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D, et al. Sarcopenia: assessment of disease burden and strategies to improve outcomes. *Clin Interv Aging*. 2018;13:913–927.

25. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. DOI: 10.7326/0003-4819-150-9-200905050-00006.

26. Lee CS, Cha R-H, Lim Y-H, Kim H, Song KH, Gu N, Yu KS, Lim CS, Han JS, Kim S, et al. Ethnic coefficients for glomerular filtration rate estimation by the modification of diet in renal disease study equations in the Korean population. *J Korean Med Sci*. 2010;25:1616–1625. DOI: 10.3346/jkms.2010.25.11.1616.

27. Oh YJ, Cha R-H, Lee SH, Yu KS, Kim SE, Kim H, Kim YS. Validation of the Korean coefficient for the modification of diet in renal disease study equation. *Korean J Intern Med*. 2016;31:344–356. DOI: 10.3904/kjim.2015.227.

28. Junge W, Wilke B, Halabi A, Klein G. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance

29. Inker LA, Okparavero A. Cystatin C as a marker of glomerular filtration rate: prospects and limitations. *Curr Opin Nephrol Hypertens*. 2011;20:631–639. DOI: 10.1097/MNH.0b013e32834b8850.

30. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. *Am J Kidney Dis*. 2013;62:595–603. DOI: 10.1053/j.ajkd.2013.03.027.

31. Grubb A, Blirup-Jensen S, Lindstrom V, Schmidt C, Althaus H, Zegers I. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med*. 2010;48:1619–1621. DOI: 10.1515/CCLM.2010.318.

32. Zhao Z, Sacks DB. Detrimental effects of not using international reference materials to calibrate cystatin C assays. *Clin Chem*. 2016;62:410–411. DOI: 10.1373/clinchem.2015.244988.

33. Voskoboev NV, Larson TS, Rule AD, Lieske JC. Importance of cystatin C assay standardization. *Clin Chem*. 2011;57:1209–1211. DOI: 10.1373/clinchem.2011.164798.

34. Stevens LA, Li S, Kurella Tamura M, Chen SC, Vassalotti JA, Norris KC, Whaley-Connell AT, Bakris GL, McCullough PA. Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations: risk factors for and complications of CKD and mortality in the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis*. 2011;57:S9–S16. DOI: 10.1053/j.ajkd.2010.11.007.

35. Larsson A, Hansson L-O, Flodin M, Katz R, Shlipak MG. Calibration of the siemens cystatin C immunoassay has changed over time. *Clin Chem*. 2011;57:777–778. DOI: 10.1373/clinchem.2010.159848.

36. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369:932–943. DOI: 10.1056/NEJMoa1214234.

37. Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J. Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol*. 2009;20:2617–2624. DOI: 10.1681/ASN.2009010025.

38. White SL, Polkinghorne KR, Atkins RC, Chadban SJ. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. *Am J Kidney Dis*. 2010;55:660–670. DOI: 10.1053/j.ajkd.2009.12.011.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

*Measurement of renal filtration markers and their calibration*

This study was conducted only for patients enrolled in a single institution, so the measurement of serum creatinine (Scr) and cystatin C (Scys) was exclusively performed in the Department of Laboratory Medicine of Seoul National University Hospital (SNUH). This laboratory has obtained accreditation from many domestic and international certification bodies such as the College of American Pathologists for quality control. However, inevitable changes occurred in the measurement of renal filtration markers, since patients were enrolled over a long time with a total enrollment period of 11 years. During the study period, we updated the automated test equipment, and following international trends, implemented standardization of the Scr measurement in the latter part of the study. Therefore, the impact of the fundamental changes in test methods should be considered.

As with most laboratories, Scr was measured with the kinetic Jaffe method, which is a colorimetric analysis using an alkaline picric reaction. Isotope dilution mass spectrometry (IDMS) traceable calibration was introduced at SNUH from April 2009 for standardized Scr measurement. Prior to that time, the crude values obtained from the Jaffe reaction were reported as they were without additional calibration. Patients enrolled before April 2009 were 217 patients, or 11.2% of all the study population, who underwent Scr measurement using the Hitachi 7600 automated analyzer (Hitachi high-technologies Co., Tokyo, Japan), Roche calibrator, and CREA reagent (Roche Diagnostics GmbH, Mannheim, Germany). The Scr value of these patients could not be directly applied to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which is the eGFR formula developed based on the standardized Scr.[25] As an alternative, we used a correction method that was

previously introduced in a reference study. Nephrologists of SNUH have published the results of calibrating the coefficients of the MDRD equation using IDMS calibration to specific values for Koreans.[26] This study was conducted at a similar time as when we enrolled patients with non-standardized Scr values in the stent registry. They used data from 151 Korean patients collected from April 2008 to February 2009. They sent forty randomly selected frozen samples to the Cleveland Clinic Reference Laboratory, who performed IDMS calibration studies of MDRD equation, to harmonize the Scr measurements of the two institutions. The formula for correcting the Scr measurements at that time to the IDMS calibrated value was: calibrated Scr (mg/dL) = 1.0734 x measured Scr - 0.2418. The Scr measurements for the period from April 2009 to December 2010, when 512 patients (26.6%) were enrolled, refined this correction formula a little more. According to the recommendations of the reagent manufacturer and the institution's own standards, the measured Scr values were multiplied by 1.07 and then subtracted by 0.2mg/dL to obtain the Scr values with IDMS calibration.[27]

