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Association between Multimorbidity and Kidney Function among Patients with Non-Dialysis-Dependent CKD: The Fukuoka Kidney Disease Registry Study

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Aim: Individuals with chronic kidney disease (CKD) have a high prevalence of comorbidities, including cardiovascular disease (CVD) and its risk factors. However, epidemiological results to assess the association between multimorbidity and kidney function among the CKD population remains limited.

Methods: We performed a cross-sectional analysis of the association between 23 comorbid conditions and reduced kidney function in 4,476 patients with non-dialysis-dependent CKD enrolled in a multicenter cohort in Japan. Reduced kidney function was defined as an estimated glomerular filtration rate of ≤ 60 mL/min/1.73 m^2.

Results: The mean age of patients was 67 years (male, 56.0%). The prevalence of hypertension, diabetes mellitus, dyslipidemia, prior CVD, cancer, and bone fracture, which are the major comorbidities, was 83.3%, 28.7%, 45.9%, 23.3%, 12.7%, and 6.3%, respectively. Multivariable-adjusted analyses revealed that age, male sex, hypertension, dyslipidemia, prior CVD, body mass index, urinary protein excretion, and underlying kidney disease were independent factors associated with reduced kidney function. Importantly, the odds ratios (ORs) for reduced kidney function increased linearly as the number of major comorbid conditions increased (OR for 1–2 conditions: 2.22, 95% confidence interval [CI]: 1.65–2.97; OR for 3–4 conditions: 3.04, 95% CI: 2.12–4.37; OR for ≥ 5 conditions: 4.37, 95% CI: 1.75–10.9). The upward trend in OR was more pronounced with cardiovascular comorbidities but not significant with non-cardiovascular comorbidities.

Conclusions: In conclusion, we observed an independent association between cardiovascular comorbidity and its risk factors and reduced kidney function. The results of this study highlight the importance of managing multimorbidity among patients with CKD.

Key words: Aging, Comorbidities, Cardiovascular disease, Epidemiology

Introduction

The prevalence of chronic kidney disease (CKD) increases dramatically in the elderly, with 30% of males and 40% of females in the general Japanese population aged 65–69 years having stage 3 CKD[1]. The number of patients with newly diagnosed end-stage kidney disease (ESKD) will increase by approximately 8% annually, and the cumulative number of patients receiving renal therapy will double to 5.44 million by 2030. This increase is expected to be particularly noticeable in Asian countries[2, 3]. Hence, CKD is increasingly recognized as a global health burden.

Epidemiological results suggest an increased risk of cardiovascular disease (CVD) morbidity and mortality in patients with CKD[4-6]. Furthermore, a meta-analysis of clinical studies evaluated the significance of CKD and confirmed that a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 and albuminuria are risk factors for all-cause mortality, cardiovascular death, and ESKD[7, 8]. Patients with

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CKD have a high prevalence of comorbidities related to risk factors for CVD, and their management is more complicated. An association between the complexity of care and life expectancy for patients with reduced kidney function has been reported[9]. Complexity in patients with CKD increases the number of medications for multiple comorbidities and may lead to a further decline in kidney function through adverse drug reactions and low adherence[10-12]. Presently, it is less clear what types of comorbidities, including CVD, are closely associated with reduced kidney function in patients with non-dialysis-dependent CKD. Furthermore, the dose–response relationship between cumulative comorbidities or polypharmacy and reduced kidney function has not been fully confirmed. A better understanding of the comorbid burden of patients with CKD would be useful to define strategies to improve care for patients with CKD. However, epidemiological results to assess the association between multimorbidity and kidney function among the CKD population are still scarce; hence, the characteristics of comorbid burden in this population are unknown.

The Fukuoka Kidney disease Registry (FKR) Study is a prospective multicenter cohort study of approximately 4,500 Japanese patients with CKD under nephrologist care. In this study, we report the characteristics of enrolled patients and comorbid conditions at baseline. We aimed to examine the association between comorbidities, including cardiovascular risk profile, and reduced kidney function and to assess the impact of multimorbidity on kidney function in Japanese patients with CKD.

Materials and Methods

Participant Selection and Recruitment

The design of the FKR Study has been described previously[13]. A total of 4,476 patients with CKD aged ≥ 16 years under nephrologist care at 12 sites were enrolled between January 2013 and March 2017. All patients who met the definition of CKD according to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines were included[14]. We analyzed data from all enrolled patients as the final study population. The study protocol was approved by the Clinical Research Ethics Committee of the Institutional Review Board at Kyushu University (approval number 469-08) and the ethics committees at all participating institutions. Written informed consent was obtained from all patients at the start of the study. This study was registered in the University Hospital Medical Information Network clinical trial registry (UMIN000007988). This study was performed following the Declaration of Helsinki. Data analysis was conducted from December 2020 to February 2021.

Clinical Parameters

Demographic and clinical data were collected from all patients at the time of enrollment. Serum levels of cystatin C, creatinine (Cr), albumin, calcium, phosphorus, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), iron, ferritin, and high-sensitivity C-reactive protein (CRP); total iron-binding capacity; and plasma levels of intact parathyroid hormone (PTH), urine protein, and urine Cr were determined via central measurements using blood and urine samples collected at enrollment. Low-density lipoprotein cholesterol (LDL-C) was determined using the Friedewald formula for patients with a TG concentration of <400 mg/dL. For patients with a TG concentration of ≥ 400 mg/dL, LDL-C values from the direct measurement method from medical records were adopted. The corrected serum calcium concentration calculation was based on the serum albumin concentration, which was in turn based on the Payne formula: corrected calcium concentration (mg/dL) = observed total calcium concentration (mg/dL) + (4.0 − serum albumin concentration [g/dL]). CKD was defined and categorized as G1–G5 according to the status of estimated GFR (eGFR) using KDIGO clinical practice guidelines[15, 16]. eGFR was calculated using the Schwartz formula in patients aged <18 years and using the following formula in patients aged >18 years[17-19]: $\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287}$ (if female, $\times 0.739$). Medications administered to the cohort participants included the following drugs; antihypertensive agents, lipid-lowering agents, uric acid-lowering agents, antiplatelet/anticoagulant agents, oral antidiabetic agents, insulin, erythropoietin-stimulating agents, iron supplements, agents for bone mineral metabolism disorders, laxatives, sodium bicarbonate, uremic toxins and potassium adsorbents, thyroid medications, glucocorticoids, immunosuppressants, antidepressants, insomnia medications, non-steroidal anti-inflammatory drugs, proton pump inhibitors, and H2 blockers.

