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ORIGINAL RESEARCH

Left Ventricular Diastolic Dysfunction and Progression of Chronic Kidney Disease: Analysis of KNOW-CKD Data

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BACKGROUND: Few studies have examined the association between the early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio (E/e') and chronic kidney disease progression.

METHODS AND RESULTS: We reviewed data from 2238 patients with nondialysis chronic kidney disease from the KNOW-CKD (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease); data from 163 patients were excluded because of missing content. A >50% decrease in estimated glomerular filtration rate from baseline, doubling of serum creatinine, or dialysis initiation and/or kidney transplantation were considered renal events. At baseline, median (interquartile range) ejection fraction and E/e' were 64.0% (60.0%–68.0%) and 9.1 (7.4–11.9), respectively. Proportions of ejection fraction <50% and E/e' ≥15 were 1.3% and 9.6%, respectively. More than one quarter of patients (27.2%) had an estimated glomerular filtration rate <30 mL/min per 1.73 m^2. During the mean 59.1-month follow-up period, 724 patients (34.9%) experienced renal events. In multivariable Cox proportional hazard regression analysis, the hazard ratio with 95% CI per 1-unit increase in E/e' was 1.027 (1.005–1.050; *P*=0.016). Penalized spline curve analysis yielded a suggested threshold of E/e' for renal events of 12; in our data set, the proportion of E/e' ≥12 was 4.1%.

CONCLUSIONS: Increased E/e' was associated with an increased hazard of renal events, suggesting that diastolic heart dysfunction is a novel risk factor for chronic kidney disease progression.

Key Words: cardiorenal syndrome ■ chronic kidney disease ■ diastolic heart dysfunction ■ early predictor ■ progression

The prevalence of heart failure (HF) in the United States and Europe has been estimated to range from 1% to 14%.[1] In Korea, the prevalence rate of HF in the adult population is 12.4 people per 1000 adults, and this rate is associated with increased socioeconomic burden.[2] HF with preserved ejection fraction (EF) is becoming increasingly common and of clinical interest,[1] and diastolic dysfunction has been proposed as the key pathophysiology underlying HF with preserved EF.[3] To accurately measure diastolic heart function, invasive catheterization is required, which is not always applicable in ordinary practice. To overcome this limitation, several echocardiographic surrogates have been suggested.[4] The early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio (E/e') has been shown to be associated with mortality and cardiovascular hospitalization.[5] However, the diagnostic accuracy of E/e' as an indicator of left ventricular (LV) filling pressure needs further research.[6]

Heart and kidneys affect each other, and the term "cardiorenal syndrome" (CRS) is used ubiquitously.

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CLINICAL PERSPECTIVE

What Is New?

- There are complex links between the heart and the kidneys; however, there were few studies to reveal the association between left ventricular dysfunction and the progression of chronic kidney disease (CKD).
- We found that among patients with nondialysis CKD, increment of early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio, measured by echocardiography, was significantly associated with the CKD progression, defined as a >50% decrease in estimated glomerular filtration rate from baseline, doubling of serum creatinine, dialysis initiation, and/or kidney transplantation.

What Are the Clinical Implications?

- The risk of CKD progression according to the increment of early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio was evident in patients with otherwise nondialysis CKD; thus, the current findings suggest that early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio might be a potential early risk factor for CKD progression.

Nonstandard Abbreviations and Acronyms

CRS	cardiorenal syndrome
E/e'	early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio
KNOW-CKD	Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease

According to Ronco et al, there are 4 distinctive types of CRS: the heart affects the kidney acutely (CRS type 1) or chronically (CRS type 2), or the kidney affects the heart acutely (CRS type 3) or chronically (CRS type 4).[7] The main pathophysiology of CRS was previously assumed to be renal ischemia secondary to forward pump failure. However, CRS can develop in patients with HF with preserved EF; diastolic dysfunction and the resultant high central venous pressure have been proposed to play important roles in the development of CRS in patients with HF with preserved EF.[8–10] Diastolic dysfunction can likely contribute to chronic kidney disease (CKD) progression as a component of CRS type 2. This possibility has not been explored in the medical literature.

Our aim in this study, therefore, was to identify the effect of diastolic dysfunction, as assessed by E/e', on the risk of progression of CKD using data from a large number of adults enrolled in the KNOW-CKD (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease).

METHODS

Data Sharing Statement

Because of ethical issues and data protection regulations, data that support the findings of the present study cannot be made publicly available.

Study Subjects

The KNOW-CKD is a multicenter prospective cohort study in Korea of 2238 patients with nondialysis CKD, stages 1 to 5, enrolled from February 2011 through January 2016. Details of the design and methods used in the KNOW-CKD have been published previously (NCT01630486 at http://www.clinicaltrials.gov).[11,12] CKD and its stages were defined using the Kidney Disease Improving Global Outcomes 2012 guidelines.[12] The study protocol was approved by the institutional review board of each participating clinical center: Seoul National University Hospital (1104-089-359), Seoul National University Bundang Hospital (B-1106/129–008), Yonsei University Severance Hospital (4-2011-0163), Kangbuk Samsung Medical Center (2011–01-076), Seoul St. Mary's Hospital (KC11OIMI0441), Gil Hospital (GIRBA2553), Eulji General Hospital (201105-01), Chonnam National University Hospital (CNUH-2011-092), and Pusan Paik Hospital (11-091) in 2011. The protocol of KNOW-CKD adhered to the principles of the Declaration of Helsinki, and written informed consent was obtained from all subjects.

Of the 2238 patients, 163 were excluded from this study: these comprised 146 patients with missing echocardiographic measures and 17 patients with missing data on medical history, blood pressure, pulse pressure, and/or body mass index. Therefore, 2075 patients were included in the final analyses (Figure 1).

