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ORIGINAL RESEARCH

Vascular Calcification as a Novel Risk Factor for Kidney Function Deterioration in the Nonelderly

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BACKGROUND: The relationship between vascular calcification and chronic kidney disease is well known. However, whether vascular calcification affects renal function deterioration remains unclear. We investigated whether kidney function deteriorated more rapidly in individuals with higher vascular calcification indicated by the coronary artery calcium score (CACS).

METHODS AND RESULTS: Individuals with a normal estimated glomerular filtration rate (>60 mL/min per 1.73 m^2) who underwent cardiac computed tomography in our institution (a tertiary teaching hospital in Cheonan, Korea) from January 2010 to July 2012 were retrospectively reviewed. All participants were aged 20 to 65 years. Among 739 patients, 447, 175, and 117 had CACSs of 0, 1 to 99, and ≥100 units, respectively. The participants were followed for 7.8 (interquartile range, 5.5–8.8) years. The adjusted annual estimated glomerular filtration rates declined more rapidly in patients in the CACS ≥100 group compared with those in the CACS 0 group (adjusted-β, −0.40; 95% CI, −0.80 to −0.03) when estimated using a linear mixed model. The adjusted hazard ratio in the CACS ≥100 group for Kidney Disease: Improving Global Outcomes criteria (a drop in estimated glomerular filtration rate category accompanied by a 25% or greater drop in estimated glomerular filtration rate) was 2.52 (1.13–5.61). After propensity score matching, more prevalent renal outcomes (13.2%) were observed in patients with a CACS of ≥100 compared with those with a CACS of 0 (1.9%), with statistical significance (P=0.004).

CONCLUSIONS: Our results showed that renal function declined more rapidly in patients with higher CACSs, suggesting that vascular calcification might be associated with chronic kidney disease progression.

Key Words: chronic kidney disease ■ coronary artery calcium ■ renal function ■ risk factor ■ vascular calcification

The prevalence of chronic kidney disease (CKD) is increasing, resulting in an increased global health burden.[1] There have been numerous efforts to prevent the progression of CKD to end-stage renal disease.[2,3] As results of these efforts, aging, male sex, race, hypertension, diabetes mellitus (DM), obesity, smoking, metabolic syndrome, and proteinuria have been identified as the traditional risk factors of CKD.[4–11] The progression of CKD to later stages or even to end-stage renal disease needs to be prevented by managing these and other yet unveiled risk factors.[12,13] In this context, several studies have revealed novel risk factors including acute kidney injury (AKI),[14] nonalcoholic fatty liver,[15] the use of proton pump inhibitors,[16,17] and sleep disturbances.[18] Because both identifying unknown risk factors for CKD and mitigating modifiable risk factors for CKD are crucial in the management of CKD patients, efforts to identify emerging risk factors for CKD should continue.[19]

Increased vascular calcification in patients with CKD is obvious and unquestionable.[20–22] Based on the association between CKD and vascular calcification, the

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CLINICAL PERSPECTIVE

What Is New?

- This study showed that a higher coronary artery calcification score was associated with rapid renal function decline.

What Are the Clinical Implications?

- Vascular calcification was considered a consequence of chronic kidney disease.
- However, vascular calcification might be a possible mechanism of chronic kidney disease pathogenesis.
- Additionally, this study endorsed the association between atherosclerosis and the rapid deterioration of renal function.

Nonstandard Abbreviations and Acronyms

CACS	coronary artery calcification scores
PSM	propensity score matching

concept of CKD-mineral bone disease has arisen[23] and vascular calcification has been thought to be a consequence of CKD.[20] As risk factors for vascular calcification, previous studies have identified not only CKD but also aging, DM, dyslipidemia, hypertension, male sex, and cigarette smoking.[24] It is not surprising that these factors are also risk factors for CKD progression.

Vascular calcification is a feature of atherosclerosis.[25] Coronary artery calcification is considered the most reliable, predictable cardiovascular marker in the asymptomatic general population, and it is useful to guide the implementation of prophylactic interventions such as statins and/or aspirin.[26] Although the risk factors for vascular calcification are also known as risk factors for CKD progression, whether severe vascular calcification contributes to a rapid decline in renal function remains unclear. Aortic arch calcification might be associated with the deterioration of renal function in patients with CKD stage 3 to 5.[27,28] However, the association between coronary artery calcification scores (CACSs) and renal deterioration has not been elucidated. Thus, the objective of this study was to investigate whether kidney function might deteriorate more rapidly in individuals with higher CACSs, an index of vascular calcification.

METHODS

The data of this study are available from the corresponding author on reasonable request.

Study Population

We retrospectively collected data from patients aged between 20 and 65 years who underwent cardiac computed tomography (CT) at our institution (Soonchunhyang University Cheonan Hospital, Cheonan, Korea) between January 2010 and July 2012 for the following reasons: (1) estimation of the risk of general anesthesia for elective surgery; (2) angina symptoms including chest pain, chest tightness, dyspnea, and dizziness without the need for an emergency evaluation because the symptoms were nonspecific or the onset of the manifestation was a long time ago; or (3) asymptomatic ECG abnormalities with a low possibility of an acute coronary syndrome such as nonspecific ST-T changes, T wave inversion, or left ventricular hypertrophy. Patients were considered eligible for this study when they had a baseline estimated glomerular filtration rate (eGFR) of ≥60 mL/min per 1.73 m^2 with follow-up eGFR data for more than 1 year. To exclude the effect of an AKI, patients with a 100% increase in serum creatinine within 30 days were classified as having AKI and excluded from the study. As our patients showed normal creatinine levels, a 50% increase in serum creatinine could lead to misinterpretation. For example, if we used a 50% increase in serum creatinine as the definition for AKI, the patients with a baseline creatinine 0.60 mg/dL, which increased to 0.91 mg/dL after 30 days, could be defined as having AKI. However, this increase could be the result of minor perturbations in the creatinine levels rather than AKI, given that studies with AKI in the outpatient setting are lacking.