The compensated Jaffe method was applied from January 2011 to ensure accuracy comparable to that measured by the IDMS method, the gold standard of Scr measurement. Since January 2011, the systematic error of the Jaffe assay due to non-creatinine chromogens was overcome by subtracting 0.3mg/dL from the Scr values obtained using the Roche updated reagent system and TBA-200FR automated analyzer (Canon Medical Systems Corporation, Tochigi, Japan) to implement the rate-blanked compensated kinetic alkaline picrate Jaffe method.[27, 28] About two-thirds (1199 patients) of the study population were enrolled after changing the automated test equipment. Based on the assumption that there are negligible systematic deviations between the Scr measurements before and after the change, we applied the Scr values from April 2009 to the CKD-EPI eGFR equation without further calibration. On the other hand, the measurements before April 2009 were corrected according to the calibration method of the reference paper,[26] and the eGFR of the registered patients was calculated using

these converted values.
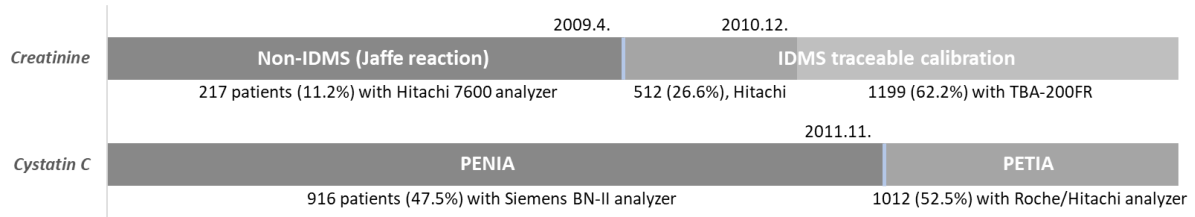
For the Scys measurement, the SNUH laboratory used nephelometry (PENIA, particle-enhanced nephelometric assay) from December 2004 to November 2011, but from then on it replaced the assay with a turbidimetric test (PETIA, particle-enhanced immunoturbidimetric assay). Both the PETIA and PENIA methods measure the Scys value using the aggregation reaction, in which cystatin C and cystatin-specific antibody react with each other to form an insoluble complex. PETIA quantifies the increase in the turbidity of the solution when cystatin C reacts with the antibody (Roche Tina-quant Generation 1 assay tested with Roche/Hitachi MODULAR P analyzer, Roche/Hitachi, Indianapolis, IN), but on the other hand, PENIA gauge the degree of light scattering as the light transmitted through the mixed solution of the insoluble cystatin C and anti-cystatin C antibody complex (N Latex assay on the Siemens BN-II analyzer, Siemens Health Care Diagnostic, Marburg, Germany).[29] Since December 2011, patients who measured the Scys using the Roche PETIA assay were 1012, 52.5% of the study population.

Just as IDMS traceable calibration introduces standardization into Scr measurement, several attempts have been made to standardize different assays to increase the reliability of Scys measurements.[29, 30] In particular, since June 2010, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) began to disseminate reference materials (ERM-DA471/IFCC) for the standardization of Scys measurement,[31] and many manufacturers and institutions introduced standardized Scys assays into their daily practice. However, the two Scys assays that had been used in SNUH were not standardized, so it is not appropriate to apply

the test results to the CKD-EPI equation, which requires standardized Scys values. The unstandardized Scys values measured by the two assays are not interchangeable with each other. Scys values measured by the PENIA assay generally tends to be slightly lower than Scys values obtained by the PETIA method.[29, 32, 33] Also, there was a so-called 'systemic drift' in PENIA test kits manufactured from 2000 to 2010, and it was reported that recently produced kits tend to measure the results slightly lower than actual values.[33-35] Therefore, it is inappropriate to use the Scys values obtained by the two methods of PETIA and PENIA to calculate the eGFR on the same line without additional correction.