Echocardiographic Measurements

Complete 2-dimensional M-mode and Doppler studies were performed via standard approaches by cardiologists of the participating hospitals who were blinded to the clinical data. M-mode examination was performed according to American Society of Echocardiography guidelines.[13] Recorded echocardiographic data were LV end-diastolic diameter, LV end-systolic diameter, interventricular septum thickness, LV posterior wall thickness, left atrial diameter, regional wall motion

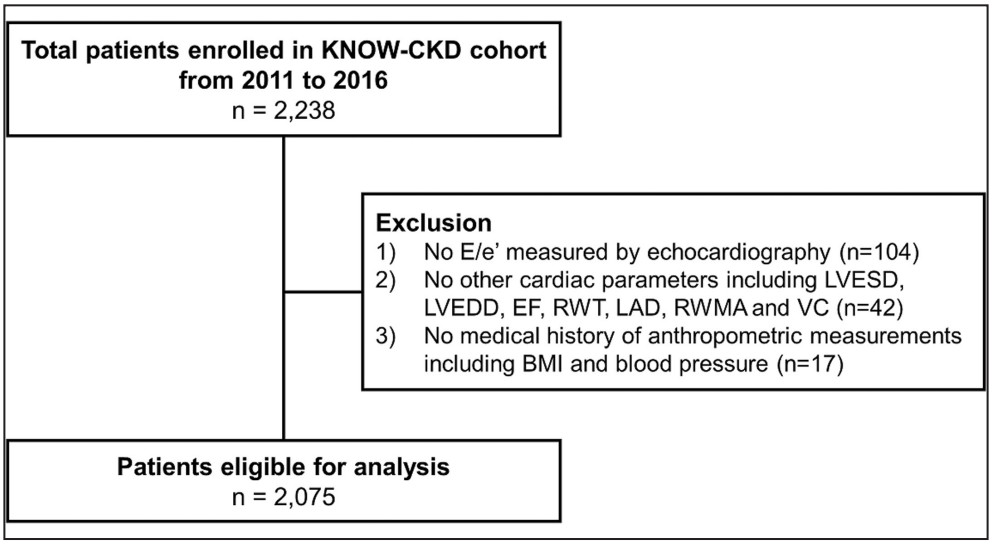

Figure 1. Flowchart of this study.
BMI indicates body mass index; E/e', early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio; EF, ejection fraction; KNOW-CKD, Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RWMA, regional wall motion abnormality; RWT, relative wall thickness; and VC, valvular calcification.

abnormality, EF, and valvular calcification. Relative wall thickness was calculated using the following formula: relative wall thickness=(2×LV posterior wall thickness)/LV end-diastolic diameter. To record early diastolic mitral inflow, pulsed-wave Doppler from the apical 4-chamber view was used. Early diastolic mitral annulus velocity was measured by tissue Doppler in the septal region of the mitral annulus, and the E/e' was calculated to measure LV filling pressure.

Clinical and Laboratory Measurements

Baseline clinical characteristics, including detailed demographic information and laboratory values at enrollment, were extracted from an electronic data management system (http://www.phaactaX.org). Body mass index was calculated as weight (kg) divided by height squared (m^2). Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg, or treatment with antihypertensive drugs. Renin-angiotensin system inhibitors included angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Diabetes was defined as fasting glucose ≥126 mg/dL or treatment with insulin or oral antidiabetic drugs. Coronary artery calcium score was measured using ECG-gated coronary multidetector computed tomography following the standard protocol of each center. Quantitative coronary artery calcium score was calculated as described by Agatston et al,[14] and the presence of coronary artery calcification was defined as coronary artery calcium score ≥100.[15] Brachial-ankle pulse wave velocity was automatically generated using a wave form analyzer (VP-1000; Collin Co, Komaki, Japan).[16] The presence of abdominal aortic calcification was defined as an abdominal aortic calcification score ≥1.[17] Blood samples for laboratory tests were obtained after overnight fasting. Serum creatinine and 25-hydroxyvitamin D levels were measured at a central laboratory (Lab Genomics, Seoul, Republic of Korea). Serum creatinine level was measured by the isotope dilution mass spectroscopy–traceable method. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[18] Voided urine samples were sent to the central laboratory for urine creatinine and protein determinations. Urine protein excretion was quantified using urinary protein/creatinine ratio (g/g).

Definition of Renal Outcomes

Progression of CKD was defined as development of renal events, defined as a >50% decrease in eGFR from baseline, doubling of serum creatinine, dialysis initiation, and/or kidney transplantation.

Statistical Analysis

Distributions of continuous variables were evaluated using the Shapiro-Wilk test. No continuous variables were normally distributed, and they are presented as median (interquartile range). Categorical variables are expressed as percentage. *P* values for trends were analyzed by Jonckheere-Terpstra tests and for categorical variables by linear-by-linear associations.

Differences were analyzed by Mann-Whitney *U* tests for nonnormally distributed continuous variables and χ^2 tests for categorical variables.