The study protocol was reviewed and approved by the institutional review board of Soonchunhyang University Cheonan Hospital (Cheonan, Korea) (IRB-No: SCHCA 2019-05-005). The study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective study design.

Measurement of Coronary Artery Calcium Score and Covariates

After the CT scan, the CACS was calculated according to a previously established method described by Agatston.[29] Patient data were collected from electronic medical records and laboratory findings. These data including age, sex, body mass index (BMI), history of hypertension, DM, or dyslipidemia, and use of renin-angiotensin system blocker (eg, angiotensin receptor blocker or angiotensin-converting enzyme inhibitor) were acquired during general medical practice by reviewing electronic medical records and medication. BMI was calculated as kilograms divided by height in meters squared. The baseline laboratory data,

including hemoglobin, serum creatinine, albumin, total cholesterol, triglycerides, uric acid, calcium, phosphorus, and proteinuria, were acquired within 3 months of undergoing cardiac CT. When the statistical analysis was performed for proteinuria, the urine protein measured by a dipstick test was graded into 4 stratifications of negative, trace, 1+, and 2+ or over, as described elsewhere.[30] However, the number of patients with urine protein values of 1+ or 2+ or over were too small. Therefore, we merged the urine protein values of 1+ and 2+ or over into 1+ or over.

Serum creatinine assays were standardized by isotope-dilution mass spectrometry, a reference method for use in the Chronic Kidney Disease Epidemiology Collaboration equation.[31] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Laboratory data outside the duration, within 3 months of undergoing cardiac CT as described previously, were considered to have no baseline values. Follow-up eGFR data were collected until July 2020.

Estimation of Annual Rate of Decline in eGFR and Renal Outcomes

The data were analyzed by computing the median rate of decline in eGFR (eGFR slope) and the time-to-event. The eGFR slope was calculated from a linear mixed model using all eGFR measurements as described elsewhere.[32] The primary renal outcome for the time-to-event analysis was defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria as a sustained drop in the GFR category accompanied by a 25% or greater drop in eGFR from baseline.[33,34] When the reduction was confirmed by measurements at least 3 months apart without recovery, it was considered that renal outcome had developed.

Statistical Analysis

All statistical analyses were performed using SPSS 26.0 for Windows (SPSS, Inc., Chicago, IL) and R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). The categorical variables are expressed as counts (percentage). The normally distributed continuous variables are expressed as the mean±SD. Otherwise, they are presented as the median (interquartile ranges). Based on the CACS, all patients were categorized into 3 groups. Patients with a CACS of 0 were assigned to the CACS 0 group. Those with a CACS of >0 were divided into 2 groups, 1 to 99 or ≥100, based on a previous CACS study.[26] The groups were compared using 1-way ANOVA for normally distributed continuous variables, the Kruskal-Wallis test for nonnormally distributed continuous variables, and Pearson's chi-square test for categorical variables. As a trend test, the linear-by-linear association test and the Jonckheere-Terpstra test were used for categorical and continuous variables, respectively. In all analyses, a P value of <0.05 was considered statistically significant.

To adjust for other covariates, covariates including age, sex, BMI, hypertension, DM, baseline eGFR, and urine dipstick protein were selected. Additional annual declines in eGFR were calculated using linear mixed models in which the fixed effects included time, eGFR, and eGFR*time. Random intercept and random slope models were used. P values and CIs of the linear mixed models were estimated by Satterthwaite approximations for degrees of freedom. For the adjusted results, confounders and the interaction terms for each confounder×time were added. Cox proportional hazards models were used to determine the association between CACSs and the risk of renal progression. Multivariable Cox proportional hazards regression analyses were conducted by stratifying to determine associations between the calcium scores and outcomes. The proportional hazards assumption was tested using Schoenfeld residuals. In the Cox regression models, statistical significance was considered when the 95% CI of a hazard ratio did not include 1.0.

Propensity score matching (PSM) with the nearest method and a 0.1 caliper was used for sensitivity analysis. In PSM, age, sex, hypertension, DM, dyslipidemia, proteinuria, BMI, albumin, baseline eGFR, and use of renin-angiotensin system blocker were matched.

RESULTS

Characteristics of Study Population

A diagram of patient enrollment is shown in Figure 1. A total of 4019 individuals underwent cardiac CT from January 2010 to July 2012. Among them, 1937 were excluded because they did not meet the age criterion (age between 20 and 65). If there were no eGFR results within 90 days of the CT scans, the patient was defined as not having a baseline eGFR and was excluded from the study. A total of 1147 patients were excluded for the following reasons: (1) 258 were missing baseline eGFR data; (2) 88 had a baseline eGFR of <60 mL/min per 1.73 m^2; (3) 518 were missing eGFR follow-up data for more than 1 year; (4) 171 had missing baseline proteinuria data; and (5) 112 had missing BMI data. Among the remaining 935 eligible patients, 93 were excluded because they were considered to have AKI, and 103 were excluded because they had concomitant diseases that could affect renal function deterioration, including congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, and any cancer. The patient cohort before excluding those with the comorbidities listed are represented in Table S1.