Comorbidity Definition

Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg and/or current use of antihypertensive agents. Diabetes mellitus was identified in subjects with a hemoglobin A1c value ≥ of 6.5% (National Glycohemoglobin Standardization Program) or diabetic nephropathy and/or current treatment with

insulin or oral antihyperglycemic drugs. Dyslipidemia was defined as an LDL-C of ≥ 140 mg/dL, an HDL-C of <40 mg/dL, a TG of ≥ 150 mg/dL, or current lipid-lowering drug use. Prior CVD was defined as a composite history of ischemic heart disease, congestive heart failure, ischemic stroke, hemorrhagic stroke, peripheral artery disease (PAD), thoracic aortic aneurysm, and abdominal aortic aneurysm. Ischemic heart disease was defined as myocardial infarction, exertional angina pectoris, and vasospastic angina pectoris as diagnosed through coronary angiography and coronary heart disease with revascularization (coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty). A past history of congestive heart failure was defined by the attending physician, regardless of hospitalization. A history of stroke was defined as a permanent neurological deficit and imaging evidence of intracranial lesions using computed tomography and magnetic resonance imaging of the brain. PAD was defined as symptoms of Fontaine class II or higher (intermittent claudication and resting leg pain), an ankle–brachial index of <0.9, arterial stenosis via imaging diagnosis, or revascularization (surgery or percutaneous angioplasty of peripheral artery). The presence or absence of atrial fibrillation was determined on the basis of medical records without distinguishing the type of atrial fibrillation (persistent or paroxysmal). Sleep apnea was diagnosed by simple/all-night polysomnography or treatment. The exclusion criteria included active malignancies; thus, a history of malignancy at baseline was defined as diagnosis and treatment on the basis of clinical symptoms, imaging, and histological evidence, and >2 years after the completion of treatment. Dementia and depression were diagnosed by the attending physician and in patients taking antidementia or antidepressant medications, respectively. Liver disease was defined as mild or severe liver dysfunction in hepatitis virus carriers, patients with chronic hepatitis or cirrhosis, and patients receiving antiviral treatment. A history of thyroid disease was defined as a diagnosis of Hashimoto's or Graves' disease or receipt of antithyroid medication or thyroid hormone replacement. A history of other comorbidities, including bone fracture, chronic obstructive pulmonary disease, and collagen disease, was identified on the basis of all available clinical data collected by clinical research coordinators (CRCs). Clinical information on each patient's health status and medication was collected from medical records using a structured data format by the CRCs in our research network. Comorbidity was evaluated using the Charlson Comorbidity Index[20]. We determined the 23 selected comorbidities for analysis on the basis of the components of the Charlson Comorbidity Index and disease information available in this cohort.

Statistical Analysis

Continuous variables are presented as median and interquartile range, whereas categorical data are presented as number and percentage. The clinical backgrounds categorized as G1–G5 according to KDIGO clinical practice guidelines were compared using trend analyses; a linear regression model was used for categorical variables and a logistic regression model for continuous variables. To determine independent associated factors of a reduced GFR, we selected covariates using a logistic regression model and a stepwise backward elimination with a P value of <0.05 for the remaining variables. In this selection, the clinically or biologically plausible risk factors for reduced GFR were included as initial candidate variables, including age, sex, smoking habit, alcohol intake, underlying kidney disease (hypertensive nephrosclerosis, diabetic nephropathy, and others), hypertension, diabetes mellitus, dyslipidemia, prior history of CVD, cancer, bone fracture, body mass index (BMI), and urinary protein-to-Cr ratio (UPCR). The final model consisted of age, sex, underlying kidney disease, hypertension, diabetes mellitus, dyslipidemia, history of CVD, BMI, and UPCR. Multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the prevalence of reduced kidney function (<60 mL/min/1.73 m^2) were estimated using this final model. Variables relevant to the categories were excluded from each model. We also plotted a box-and-whisker diagram showing the association between the number of comorbidities and eGFR and tested this association in a multivariable-adjusted linear regression model with eGFR as the dependent variable. To assess the effect of the number of medications on reduced kidney function, we evaluated the multivariate ORs for reduced eGFR in each of the categorical groups classified according to the number of medications (0, 1–2, 3–4, 5–6, and ≥ 7). Statistical analyses were undertaken using SAS v9.4 (SAS Institute, Cary, NC, USA) and STATA v16 (Stata, College Station, TX, USA). A P value of <0.05 (two-tailed) was considered statistically significant.

Results

Demographics and Baseline Characteristics

Table 1 presents the patients' baseline characteristics according to CKD stages. The mean age of patients was 67 (15.9) years (female, 44.0%). The distribution of CKD stages was 259 (5.8%), 825 (18.4%), 834 (18.6%), 934 (20.9%), 1,093 (24.4%),