Patients were stratified into 4 quartiles according to E/e'. Death before renal events was treated as a censored observation for renal events. For survival analysis, Kaplan-Meier curve analysis was used, and statistical significance was calculated using the log-rank test. To evaluate the independent association between E/e' and renal outcomes in this study, Cox proportional hazard regression analyses were performed, and results are reported as hazard ratios (HRs) and 95% CIs. For continuous variables that did not satisfy the proportional hazard assumption, we used a categorized version of the variable based on median values. Covariates in multivariable analyses were chosen on the basis of clinical and statistical relevance, and only participants without missing values were included. The relationship between E/e' and renal events was plotted using the penalized smoothing spline method, using the "pspline" package in R (version 3.03). $P<0.05$ was considered statistically significant. All analyses, unless otherwise specified, were performed using R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics of Enrolled Participants

Mean age of the 2075 patients was 55.0 years, and 60.9% of the patients were men. Causes of CKD were diabetic nephropathy in 23.1% of patients, hypertensive nephropathy in 18.2% of patients, glomerulonephritis in 35.7% of patients, and other causes in 23.0% of patients. Median eGFR was 46.2 mL/min per 1.73 m^2, and median urinary protein/creatinine ratio was 0.5 g/g creatinine. Median E/e' was 9.1, and the proportions of EF <50% and E/e' ≥15 were 1.3% and 9.6%, respectively. Proportion of enrolled patients with eGFR <30 mL/min per 1.73 m^2 was 27.2%. During the mean 59.1-month follow-up period, 724 patients (34.9%) experienced renal events.

Baseline Characteristics of Enrolled Participants According to E/e' Quartile

We compared the baseline characteristics of E/e' quartiles (Table 1). As E/e' quartile increased, age and proportion of comorbidities (hypertension, diabetes, administration of diuretics, β blockers, calcium channel blockers, and statins) increased. In contrast, the proportions of male patients and current smokers decreased with higher E/e' quartile. LV chamber size, relative wall thickness, and left atrial diameter were higher and regional wall motion abnormality, coronary artery calcification, previous percutaneous coronary intervention, and valvular calcification were more common for higher E/e' quartile groups. Unexpectedly, however, EF was also higher for the higher E/e' quartile groups. As E/e' quartile increased, afterload markers of systolic BP, pulse pressure, and brachial-ankle pulse wave velocity increased. Patients in higher E/e' quartile groups had more severe kidney damage (decreased eGFR and increased urinary protein/creatinine ratio), increased fasting glucose, and increased inflammation (increased white blood cell count and hsCRP [high-sensitivity C-reactive protein]) than those in lower E/e' quartile groups.

Renal Outcomes According to E/e' Quartile

We compared renal survival according to E/e' quartile. Estimated mean (SE) renal survival lengths were 61.5 (1.23) months, 59.7 (1.27) months, 57.1 (1.28) months, and 47.3 (1.29) months in the first through fourth E/e' quartiles, respectively (log-rank $P<0.001$; Figure 2). The fourth E/e' quartile had the shortest renal survival compared with the first through third E/e' quartiles. We performed multivariable Cox proportional hazard regression analysis to adjust for the effects of confounders (Table 2). In the fully adjusted model (model 2), a 1-unit increase in E/e' was associated with an increased hazard of renal events (HR, 1.021 [95% CI, 1.000–1.045]; $P=0.048$). Furthermore, the HR of renal outcomes was significantly high for the highest E/e' quartile in the full model (quartile 4: HR, 1.302 [95% CI, 1.001–1.693]; $P=0.049$).

Sensitivity Analysis According to E/e'

We performed sensitivity analysis using higher quantile values: octiles, noniles, deciles, and 11-quantiles (Figure S1). The 8th octile (>14.0), 9th nonile (>14.2), 10th decile (>14.75), and 11th 11-quantile (>15.0) consistently showed an increased hazard of renal events compared with the lowest quantiles, suggesting that the hazard of renal events increased only when E/e' was profoundly high. In penalized spline curve analysis, the lower line of the 95% CI was above the HR 1.0 when E/e' was >12 based on visual inspection (Figure 3).

DISCUSSION

Decreased renal function is associated with increased risk of cardiovascular hospitalization and all-cause mortality in patients with CKD.[19] Therefore, delaying progression is of utmost importance in treating patients with CKD. According to the 2012 Kidney Disease Improving Global Outcomes guidelines, BP control