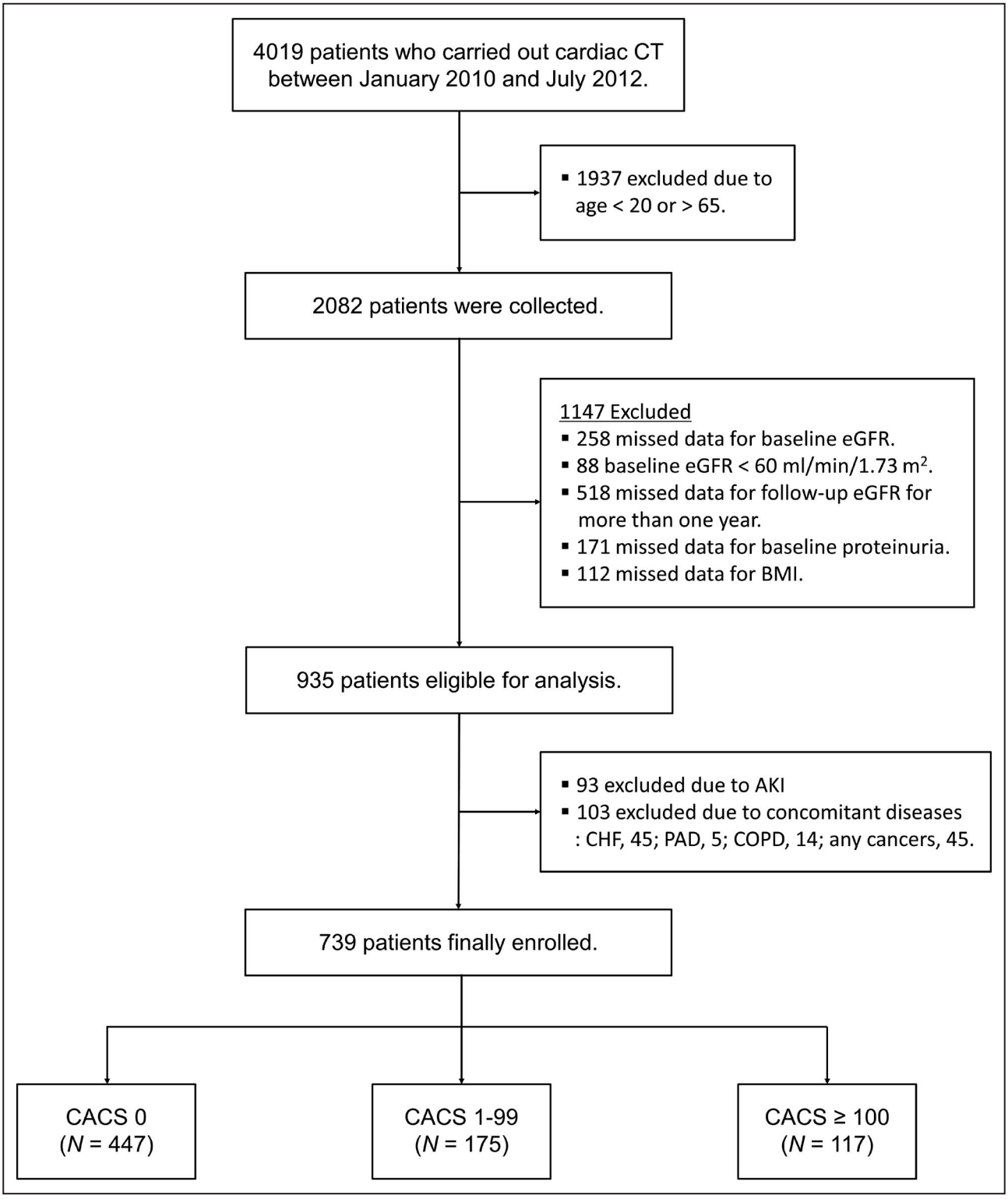

Figure 1. Flow chart outlining patient enrollment.
The patients were grouped into tertiles according to calcium scores of CACS 0, CACS 1 to 99, and CACS ≥100. AKI indicates acute kidney injury; BMI, body mass index; CACS, coronary artery calcium score; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CT, computed tomography; eGFR, estimated glomerular filtration rate; and PAD, peripheral artery disease.

The remaining 739 patients were followed for a median of 7.8 (5.5–8.8) years. Of these patients, 447 had a CACS of 0 (CACS 0 group). The patients with CACS of >0 were categorized into 2 groups, the CACS 1 to 99 group and the CACS ≥100 group (Table 1). The patients with higher CACSs were

Table 1. Baseline Characteristics According to Stratification of CACS (N=739)

Variables	CACS 0 (n=447)	CACS 1–99 (n=175)	CACS ≥100 (n=117)	*P* Value
Age, y	52 (47–57)	56 (53–61)	60 (55–62)	<0.001
Male sex, n (%)	222 (49.7)	103 (58.9)	90 (76.9)	<0.001
Body mass index, kg/m^2	24.6 (22.7–26.9)	25.3 (23.2–27.7)	25.7 (23.8–27.2)	0.006
Hypertension, n (%)	196 (43.8)	104 (59.4)	90 (76.9)	<0.001
Diabetes mellitus, n (%)	97 (21.7)	67 (38.3)	59 (50.4)	<0.001
Dyslipidemia, n (%)	116 (26.0)	82 (46.9)	75 (64.1)	<0.001
Hemoglobin, g/dL	14.0 (13.0–15.3)	13.9 (12.9–15.0)	14.1 (13.1–15.2)	0.795
Urea nitrogen, mg/dL	12.6 (10.3–15.5)	13.6 (11.1–16.8)	13.9 (11.8–16.4)	0.001
Creatinine, mg/dL	0.7 (0.6–0.8)	0.7 (0.6–0.9)	0.8 (0.7–0.9)	<0.001
Albumin, g/dL	4.6 (4.4–4.8)	4.5 (4.2–4.8)	4.5 (4.3–4.7)	0.001
Aspartate aminotransaminase, IU/L	22 (18–28)	22 (18–28)	23 (20–30)	0.035
Alanine aminotransaminase, IU/L	22 (15–31)	23 (16–33)	23 (18–33)	0.136
Total bilirubin, mg/dL	0.5 (0.4–0.7)	0.5 (0.3–0.6)	0.5 (0.3–0.7)	0.256
Total cholesterol, mg/dL	186 (161–212)	183 (160–210)	179 (142–212)	0.161
Non-high-density lipoprotein cholesterol, mg/dL	138 (114–167)	138 (116–171)	135 (101–168)	0.376
Triglycerides, mg/dL	127 (88–188)	137 (95–208)	147 (107–206)	0.007
Uric acid, mg/dL	4.6 (3.7–5.6)	4.9 (4.0–5.8)	5.2 (4.4–6.3)	0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	104.9 (99.2–111.7)	101.1 (95.1–107.0)	99.2 (93.7–104.0)	<0.001
Renin-angiotensin system blocker, n (%)	90 (20.1)	38 (21.7)	41 (35.0)	0.003
Urine dipstick protein				0.045
Negative	361 (80.8)	136 (77.7)	81 (69.2)	
Trace	74 (16.6)	29 (16.6)	29 (24.8)	
1+ or over	12 (2.7)	10 (5.7)	7 (6.0)	
Follow-up duration, y	7.8 (5.5–8.8)	7.8 (5.0–8.7)	8.1 (6.6–9.0)	0.117

