Cystatin C-Based eGFR Is a Superior Prognostic Parameter to Creatinine-Based eGFR in Post-Endovascular Therapy Peripheral Artery Disease Patients

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Background: Kidney dysfunction is reportedly associated with adverse outcome in patients with peripheral artery disease (PAD). Estimated glomerular filtration rate (eGFR), a recently popularized index for assessing kidney function, is calculated using serum creatinine or cystatin C. Compared with creatinine-based eGFR (eGFR_{cr}), cystatin C-based eGFR (eGFR_{cys}) is less affected by age, gender, and muscle mass. We hypothesized that eGFR_{cys} is a feasible prognostic biomarker despite muscle sarcopenia in patients with PAD.

Methods and Results: We calculated both eGFR_{cr} and eGFR_{cys} according to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline in 234 PAD patients who underwent endovascular therapy. Patients were prospectively followed during a median follow-up period of 964 days for the endpoint of major adverse cardiovascular and cerebrovascular events (MACCE). On multivariate Cox proportional hazard analysis eGFR_{cys}, but not eGFR_{cr}, was an independent predictor of MACCE. The C index was larger for eGFR_{cys} than eGFR_{cr} (0.69 vs. 0.57, $P=0.0006$). On Kaplan-Meier analysis the incidence of MACCE was increased with advancing chronic kidney disease stage based on eGFR_{cys}, but not on eGFR_{cr}, in patients with PAD. Net reclassification index was improved with the addition of eGFR_{cys} to basic predictors.

Conclusions: Compared with eGFR_{cr}, eGFR_{cys} may be a more reliable biomarker for MACCE and patient risk stratification. (*Circ J* 2015; **79**: 2480–2486)

Key Words: Creatinine-based eGFR; Cystatin C-based eGFR; Muscle sarcopenia; Peripheral artery disease

Peripheral artery disease (PAD) is an athero-occlusive disease affecting the lower limb arteries, leading to impaired morbidity. The presence of PAD is an independent predictor of cardiovascular events.^{1–3} Despite advances in medical therapy, patients with PAD have a 3-fold higher risk of all-cause and cardiovascular mortality compared with healthy controls.⁴ Therefore, early identification and risk stratification of PAD patients is becoming increasingly important. Although reduced lower extremity performance has been reported to be associated with morbidity and mortality, little is known about useful biomarkers for predicting major adverse cardiovascular and cerebrovascular events (MACCE) in PAD patients.

Kidney dysfunction is closely associated with PAD development.^{5,6} Estimated glomerular filtration rate (eGFR) is a well-established marker for kidney function. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline, creatinine-based eGFR (eGFR_{cr}) is recommended for initial GFR assessment,⁷ but eGFR_{cr} is thought to be inaccurate for

detecting small decreases in GFR because of the non-linear relationship between creatinine concentration and GFR.⁸ In addition, eGFR_{cr} is often inaccurate when estimating GFR because it is affected by several factors such as age, gender, and muscle mass.^{9,10}

Cystatin C, a 13-kD basic protein, is a cysteine protease inhibitor synthesized by all nucleated cells and released into the blood at a relatively constant rate. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubule, and not secreted. Therefore, cystatin C is a useful marker for glomerular function. Although the precise mechanism remains to be clarified, elevated serum cystatin C has been reported to be associated with the development of stroke, ischemic heart disease (IHD), heart failure, aortic abdominal aneurysm, and PAD because it is related to worsening atherogenesis, inflammation, cardiac remodeling, and deteriorating kidney function.^{11–15} Cystatin C-based eGFR (eGFR_{cys}) is used to assess mild kidney dysfunction because it is less affected by age, gender, and

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Table 1. Clinical PAD Patient Characteristics (n=234)

Variables	All patients (n=234)	Event free (n=180)	MACCE (n=54)	P-value
Age (years)	75±8	74±9	77±7	0.0071
M/F	193/41	147/33	46/8	0.5508
BMI (%)	21.9±3.1	22.2±2.9	21.0±3.6	0.0198
FFMI (%)	17.8±1.5	17.9±1.5	17.4±1.7	0.0393
Hypertension	192 (82)	148 (82)	44 (81)	0.7222
Diabetes mellitus	110 (47)	81 (45)	29 (54)	0.3313
Hyperlipidemia	154 (66)	123 (68)	31 (57)	0.0912
Previous IHD	70 (30)	43 (24)	27 (50)	0.0004
AP/OMI/AP+OMI	36/18/16	24/11/8	12/7/8	0.0025
Prior PCI	48 (21)	31 (17)	17 (31)	0.0290
Prior CABG	18 (8)	8 (4)	10 (19)	0.0008
Medical	9 (4)	6 (5)	3 (6)	0.4782
Previous cerebrovascular disease	44 (19)	30 (17)	14 (26)	0.1489
Fontaine II/III/IV	181/27/26	148/20/12	33/7/14	<0.0001
Endovascular therapy				
Iliac artery	160 (68)	128 (71)	32 (59)	0.1005
Femoropopliteal artery	139 (59)	101 (56)	38 (70)	0.0613
Tibial or peroneal artery	30 (13)	16 (9)	14 (26)	0.0010
Stent	216 (92)	166 (94)	50 (93)	0.9953
Pre-treatment ABI	0.58±0.18	0.58±0.19	0.59±0.15	0.8387
Post-treatment ABI	0.89±0.19	0.90±0.18	0.87±0.23	0.4302
Kidney function				
Crea (mg/dl)	0.87±0.30	0.84±0.27	0.94±0.38	0.0542
eGFRcr (ml/min/1.73 m ²)	70±22	71±22	66±25	0.1780
Cystatin C (mg/L)	1.16±0.34	1.11±0.31	1.32±0.40	<0.0001
eGFRcys (ml/min/1.73 m ²)	63±20	66±20	54±17	<0.0001
Medication				
Aspirin	165 (71)	122 (68)	43 (80)	0.0939
Clopidogrel	143 (61)	110 (61)	33 (61)	>0.9999
Other antiplatelet drug	107 (46)	80 (44)	27 (50)	0.4723
ACEI and/or ARB	142 (61)	105 (58)	37 (69)	0.1790
CCB	129 (55)	102 (57)	27 (50)	0.3876
Statin	123 (53)	97 (54)	26 (48)	0.4587

Data given as mean±SD or n (%). ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitors; AP, angina pectoris; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blockers; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; FFMI, fat-free mass index; IHD, ischemic heart disease; OMI, old myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; MACCE, major adverse cardiovascular and cerebrovascular events.

muscle mass when compared with eGFRcr.^{9,16} According to the KDIGO guideline, GFR should be calculated using serum cystatin C in patients with certain conditions, such as extreme muscle mass loss. It remains to be determined, however, whether eGFRcys can predict clinical outcome in patients with PAD.

In the present study, we tested the hypothesis that eGFRcys is a feasible prognostic parameter in patients with PAD despite muscle sarcopenia.

Methods

Subjects

This was a prospective study of 234 de novo patients who were admitted to hospital for PAD treatment. PAD was diagnosed by 2 physicians according to ankle-brachial index (ABI) and computed tomography angiography. Endovascular therapy (EVT) was performed by experienced cardiologists according

to the Trans-Atlantic Inter-Society Consensus II (TASC II) guideline recommendation. Optimized medical therapy was independently administered based on symptom improvement by physicians who were blinded to the biochemistry results. Exclusion criteria were acute coronary syndrome within the 3 months preceding admission, hemodialysis, thyroid disease, and malignant disease. Demographic and clinical data including age, gender, and ABI were collected from patient medical records and interviews. Medications and ABI at discharge were recorded from the hospital medical records.

Ethics

The study protocol was approved by the institutional ethics committee of Yamagata University School of Medicine, and all participants provided written informed consent. All procedures were performed in accordance with the Helsinki Declaration.

Figure 1. Relationship between cystatin C-based estimated glomerular filtration rate (eGFRcys) and creatinine-based eGFR (eGFRcr) in patients with Fontaine class (A) II, (B) III, and (C) IV. There was a close relationship between eGFRcys and eGFRcr in patients with (A,B) Fontaine classes II and III. (C) There was a moderate relationship between eGFRcys and eGFRcr in patients with Fontaine class IV.

Kidney Function

Blood samples were obtained in the early morning before the first EVT. Serum cystatin C was measured using sandwich enzyme-linked immunosorbent assay with 2 distinct anti-human cystatin C-specific monoclonal antibodies (human cystatin C, KRKA, Novo Mesto, Slovenia), as previously reported.^{9,16}

eGFRcr was calculated using the following equations: eGFRcr in male subjects = $194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287}$; eGFRcr in female subjects = $194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$.¹⁷

eGFRcys was calculated using the following equations: eGFRcys in male subjects = $104 \times \text{cystatin C}^{-1.019} \times 0.996^{\text{Age}-8}$; eGFRcys in female subjects = $(104 \times \text{cystatin C}^{-1.019} \times 0.996^{\text{Age}} \times 0.929) - 8$.¹⁸

Marker for Muscle Sarcopenia

Fat-free mass (FFM), a marker for sarcopenia, was estimated using the following equation: $\text{FFM (kg)} = 7.38 + 0.02908 \times \text{urinary creatinine}$. FFM was normalized by the square of patient height in meters to obtain the FFM index (FFMI).^{19,20}

Measurement

Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or anti-hypertensive med-

ication use. Diabetes mellitus was defined as glycosylated hemoglobin A1c $\geq 6.5\%$ (National Glyco Hemoglobin Standardization Program), or anti-diabetes medication use. Hyperlipidemia was defined as total cholesterol ≥ 220 mg/dl, triglyceride ≥ 150 mg/dl, or anti-hyperlipidemic drug use.

Endpoint and Follow-up

All subjects were prospectively followed by telephone or medical records twice a year for a median period of 964 days (IQR, 493–1,501 days; longest follow-up, 1,750 days). The endpoint was MACCE including all-cause death and rehospitalization due to cardiovascular and cerebrovascular disease such as stroke, IHD, heart failure, aortic abdominal aneurysm, and the development of critical limb ischemia (CLI) and amputation.

Statistical Analysis

Data are given as mean $\pm$ SD. Continuous and categorical variables were compared using t-test and chi-squared test, respectively. Differences between 3 groups were analyzed using analysis of variance with Fisher's least significant difference test. MACCE receiver operating characteristics curves (ROC) were constructed and used as a measure of the predictive accuracy of eGFRcys and eGFRcr for MACCE. Cox proportional

hazard analysis was performed to identify independent predictors for MACCE, and significant predictors selected on univariate analysis were entered into multivariate analysis. Survival curves were constructed with the Kaplan-Meier method and compared using log-rank test. In addition, we calculated the net reclassification index (NRI) and integrated discrimination index (IDI) to measure the quality of improvement for correct reclassification following the addition of eGFRcys to the model. $P < 0.05$ was considered statistically significant. All statistical analysis was performed with a standard program package (JMP version 8; SAS Institute, Cary, NC, USA and R 3.0.2 with additional packages including Rcmdr, Epi, pROC, and PredictABEL).

Results

Clinical Characteristics vs. Presence of MACCE

During the follow-up period, there were 54 MACCE, including 10 all-cause deaths, 33 re-hospitalizations due to cardiovascular and cerebrovascular disease, and 11 re-hospitalizations due to CLI development and amputation.

Patient baseline characteristics are listed in Table 1. There were 193 men and 41 women. Mean eGFRcys and eGFRcr were 63 and 70 mL/min/1.73 m², respectively. Patients with MACCE were older and had a more severe Fontaine class than those without MACCE. They also had higher prevalence of previous IHD and tibial or peroneal artery occlusion. Body mass index (BMI), FFMI, and eGFRcys were lower in patients with MACCE than in those without MACCE. There were no

significant differences in gender, prevalence of hypertension, diabetes mellitus, hyperlipidemia, and previous cerebrovascular disease, pre- and post-treatment ABI, eGFRcr, or medication at discharge between patients with and without MACCE.

eGFRcys and eGFRcr vs. Fontaine Class

As shown in Figures 1A and B, there was a close relationship between eGFRcys and eGFRcr in patients with Fontaine class II and III. In contrast, there was a moderate relationship between eGFRcys and eGFRcr in patients with Fontaine class IV (Figure 1C). In patients with Fontaine class IV, eGFRcr tended to be higher than eGFRcys.

Fontaine Class and eGFRcys, eGFRcr, and FFMI

Patients with Fontaine class IV had lower eGFRcys than those with Fontaine class II (Figure 2A), whereas eGFRcr did not significantly differ with Fontaine class (Figure 2B). As FFMI decreased with advancing Fontaine class (Figure 2C), severe PAD patients were more likely to have muscle sarcopenia.

eGFRcys ROC to Predict MACCE

ROC analysis was performed to compare the prognostic capabilities of eGFRcys and eGFRcr (Figure 3). The cut-offs of eGFRcys and eGFRcr were 59 and 57 mL/min/1.73 m², respectively. The C indexes of eGFRcys and eGFRcr were 0.69 and 0.57, respectively. The significantly higher eGFRcys C index suggests that eGFRcys had superior prognostic capacity to eGFRcr in patients with PAD.

eGFRcys and MACCE in PAD Patients

We performed univariate and multivariate Cox proportional hazard regression analyses in patients with PAD to identify predictors of MACCE. On univariate analysis, eGFRcys was significantly related to MACCE in patients with PAD. Furthermore, age, BMI, FFMI, previous IHD, and CLI were also related to MACCE (Table 2). On multivariate Cox proportional hazard regression analysis, eGFRcys, but not eGFRcr, was an independent predictor for MACCE after adjustment for age, FFMI, previous IHD, and CLI (hazard ratio, 0.55; 95% confidence interval: 0.39–0.79; $P=0.0015$; Table 2).

Risk Stratification

Patients were stratified into 3 groups based on eGFRcys according to the chronic kidney disease (CKD) guideline:²¹ normal or high; mildly decreased; and decreased eGFRcys (≥ 90 , 60–89, and <60 ml/min/1.73 m², respectively). On Kaplan-Meier analysis the prevalence of MACCE increased with advancing CKD stage based on eGFRcys (Figure 4A). Conversely, the prevalence of MACCE did not differ with CKD stage based on eGFRcr (Figure 4B).

Improvement of Reclassification After Addition of eGFRcys to Predict MACCE

We evaluated NRI and IDI to examine whether model fit and discrimination improve with addition of eGFRcys to the basic predictors such as age, BMI, FFMI, previous IHD, previous cerebrovascular disease and CLI. NRI and IDI were significantly improved by adding eGFRcys to the basic predictors (Table 3).

Discussion

The new and important findings from this study are as follows: (1) PAD patients with MACCE had lower eGFRcys than those

Table 2. Predictors of MACCE in PAD Patients			
Variables	HR	95% CI	P-value
Univariate analysis			
Age (per 1-year increase)	1.05	1.02–1.09	0.0035
Gender	0.94	0.44–1.98	0.8625
BMI (per 1-SD increase)	0.63	0.47–0.83	0.0014
FFMI (per 1-SD increase)	0.67	0.50–0.88	0.0053
Hypertension	1.14	0.59–2.25	0.6672
Diabetes mellitus	1.32	0.76–2.25	0.3049
Hyperlipidemia	1.59	0.93–2.73	0.0895
Previous IHD	2.44	1.45–4.17	0.0011
Previous cerebrovascular disease	1.75	0.93–3.23	0.0829
CLI	4.18	2.30–7.63	<0.0001
eGFRcr (per 1-SD increase)	0.84	0.63–1.12	0.2485
eGFRcys (per 1-SD increase)	0.52	0.38–0.71	<0.0001
Pre-treatment ABI	1.59	0.24–10.78	0.6334
Post-treatment ABI	0.49	0.08–2.86	0.4290
Multivariate analysis			
Age (per 1-year increase)	1.01	0.97–1.05	0.6184
FFMI (per 1-SD increase)	0.74	0.56–0.98	0.0346
Previous IHD	2.80	1.63–4.85	0.0002
CLI	2.66	1.39–5.12	0.0032
eGFRcys (per 1-SD increase)	0.55	0.39–0.79	0.0015

CI, confidence interval; CLI, critical limb ischemia; HR, hazard ratio. Other abbreviations as in Table 1.

Table 3. Addition of eGFRcys for Prediction of MACCE		
	Baseline model	Baseline model+eGFRcys
C index (P-value)	0.771	0.806 (0.0777)
NRI (95% CI, P-value)	Reference	0.4150 (0.1182–0.7118, 0.0061)
IDI (95% CI, P-value)	Reference	0.0453 (0.0101–0.0805, 0.0117)

Baseline model includes age, BMI, FFMI, previous IHD, previous cerebrovascular disease, and CLI. IDI, integrated discrimination index; NRI, net reclassification index. Other abbreviations as in Tables 1,2.

without MACCE; (2) eGFRcr tended to be higher than eGFRcys in patients with Fontaine class IV who had muscle sarcopenia; (3) the C index of eGFRcys was higher than that for eGFRcr; (4) eGFRcys, but not eGFRcr, was an independent predictor for MACCE in patients with PAD; (5) the prevalence of MACCE increased with advancing CKD stage based on eGFRcys but not eGFRcr; and (6) the prediction model with eGFRcys had improved prognostic capacity for patients with PAD.

GFR and Muscle Sarcopenia

Precise assessment of kidney function is important because kidney dysfunction is associated with tolerance of contrast media, PAD development, and clinical outcome in patients with PAD.^{22–24} Given that eGFR is simple and easy to calculate, eGFRcr is the most prevalent index for assessing overall kidney function. A previous study, however, proposed that eGFRcr is often overestimated in individuals with reduced muscle mass. Overestimated eGFRcr has a U-shaped association with actual GFR and mortality in the general population.^{25,26} Patients with severe PAD are likely to have muscle sarcopenia due to intermittent claudication, rest pain, and CLI.²⁷ In the present study, PAD severity was significantly associated with muscle sarcopenia, as measured with FFMI. Therefore, it is possible that eGFRcys is superior to eGFRcr for evaluating kidney function

in patients with PAD because eGFRcys is less affected by muscle sarcopenia.

eGFRcys and Clinical Outcome

Several reports indicated that eGFRcys could provide better estimates for clinical risk at GFR ≥ 60 ml/min/1.73 m², and that it is linearly associated with mortality.^{26,28} In CKD patients, eGFRcys has been associated with a higher risk for cardiovascular disease development and mortality.^{29–31} Earlier publications demonstrated that eGFRcys can more accurately predict clinical outcome than eGFRcr and that eGFRcys-based CKD staging can improve risk stratification of end-stage renal disease in patients with diabetes mellitus.^{31,32} Similarly, in the present study eGFRcys was found to have superior prognostic value to eGFRcr and can be used to risk stratify PAD patients more precisely than eGFRcr.

Conversely, we performed subgroup analysis in patients without CLI to examine whether eGFRcr can predict MACCE, because these patients did not have advanced muscle sarcopenia. Interestingly, eGFRcr was significantly associated with MACCE on multivariate Cox proportional hazard regression analysis (Table S1). Therefore, muscle sarcopenia and CLI are important factors to determine the appropriate eGFR.

Clinical Perspective

eGFRcys measurement according to KDIGO guideline is recommended for patients with PAD who undergo amputation. Measurement of eGFRcys may also be useful in PAD patients with muscle sarcopenia, who are at high risk of amputation.

Study Limitations

These results should be interpreted with regard to the small number of study subjects. The ROC curves are highly dependent on study population, and the findings may be different in another set of patients. Further studies with larger cohorts are necessary to better delineate the prognostic value of eGFRcys in patients with PAD.

Conclusions

eGFRcys had superior prognostic value to eGFRcr in PAD patients with muscle sarcopenia. eGFRcys is a feasible biomarker for risk stratification and prediction of morbidity and mortality in patients with PAD.

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Conflict of Interest

None.

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Supplementary Files

Supplementary File 1

Table S1. Predictors of MACCE in PAD patients without CLI

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-0762