Table 1. Baseline Characteristics According to E/e' Quartile

Characteristic	N	Quartile 1 (≤7.4) (N=526)	Quartile 2 (>7.4 and <9.1) (N=518)	Quartile 3 (>9.1 and <11.9) (N=522)	Quartile 4 (>11.9) (N=521)	*P* value	*P* value for trend
Age, y	2075	47.0 (38.0–56.0)	52.5 (42.0–61.0)	56.0 (49.0–64.0)	61.0 (53.0–67.0)	<0.001	<0.001
Male sex, n (%)	2075	344 (66.0)	328 (63.3)	311 (60.0)	281 (54.2)	0.001	0.001
Current smoking, n (%)	2075	99 (19.0)	101 (19.5)	75 (14.5)	57 (11.0)	<0.001	<0.001
Hypertension, n (%)	2075	479 (91.9)	500 (96.5)	495 (95.6)	510 (98.5)	<0.001	<0.001
Diabetes, n (%)	2075	74 (14.2)	120 (23.2)	204 (39.4)	295 (56.9)	<0.001	<0.001
Body mass index, kg/m^2	2075	23.6 (21.2–25.7)	24.2 (22.3–26.0)	24.4 (22.4–26.7)	25.2 (23.1–27.5)	<0.001	<0.001
RAS inhibitors, n (%)	2075	442 (84.8)	442 (85.3)	443 (85.5)	445 (85.9)	0.97	0.97
Diuretics, n (%)	2075	110 (21.1)	131 (25.3)	175 (33.8)	232 (44.8)	<0.001	<0.001
β Blockers, n (%)	2075	78 (15.0)	116 (22.4)	127 (24.5)	201 (38.8)	<0.001	<0.001
Calcium channel blockers, n (%)	2075	158 (30.3)	194 (37.5)	230 (44.4)	299 (57.7)	<0.001	<0.001
Statins, n (%)	2075	209 (40.1)	253 (48.8)	303 (58.5)	313 (60.4)	<0.001	<0.001
Cardiac parameters							
LVESD, mm	2075	30.0 (28.0–32.3)	30.0 (27.7–33.0)	30.0 (27.0–33.0)	30.5 (28.0–34.0)	<0.001	0.007
LVEDD, mm	2075	48.0 (45.0–50.1)	48.6 (45.7–51.6)	49.0 (46.0–52.0)	50.0 (46.0–52.2)	<0.001	<0.001
Ejection fraction, %	2075	63.0 (59.0–66.9)	64.0 (60.9–67.7)	64.7 (61.0–68.0)	65.0 (60.0–69.0)	0.002	0.001
Relative wall thickness	2075	0.4 (0.3–0.4)	0.4 (0.3–0.4)	0.4 (0.3–0.4)	0.4 (0.4–0.4)	<0.001	<0.001
LAD, mm	2075	35.0 (32.0–39.0)	37.0 (33.0–40.0)	38.0 (35.0–42.0)	40.0 (37.0–44.0)	<0.001	<0.001
E/e'	2075	6.3 (5.6–7.0)	8.2 (7.8–8.7)	10.2 (9.7–11.0)	14.0 (12.6–16.1)	<0.001	<0.001
RWMA, n (%)	2075	9 (1.7)	5 (1.0)	20 (3.9)	27 (5.2)	<0.001	<0.001
Valvular calcification, n (%)	2075	19 (3.6)	35 (6.8)	39 (7.5)	90 (17.4)	<0.001	<0.001
Coronary artery calcification, n (%)	1976	51 (10.0)	90 (17.9)	124 (25.3)	195 (41.2)	<0.001	<0.001
Previous PCI, n (%)	2075	7 (1.3)	7 (1.4)	23 (4.4)	30 (5.8)	<0.001	<0.001
Vascular parameters							
Systolic BP, mm Hg	2075	123.0 (113.0–131.0)	126.0 (116.0–135.0)	128.0 (120.0–139.0)	131.0 (120.0–141.0)	<0.001	<0.001
Diastolic BP, mm Hg	2075	77.0 (70.0–83.0)	79.0 (70.0–85.0)	77.0 (69.0–84.0)	77.0 (69.0–83.0)	0.142	0.834
Pulse pressure, mm Hg	2075	47.0 (40.0–52.0)	48.0 (40.0–55.0)	51.0 (43.0–59.0)	55.0 (47.0–64.0)	<0.001	<0.001
baPWV, cm/sec	1894	1342.0 (1218.8–1492.5)	1400.0 (1254.5–1598.5)	1514.5 (1340.8–1727.2)	1681.8 (1438.0–1902.0)	<0.001	<0.001
Abdominal aortic calcification, n (%)	2075	112 (21.5)	131 (25.3)	189 (36.5)	258 (49.8)	<0.001	<0.001
Phosphorus, mg/dL	2058	3.5 (3.1–3.9)	3.6 (3.2–4.0)	3.7 (3.3–4.0)	3.8 (3.4–4.3)	<0.001	<0.001
Calcium, mg/dL	2062	9.2 (9.0–9.5)	9.2 (8.8–9.5)	9.2 (8.8–9.4)	9.1 (8.7–9.4)	<0.001	<0.001
Intact PTH, pg/mL	1765	47.5 (29.7–72.1)	46.0 (31.4–80.0)	51.7 (34.6–84.1)	62.0 (39.2–101.6)	<0.001	<0.001
25-Hydroxyvitamin D, ng/mL	2036	17.1 (13.1–21.9)	16.9 (13.4–21.6)	16.2 (12.8–20.8)	15.0 (11.7–19.6)	<0.001	<0.001
Active vitamin D, n (%)	2075	7 (1.3)	9 (1.7)	12 (2.3)	23 (4.4)	0.006	0.006
Oral vitamin D3, n (%)	2075	23 (4.4)	34 (6.6)	26 (5.0)	25 (4.8)	0.426	0.426
Phosphate binder, n (%)	2075	41 (7.9)	52 (10.0)	33 (6.4)	51 (9.8)	0.109	0.109
Laboratory parameters							
Creatinine, mg/dL	2075	1.3 (0.9–1.9)	1.4 (1.0–2.0)	1.5 (1.1–2.2)	1.8 (1.3–2.7)	<0.001	<0.001
eGFR, mL/min per 1.73 m^2	2075	60.9 (36.4–92.6)	52.6 (32.1–82.2)	45.8 (28.5–67.1)	34.6 (22.3–51.1)	<0.001	<0.001

(*Continued*)

Table 1. (Continued)

Characteristic	N	Quartile 1 (≤7.4) (N=526)	Quartile 2 (>7.4 and <9.1) (N=518)	Quartile 3 (>9.1 and <11.9) (N=522)	Quartile 4 (>11.9) (N=521)	*P* value	*P* value for trend
UPCR, g/g creatinine	2008	0.3 (0.1–0.8)	0.4 (0.1–1.2)	0.5 (0.2–1.5)	1.0 (0.3–2.7)	<0.001	<0.001
Fasting glucose, mg/dL	2055	96.0 (90.0–105.0)	98.0 (91.0–108.0)	102.0 (93.0–123.0)	106.0 (93.0–131.5)	<0.001	<0.001
Serum albumin, g/dL	2064	4.3 (4.1–4.5)	4.3 (4.0–4.5)	4.2 (4.0–4.5)	4.1 (3.9–4.4)	<0.001	<0.001
Cholesterol, mmol/L	2062	173.0 (151.0–201.0)	170.0 (147.0–194.0)	169.0 (147.0–196.0)	171.0 (142.0–201.0)	0.129	0.103
White blood cells, $\times 10^3/\mu L$	2050	6.3 (5.2–7.5)	6.2 (5.1–7.5)	6.3 (5.3–7.7)	6.4 (5.4–7.9)	0.063	0.019
CRP, mg/dL	1932	0.5 (0.2–1.4)	0.6 (0.2–1.7)	0.6 (0.2–1.5)	0.9 (0.3–2.0)	0.506	0.409