Table 1. General characteristics of patients according to CKD stages

	All patients	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5	*P* value
No. of patients	4,476	1,084	834	934	1,093	531	
Age, years	67 (55–76)	50 (38–65)	65 (56–73)	70 (62–78)	73 (64–80)	72 (64–79)	<0.001
Sex (female), %	44.0	55.5	45.9	36.8	38.8	40.7	<0.001
Smoking history							
Never smokers, %	47.6	12.9	9.3	9.5	11.4	12.1	<0.001
Current smokers, %	11.2	57.9	52.1	45.9	41.5	36.6	0.57
Former smokers, %	41.2	29.1	38.6	44.5	47.1	51.3	<0.001
Drinking history							
Never drinkers, %	38.8	37.2	36.8	38.1	40.8	29.9	0.02
Current drinkers, %	48.6	55.3	55.6	47.8	43.0	56.0	<0.001
Former drinkers, %	12.6	7.5	7.6	14.2	16.3	14.2	<0.001
Underlying kidney disease							
Biopsy proven primary CGN, %	34.9	11.5	13.7	16.9	16.0	19.0	<0.001
CGN without biopsy, %	14.4	70.4	44.2	32.8	13.0	7.3	<0.001
Diabetic nephropathy, %	11.2	1.4	5.6	10.6	17.9	30.9	<0.001
Hypertensive nephrosclerosis, %	21.6	4.0	16.7	36.8	33.9	26.2	<0.001
Other, %	17.9	12.7	19.8	2.8	19.2	16.6	0.80
Anthropometric data							
Height, cm	160 (154–167)	161 (155–168)	161 (154–168)	161 (154–167)	160 (153–166)	160 (153–166)	<0.001
Body weight, kg	59 (51.3–67.6)	58.5 (51.6–68.5)	60.3 (52–68.6)	60.5 (52–68)	58 (50–67)	58 (50–65)	<0.001
BMI, kg/m^2	22.9 (20.6–25.6)	22.6 (20.3–25.9)	23.2 (20.9–26.0)	23.2 (21.0–25.7)	22.8 (20.5–25.4)	22.6 (20.4–24.9)	0.05
Blood pressure							
Systolic, mmHg	130 (119–142)	124 (113–135)	130 (120–140)	130 (120–142)	132 (121–144)	135 (126–147)	<0.001
Diastolic, mmHg	74 (67.3–82)	74 (66–82)	76 (70–84)	74 (68–82)	73 (65–81)	72 (65–80)	<0.001
Blood pressure <130/80 mmHg, %	41.7	54.6	41.0	39.8	37.1	29.4	<0.001
Blood pressure <140/90 mmHg, %	68.5	79.2	69.5	67.9	64.2	54.8	<0.001
Kidney parameters							
Serum Cr, mg/dL	1.29 (0.88–2.09)	0.70 (0.61–0.83)	1.02 (0.87–1.15)	1.36 (1.22–1.54)	2.13 (1.83–2.50)	4.09 (3.53–4.98)	<0.001
Serum cystatin C, mg/L	1.43 (0.96–2.26)	0.79 (0.69–0.92)	1.08 (0.97–1.23)	1.49 (1.30–1.72)	2.30 (1.97–2.62)	3.53 (3.10–4.00)	<0.001
eGFR, mL/min/1.73 m^2	40.1 (23.4–59.2)	76.9 (67.8–89.2)	51.5 (48.0–55.3)	37.3 (33.9–41.5)	22.8 (19.1–26.4)	11.3 (9.2–13.2)	<0.001
UPCR, g/gCr	0.40 (0.11–1.30)	0.16 (0.07–0.53)	0.17 (0.07–0.64)	0.31 (0.10–1.03)	0.69 (0.27–1.93)	1.83 (0.93–3.54)	<0.001
UACR, mg/gCr	206.5 (35.7–794.5)	76.6 (15.2–348.3)	84.5 (16.7–396.6)	158.2 (30.6–645.9)	381 (108.8–1119.1)	942.3 (430.6–2070.1)	<0.001
Lipids, uric acid, hemoglobin A1c, CRP, and albumin							
Total cholesterol, mg/dL	191 (167–217)	199 (178–223)	198 (175–221)	163 (169–217)	183 (158–212)	172 (149–199)	<0.001
LDL-C, mg/dL	104.4 (84.7–125.8)	109 (91.8–129.8)	108.6 (89.8–129.6)	105.4 (86.4–125/0)	100.2 (80.0–122.0)	91.7 (71.4–115.2)	<0.001
HDL-C, mg/dL	56 (45–70)	63 (52–77)	58 (47–72)	56 (12–69)	52 (10–66)	49 (39–60)	0.01
Triglycerides, mg/dL	120 (87–171)	107 (77–156)	122 (87–174)	125 (91–170)	125 (91–180)	126 (92–168)	<0.001
Uric acid, mg/dL	6.1 (5.2–7.1)	5.4 (4.5–6.4)	6.1 (5.3–6.9)	6.4 (5.6–7.3)	6.4 (5.6–7.5)	6.6 (5.6–7.7)	<0.001
Hemoglobin A1c, %	6.0 (5.6–6.4)	5.8 (5.5–6.2)	6.0 (5.6–6.4)	6.0 (5.7–6.5)	6.1 (5.7–6.6)	5.9 (5.2–6.5)	<0.001
CRP, mg/dL	0.05 (0.02–0.12)	0.04 (0.02–0.09)	0.05 (0.02–0.11)	0.06 (0.03–0.13)	0.07 (0.03–0.15)	0.06 (0.03–0.16)	0.01
Serum albumin, g/dL	4.1 (3.8–4.3)	4.2 (4.0–4.5)	4.2 (3.9–4.4)	4.1 (3.8–4.3)	3.9 (3.7–4.2)	3.8 (3.5–4.1)	<0.001
Anemia parameters and iron status							
Hemoglobin, g/dL	12.7 (11.3–14.1)	13.9 (13.0–15.0)	13.7 (12.6–14.8)	12.8 (11.6–14.1)	11.6 (10.7–12.7)	10.8 (10.1–11.7)	<0.001
Iron, μg/mL	84 (65–106)	90 (68–115)	93 (71–113)	84 (66–106)	78 (61–95)	77 (59–94)	<0.001
Transferrin saturation, %	28.6 (22.0–36.1)	28.4 (21.6–36.5)	30.3 (22.7–37.1)	28.3 (21.9–36.0)	27.9 (21.6–35.0)	29.8 (22.9–36.8)	0.87
Ferritin, ng/mL	100 (46.1–186)	77.4 (29.3–157)	94.7 (48.2–171)	99 (47.3–181)	109 (51.6–198)	137 (75.9–248)	<0.001
MBD parameters and electrolytes							
Corrected calcium, mg/dL	9.3 (9.0–9.5)	9.2 (9.0–9.5)	9.3 (9.1–9.5)	9.4 (9.1–9.6)	9.3 (9.0–9.6)	9.0 (8.6–9.4)	<0.001
Phosphorus, mg/dL	3.4 (3.0–3.9)	3.3 (2.9–3.7)	3.3 (2.9–3.7)	3.3 (2.9–3.7)	3.5 (3.1–3.9)	4.2 (3.3–4.8)	<0.001
Intact PTH, pg/mL	67 (46–110)	48 (37–62)	55 (42–71)	65 (48–88)	104 (71.5–152)	221 (141–334)	<0.001
Serum sodium, mEq/L	141 (139–142)	141 (140–142)	141 (140–142)	141 (139–142)	141 (139–142)	140 (138–142)	<0.001
Serum potassium, mEq/L	4.4 (4.1–4.7)	4.1 (3.9–4.4)	4.3 (4.0–4.6)	4.4 (4.1–4.7)	4.6 (4.3–4.9)	4.7 (4.3–5.0)	<0.001

Abbreviations: CKD, chronic kidney disease; CGN, chronic glomerulonephritis; BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-to-creatinine ratio; UACR, urinary albumin-to-creatinine ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; MBD, mineral bone disorders; PTH, parathyroid hormone. Values are presented as median (interquartile range) or percentage.

				Categories for albuminuria, description and interval			
				A1	A2	A3	No. (%)
				Normal or slight increase	Moderate increase	Severe increase	
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	>300 mg/g >30 mg/mmol	
GFR categories (mL/min/1.73m²), description and range	G1	Normal or high	≥90	2.3%	2.2%	1.3%	253 (5.8)
	G2	Slight decrease	60-89	6.4%	7.1%	5.2%	805 (18.6)
	G3a	Slight-moderate decrease	45-59	6.3%	7.1%	5.4%	814 (18.8)
	G3b	Moderate-severe decrease	30-44	5.2%	7.6%	8.2%	908 (21.0)
	G4	Severe decrease	15-29	2.6%	7.9%	13.6%	1045 (24.1)
	G5	Kidney failure	<15	0.2%	2.1%	9.5%	509 (11.7)
No. (%)				993 (22.9)	1,469 (33.9)	1,872 (43.2)	4,334 (100)

Low risk (if no other markers of CKD)
Moderate risk
High risk
Very high risk

Fig. 1. Classification of chronic kidney disease using GFR and ACR categories (KDIGO 2012)
Abbreviations: GFR, glomerular filtration rate; ACR, albumin-to-creatinine rate.

and 531 (11.9%) for G1, G2, G3a, G3b, G4, and G5, respectively. The percentage of former smokers increased with CKD progression, whereas the percentage of never smokers decreased. The proportion of drinkers increased with CKD progression in both former and current smokers. Of the 4,476 patients, 2,204 patients (49.3%) had chronic glomerulonephritis (CGN), and 1,561 patients (34.9%) had biopsy-proven CGN. Other causes of kidney disease included diabetic nephropathy in 502 patients (11.2%) and hypertensive nephrosclerosis in 969 patients (21.6%), whereas the remaining 801 patients (17.9%) had other causes. In the earlier CKD stages (G1 and G2), 81.9% of patients had CGN as the cause of kidney disease. By contrast, the proportion of patients with diabetic nephropathy and hypertensive nephrosclerosis as the cause of kidney disease increased to 30.9% and 26.2% in stage G5, respectively. The mean BMI was 22.9 kg/m^2. The mean systolic and diastolic blood pressures of patients were 130 and 74 mmHg, respectively.