To solve this problem, we adopted a calibration method to standardized Scys values in a reference study that examined the revised CKD-EPI equation.[36] In this study, data from several sources not only differed from the assay kits or automated equipment used for Scys measurement but also varied in their study period. The researchers pooled data from these studies, data of PENIA and PETIA assays were converted to standardized Scys values using different conversion formulas for each assay and specified study period. These data included studies that used the same vendor assays as those used by the SNUH laboratory. We chose two equations that were used to standardize measured Scys values at a time similar to when the SNUH laboratory performed Scys assays for the registry data. To standardize the Scys values obtained by the PENIA method, we selected the conversion equation for the ARIC (Atherosclerosis Risk in Communities Study) which collected data in 2008 using the same Siemens BN-II system as our study: IFCC Scys (mg/L) = 1.12 x (0.083 + (0.914 x measured Scys)).[37] We then selected the AusDiab (Australian Diabetes, Obesity, and Lifestyle Study), which measured the Scys values in 2010 using the Roche immunoturbidimetric assay, to transform the PETIA assay results: IFCC Scys (mg/L) = 1.12 x (-0.25 + (1.07 x measured Scys)).[38] Both the ARIC study and the AusDiab study had more female patients than our prospective cohort (respectively 57.1% and 55.2% vs. 29.2%). Patients included in the

AusDiab study had a similar renal function on average with our patients (standardized Scr-based MDRD equation, 78.9 ± 15.2 vs. $79.7 \pm 27.1 \text{mL/min/1.73m}^2$). In contrast, patients in the ARIC study had generally higher eGFR than our cohort, with an average eGFR of $84.0 \pm 17.0 \text{mL/min/1.73m}^2$ in the lowest quartile patients with relatively low renal function. But instead, unlike other source studies that adopted the PENIA method, the ARIC study used the same BN-II system as ours. Also, systemic drift had the least impact because the ARIC study most recently measured Scys. Thus, in addition to the AusDiab study, we adopted the conversion formula of the ARIC study as the standardization method for our research.

Calculation of the Scr- and Scys-based eGFR

Using the standardized Scr and Scys values as described above, we retrospectively evaluated the renal function of the study subjects. The equations for calculating eGFR were as follows.

CKD-EPI creatinine equation (2009)[25]:

$$\text{eGFR} = 141 \times \min\left(\frac{\text{Scr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\text{Scr}}{\kappa}, 1\right)^{-1.209} \times 0.993^{\text{Age}} \text{ [x 1.018 (if female)]}$$

Abbreviations and units are as follows; eGFR (estimated glomerular filtration rate, mL/min/1.73m^2), Scr (standardized serum creatinine, mg/dL), $\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.329$ (females) or -0.411 (males), min = the minimum of Scr/κ or 1, max = the maximum of Scr/κ or 1, and age in years.

CKD-EPI cystatin C equation (2012)[31]:

$$\text{eGFR} = 133 \times \min\left(\frac{\text{Scys}}{0.8}, 1\right)^{-0.499} \times \max\left(\frac{\text{Scys}}{0.8}, 1\right)^{-1.328} \times 0.996^{\text{Age}} \text{ [x 0.932 (if female)]}$$

Abbreviations and units are as follows; Scys (standardized serum cystatin C, mg/L), min = the minimum of Scys/0.8 or 1, max = the maximum of Scys/0.8 or 1, and age in years.

Table S1. Comparison of baseline characteristics between study participants and non-participants.

	Total eligible population (n=3365)	Participants (n=1928, 57.3%)	Non-participants (n=1437, 42.7%)	P value
Demographics and risk factors				
Men	2383 (70.8%)	1365 (70.8%)	1018 (70.8%)	>0.999
Age (year)	65.5 ± 10.4	65.2 ± 9.9	65.8 ± 10.9	0.093
BMI (kg/m^2)	24.5 ± 3.1	24.9 ± 3.0	24.1 ± 3.3	<0.001
Hypertension	2217 (65.9%)	1321 (68.5%)	896 (62.4%)	<0.001
Diabetes mellitus	1322 (39.3%)	774 (40.1%)	548 (38.1%)	0.252
History of myocardial infarction	267 (7.9%)	168 (8.7%)	99 (6.9%)	0.061
Previous revascularization	698 (20.7%)	395 (20.5%)	303 (21.1%)	0.704
History of cerebrovascular accident	326 (9.7%)	189 (9.8%)	137 (9.5%)	0.840
Dyslipidemia or statin user	2294 (68.2%)	1431 (74.2%)	863 (60.1%)	<0.001
Current smoker	778 (23.1%)	419 (21.7%)	359 (25.0%)	0.030
Presented as acute MI	753 (22.4%)	160 (8.3%)	593 (41.3%)	<0.001