The data are presented as median (interquartile range) or count (%) as appropriate. *P* values were calculated using the Kruskal-Wallis test and Pearson's χ^2 test for categorical variables. There was 1 (0.1%) missing urea nitrogen, albumin, and total bilirubin value; 7 (0.9%) missing total cholesterol and triglyceride values; 100 (13.5%) missing non-high-density lipoprotein cholesterol values; and 120 (16.2%) missing uric acid values. CACS indicates coronary artery calcium score.

older, and there were more men, higher baseline creatinine levels, and a higher prevalence of hypertension, DM, and dyslipidemia. However, the levels of albumin and total cholesterol were lower in these patients (Table 1). The patients included in the higher CACS group had lower eGFRs and more prominent proteinuria than those in the CACS 0 group.

Table 2. Estimation of Additional Annual eGFR Changes According to the Stratification of CACS (N=739)

	Additional Annual eGFR Change, mL/min/1.73 m^2 per y		
	Model 1*	Model 2†	Model 3‡
CACS 0	Reference	Reference	Reference
CACS 1–99	−0.24 (−0.56 to 0.08)	−0.34 (−0.67 to 0.02)§	−0.26 (−0.59 to 0.07)
CACS ≥100	−0.45 (−0.82 to −0.10)§	−0.60 (−0.98 to −0.22)‖	−0.40 (−0.80 to −0.03)§

Additional annual eGFR changes with 95% CIs were calculated by linear mixed models. The fixed effects included time, eGFR, and eGFR*time. For the adjusted results, confounders and interaction terms for each confounder × time were added. CACS indicates coronary artery calcium score; and eGFR, estimated glomerular filtration rate.

*Model 1: not adjusted.

†Model 2: adjusted for age, sex, and body mass index.

‡Model 3: adjusted for Model 2 variables plus diabetes mellitus, hypertension, dyslipidemia, urine dipstick protein, and use of renin-angiotensin system blocker.

§$P<0.05$.

‖$P<0.01$.

Table 3. Hazard Ratios for Renal Outcomes According to CACS (N=739)

CACS	N	No. of Event	Model 1*	Model 2†	Model 3‡
CACS 0	447	17 (3.8)	Reference	Reference	Reference
CACS 1–99	175	13 (7.4)	2.10 (1.02–4.33)§	2.06 (0.97–4.38)	1.53 (0.71–3.33)
CACS ≥100	117	16 (13.7)	3.49 (1.76–6.91)‖	3.41 (1.58–7.35)¶	2.52 (1.13–5.61)§

Hazard ratios (95% CI) were determined by multivariable Cox proportional hazard models adjusted for confounding variables. Renal outcome was based on Kidney Disease: Improving Global Outcomes criteria, which were defined by a sustained drop in the GFR category accompanied by a 25% or greater drop in the eGFR from baseline. CACS indicates coronary artery calcium score; and eGFR, estimated glomerular filtration rate.

*Model 1: not adjusted.

†Model 2: adjusted for age, sex, and body mass index.

‡Model 3: adjusted for Model 2 variables plus diabetes mellitus, hypertension, dyslipidemia, baseline estimated glomerular filtration rate, urine dipstick protein, and use of renin-angiotensin system blocker.

§$P<0.05$.

‖$P<0.001$.

¶$P<0.01$.

Annual Rates of Decline in eGFR

The additional rates of annual eGFR decline were faster in patients with higher CACSs than in the CACS 0 group (Table 2). In the unadjusted models, the patients with a CACS of ≥100 showed a more rapid decline in the eGFR of −0.45 (−0.82 to −0.10). In the final model adjusted for age, sex, BMI, DM, hypertension, dyslipidemia, baseline eGFR, proteinuria, and use of renin-angiotensin system blocker, the rates of eGFR decline were more rapid in the group with a CACS of ≥100 than in the CACS 0 group by −0.40 (−0.80 to −0.03).

Association Between CACS and Risk of Renal Outcome

Patients in the CACS ≥100 group experienced 16 (13.6%) events among 117 patients based on the KDIGO criteria (Table 3). However, only 3.8% of the 447 patients in the CACS 0 group experienced an event. In the CACS ≥100 group, a nearly 2.5-fold increased hazard ratio was observed after adjustment for other covariates. The hazard ratio increased log-linearly up to CACS 300, then slightly decreased (Figure 2).