Continuous variables are reported as medians (interquartile ranges), and categorical variables are reported as numbers (percentages).

baPWV indicates brachial-ankle pulse wave velocity; BP, blood pressure; CRP, C-reactive protein; E/e', early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; PCI, percutaneous coronary intervention; PTH, parathyroid hormone; RAS, renin-angiotensin system; RWMA, regional wall motion abnormality; and UPCR, urine protein/creatinine ratio.

using renin-angiotensin system inhibitors, glycemic control, reduced protein and salt intake, and lifestyle modifications are recommended to prevent the progression of CKD.[20] To enhance the effect of these approaches, identification of patients at high risk of CKD progression is crucial.

There are also complex links between the heart and the kidneys, and the precise pathophysiological mechanisms of these associations remain elusive.[21] However, as the concept of CRS has gained clinical interest,[7] several possibilities have been introduced. In particular, decreased renal perfusion attributable to impairment of left ventricular systolic or diastolic function is thought to lead to decreased cardiac output and stroke volume.[8–10] Thus, it is expected that patients with CKD with left ventricular dysfunction are at

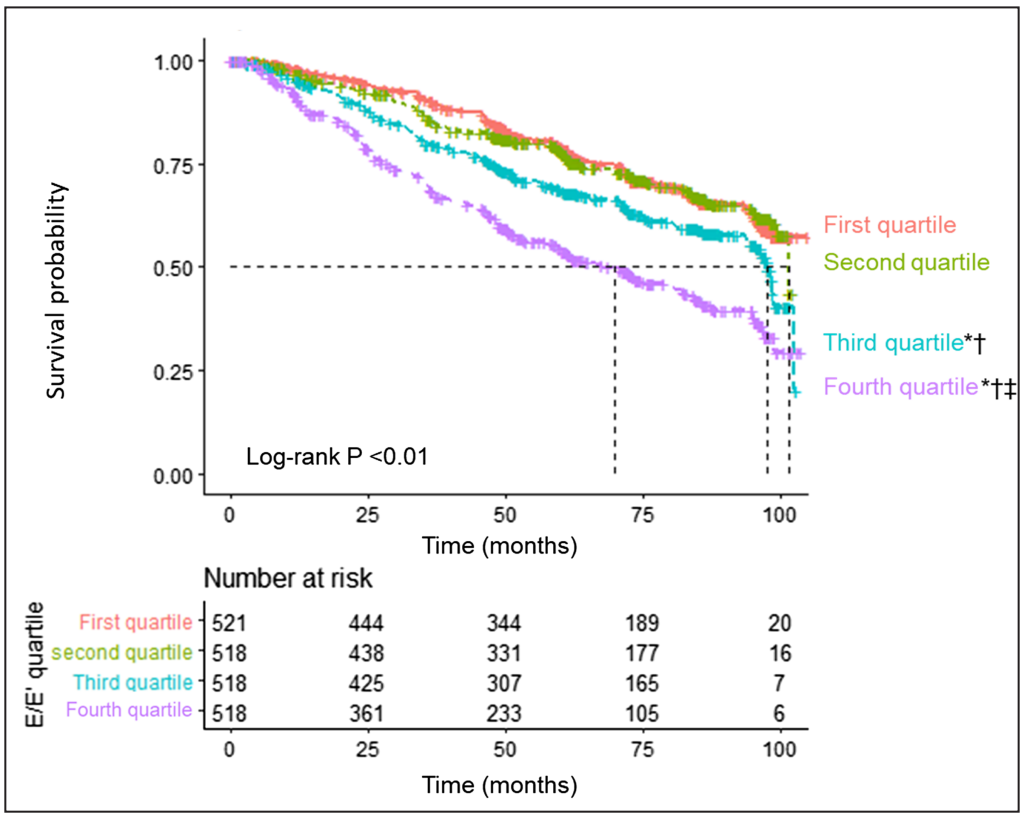

Figure 2. Kaplan-Meier survival curve of quartiles of early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio (E/e').

*P<0.05, †P<0.05, and ‡P<0.05 compared with first, second, and third quartiles, respectively, of E/e' group using the log-rank test.

Table 2. HRs of E/e' for Adverse Renal Outcomes

Variable	Univariate (n=2075)		Model 1 (n=1887)		Model 2 (n=1887)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
E/e' (per 1-unit increase)	1.078 (1.062–1.095)	<0.001	1.023 (1.002–1.045)	0.033	1.021 (1.000–1.045)	0.048
E/e' quartile (vs quartile 1)	Reference		Reference		Reference	
Quartile 2	1.033 (0.819–1.303)	0.783	0.913 (0.714–1.168)	0.469	0.947 (0.740–1.212)	0.665
Quartile 3	1.460 (1.174–1.814)	0.001	1.196 (0.937–1.528)	0.151	1.211 (0.946–1.551)	0.129
Quartile 4	2.394 (1.948–2.942)	<0.001	1.329 (1.026–1.721)	0.031	1.302 (1.001–1.693)	0.049