The median eGFR was 40.1 mL/min/1.73 m^2. The median UPCR and median urinary albumin-to-Cr ratio were 0.40 g/gCr and 206.5 mg/gCr, respectively. The group with a lower eGFR had lower total cholesterol, LDL-C, and HDL-C levels but higher TG levels. There was a trend toward higher uric acid and CRP levels and lower albumin levels in the low eGFR group compared with the high eGFR group. The low eGFR group had lower levels of hemoglobin, serum iron, and calcium but higher levels of ferritin, phosphorus, intact PTH, and potassium. Use of antihypertensives, lipid-lowering drugs, insulin, urate-lowering drugs, antiplatelet/anticoagulants, erythropoiesis-stimulating agents, mineral bone disorders-related drugs, uremic toxins, and potassium adsorbents was higher in the low eGFR group compared with the high eGFR group **(Supplementary Table 1)**. **Fig. 1** shows the distribution of enrolled patients stratified by eGFR and albuminuria[10]. Risk rankings for adverse outcomes based on eGFR and albuminuria levels stratified 8.6%, 15.6%, 18.7%, and 57.0% of the total cohort as mild, moderate, severe, and very severe, respectively. As **Fig. 2** shows, the number of medications increased linearly with the progression of the CKD stage, and a significant dose–response relationship between polypharmacy and reduced eGFR was observed in the multivariable-adjusted model **(Table 6)**.

Independent Associated Factors of Reduced Kidney Function

Table 2 lists the multivariable independent associated factors of an eGFR <60 mL/min/1.73 m^2. Logistic regression revealed that older age (OR for 10 year increment, 1.78; 95% CI, 1.68–1.90), male sex (OR, 1.25; 95% CI, 1.05–1.50), underlying kidney disease (OR for others, 3.46; 95% CI: 2.74–4.38; OR for hypertensive nephrosclerosis, 5.94; 95% CI, 4.22–8.37; and OR for diabetic nephropathy, 9.59; 95% CI, 5.39–17.1), history of CVD (OR, 1.68; 95% CI, 1.26–2.40), hypertension (OR, 2.68; 95% CI, 2.15–

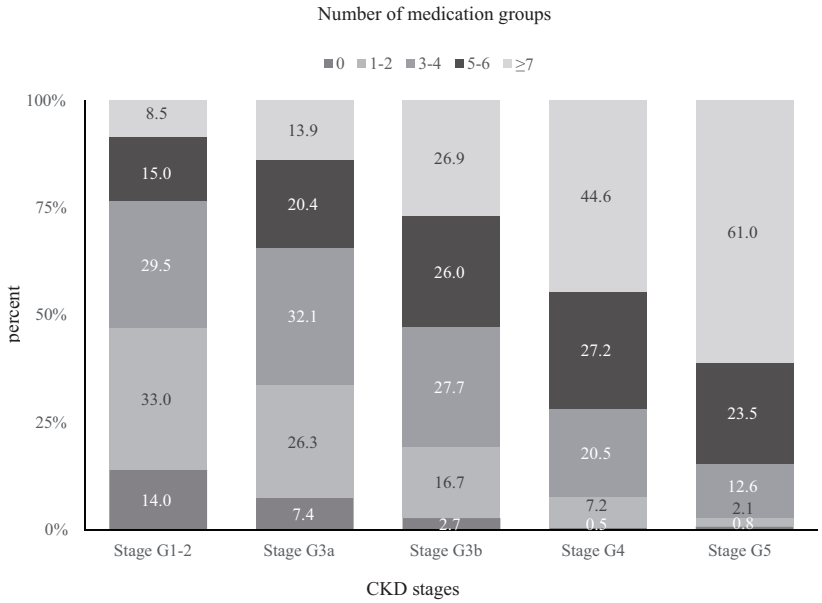

Fig. 2. Distribution of the number of CKD-related medications by CKD stages

Abbreviation: CKD, chronic kidney disease.

Table 2. Multivariable independent associated factors for estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2

Variable	Adjusted odds ratio (95% CI)[a]	*P* value
Age (per 10-year increment)	1.78 (1.68–1.90)	<0.001
Men (vs. women)	1.25 (1.05–1.50)	0.012
Underlying kidney disease		
Others (vs. CGN)	3.46 (2.74–4.38)	<0.001
Hypertensive nephrosclerosis (vs. CGN)	5.94 (4.22-8.37)	<0.001
Diabetic nephropathy (vs. CGN)	9.59 (5.39–17.1)	<0.001
Cardiovascular disease (vs. without)	1.68 (1.26–2.40)	<0.001
Hypertension (vs. without)	2.68 (2.15–3.34)	<0.001
Diabetes mellitus (vs. without)	0.71 (0.56–0.90)	0.005
Dyslipidemia (vs. without)	1.28 (1.07–1.54)	0.008
Body mass index (per 5-kg/m^2 decrement)	1.20 (1.07–1.34)	0.001
Urinary protein excretion (per 1-g/gCr increment)	1.47 (1.34–1.62)	<0.001

Abbreviations: CGN, chronic glomerulonephritis; CI, confidence interval.
Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg and/or current use of antihypertensive agents.
Diabetes mellitus was identified in patients with a hemoglobin A1c value ≥ 6.5% (National Glycohemoglobin Standardization Program), whose underlying kidney disease was diabetic nephropathy, and/or who were receiving treatment with insulin or oral antihyperglycemic drugs.
Dyslipidemia was defined as a triglyceride concentration ≥ 150 mg/dL, a low-density lipoprotein cholesterol concentration ≥ 140 mg/dL, a high-density lipoprotein cholesterol concentration < 40 mg/dL, or use of lipid-lowering medication.
Cardiovascular disease was defined as a composite of ischemic heart disease, congestive heart failure, ischemic stroke, hemorrhagic stroke, peripheral artery disease, thoracic aortic aneurysm, and abdominal aortic aneurysm.
[a]Variables were selected by a logistic regression model using a stepwise backward method with $P<0.05$ for remaining variables to determine the independent associated factors for estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2.

3.34), diabetes mellitus (OR, 0.71; 95% CI, 0.56–0.90), dyslipidemia (OR, 1.28; 95% CI, 1.07–1.54), lower BMI (OR for 5 kg/m^2 decrement, 1.20; 95% CI, 1.07–1.34), and higher UPCR (OR for 1 g/gCr increment, 1.47; 95% CI, 1.34–1.62) were independently associated with a reduced eGFR.

Table 3. Prevalence of major comorbid conditions of patients according to CKD stages

	All patients	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5	*P* value
Hypertension, %	83.3	63.0	81.8	90.8	95.3	96.4	<0.001
Diabetes mellitus, %	28.7	15.5	20.4	29.2	38.4	47.7	<0.001
Dyslipidemia, %	45.9	39.9	46.9	47.1	49.4	50.1	<0.001
Cardiovascular disease, %	23.3	6.7	14.7	25.5	37.9	36.6	<0.001
Ischemic heart disease, %	10.8	2.7	7.3	12.6	16.4	17.9	<0.001
Congestive heart failure, %	3.0	0.3	0.4	3.5	5.7	5.9	<0.001
Ischemic stroke, %	9.1	2.9	5.9	8.7	15.7	14.2	<0.001
Hemorrhagic stroke, %	2.0	0.7	1.1	2.4	3.5	2.6	<0.001
Peripheral artery disease, %	3.2	0.9	1.1	3.6	5.1	6.6	<0.001
Thoracic aortic aneurysm, %	0.9	0.0	0.7	1.0	1.6	1.3	<0.001
Abdominal aortic aneurysm, %	2.1	0.4	0.6	2.5	3.5	4.5	<0.001
Cancer, %	12.7	5.3	11.3	17.5	15.8	15.1	<0.001
Bone fracture, %	6.3	4.1	6.2	6.3	6.9	9.8	<0.001
Frequency (no. of conditions)							
0	7.4	21.7	8.0	3.2	1.9	0.8	<0.001
1–2	59.7	66.2	68.6	60.3	50.7	46.1	<0.001
3–4	28.9	11.5	22.6	32.0	40.3	44.6	<0.001
≥ 5	4.0	0.6	0.8	4.5	7.1	8.5	<0.001
Charlson Comorbidity Index	1.16 (1.45)	0.51 (0.98)	0.84 (1.21)	1.27 (1.43)	1.65 (1.60)	1.79 (1.61)	<0.001