Left ventricular ejection fraction (%)	57.4 ± 10.4	59.4 ± 9.3	54.8 ± 11.3	<0.001

Angiographic and procedural characteristics

Extent of coronary artery disease				0.444
1-VD	1051 (31.2%)	600 (31.1%)	451 (31.4%)	
2-VD	1143 (34.0%)	671 (34.8%)	472 (32.8%)	
3-VD	1171 (34.8%)	657 (34.1%)	514 (35.8%)	
LM disease	356 (10.6%)	201 (10.4%)	155 (10.8%)	0.779
Multiple target lesions	1041 (30.9%)	561 (29.1%)	480 (33.4%)	0.008
Intervention for type B2/C lesion	2884 (85.7%)	1647 (85.4%)	1237 (86.1%)	0.625
Intervention for in-stent restenosis	194 (5.8%)	105 (5.4%)	89 (6.2%)	0.398
Intervention for bifurcation lesion	2098 (62.3%)	1180 (61.2%)	918 (63.9%)	0.121
Side branch treatment	464 (13.8%)	261 (13.5%)	203 (14.1%)	0.660
Procedural success	3348 (99.5%)	1922 (99.7%)	1426 (99.2%)	0.111

Values are described as numbers (%) or mean ± standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; LM, left main; MI, myocardial infarction; PCI,

percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; VD, vessel disease.

Table S2. Baseline characteristics of study population according to 3-year mortality.

	Total population (n=1928)	Mortality (+) (n=102, 5.3%)	Mortality (-) (n=1826, 94.7%)	P value
Demographics and risk factors				
Men	1365 (70.8%)	77 (75.5%)	1288 (70.5%)	0.284
Age (year)	65.2 ± 9.9	70.8 ± 9.8	64.9 ± 9.9	<0.001
Age ≥65	1086 (56.3%)	81 (79.4%)	1005 (55.0%)	<0.001
Hypertension	1321 (68.5%)	77 (75.5%)	1244 (68.1%)	0.119
Diabetes mellitus	774 (40.1%)	54 (52.9%)	720 (39.4%)	0.007
History of myocardial infarction	168 (8.7%)	13 (12.7%)	155 (8.5%)	0.138
Previous revascularization	395 (20.5%)	22 (21.6%)	373 (20.4%)	0.781
History of cerebrovascular accident	189 (9.8%)	18 (17.6%)	171 (9.4%)	0.006
Dyslipidemia or statin user	1431 (74.2%)	64 (62.7%)	1367 (74.9%)	0.006
Current smoker	419 (21.7%)	24 (23.5%)	395 (21.6%)	0.651
Presented as acute MI	160 (8.3%)	18 (17.6%)	142 (7.8%)	<0.001
Left ventricular ejection fraction (%)	59.3 ± 9.3	53.9 ± 14.1	59.7 ± 8.8	<0.001

Angiographic and procedural characteristics

Extent of coronary artery disease				0.009
1-VD	600 (31.1%)	21 (20.6%)	579 (31.7%)	
2-VD	671 (34.8%)	33 (32.4%)	638 (34.9%)	
3-VD	657 (34.1%)	48 (47.1%)	609 (33.4%)	
LM disease	201 (10.4%)	18 (17.6%)	183 (10.0%)	0.014
Multiple target lesions	561 (29.1%)	35 (34.3%)	526 (28.8%)	0.233
Intervention for type B2/C lesion	1647 (85.4%)	90 (88.2%)	1557 (85.3%)	0.409
Intervention for in-stent restenosis	105 (5.4%)	11 (10.8%)	94 (5.1%)	0.015
Intervention for bifurcation lesion	1180 (61.2%)	63 (61.8%)	1117 (61.2%)	0.905
Side branch treatment	261 (13.5%)	16 (15.7%)	245 (13.4%)	0.515
Procedural success	1922 (99.7%)	101 (99.0%)	1821 (99.7%)	0.212
Medications at discharge				
Aspirin	1916 (99.4%)	100 (98.0%)	1816 (99.5%)	0.130
Clopidogrel	1906 (98.9%)	100 (98.0%)	1806 (98.9%)	0.423
Dual antiplatelet therapy	1899 (98.5%)	100 (98.0%)	1799 (98.5%)	0.697

Beta blockers	1019 (52.9%)	55 (53.9%)	964 (52.8%)	0.824
ACE inhibitors	246 (12.8%)	18 (17.6%)	228 (12.5%)	0.128
ARBs	743 (38.5%)	43 (42.2%)	700 (38.3%)	0.440
Statins	1716 (89.0%)	72 (70.6%)	1644 (90.0%)	<0.001
CCBs	669 (34.7%)	36 (35.3%)	633 (34.7%)	0.897
Body habitus, Scr, Scys and eGFR				
Body weight (kg)	66.0 ± 10.3	62.8 ± 10.2	66.2 ± 10.3	0.001
BMI (kg/m^2)	24.9 ± 2.9	23.7 ± 3.2	24.9 ± 2.9	<0.001
Scr (mg/dL)	1.11 ± 1.11	1.86 ± 2.17	1.07 ± 1.00	<0.001
Scys (mg/dL)	1.00 ± 0.81	1.81 ± 1.68	0.96 ± 0.71	<0.001
eGFR (mL/min/1.73m^2)				
by Scr-based CKD-EPI equation	78.7 ± 23.0	62.7 ± 31.5	79.6 ± 22.1	<0.001
by Scys-based CKD-EPI equation	89.8 ± 26.7	62.3 ± 34.3	91.3 ± 25.4	<0.001
Baseline renal dysfunction				
eGFR <60 by Scr-based CKD-EPI equation	347 (18.0%)	39 (38.2%)	308 (16.9%)	<0.001
eGFR <60 by Scys-based CKD-EPI equation	259 (13.4%)	42 (41.2%)	217 (11.9%)	<0.001