HRs and 95% CIs were determined using Cox proportional hazard regression analysis. In multivariable analysis, covariates in model 1 were age, sex, body mass index, current smoking, chronic diseases, categorized systolic and diastolic blood pressure by median value, fasting glucose, total cholesterol, other cardiac variables (regional wall motion abnormality, ejection fraction, calcifications of cardiac valves and coronary arteries, history of coronary stenting, and relative wall thickness), vascular variables (abdominal aortic calcification and categorized pulse pressure, brachial-ankle pulse wave velocity, calcium and phosphorous, intact parathyroid hormone, and 25-hydroxyvitamin D by median value), medications (renin-angiotensin system inhibitors, diuretics, β blockers, calcium channel blockers, statins, oral vitamin D3, active vitamin D, and phosphate binders), white blood cell count, albumin categorized by median value, and urine protein/creatinine ratio. Covariates in model 2 were variables in model 1 plus baseline renal function represented by chronic kidney disease stage. E/e' indicates early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio; and HR, hazard ratio.

increased risk of progression of CKD. We performed the current study to identify the effect of increments in E/e' on potential renal risk, as E/e' is the most validated surrogate marker of left ventricular diastolic dysfunction,[4] and found that increased E/e' was associated with increased risk of future renal events.

In this study, a 1-unit increase in E/e' was associated with a 2.1% increased hazard of renal event development (Table 2), suggesting that patients with left ventricular diastolic dysfunction are at increased risk of CKD progression. However, the relationship between E/e' and renal events was not simple because there were not strong statistical associations between E/e' quartiles and renal events. In sensitivity analysis of higher quantiles, a significant association between renal hazards and increased E/e' was found, but only when E/e' was profoundly high, suggesting a nonlinear association between E/e' and renal events. In penalized spline curve analysis, the suggested threshold of E/e' for renal events was ≈12 based on visual inspection. Although there was a difference between the thresholds for increased HR of adverse renal outcomes in our 2 statistical analyses, the number of patients with high E/e' was small in this study. Therefore, further analysis is necessary to determine thresholds with clinical significance.

Even when advanced CKD was defined as an eGFR of <30 mL/min per 1.73 m^2, we did not find a significant association between E/e' and renal outcomes in subgroup analysis. In particular, there was no significant difference in the main outcomes according to renal function. This finding means that the risk of adverse renal outcomes according to an increase in E/e' is not consistent with the effects of uremic cardiomyopathy. Rather, it might be attributable to diastolic dysfunction induced by increased intermyocardiocytic fibrosis,[22] which can be explained not only by uremic toxins,[23] but also by insulin resistance[24] or disruption of bone mineral metabolism.[25] Because variables associated with afterload (systolic BP, pulse pressure, and brachial-ankle pulse wave velocity; data not shown) did not modify the association between E/e' and renal events, and increased E/e' was not associated with an increased incidence of renal outcomes in patients with a thickened myocardium, the relationship between E/e' and renal events is unlikely to be secondary to the hazard from increased concentric cardiac stress. Because the association between E/e' and renal events was not influenced by inflammation (white blood cell count and hsCRP; data not shown) or cardiac chamber size (left atrial diameter and LV end-diastolic diameter; LV end-diastolic diameter data not shown), we postulate that the renal hazard posed by increased E/e' is attributable to hemodynamic changes resulting from increased central venous pressure, decreased renal perfusion pressure, and resultant renal ischemia, as previously suggested for CRS.[8–10] However, we did not measure central venous pressure; therefore, further studies with additional cardiac measurements, including central venous pressure, are needed to test this hypothesis.

In this study, we identified an unexpected positive association between E/e' and EF, as shown in Table 1. In a scatterplot constructed using the locally weighted scatterplot smoothing method (Figure S2A), the overall association between E/e' and EF was inverted and U shaped, which was confirmed in a multivariable generalized additive model plot (Figure S2B), indicating a compensatory increase in systolic heart function during the early process of diastolic heart dysfunction. In this study, most cardiac dysfunction was assumed to be subclinical because the rates of overt systolic (EF <50%, 1.3%) and left ventricular diastolic (E/e' ≥15, 9.6%) dysfunction were low.[1,4] Therefore, we hypothesize that compensatory systolic hyperfunction is a subclinical cardiac adaption to deterioration in diastolic heart function.