Abbreviations: CKD, chronic kidney disease. Values are presented as mean (standard deviation) or percentage.
Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg and/or current use of antihypertensive agents. Diabetes mellitus was identified in patients with a hemoglobin A1c value ≥ 6.5% (National Glycohemoglobin Standardization Program), whose underlying kidney disease was diabetic nephropathy, and/or who were receiving treatment with insulin or oral antihyperglycemic drugs.
Dyslipidemia was defined as a triglyceride concentration ≥ 150 mg/dL, a low-density lipoprotein cholesterol concentration ≥ 140 mg/dL, a high-density lipoprotein cholesterol concentration <40 mg/dL, or use of lipid-lowering medication. Cardiovascular disease was defined as a composite of ischemic heart disease, congestive heart failure, ischemic stroke, hemorrhagic stroke, peripheral artery disease, thoracic aortic aneurysm, and abdominal aortic aneurysm.

Comorbidities Associated with Reduced Kidney Function

As **Table 3** shows, the prevalence of major comorbid conditions, including hypertension, diabetes mellitus, dyslipidemia, prior CVD, cancer, and bone fracture was 3,727 (83.3%), 1,285 (28.7%), 2,055 (45.9%), 1,041 (23.3%), 567 (12.7%), and 282 (6.3%), respectively. The proportion of patients with these comorbidities was significantly increased in the group with advanced CKD **(Supplementary Table 2)**. Importantly, the cumulative number of comorbidities increased, and the Charlson Comorbidity Index increased in the population with a reduced eGFR (*P* for trend, <0.001). **Table 4** shows the prevalence and association of comorbidities with an eGFR of <60 mL/min/1.73 m^2. Of all cardiovascular comorbidities, hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, and congestive heart failure were associated with elevated ORs with an eGFR of <60 mL/min/1.73 m^2. For non-cardiovascular comorbidities, cancer was a significant risk factor for decreased kidney function, whereas collagen disease and liver disease were associated with lowered ORs with an eGFR of <60 mL/min/1.73 m^2. Sensitivity analysis revealed a clearer dose–response relationship between reduced GFR and comorbidity in the model using an eGFR of <45 mL/min/1.73 m^2 as the dependent variable **(Supplementary Table 3)**. **Supplementary Fig. 1** shows the dose–response association between eGFR and the number of comorbidities. Furthermore, a significant association between eGFR and comorbidity categories was identified in the multivariable-adjusted linear regression model with eGFR as the dependent variable **(Supplementary Table 4)**.

Multimorbidity and Reduced Kidney Function

Table 5 demonstrates the association between multimorbidity and reduced eGFR. Compared with the reference group without any comorbidities, adjusted ORs increased linearly as the cumulative number of conditions increased (all 23 registered comorbidities: OR for 1–2 conditions, 2.11; 95% CI, 1.54–3.41; OR for 3–4 conditions, 2.38; 95% CI, 1.66–3.41; and OR for ≥ 5 conditions, 2.94; 95% CI: 1.74–4.97; and major comorbidities: OR for 1–2 conditions, 2.22; 95% CI, 1.65–2.97; OR for 3–4 conditions, 3.04; 95% CI, 2.12–4.37; and OR for ≥ 5

Table 4. Comorbidities associated with an eGFR < 60 mL/min/1.73 m^2

Comorbidities	No. (%) of included subjects	Prevalence of subjects with an eGFR < 60 mL/min/1.73 m^2 (%)	Adjusted odds ratio (95% CI)	*P* value
Cardiovascular risk factors				
Hypertension (vs. without)	3,727 (83.3)	81.9	2.68 (2.15–3.34)	< 0.001
Diabetes mellitus (vs. without)	1,285 (28.7)	86.9	0.71 (0.56–0.90)	0.005
Dyslipidemia (vs. without)	2,055 (45.9)	79.1	1.28 (1.07–1.54)	0.01
Sleep apnea syndrome (vs. without)	61 (1.4)	83.6	1.04 (0.46–2.33)	0.93
Atrial fibrillation (vs. without)	282 (5.5)	92.2	1.08 (0.63–1.85)	0.79
Cardiovascular disease (vs. without)	1,041 (23.3)	93.0	1.68 (1.26–2.40)	< 0.001
Ischemic heart disease (vs. without)	481 (10.8)	94.0	1.63 (1.05–2.51)	0.03
Congestive heart failure (vs. without)	132 (3.0)	97.7	5.04 (1.52–16.7)	0.01
Ischemic stroke (vs. without)	408 (9.1)	92.4	1.40 (0.92–2.14)	0.12
Hemorrhagic stroke (vs. without)	90 (2.0)	92.2	1.62 (0.70–3.75)	0.26
Peripheral artery disease (vs. without)	144 (3.2)	93.1	1.18 (0.53–2.63)	0.68
Thoracic aortic aneurysm (vs. without)	39 (0.9)	92.3[a]	1.85 (0.53–6.47)[a]	0.33[a]
Abdominal aortic aneurysm (vs. without)	94 (2.1)	95.7	1.63 (0.56–4.61)	0.38
Non-cardiovascular disease (vs. without)	3,392 (75.8)	83.3	1.01 (0.83–1.23)	0.93
Cancer (vs. without)	567 (12.7)	90.0	1.41 (1.02–1.94)	0.04
Bone fracture (vs. without)	282 (6.3)	84.4	0.93 (0.63–1.38)	0.73
Collagen disease (vs. without)	167 (3.7)	70.1	0.54 (0.36–0.82)	0.004
Rheumatoid arthritis (vs. without)	112 (2.5)	73.2	0.61 (0.36–1.03)	0.06
Thyroid disease (vs. without)	206 (4.6)	83.0	1.26 (0.82–1.96)	0.29
Liver disease (vs. without)	227 (5.1)	76.2	0.65 (0.45–0.94)	0.02
COPD (vs. without)	129 (4.3)	79.2	0.70 (0.45–1.10)	0.13
Gastroduodenal ulcer (vs. without)	108 (2.4)	87.0	1.30 (0.68–2.51)	0.43
Depression (vs. without)	103 (2.3)	81.6	1.38 (0.74–2.60)	0.31
Dementia (vs. without)	52 (1.16)	98.1	3.94 (0.50–31.0)	0.19
Hemiplegia (vs. without)	46 (1.0)	97.8	3.18 (0.42–24.1)	0.26