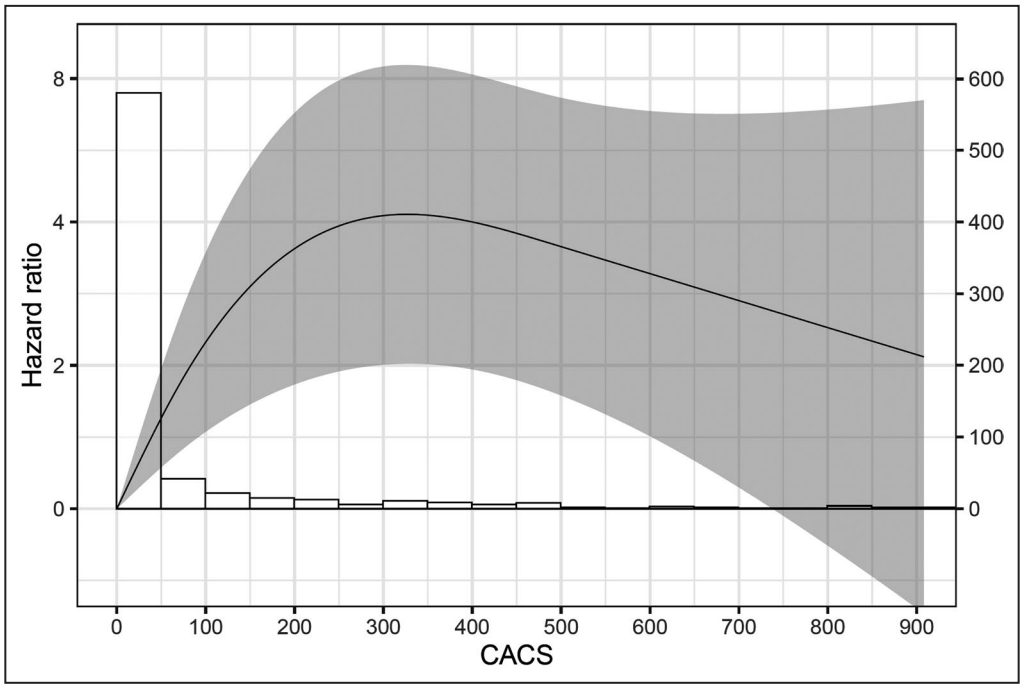

Figure 2. A restricted cubic spline of CACS and adjusted hazard ratio of renal outcome.
Curves represent adjusted hazard ratio (natural log-transformed) and the 95% CIs (shaded area) based on restricted cubic splines for CACS. The model was adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, proteinuria, body mass index, baseline estimated glomerular filtration rate, and use of renin-angiotensin system blocker. CACS indicates coronary artery calcium score.

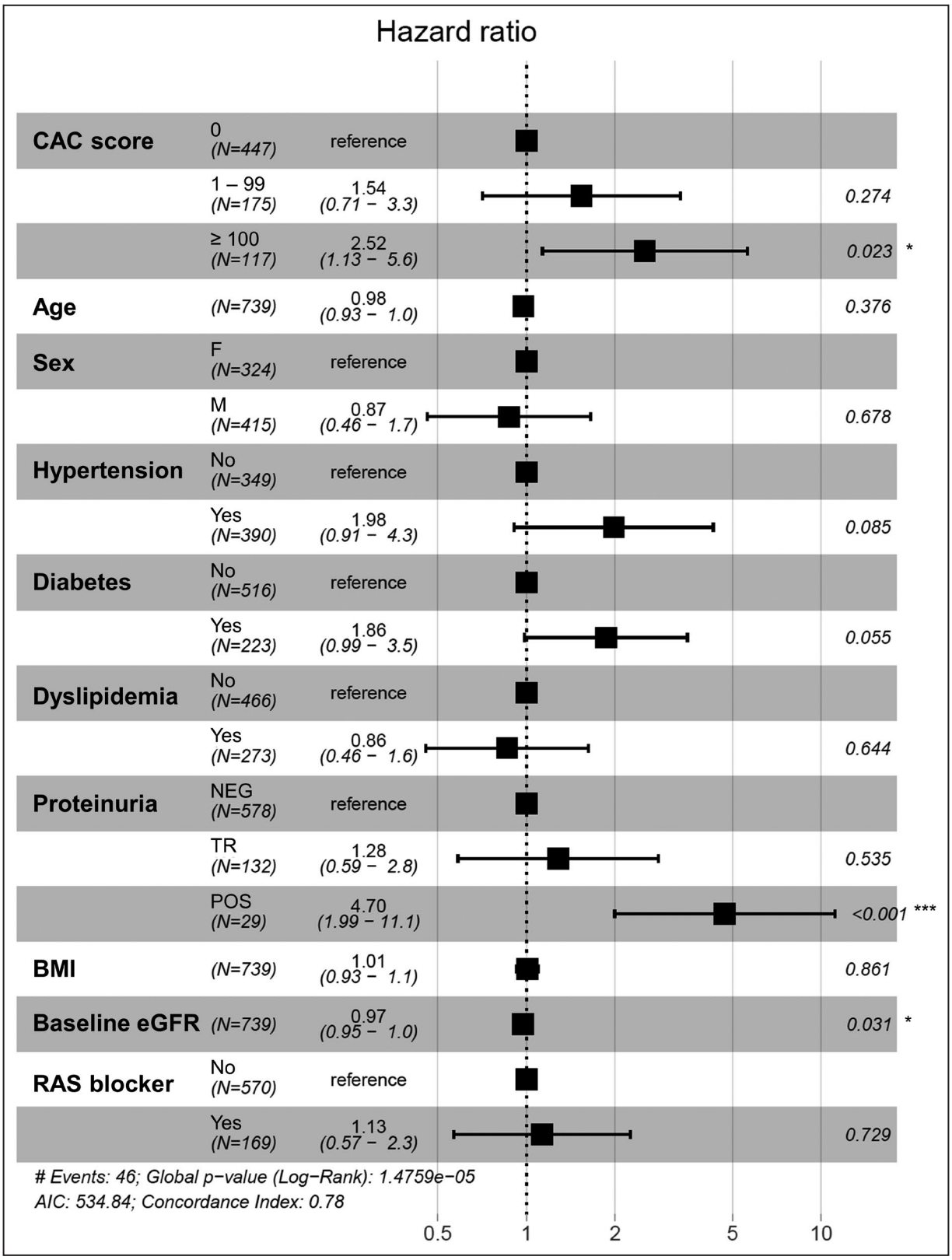

Figure 3. Hazard ratio plot of variables associated with renal outcome defined by KDIGO criteria.
Squares indicate hazard ratio; error bars, 95% CIs;. dotted line, a line of hazard ratio 1. *P<0.05, ***P<0.001). AIC indicates Akaike's information criterion; BMI, body mass index; CAC, coronary artery calcium; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; and RAS, renin-angiotensin system.