Scr/Scys	1.10 ± 0.26	0.98 ± 0.28	1.11 ± 0.25	<0.001
eGFRcys/eGFRcr	1.16 ± 0.23	1.01 ± 0.28	1.17 ± 0.22	<0.001

Values are described as numbers (%) or mean ± standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; EPI, Epidemiology Collaboration; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; Scr, serum creatinine; Scys, serum cystatin C; STEMI, ST-segment elevation myocardial infarction; VD, vessel disease.

Table S3. Baseline characteristics of study population according to muscle mass estimated by ratio of estimated glomerular filtration rate by serum cystatin C to creatinine.

	Total population (n=1928)	Low-MM (n=601, 31.2%)	Normal-MM (n=1327, 68.8%)	P value
Demographics and risk factors				
Men	1365 (70.8%)	459 (76.4%)	906 (68.3%)	<0.001
Age (year)	65.2 ± 9.9	66.7 ± 10.3	64.5 ± 9.7	<0.001
Age ≥65	1086 (56.3%)	379 (63.1%)	707 (53.3%)	<0.001
Hypertension	1321 (68.5%)	435 (72.4%)	886 (66.8%)	0.014
Diabetes mellitus	774 (40.1%)	265 (44.1%)	509 (38.4%)	0.017
History of myocardial infarction	168 (8.7%)	69 (11.5%)	99 (7.5%)	0.004
Previous revascularization	395 (20.5%)	115 (19.1%)	280 (21.1%)	0.322
History of cerebrovascular accident	189 (9.8%)	55 (9.2%)	134 (10.1%)	0.517
Dyslipidemia or statin user	1431 (74.2%)	430 (71.5%)	1001 (75.4%)	0.071
Current smoker	419 (21.7%)	158 (26.3%)	261 (19.7%)	0.001
Presented as acute MI	160 (8.3%)	51 (8.5%)	109 (8.2%)	0.841

Left ventricular ejection fraction (%)	59.3 ± 9.3	58.1 ± 10.8	59.9 ± 8.5	0.001
Angiographic and procedural characteristics				
Extent of coronary artery disease				0.892
1-VD	600 (31.1%)	183 (30.4%)	417 (31.4%)	-
2-VD	671 (34.8%)	213 (35.4%)	458 (34.5%)	-
3-VD	657 (34.1%)	205 (34.1%)	452 (34.1%)	-
LM disease	201 (10.4%)	62 (10.3%)	139 (10.5%)	0.916
Multiple target lesions	561 (29.1%)	188 (31.3%)	373 (28.1%)	0.155
Intervention for type B2/C lesion	1647 (85.4%)	505 (84.0%)	1142 (86.1%)	0.241
Intervention for in-stent restenosis	105 (5.4%)	39 (6.5%)	66 (5.0%)	0.174
Intervention for bifurcation lesion	1180 (61.2%)	379 (63.1%)	801 (60.4%)	0.260
Side branch treatment	261 (13.5%)	89 (14.8%)	172 (13.0%)	0.272
Procedural success	1922 (99.7%)	598 (99.5%)	1324 (99.8%)	0.319
Medications at discharge				
Aspirin	1916 (99.4%)	594 (98.8%)	1322 (99.6%)	0.058
Clopidogrel	1906 (98.9%)	593 (98.7%)	1313 (98.9%)	0.597

Dual antiplatelet therapy	1899 (98.5%)	590 (98.2%)	1309 (98.6%)	0.428
Beta blockers	1019 (52.9%)	323 (53.7%)	696 (52.4%)	0.598
ACE inhibitors	246 (12.8%)	93 (15.5%)	153 (11.5%)	0.016
ARBs	743 (38.5%)	227 (37.8%)	516 (38.9%)	0.641
Statins	1716 (89.0%)	522 (86.9%)	1194 (90.0%)	0.042
CCBs	669 (34.7%)	211 (35.1%)	458 (34.5%)	0.800
Body habitus, Scr, Scys and eGFR				
Body weight (kg)	66.0 ± 10.3	65.3 ± 10.2	66.4 ± 10.4	0.047
BMI (kg/m^2)	24.9 ± 2.9	24.6 ± 3.1	25.0 ± 2.9	0.008
Scr (mg/dL)	1.11 ± 1.11	1.06 ± 0.95	1.14 ± 1.17	0.158
Scys (mg/dL)	1.00 ± 0.81	1.19 ± 0.96	0.92 ± 0.72	<0.001
eGFR (mL/min/1.73m^2)				
by Scr-based CKD-EPI equation	78.7 ± 23.0	81.5 ± 24.4	77.4 ± 22.2	<0.001
by Scys-based CKD-EPI equation	89.8 ± 26.7	77.1 ± 26.9	95.6 ± 24.5	<0.001
Baseline renal dysfunction				
eGFR <60 by Scr-based CKD-EPI equation	347 (18.0%)	98 (16.3%)	249 (18.8%)	0.193