Abbreviations: eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CI, confidence interval.
Denominator was 4,476 patients.
Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg and/or current treatment with antihypertensive agents.
Diabetes mellitus was identified in patients with a hemoglobin A1c value ≥ 6.5% (National Glycohemoglobin Standardization Program), whose underlying kidney disease was diabetic nephropathy, and/or who were receiving treatment with insulin or oral antihyperglycemic drugs.
Dyslipidemia was defined as a triglyceride concentration ≥ 150 mg/dL, a low-density lipoprotein cholesterol concentration ≥ 140 mg/dL, a high-density lipoprotein cholesterol concentration < 40 mg/dL, or use of lipid-lowering medication.
Cardiovascular disease was defined as a composite of ischemic heart disease, congestive heart failure, ischemic stroke, hemorrhagic stroke, peripheral artery disease, thoracic aortic aneurysm, and abdominal aortic aneurysm.
Adjusted using the final selected model (age, sex, underlying kidney disease, hypertension, diabetes mellitus, dyslipidemia, history of cardiovascular disease, body mass index, and urinary protein excretion). Variables relevant to the categories were excluded from each model.
[a] eGFR < 50 mL/min/1.73 m^2 was the cutoff value.

conditions, 4.37; 95% CI: 1.75–10.9). This upward trend was most pronounced with cardiovascular comorbidities (OR for 1–2 conditions, 2.34; 95% CI, 1.76–3.11; OR for 3–4 conditions, 3.29; 95% CI, 2.26–4.78; and OR for ≥ 5 conditions, 7.12; 95% CI, 2.05–24.7). There was no significant association between the cumulative number of non-cardiovascular comorbidities and reduced eGFR (*P* for trend, 0.93). As **Fig. 2** shows, the number of medications increased linearly with the progression of the CKD stage, and a significant dose–response relationship between polypharmacy and reduced eGFR was observed in the multivariable-adjusted model **(Table 6)**.

Discussion

The FKR Study is an observational cohort study of Japanese patients with non-dialysis-dependent CKD under nephrologist care. This cohort includes approximately 4,500 outpatients with CKD stages

Table 5. The association between multimorbidity and reduced eGFR (<60 mL/min/1.73 m^2)

	No. (%) of included patients	Prevalence of patients with an eGFR <60 mL/min/1.73 m^2 (%)	Adjusted odds ratio (95% CI)	*P* value
All 23 registered comorbidities, No. of conditions				
0	304 (6.8)	31.9	1.00 (reference)	<0.001
1–2	2,286 (51.1)	71.3	2.11 (1.54–2.91)	
3–4	1,473 (32.9)	87.0	2.38 (1.66–3.41)	
≥ 5	413 (9.2)	92.7	2.94 (1.74–4.97)	
Major comorbidities, No. of conditions				
0	357 (8.0)	31.5	1.0 (reference)	<0.001
1–2	2,652 (59.2)	72.9	2.22 (1.65–2.97)	
3–4	1,289 (28.8)	90.3	3.04 (2.12–4.37)	
≥ 5	178 (4.0)	96.7	4.37 (1.75–10.9)	
Cardiovascular comorbidities, No. of conditions				
0	382 (8.5)	33.0	1.00 (reference)	<0.001
1–2	2,844 (63.6)	74.0	2.34 (1.76–3.11)	
3–4	1,110 (24.8)	91.4	3.29 (2.26–4.78)	
≥ 5	140 (3.1)	97.9	7.12 (2.05–24.7)	
Non-cardiovascular comorbidities, No. of conditions				
0	2,945 (65.8)	71.9	1.00 (reference)	0.93
1	1,112 (24.8)	83.5	1.09 (0.88–1.36)	
2	325 (7.3)	82.5	0.80 (0.56–1.14)	
≥ 3	94 (2.1)	83.0	0.78 (0.42–1.46)	

Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.
Major comorbid conditions included hypertension, diabetes, dyslipidemia, prior cardiovascular disease, cancer, and bone fracture.
Adjusted using the final selected model, which included age, sex, underlying kidney disease, hypertension, diabetes mellitus, dyslipidemia, history of cardiovascular disease, body mass index, and urinary protein excretion. Variables relevant to the categories were excluded from each model.

Table 6. The association between the number of medications and reduced eGFR (<60 mL/min/1.73 m^2)

No. of medications	No. (%) of included patients	Prevalence of patients with an eGFR <60 mL/min/1.73 m^2 (%)	Adjusted odds ratio (95% CI)	*P* value
0	248 (5.5)	38.7	1.0 (reference)	<0.001
1–2	882 (18.4)	56.6	1.29 (0.87–1.92)	
3–4	1,138 (25.4)	71.9	1.96 (1.31–2.92)	
5–6	997 (22.3)	83.8	2.36 (1.54–3.62)	
≥ 7	1,271 (28.4)	92.7	3.39 (2.13–5.40)	

Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.
Adjusted using the final selected model, which included age, sex, underlying kidney disease, hypertension, diabetes mellitus, dyslipidemia, history of cardiovascular disease, body mass index, and urinary protein excretion.

G1–G5. A multivariable analysis revealed that lifestyle-related diseases, such as hypertension, diabetes mellitus, dyslipidemia, and a history of CVD, were independent factors associated with reduced kidney function. Interestingly, an independent linear association between the cumulative number of comorbidities and eGFR reduction was observed. The findings from this study provide a comprehensive understanding of demographics and highlight the importance of managing multimorbidity among patients with CKD under nephrologist care in Japan.

Patients with advanced CKD stages were older, more likely to have diabetes mellitus and cancer, and more likely to have high blood pressure levels, coronary artery disease, heart failure, and PAD. These data demonstrate the high disease burden of chronic diseases among older adults with comorbidities associated with CKD. Comorbidities, including CVD, are a major source of morbidity and healthcare costs for hospitalized elderly patients[21]. Furthermore,

CKD influences diagnosis and treatment decisions for these other comorbidities[22]. Thus, early detection of CKD and appropriate management of chronic diseases may be a useful strategy to prevent adverse outcomes caused by these comorbidities.

A multivariable analysis revealed an independent association between reduced kidney function and comorbidities, including lifestyle-related disease and CVD risk factors. The high prevalence of cardiovascular risk factors in patients with advanced CKD suggests that the underlying cause of CKD may be a form of diffuse atherosclerotic vascular disease, as well as cardiac and other vascular diseases. This hypothesis is consistent with prior pathophysiological and epidemiological studies[23, 24]. The strong association between CKD and CVD suggests not only that both conditions share risks but also that CKD itself may promote a complex cardiovascular risk condition[5, 25, 26]. Longitudinal investigations are needed to more fully explore this hypothesis.

Tonelli *et al.* assessed medical complexity using nine markers (including the number of comorbidities, number of prescription medications, presence of psychiatric disorders, number of types of physicians involved in each patient's care, and number of physicians involved in each patient's care) and found that patients with CKD had the highest complexity, leading to an increased risk of death[9]. The authors concluded that intensive risk management is recommended for patients with CKD at high risk for comorbid CVD. However, such intensive management has a negative aspect, which may lead to complexity of care because of the increased number of medications. An increase in the number of medications can lead to adverse effects[11] and reduced kidney function due to poor adherence[12]. Indeed, in our study, we found a significant dose–response relationship between the cumulative number of complications (especially cardiovascular complications) and reduced eGFR. These findings suggest that complications in patients with impaired kidney function are mainly due to increased cardiovascular burden, and therefore, an increase in the number of medications may have an unfavorable impact on kidney function through adverse effects and reduced adherence. A longitudinal study of our cohort needs to be further investigated to determine what practice patterns regarding medication use are protective for kidney outcomes.