In addition to the CACS, the baseline eGFR and proteinuria were associated with an increased hazard ratio for the renal outcome as defined by the KDIGO criteria (Figure 3). More rapid deterioration of renal function was observed in the CACS ≥100 group compared with the CACS 0 group (Figure 4).

Sensitivity Analyses

There were dissimilarities between the groups. Although the models were adjusted for other covariates, rather large differences between the groups might have induced bias even after the adjustment. These biases could be reduced using PSM.[35] Other covariates were identical between the CACS 0 and CACS ≥100 groups after PSM (Table 4). More prevalent renal outcomes were observed in the CACS ≥100 group (14 patients, 13.2%) when compared with the CACS 0 group (2 patients, 1.9%), with statistical significance (*P*=0.004).

Figure 5 depicts the eGFR trajectories of the 2 propensity-score-matched groups (CACS of 0 versus CACS ≥100) with fitted lines and 95% CIs. The fitted line of the eGFR trajectories was nearly linear. The eGFR declined more rapidly in CACS ≥100 group, although there was no difference in the baseline eGFR between 2 propensity-score-matched groups (Table 4).

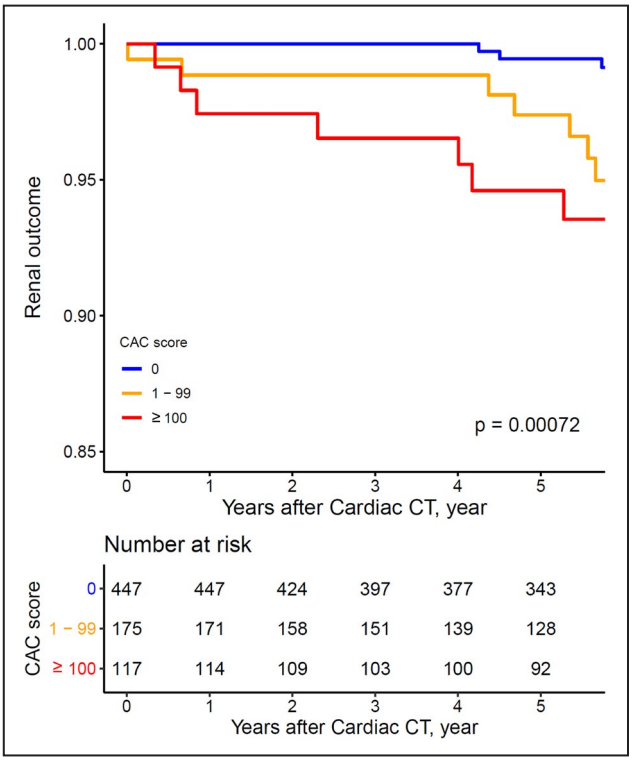

Figure 4. Kaplan-Meier curve of renal outcomes according to CACS groups.
The probability of renal outcome development in the entire cohort is presented. Renal outcomes were defined by KDIGO criteria as a sustained drop in the GFR category accompanied by a 25% or greater drop in the eGFR from baseline. CAC indicates coronary artery calcium; CT, computed tomography; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

DISCUSSION

To the best of our knowledge, this was the first study to show a relationship between CACS, a representative marker of vascular calcification, and renal function deterioration in nonelderly individuals with normal eGFRs. It is broadly appreciated that vascular calcification, including coronary artery calcification, is attributed to CKD.[36] As mentioned previously, previous studies have shown that the presence of aortic arch calcification was associated with the faster deterioration of renal function in patients with CKD stage 3 to 5.[27,28] Beyond such previous knowledge, our results consolidated evidence that renal function declined more rapidly in patients with higher CACSs and that vascular calcification could also be a risk factor for CKD. Putative mechanisms to explain our results remain unclear. Nonetheless, our results raised a scientific dilemma regarding the relationship between vascular calcification and CKD. The genetic and metabolic characteristics of the individuals may explain the association between higher vascular calcification and the rapid decline in renal function.

There is a direct relationship between atherosclerosis and the rapid deterioration of renal function. In a previous study, a higher atherosclerotic burden based on the intima-media thickness of the common carotid arteries resulted in an accelerated decrease in renal size and function with increasing age.[37] The effect of atherosclerosis on microvascular rarefaction[38] can also explain our novel findings. Autopsy studies found that systemic atherosclerosis was associated with renal atherosclerosis and that it increased the rate of global glomerulosclerosis.[39,40] It has been reported that renal function declined faster in patients with severe arteriosclerosis or arteriolosclerosis after tumor nephrectomy.[41] Patients with abdominal aortic calcification have shown delayed renal function recovery after undergoing living donor kidney transplantation.[42]

The relationship between atherosclerosis and the rapid decline in renal function may be explained indirectly by arterial stiffness because atherosclerosis is associated with arterial stiffness.[43] Previous studies have shown that patients with arterial stiffness have more rapid renal function decline and a higher incidence of CKD.[44,45] The renal resistive index measured by Doppler ultrasonography correlates well with renal arteriolosclerosis[46,47] and is a predictive factor for renal progression.[48,49] Arterial stiffness caused by atherosclerosis exposes glomerular capillaries to the detrimental effect of higher pulse pressure, resulting

Table 4. Hazard Ratios for Renal Outcomes According to CACS After Propensity Score Matching (N=212)