eGFR <60 by Scys-based CKD-EPI equation	259 (13.4%)	140 (23.3%)	119 (9.0%)	<0.001
Scr/Scys	1.10 ± 0.26	0.89 ± 0.17	1.20 ± 0.23	<0.001
eGFRcys/eGFRcr	1.16 ± 0.23	0.94 ± 0.14	1.26 ± 0.18	<0.001

Values are described as numbers (%) or mean ± standard deviation.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; EPI, Epidemiology Collaboration; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LM, left main; Low-MM, low muscle mass; MI, myocardial infarction; PCI, percutaneous coronary intervention; Scr, serum creatinine; Scys, serum cystatin C; STEMI, ST-segment elevation myocardial infarction; VD, vessel disease.

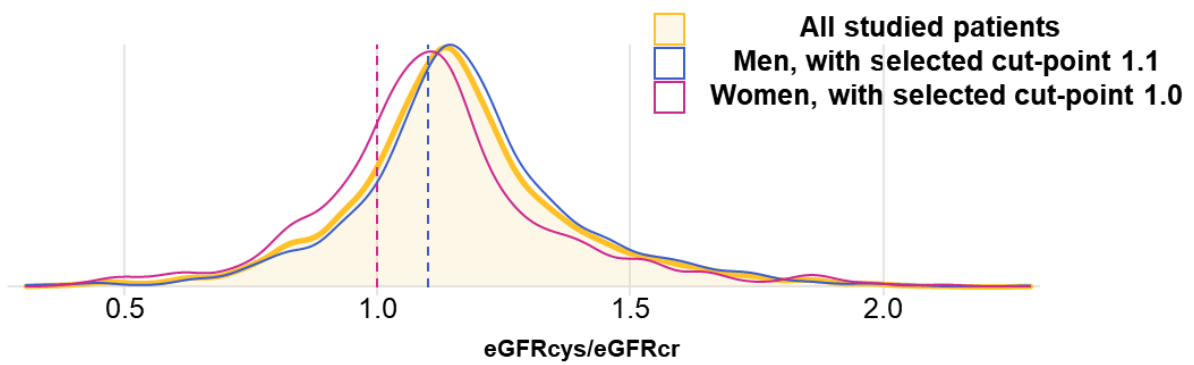**Figure S1. Association of Low Muscle Mass with 3-Year Risk of All-Cause Death.**
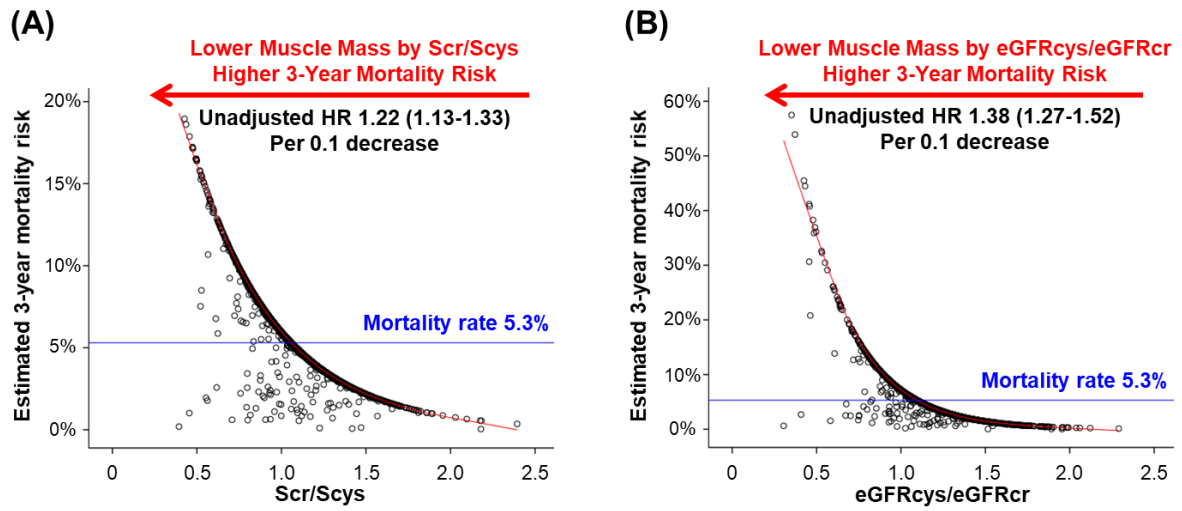
eGFR, estimated glomerular filtration rate; HR, hazard ratio; Scr, serum creatinine; Scys, serum cystatin C.