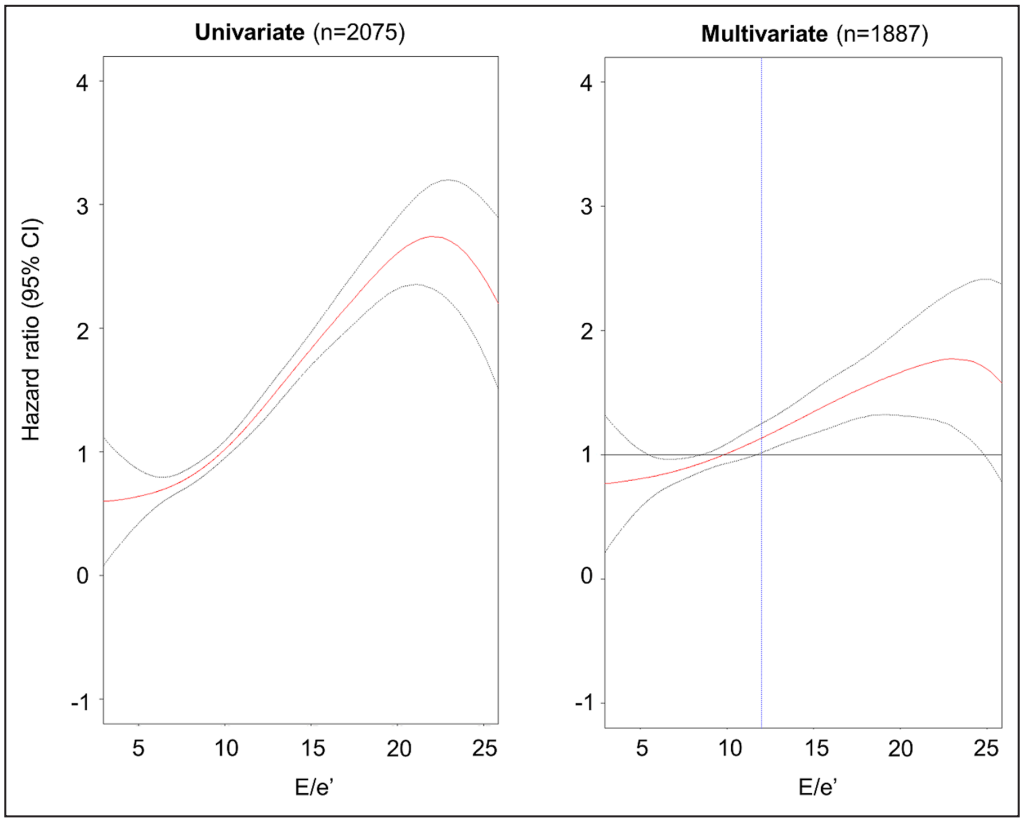

Figure 3. Penalized smoothing splines showing the relationship between early diastolic mitral inflow velocity/early diastolic mitral annulus velocity ratio (E/e') and adverse renal outcomes. Upper (≥25) and lower 0.5% (<3.8) values of E/e' were truncated. The red line indicates the hazard ratio (HR), and the black dotted line indicates the 95% CI at which E/e' influenced adverse renal outcomes. HR and 95% CI were determined using Cox proportional hazard regression analysis. In multivariable analysis, covariates were age, sex, current smoking, chronic diseases, body mass index, categorized systolic and diastolic blood pressure by median value, fasting glucose, total cholesterol, other cardiac variables (regional wall motion abnormality, ejection fraction, calcifications of cardiac valves and coronary arteries, history of coronary stenting, and relative wall thickness), vascular variables (abdominal aortic calcification and categorized pulse pressure, brachial-ankle pulse wave velocity, calcium and phosphorous, intact parathyroid hormone, and 25-hydroxyvitamin D by median value), medications (renin-angiotensin system inhibitors, diuretics, β blockers, calcium channel blockers, statins, oral vitamin D_3, active vitamin D, and phosphate binders), white blood cell count, albumin categorized by median value, urine protein/creatinine ratio, and chronic kidney disease stage.

The study had several limitations. First, echocardiographic measures were not homogeneous because they were measured by different cardiologists and machines in the participating hospitals. Furthermore, we only used septal E/e' values, and the threshold of lateral E/e' should be studied further because the value of lateral E/e' is generally lower than that of septal E/e'.[4] Nonetheless, this limitation would only have slightly affected the study results because the renal hazard of increased E/e' increased steadily after a certain E/e' based on penalized spline curve analysis. Second, the diagnostic accuracy of E/e' as a surrogate of LV filling pressure is controversial.[5,6] Therefore, it is controversial whether the renal hazard of increased E/e' can be interpreted as the renal hazard of diastolic dysfunction. Although evaluation of left ventricular diastolic dysfunction includes various noninvasive echocardiographic indexes, including E/e', mitral septal and lateral velocities, left atrial volume, and tricuspid regurgitation velocity,[26] the present study used a single marker, E/e'. This needs to be considered when interpreting the results of this study. Nonetheless, as E/e' is the most validated surrogate of diastolic heart function,[3,5,27,28] it is reasonable to conclude that left ventricular diastolic dysfunction is predictive of CKD progression based on the results of the present study.

Third, we did not analyze data on central venous pressure, right ventricular pressure, or renal perfusion pressure because the KNOW-CKD was not primarily

designed to assess the association between renal risk and diastolic heart dysfunction.

In conclusion, increased E/e' was associated with increased risk of CKD progression, suggesting that diastolic heart dysfunction is a novel risk factor for CKD progression. Because the renal hazard of increased E/e' was most evident in patients with otherwise non-dialysis CKD, this ratio can be used as an early risk factor for CKD progression. Future prospective studies are needed to confirm our study findings.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figures S1-S2