Variables	CACS 0 (n=106)	CACS ≥100 (n=106)	*P* Value
Renal outcome, n (%)*	2 (1.9)	14 (13.2)	0.004
Age, y	58 (54–62)	59 (55–62)	0.900
Male sex, n (%)	77 (72.6)	79 (74.5)	0.876
BMI, kg/m^2	25.1 (23.5–27.1)	25.9 (23.8–27.3)	0.420
Hypertension, n (%)	78 (73.6)	79 (74.5)	0.999
DM, n (%)	43 (40.6)	48 (45.3)	0.579
Dyslipidemia, n (%)	56 (52.8)	65 (61.3)	0.267
Hemoglobin, g/dL	14.4 (13.3–15.4)	14.0 (13.0–15.3)	0.156
Urea nitrogen, mg/dL	13.6 (10.7–16.7)	13.7 (11.4–16.3)	0.875
Creatinine, mg/dL	0.8 (0.7–0.9)	0.9 (0.7–1.0)	0.094
Albumin, g/dL	4.5 (4.2–4.8)	4.5 (4.3–4.7)	0.571
Aspartate aminotransaminase, IU/L	24 (19–30)	23 (20–30)	0.863
Alanine aminotransaminase, IU/L	23 (17–35)	23 (17–32)	0.876
Total bilirubin, mg/dL	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.661
Total cholesterol, mg/dL	187±42	180±43	0.241
Non-HDL cholesterol, mg/dL†	136 (113–173)	135 (109–169)	0.438
Triglycerides, mg/dL	140 (104–223)	147 (108–205)	0.606
Uric acid, mg/dL†	4.9±1.2	5.2±1.4	0.097
eGFR, mL/min per 1.73 m^2	90.5 (79.6–97.6)	89.9 (70.2–95.4)	0.186
RAS blocker, n (%)	30 (28.3)	35 (33.0)	0.551
Urine dipstick protein			
Negative	77 (70.6)	78 (71.6)	0.987
Trace	26 (23.9)	25 (22.9)	
1+ or over	6 (5.5)	6 (5.5)	
Follow-up duration, y	8.1 (5.5–9.0)	8.0 (6.6–9.0)	0.783

Propensity score matching was done using covariates, including age, sex, hypertension, DM, dyslipidemia, proteinuria, BMI, albumin, baseline eGFR, and use of RAS blocker, as matching variables. The data are presented as median (interquartile range) or count (%) as appropriate. *P* values were calculated using the Kruskal-Wallis test and Pearson's chi-square test for categorical variables. BMI indicates body mass index; CACS, coronary artery calcium score; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and RAS, renin-angiotensin system.

*Renal outcome was based on Kidney Disease: Improving Global Outcomes criteria, which were defined by a sustained drop in the GFR category accompanied by a 25% or greater drop in the eGFR from baseline.

†There were 26 (11.9%) missing non-HDL cholesterol values and 17 (7.8%) missing uric acid values.

in glomerular sclerosis.[50] Thus, arterial stiffness is a putative mechanism underlying the association between vascular calcification and rapid renal function decline.[51] Evidence suggests that renal function deteriorates rapidly in patients with higher vascular calcification because vascular calcification is a clinical marker of atherosclerosis.[52]

Chronic inflammation has a causal relationship with vascular calcification.[25] A previous study using fluorodeoxyglucose-positron emission tomography coupled with CT reported that arterial inflammation preceded calcification in human atherosclerosis.[53] Therefore, systemic inflammation may be more severe in patients with more severe vascular calcification.[54] The molecular mechanisms by which inflammation induces vascular calcification have been reported in several studies.[55] Because renal function deteriorates rapidly in patients with higher systemic inflammation,[56] renal function might decline faster in patients with higher CACSs.

Several metabolic and genetic components that affect vascular calcification might be associated with the rapid renal progression in patients with higher CACSs. Ahlqvist et al[57] reported that patients with DM manifesting with the highest insulin resistance showed the most rapid decline in renal function. In nondiabetic patients, metabolic syndrome including obesity and insulin resistance also showed a causal relationship with a rapid decrease in renal function.[8,11,58] The correlation between hepatic steatosis and CKD has been reported.[59] In addition, patients with nonalcoholic fatty liver disease showed faster decreases in renal function.[15] Moreover, metabolically healthy obese patients had higher CACSs than metabolically healthy patients with normal weight.[36] In addition, aging and cellular senescence

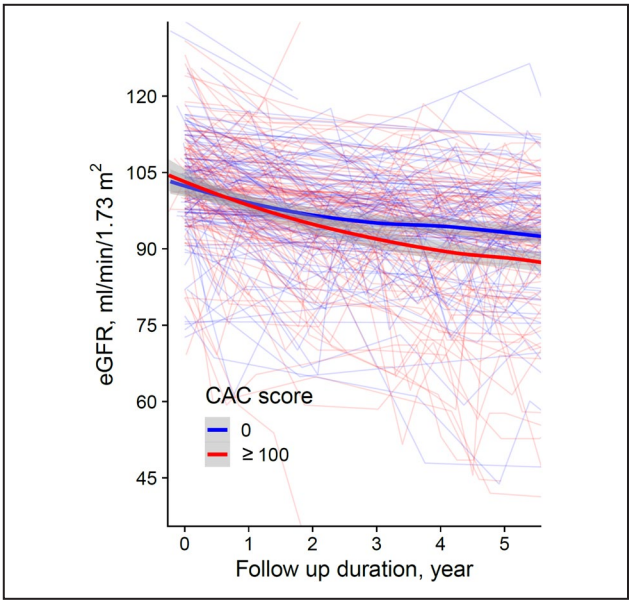

Figure 5. Depicted lines of each patient and the fitted lines of eGFR of each group (N=212).
The patients were matched using propensity score matching. The lines of each patient depict the eGFR with time-acquired serum creatinine levels. The fitted lines of eGFR of each group were calculated using a generalized additive model and drawn with 95% CIs. CAC indicates coronary artery calcium; and eGFR, estimated glomerular filtration rate.

will contribute CKD and vascular calcification.[60,61] In the CRIC (Chronic Renal Insufficiency Cohort) study, several loci were discovered to be associated with CAC in CKD patients.[62] Similarly, in the MESA study (Multi-Ethnic Study of Atherosclerosis), genome-wide association studies revealed associations between several single nucleotide polymorphisms and CAC,[63] including COL4A1 in both studies. Recent studies have continuously uncovered genetic relationships between CKD and other vascular diseases.[64,65] Given these previous reports, the correlation between vascular calcification and rapid renal progression can be explained by metabolic and genetic components.