**Figure S2. Distribution of Scr/Scys and eGFRcys/eGFRcr by Sex.**
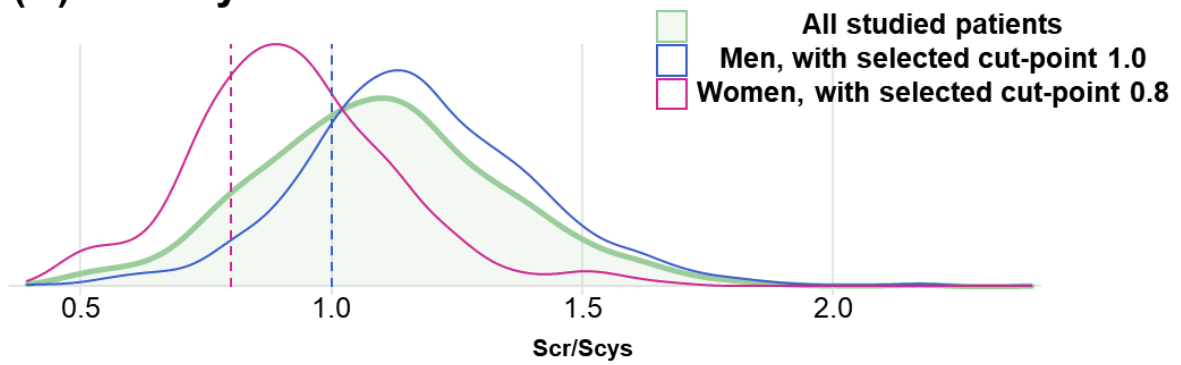
eGFR, estimated glomerular filtration rate; Scr, serum creatinine; Scys, serum cystatin C.

Figure S3. Time-dependent ROC Analysis and Optimal Discriminative Cut-Points for 3-Year Mortality.

Time-dependent ROC analysis and optimal discriminative cut-points for clinical events

		1st quartile	All-cause mortality			Selected cut-points	
			Optimal cutoff value	P-value	Cumulative percent (%)	Cut-off value	Cumulative percent (%)
Scr/Scys	All studied patients	0.884	0.979	1.9519×10^{-5}	31.59	1.0	34.75
	Men	0.986	1.006	6.4558×10^{-7}	21.54	1.0	20.66
	Women	0.789	0.837	0.0015	33.75	0.8	25.93
eGFRcys/eGFRcr	All studied patients	0.976	1.029	3.2581×10^{-11}	23.08	1.0	18.88
	Men	1.012	1.092	4.9388×10^{-9}	31.28	1.1	33.70
	Women	0.971	1.008	1.0537×10^{-5}	27.71	1.0	25.40

cf. The cut-off values of the surrogates were rounded off to avoid over-fitting and make the surrogates more practical and easy to apply. We have chosen cut-point values to be more predictable, especially for 3-year all-cause mortality.
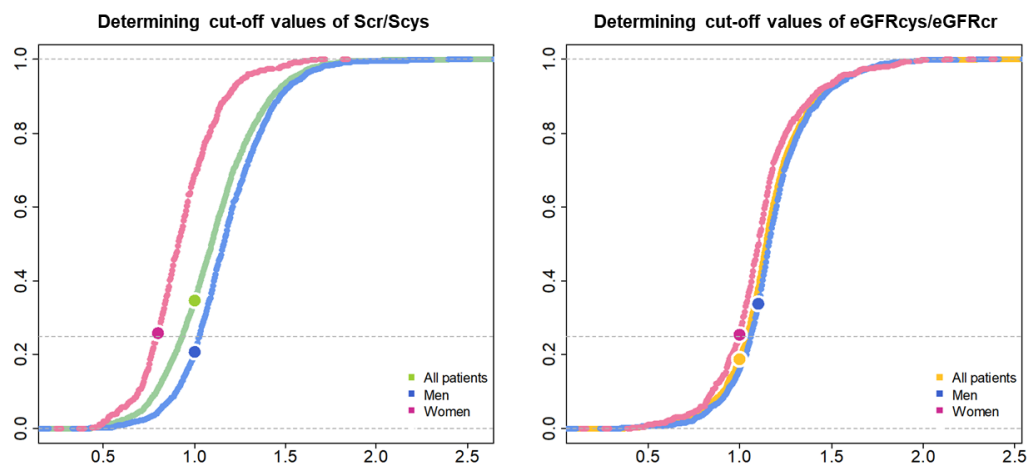
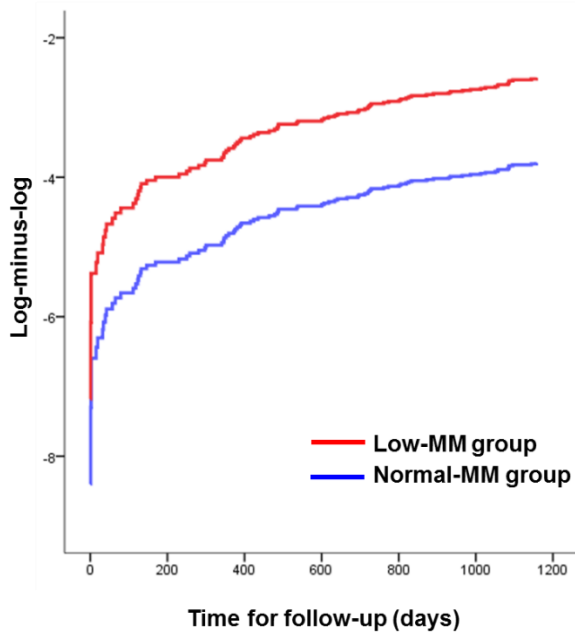ROC, receiver operating characteristics; otherwise as in Figure S2.

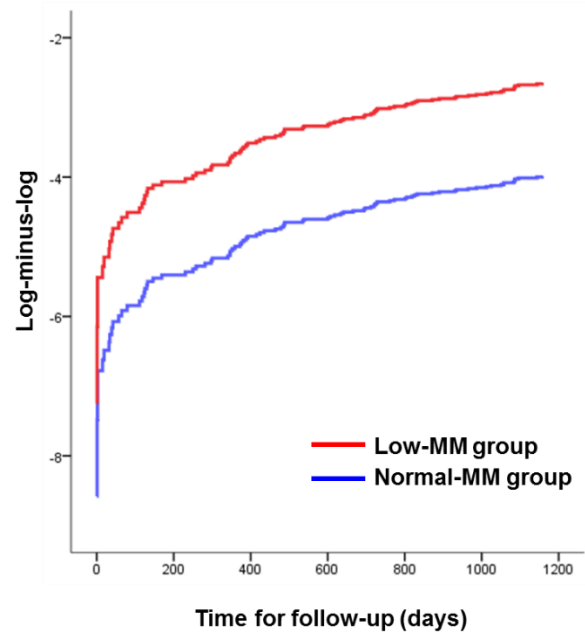**Figure S4. Determining Best Cut-Off Values using U Statistics according to Sex.**
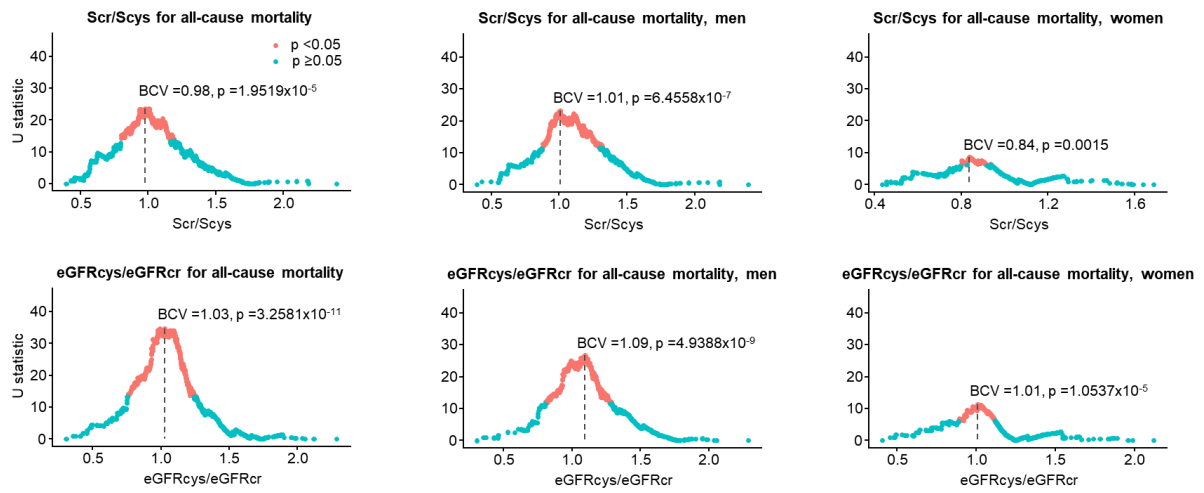
BCV, best cut-off value; otherwise as in Figure S2.

Figure S5. Log-Minus-Log Curves of All-Cause Mortality.

eGFR, estimated glomerular filtration rate; Low-MM, low muscle mass; Scr, serum creatinine;

Scys, serum cystatin C.