Ethnic differences exist in terms of susceptibility to CVD. Previous epidemiological studies have found that Western populations have a higher incidence of ischemic heart diseases, such as myocardial infarction and angina pectoris[27-29]. The crude prevalence of prior ischemic heart disease in our cohort was 10.8%, similar to the 13.4% observed in the CKD-JAC study in Japan but less than the 26.0% observed in the Chronic Renal Insufficiency Cohort study in the United States[30, 31]. Previous stroke was found in 11.1% of patients in our cohort, similar to the CKD-JAC study (11.5%), but the prevalence of stroke in individuals with an eGFR 30–60 mL/min/1.73 m^2 in the German CKD cohort deviated significantly to 37.2%[32]. The incidence of CVD, including stroke, may be less common in Japanese patients with CKD compared with Caucasians. A prospective survey of our cohort will also provide new insights into ethnic differences in CVD burden among CKD populations.

Multivariable-adjusted models showed an inverse association between diabetes and reduced kidney function (eGFR <60 mL/min/1.73 m^2). To address multicollinearity, we performed a sensitivity analysis excluding diabetic nephropathy from the model, but the OR of diabetes for reduced GFR was not significant (OR, 1.05, 95% CI, 0.85–1.30). We speculate that a possible explanation for these findings observed in this cross-sectional study is that the influence of diabetes may have been diluted by the uniqueness of the participants in this cohort, which was restricted to patients with CKD. Future longitudinal studies of this cohort will reveal the definitive association between diabetes and kidney function.

Our study has several limitations. First, we did not perform Cr clearance measurements or urine protein measurements through 24 h urine collection. However, given that routine practice is based on spot urinalysis, evidence based on opportunistic testing may be useful in real-world practice. Second, there is the possibility of misclassification of underlying kidney disease. Nevertheless, the biopsy diagnosis rate in our cohort was relatively high (37%); thus, a highly accurate estimate could be expected. Finally, this study is cross-sectional and cannot address causality. A longitudinal study of this cohort should elucidate the association between comorbidities and the prognosis of Japanese patients with CKD.

Conclusions

In conclusion, CKD is associated with a higher prevalence of comorbid conditions. Importantly, patients with CKD are at a higher risk of comorbid CVD and require intensive monitoring and risk management. Based on these findings, emphasis should be placed on preventing adverse outcomes in patients with CKD through comprehensive multimorbidity risk management. We believe that this

study could provide a better knowledge of demographics and multimorbidity among patients with CKD under nephrologist care in Japan.

Authors' Contributions

S.T. and T.N. contributed to the study design, acquisition of data, statistical analysis, interpretation of data, and drafting of the manuscript. H.H contributed to the study design, statistical analysis, interpretation of data, and drafting of the manuscript. K.T. and T.K. contributed to the critical revision of the manuscript and study supervision. All authors provided critical reviews of the manuscript and approved the final version.

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Conflict of Interest

The authors declare that they have no relevant

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Supplementary Table 1. Baseline treatment status of the participants according to CKD stages

	All patients	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5	*P* value
Antihypertensive agents							
ACE inhibitors, %	9.1	6.7	10.1	11.3	10.2	6.6	0.30
ARBs, %	65.4	50.7	61.2	68.2	75.8	79.6	<0.001
Combined ACE inhibitors and ARBs, %	4.4	3.0	5.1	5.2	4.7	4.3	0.13
Calcium channel blockers, %	48.7	24.6	38.4	52.3	64.9	75.1	<0.001
Beta blockers, %	15.2	4.4	10.0	15.8	23.2	28.0	<0.001
Alfa blockers, %	6.1	1.2	2.5	5.5	9.5	16.0	<0.001
Diuretics, %	21.1	4.7	11.2	22.9	33.7	41.1	<0.001
Lipid-, glucose-, and uric acid-lowering therapy and antiplatelet/anticoagulant therapy							
Statins, %	40.2	31.5	40.7	45.5	42.7	43.0	<0.001
Insulin, %	6.4	1.8	2.9	5.6	9.4	16.6	<0.001
Sulfonylureas, %	3.0	0.7	2.8	4.6	4.4	2.3	<0.001
Biguanides, %	1.6	1.9	2.2	2.4	0.9	0.0	0.002
α-glucosidase inhibitors, %	4.9	1.6	3.1	6.3	7.0	7.6	<0.001
Dipeptidyl peptidase-4 inhibitors, %	12.7	5.3	9.2	12.9	18.7	20.6	<0.001
Uric acid-lowering agents, %	41.1	9.8	27.2	45.1	67.1	67.2	<0.001
Antiplatelets, %	18.3	4.5	10.7	20.5	29.6	31.1	<0.001
Warfarin, %	6.0	2.3	3.7	7.4	9.8	7.0	<0.001
Treatment for anemia							
ESAs, %	14.0	0.2	1.1	6.3	23.0	57.6	<0.001
Iron, %	7.3	3.5	3.6	5.1	10.6	18.3	<0.001
Treatment for MBD, acidosis, uremic toxin, and hyperkalemia							
Phosphate binders, %	1.4	0.1	0.4	0.5	0.9	8.1	<0.001
Vitamin D3, %	10.8	11.0	8.3	9.0	11.0	17.4	0.002
Sodium bicarbonate, %	4.6	0.0	0.5	1.4	7.5	20.2	<0.001
Carbonic absorbent, %	4.9	0.0	0.5	2.4	7.6	21.1	<0.001
Ion exchange resins, %	11.3	0.3	2.1	5.4	20.6	39.6	<0.001

Abbreviations: CKD, chronic kidney disease; ARBs, Angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; ESAs, erythropoiesis-stimulating agents; MBD, mineral bone disorders. Values are given as percentage.

Supplementary Table 2. Prevalence of all registered 23 comorbidities of the participants according to CKD stages

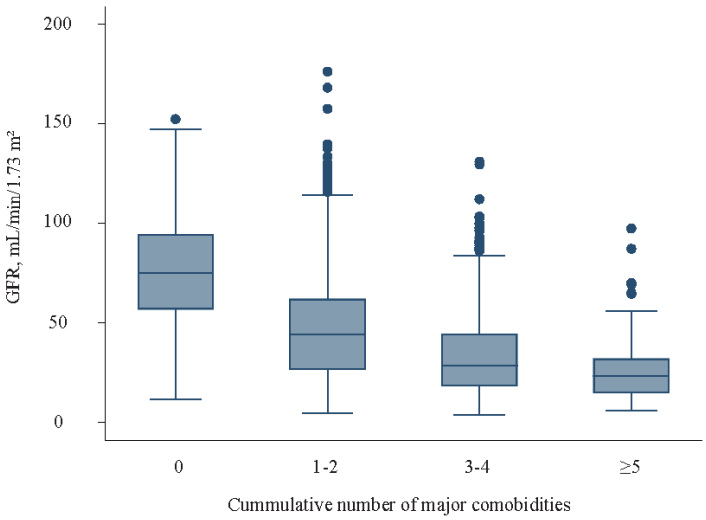
	All patients	Stage G1–2	Stage G3a	Stage G3b	Stage G4	Stage G5	*P* value
Hypertension, %	83.3	63.0	81.8	90.8	95.3	96.4	<0.001
Diabetes mellitus, %	28.7	15.5	20.4	29.2	38.4	47.7	<0.001
Dyslipidemia, %	45.9	39.9	46.9	47.1	49.4	50.1	<0.001
Cardiovascular disease, %	22.0	6.4	13.9	23.8	35.8	35.5	<0.001
Ischemic heart disease, %	10.8	2.7	7.3	12.6	16.4	17.9	<0.001
Congestive heart failure, %	3.0	0.3	0.4	3.5	5.7	5.9	<0.001
Ischemic stroke, %	9.1	2.9	5.9	8.7	15.7	14.2	<0.001
Hemorrhagic stroke, %	2.0	0.7	1.1	2.4	3.5	2.6	<0.001
Peripheral artery disease, %	3.2	0.9	1.1	3.6	5.1	6.6	<0.005
Thoracic aortic aneurysm, %	0.9	0.0	0.7	1.0	1.6	1.3	<0.001
Abdominal aortic aneurysm, %	2.1	0.4	0.6	2.5	3.5	4.5	<0.001
Atrial fibrillation, %	5.5	1.8	3.8	7.0	8.7	6.2	<0.001
Sleep apnea syndrome, %	1.4	0.9	1.2	1.0	2.3	1.3	0.05
Cancer, %	12.7	5.3	11.3	17.5	15.8	15.1	<0.001
Bone fracture, %	6.3	4.1	6.2	6.3	6.9	9.8	<0.001
Collagen disease, %	3.7	5.4	4.1	4.5	4.3	3.8	0.11
Rheumatoid arthritis, %	2.5	2.8	2.4	2.1	2.7	2.3	0.73
Thyroid disease, %	4.6	3.2	5.2	3.8	5.4	6.4	0.01
Liver disease, %	5.1	5.0	5.8	4.7	5.2	4.0	0.58
COPD, %	4.3	3.7	3.9	5.1	5.5	2.5	0.57
Gastroduodenal ulcers, %	2.4	1.3	1.7	2.8	3.7	2.7	0.001
Depression, %	2.3	1.8	1.9	3.4	1.7	3.2	0.18
Dementia, %	1.2	0.1	0.7	2.0	1.5	1.9	<0.001
Hemiplegia, %	1.0	0.1	0.6	0.8	2.1	1.9	<0.001
Frequency (no. of conditions)							
0	6.8	19.1	6.4	2.6	1.6	0.6	<0.001
1–2	51.1	60.5	61.0	51.0	40.0	38.8	<0.001
3–4	32.9	17.6	27.6	35.7	43.8	45.2	<0.001
≥ 5	9.2	2.8	5.0	10.7	14.6	15.4	<0.001
Charlson comorbidity index	1.16 (1.45)	0.51 (0.98)	0.84 (1.21)	1.27 (1.43)	1.65 (1.60)	1.79 (1.61)	<0.001

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease. Values are presented as mean (standard deviation) or percentage.
Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg and/or current use of antihypertensive agents.
Diabetes mellitus was identified in patients with a hemoglobin A1c value ≥ 6.5% (National Glycohemoglobin Standardization Program), whose underlying kidney disease was diabetic nephropathy, and/or who received treatment with insulin or oral antihyperglycemic drugs.
Dyslipidemia was defined as a triglyceride concentration ≥ 150 mg/dL, a low-density lipoprotein cholesterol concentration ≥ 140 mg/dL, a high-density lipoprotein cholesterol concentration < 40 mg/dL, or use of lipid-lowering medication.
Cardiovascular disease was defined as a composite of ischemic heart disease, congestive heart failure, ischemic stroke, hemorrhagic stroke, peripheral artery disease, thoracic aortic aneurysm, and abdominal aortic aneurism.

Supplementary Table 3. The association between multimorbidity and reduced eGFR ≤ 45 and ≤ 30 mL/min/1.73 m^2

No. of comorbid conditions	No. (%) of included subjects	eGFR ≤ 45 mL/min /1.73 m^2			eGFR ≤ 30 mL/min /1.73 m^2		
		Prevalence of subjects with eGFR ≤ 45 mL/min/1.73 m^2 (%)	Adjusted odds ratio (95% CI)	*P* value	Prevalence of subjects with eGFR ≤ 30 mL/min/1.73 m^2 (%)	Adjusted odds ratio (95% CI)	*P* value
All registered 23 comorbidities							
0	304 (6.8)	14.5	1.0 (reference)		6.6	1.0 (reference)	
1–2	2,286 (51.1)	51.1	2.63 (1.80–3.84)	<0.001	28.2	3.71 (2.17–6.86)	<0.001
3–4	1,473 (32.9)	71.4	3.46 (2.33–5.14)		48.8	5.05 (2.92–9.40)	
≥ 5	413 (9.2)	82.6	4.94 (3.08–7.93)		58.4	5.85 (3.27–11.2)	
Major comorbidities							
0	357 (8.0)	15.4	1.0 (reference)		7.0	1.0 (reference)	
1–2	2,652 (59.2)	51.4	2.91 (2.07–4.10)	<0.001	30.1	4.21 (2.51–7.08)	<0.001
3–4	1,289 (28.8)	75.7	4.25 (2.93–6.15)		52.5	5.89 (3.45–10.1)	
≥ 5	178 (4.0)	92.7	11.7 (5.76–23.73)		69.1	8.77 (4.66–16.5)	
Cardiovascular comorbidities							
0	382 (8.5)	17.0	1.0 (reference)		7.6	1.0 (reference)	
1–2	2,844 (63.6)	52.6	2.79 (2.03–3.84)	<0.001	30.8	3.86 (2.41–6.18)	<0.001
3–4	1,110 (24.8)	78.0	4.32 (3.01–6.18)		55.3	5.93 (3.62–9.69)	
≥ 5	140 (3.1)	94.3	15.5 (6.52–37.0)		74.3	11.3 (6.07–21.7)	
Non-cardiovascular comorbidities							
0	2,945 (65.8)	52.6	1.0 (reference)		33.2	1.0 (reference)	
1	1,112 (24.8)	66.7	1.16 (0.97–1.39)	0.88	42.7	1.01 (0.86–1.20)	0.42
2	325 (7.3)	62.5	0.79 (0.59–1.04)		39.4	0.82 (0.62–1.08)	
≥ 3	94 (2.1)	69.2	1.09 (0.65–1.84)		45.7	0.99 (0.61–1.60)	

Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.
Major comorbid conditions included hypertension, diabetes, dyslipidemia, prior cardiovascular disease, cancer, and bone fracture.
Adjusted using the final selected model, which included age, sex, underlying kidney disease, hypertension, diabetes mellitus, dyslipidemia, history of cardiovascular disease, body mass index, and urinary protein excretion.
The variable relevant to the categories was excluded from each model.



Supplementary Fig. 1. Box-and-whisker plots showing the association between the cumulative number of major comorbidities and eGFR
Abbreviation: GFR, glomerular filtration rate.

Supplementary Table 4. The association between major comorbidities and eGFR in multivariable-adjusted linear regression model

Major comorbidities, no. of conditions	0	1–2	3–4	≥ 5	*P* value
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Unadjusted eGFR, mL/min/1.73 m²	74.9 (72.1–77.7)	46.5 (45.5–47.5)	33.2 (32.1–34.3)	25.8 (23.7–27.9)	<0.001
Adjusted eGFR, mL/min/1.73 m²	57.8 (55.5–60.1)	44.0 (43.2–44.7)	40.9 (39.8–42.0)	39.4 (36.4–42.3)	<0.001

Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.
Major comorbid conditions included hypertension, diabetes, dyslipidemia, prior cardiovascular disease, cancer, and bone fracture. Adjusted for age, sex, underlying kidney disease, body mass index, and urinary protein excretion.