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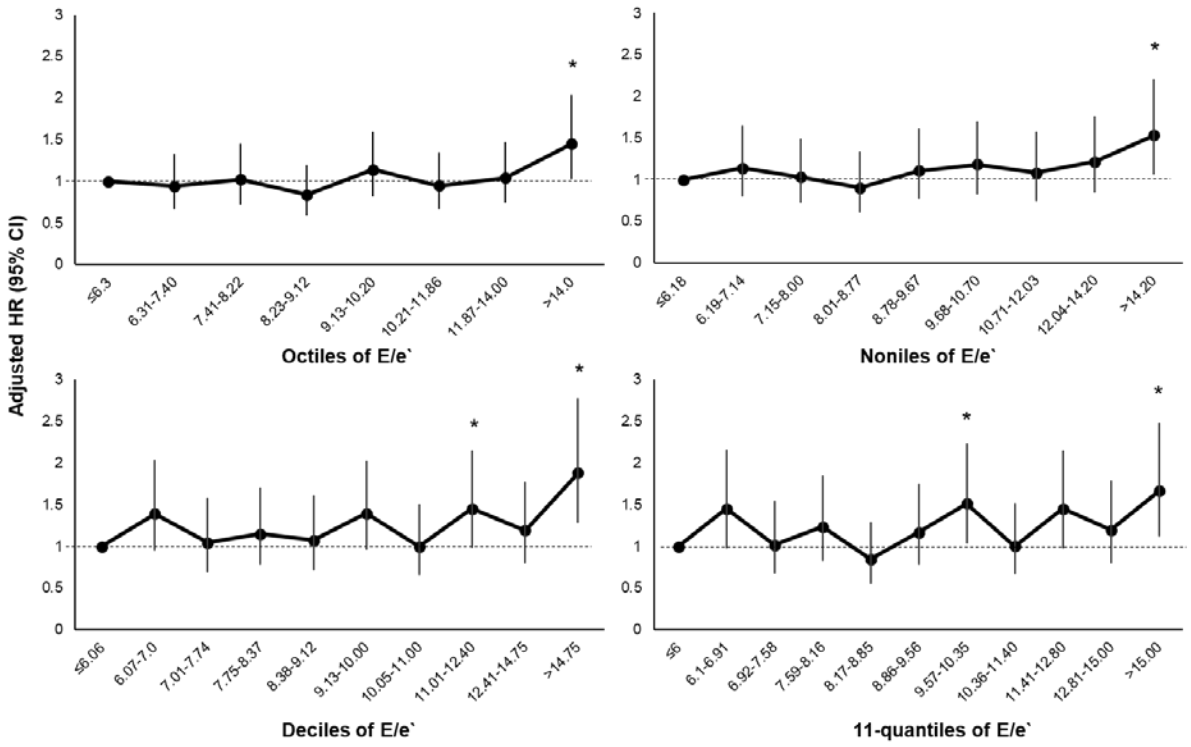
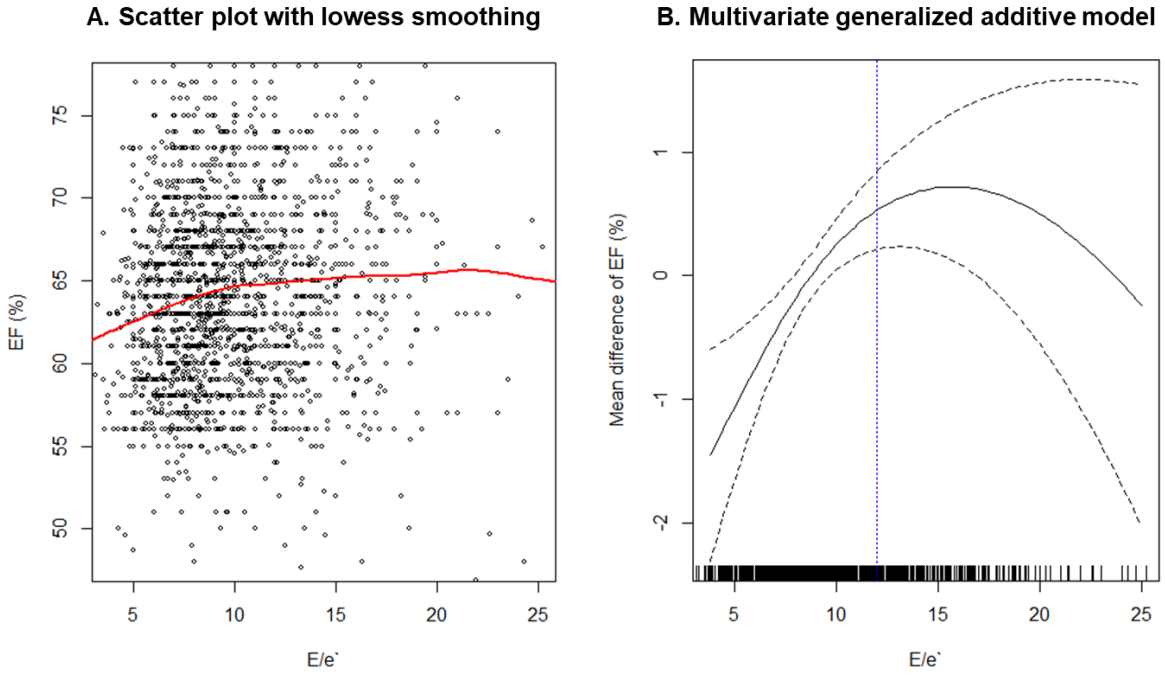
SUPPLEMENTAL MATERIAL

Figure S1. Sensitivity analysis of the hazard of E/e` on adverse renal outcome according to various quintiles.



Adjusted HR and 95% CI were analyzed using multivariate Cox proportional hazard regression analysis, entering into age, sex, current smoking, chronic diseases (body mass index, categorized systolic and diastolic blood pressure by median value, fasting glucose, and total cholesterol), other cardiac variables (regional wall motion abnormality, ejection fraction, calcifications of cardiac valve and coronary artery, history of coronary stenting, and relative wall thickness), and vascular variables (abdominal aortic calcification and categorized pulse pressure, brachial to ankle pulse wave velocity, calcium and phosphorous, intact parathyroid hormone, and 25-hydroxyvitamin D by median value), medications (renin angiotensin system inhibitor, diuretics, beta blocker, calcium channel blocker, statin, oral vitamin D3, active vitamin D, and phosphate binder), white blood cells, categorized albumin by median value, and urine protein to creatinine ratio), and chronic kidney disease stage. * < 0.05 when compared to the first quintile.

Figure S2. Association between E/e` and ejection fraction.



Upper (≥25) and lower (<3.8) one percentage of E/e` and upper (≥77%) and lower (<48%) of EF (ejection fraction) were truncated. In panel A, the red line indicated in the scatter plot is the lowess regression curve. In panel B, the dashed line indicates 95% confidential intervals for value of the smoothed EF using multivariate generalized additive model analysis after adjusting with full model (model 2) in Table 2.