Previous studies have suggested that CACS is increased during renal function deterioration and considered as a bystander in CKD and that it is determined by well-known traditional risk factors such as age, DM, hypertension, and dyslipidemia rather than a cause of CKD. However, the prognosis can vary even in individuals of similar age and comorbidities. Similarly, CACS has been used to determine the role of statins in the prevention of cardiovascular disease.[66] It can be used as a novel marker to explain the differences between individuals who have similar traditional risk factors for renal progression.

Our study had several limitations. First, this was a retrospective study that could lead to bias. Thus, we performed PSM to reduce bias. Despite these efforts, not all possible bias could be eliminated. Second, a history of smoking, considered a risk factor for renal progression, was not investigated in this study. Third, creatinine-based eGFRs rather than measured GFRs were used. In patients with normal GFRs, creatinine-based eGFRs could erroneously reflect the real renal function. The disadvantage of using creatinine-based eGFRs is that even a small perturbation in the creatinine level can cause a large change in the eGFR.[67] Thus, we defined renal progression when the reduction in eGFR lasted more than 3 months without recovery. It is important to recognize that eGFR does not recover after 3 months. This made our study robust. Furthermore, only patients between the ages of 20 and 65 were included. Thus, the validity of creatinine-based eGFRs was assumed to be sufficient. Fourth, death, a competing risk for end-stage renal disease, was not evaluated because confirming death directly using the personal identification number of an individual is prohibited by local law. Fifth, we could not explain a reason that the decline in the hazard ratio in patients with CACS of ≥300. However, it was considered that this result was attributed to fewer patients with higher CACS and that mortality might affect our results as a competing risk, which probably resulted in a reversed association between CACS and renal outcome in patients with CACS of ≥300.

CONCLUSIONS

In conclusion, our study showed that renal function declined more rapidly in patients with higher CACSs, although the causality was not elucidated and the reverse association in patients with CACS ≥300 should be noted. Our results suggest that vascular calcification represented by the CACS was associated with rapid renal progression, not just a consequence of CKD. Although our observations should be validated by other studies before vascular calcification is used as a risk factor for rapid renal progression, our findings shed light on the possible mechanisms of CKD pathogenesis.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics according to stratification of coronary artery calcium score (N = 842).

Variables	CACS 0 (N = 485)	CACS 1 – 99 (n = 209)	CACS ≥ 100 (n = 148)	*P*-value
Age, years	53 (47 – 58)	56 (52 – 61)	60 (55 – 63)	< .001
Male, number (%)	237 (48.9)	124 (59.3)	115 (77.7)	< .001
BMI, kg/m^2	24.7 (22.7 – 27.0)	25.3 (23.1 – 27.9)	25.6 (23.6 – 27.2)	.009
HTN, number (%)	218 (44.9)	122 (58.4)	112 (75.7)	< .001
DM, number (%)	105 (21.6)	80 (38.3)	78 (52.7)	< .001
CHF, number (%)	13 (2.7)	12 (5.7)	20 (13.5)	< .001
PAD, number (%)	1 (0.2)	1 (0.5)	3 (2.0)	0.040
COPD, number (%)	7 (1.4)	2 (1.0)	5 (3.4)	0.179
Cancer, number (%)	18 (3.7)	20 (9.6)	7 (4.7)	0.007
Hemoglobin, g/dL	14.0 (13.0 – 15.3)	13.9 (13.0 – 15.0)	14.0 (13.0 – 15.1)	.867
Urea nitrogen, mg/dL	12.6(10.4 – 15.6)	13.6 (11.1 – 16.9)	14.3 (11.8 – 16.4)	< .001
Creatinine, mg/dL	0.7 (0.6 – 0.8)	0.7 (0.6 – 0.9)	0.8 (0.7 – 0.9)	< .001
Albumin, g/dL	4.6 (4.3 – 4.8)	4.5 (4.2 – 4.7)	4.5 (4.2 – 4.7)	< .001
AST, IU/L	22 (18 – 28)	22 (18 – 28)	23 (20 – 31)	.055
ALT, IU/L	22 (15 – 30)	23 (16 – 33)	24 (18 – 31)	.072
Total bilirubin, mg/dL	0.5 (0.4 – 0.7)	0.5 (0.4 – 0.7)	0.5 (0.3 – 0.7)	.409
Total cholesterol, mg/dL	187 (161 – 214)	184 (161 – 209)	176 (141 – 209)	.018
Non-HDL cholesterol, mg/dL	138 (114 – 167)	138 (115 – 167)	133 (101 – 167)	.227
Triglycerides, mg/dL	129 (89 – 190)	148 (98 – 214)	146 (102 – 203)	.015
Uric acid, mg/dL	4.6 (3.7 – 5.6)	4.7 (4.0 – 5.8)	5.2 (4.3 – 6.3)	< .001
eGFR, mL/min/1.73 m^2	104.8 (98.7 – 111.6)	100.6 (94.5 – 107.0)	99.4 (93.2 – 104.1)	< .001
Urine dipstick protein				.029
Negative	390 (80.4)	159 (76.1)	103 (69.6)	
Trace	82 (16.9)	40 (19.1)	34 (23.0)	
1+ or over	13 (2.7)	10 (4.8)	11 (7.4)	
Follow-up duration, years	7.7 (5.1 – 8.8)	7.8 (5.0 – 8.8)	8.1 (5.5 – 9.1)	.224

Data are presented as median (interquartile range) or count (%) as appropriate. *P*-values are calculated using Kruskal-Wallis test and Pearson's Chi-squared test for categorical variables.
There were 1 (0.1%) missing urea nitrogen, albumin, and total bilirubin, 7 (0.8%) missing total cholesterol and triglycerides, 120 (14.3%) missing non-HDL cholesterol, and 125 (14.9%) missing uric acid.
CACS, coronary artery calcium score; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate.