Heart and Vessels (2019) 34:1440–1455
https://doi.org/10.1007/s00380-019-01375-4

ORIGINAL ARTICLE

Low HDL cholesterol as a predictor of chronic kidney disease progression: a cross-classification approach and matched cohort analysis

Keiko Kawachi[1] · Hiroshi Kataoka[1,2] · Shun Manabe[1] · Toshio Mochizuki[1] · Kosaku Nitta[1]

Received: 28 August 2018 / Accepted: 8 March 2019 / Published online: 14 March 2019

Abstract

Emerging epidemiological evidence indicates that low serum high-density lipoprotein cholesterol (HDL-C) levels are associated with the risk of progression of chronic kidney disease (CKD). However, the differences in the influence of serum HDL-C levels on CKD progression in different subcohorts have rarely been examined in detail in previous studies. The aim of this study was to investigate the significance of low serum HDL-C levels as a predictor of disease progression in CKD patients according to sub-analyses using a cross-classified subcohort. We reviewed data obtained from 120 CKD patients. Prognostic factors for renal outcome were identified by the multivariate Cox proportional hazards method. Kaplan–Meier analysis was performed to assess disease progression, which was defined as a > 30% decline in the glomerular filtration rate (GFR), or end-stage renal disease. The mean age of the included participants was 58.3 ± 13.6 years. The subjects were divided into two groups (low HDL-C vs. high HDL-C). The median follow-up period was 112.8 months. The kidney survival rate in the low HDL-C group was significantly lower than that in the high HDL-C group ($P < 0.0001$). However, the age-stratified analysis showed no difference between the two groups in the cohort of patients ≥ 70 years old. Multivariate Cox regression analyses showed a significant association between low HDL-C [hazard ratio (HR) 4.80, $P = 0.009$] and a ≥ 30% eGFR decline or ESRD. This association was more evident in the cohort of patients < 70 years old (HR 4.96, $P = 0.0165$), especially the female subcohort (HR 13.86, $P = 0.0033$). Multivariate analysis showed a significant correlation between visceral fat area and serum HDL-C levels among both male ($P = 0.0017$) and female ($P = 0.0449$) patients. In a propensity score-matched cohort (patients < 70 years old), the kidney survival rate of CKD patients was significantly lower in the low HDL-C group than in the high HDL-C group ($P = 0.0364$). A low serum HDL-C level is a significant predictor of CKD progression, especially in female patients with CKD under 70 years of age. This finding is of importance to clinicians when determining the expected prognosis of CKD in patients.

Keywords Chronic kidney disease (CKD) · High-density lipoprotein cholesterol (HDL-C) · Propensity score matching · Cross-classification approach · Female

Introduction

The relationship between serum high-density lipoprotein cholesterol (HDL-C) and chronic kidney disease (CKD) is gaining attention. Patients with CKD generally have low serum HDL-C and high serum triglyceride (TG) levels, and normal or low low-density lipoprotein cholesterol (LDL-C) levels. An atherogenic profile may underlie these findings [1]. Emerging epidemiological evidence indicates that low serum HDL-C levels are associated with the risk of development and progression of CKD [2–6]. However, this remains a matter of debate [7–10].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00380-019-01375-4) contains supplementary material, which is available to authorized users.

✉ Hiroshi Kataoka
kataoka@twmu.ac.jp

[1] Department of Medicine, Kidney Center, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

[2] Clinical Research Division for Polycystic Kidney Disease, Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan

A recent study by Bowe et al. [11] investigated the associations between HDL-C levels and various CKD end points in a cohort of 1,943,682 male veterans from the USA with normal kidney function [estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2] at study initiation. Subjects with HDL-C levels < 30 mg/dL had a 10–20% higher risk of CKD progression than did subjects with HDL-C levels ≥ 40 mg/dL during a median follow-up of 9 years. In contrast, Rahman et al. [10] reported that none of the lipid parameters—particularly, HDL-C levels—were independently associated with the progression of kidney disease defined as a composite end point of end-stage renal disease (ESRD) or 50% decline in eGFR from baseline in a prospective cohort of 3939 adults with CKD and an average eGFR of 44.9 mL/min/1.73 m^2 followed up for a median of 4.1 years.

The results of a systematic review and meta-analysis of 18 trials supported the use of a statin in the treatment of non-dialysis CKD patients on the basis of reductions in mortality and cardiovascular events, but they provided no evidence of a benefit with respect to CKD progression [12]. Mendelian randomization for strengthening causal inference in observational studies has recently been used to assess the causality of risk factors that have a genetic predisposition on real outcomes [13]. Coassin et al. [9] reported that HDL cholesterol did not causally influence eGFR and proposed a pleiotropic effect using a Mendelian randomization analysis. On the other hand, Lanktree et al. [14] recently applied a Mendelian randomization analysis to show that a genetically higher serum HDL-C level is causally associated with better kidney function.

Meanwhile, subgroup analyses, such as stratification and cross-classification analyses, although rarely reported, may contribute to clarifying such controversial issues. Investigations utilizing the cross-classification approach can produce results closely reflecting the "real clinical world" and may facilitate patient-centered medicine in a medical setting [15]. We, therefore, investigated the relationship between low serum HDL-C levels and kidney disease progression in CKD patients using stratification and cross-classification analyses.

Materials and methods

Study population

Of the 2012 outpatients visiting the Kidney Center at Tokyo Women's Medical University between August 2006 and August 2007, 201 with CKD who agreed to participate in the study and underwent abdominal computed tomography (CT) and carotid ultrasonography were recruited. CKD was diagnosed according to previously described criteria [16]. Among them, the patients treated with antidyslipidemic agents were excluded from participation. The remaining 120 patients were ultimately enrolled in the present study (Fig. 1).

The patients were divided according to their serum HDL-C level at baseline into a low HDL-C group, i.e., a group comprising male patients whose serum HDL-C value was ≤ 43 mg/dL and female patients whose serum HDL-C value was ≤ 48 mg/dL, and a high HDL-C group, i.e., a group comprising male patients whose serum HDL-C value was > 43 mg/dL and female patients whose HDL-C value > 48 mg/dL.

The subjects' human rights and protection of personal information were well considered. All the relevant staff responsible for the trial adhered to the Helsinki Declaration (amended October 2013) and the Ethical Guidelines for Clinical Studies (revised Feb 28, 2017, referred to hereafter as the Clinical Studies Ethical Guidelines) in the execution of this study. This cohort study was approved by the Medical Ethics Committee of the Tokyo Women's Medical University (#4599). All participants gave their informed consent at the time of entry.

Measurement of covariates

During a regular outpatient clinic visit, each subject underwent anthropometric and physical examinations that included blood pressure (BP), body height, body weight, visceral fat area (VFA), subcutaneous fat area (SFA), and maximum carotid intima-media thickness (IMT) measurements. BP was measured in triplicate with a mercury sphygmomanometer, and the average value was used in the analysis. VFA and SFA were measured by CT, and IMT was measured by carotid ultrasonography. Details of the measurement techniques are described below. All biochemical analyses

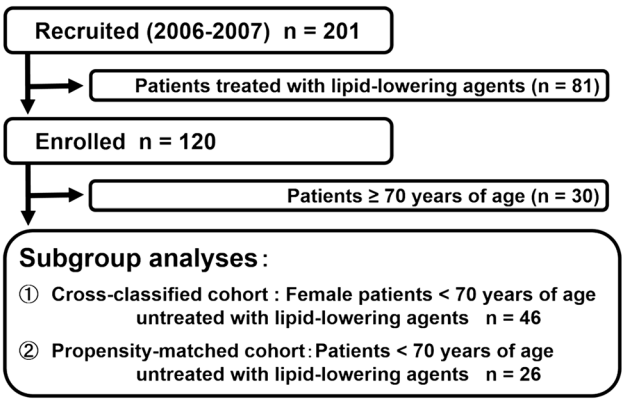

Fig. 1 Flowchart of patient selection. From the 201 screened patients, 81 who did not meet the entry criteria were excluded, and the remaining 120 were enrolled in this study. Subgroup analyses, based on age under 70 years, were performed as shown

were performed on samples obtained after an overnight fast. Serum creatinine levels were measured enzymatically. The eGFR was calculated using the previously described formula for Japanese patients [17].

The impact of concomitant drug use and comorbidities at entry was also assessed [18]. The drugs being taken concomitantly by the patients were antihypertensive drugs, diuretics, and drugs for the treatment of hyperuricemia and diabetes mellitus.

The baseline parameters assessed in this study were age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), body mass index (BMI), VFA, SFA, IMT, eGFR, hemoglobin concentration, serum levels of albumin, uric acid (UA), total cholesterol (TC), LDL-C, HDL-C, and TG values. Comorbidities were recorded as positive on the basis of the criteria listed below. The subjects were followed up until July 2016.

Abdominal CT examination

A multidetector-row CT examination was performed using a GE LightSpeed (GE Healthcare, Milwaukee, Wisconsin, USA). An index image was obtained before scanning, and the umbilicus to L4–5 level was identified as described previously [19, 20]. Horizontal images were obtained at 400 mA and 120 kVp, with a scan time of 1.0 s. The range of CT values covered the optimal range for adipose tissue, i.e., from −150 to −40.14. Data were stored and analyzed with GE advantage workstation Ver.4.0.

Carotid ultrasonography

An experienced examiner blinded to the patient data performed high-resolution duplex carotid ultrasonography with a 7.5-MHz duplex scanner (Aplio XG; Toshiba, Tokyo, Japan) as described previously [21, 22]. The common and internal carotid arteries were scanned cross-sectionally and longitudinally to estimate the presence and distribution of atherosclerotic plaques. The entire lengths of both common carotid arteries and both internal carotid arteries were scanned up to approximately 20 mm distal to the tip of the carotid bifurcation. IMT measurements were obtained to identify the thickest region of the arterial wall according to an international consensus report [23].

Definition of comorbidities and primary causes of CKD

Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or taking an antihypertensive agent. Hyperuricemia was defined as a serum UA level ≥ 7.0 mg/dL or taking an antihyperuricemic agent. Diabetes mellitus was defined as HbA1C ≥ 6.5%, a history of diagnosis of diabetes mellitus, or taking an antidiabetic agent. Hypertriglyceridemia was defined as a serum TG level ≥ 150 mg/dL. Low HDL-C was defined as a serum HDL-C level ≤ 43 mg/dL among male patients and ≤ 48 mg/dL among female patients. High LDL-C was defined as a serum LDL-C level ≥ 140 mg/dL. High TC was defined as a serum TC level ≥ 220 mg/dL.

Diabetic nephropathy, chronic glomerulonephritis and nephrosclerosis were defined by biopsies or by a clinical diagnosis by the physician in charge.

Definition of subcohorts

Two conventional attributes of CKD, age (≥ 70 vs. < 70) [24] and sex (male vs. female) [25], were used for stratification analyses and cross-classification analyses. In this study, we initially examined the prognostic factors of CKD in the total cohort and subsequently divided the patients into two subcohorts by age and sex. Finally, we made four subcohorts by multiplying the two attributes for cross-classification. As patients were categorized into four mutually exclusive prespecified subcohorts on the basis of cross-classification, we were able to investigate the progression of CKD in a total of four subcohorts.

Outcome evaluation (end point)

The outcome variable of interest was kidney disease progression, which was defined as a ≥ 30% decline in eGFR [26] from baseline or the development of ESRD requiring dialysis.

Statistical analysis

Continuous variables are reported as mean ± standard deviation or as medians (interquartile ranges). Categorical variables are reported as percentages, unless otherwise stated. Group differences were evaluated using an unpaired *t* test, the Mann–Whitney *U* test, the Chi-square test, or Fisher's exact test.

The correlations between serum HDL-C values and the other variables were assessed using Pearson's correlation coefficients. The optimal cutoff serum HDL-C value for discriminating a ≥ 30% eGFR decline or ESRD during follow-up examinations was determined by receiver operating characteristic (ROC) analysis. Prognostic variables for renal outcome were assessed by univariate and multivariate Cox proportional hazards methods. Univariate Cox regression analyses were performed, and variables with *P* values < 0.1, age, sex, and eGFR were candidates for multivariate analyses. Kidney disease progression, defined as a ≥ 30% eGFR decline or development of ESRD, and interval estimates between the low HDL-C and high HDL-C groups were

estimated by the Kaplan–Meier method and evaluated by the log-rank test.

To further assess whether associations were consistent across clinically matched subgroups, we fit propensity score-matched models that included several potential modifying variables (age, sex, eGFR, MBP) and performed subgroup analyses. The caliper-matching method was used with a maximum tolerance level of 0.1. Standardized differences were estimated to assess the appropriateness of matching, and 95% confidence intervals (CIs) were calculated. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using the JMP Pro ver.12.1.0 software program (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The 120 subjects consisted of 60 male patients and 60 female patients, and their mean age at baseline was 58.6 ± 13.6 years (range 24–84 years). As shown in Table 1, the mean SBP was 125.7 ± 7.4 mmHg, DBP 76.4 ± 6.4 mmHg, MBP 92.8 ± 6.5 mmHg, BMI 23.7 ± 3.6 kg/m^2, VFA 119.6 ± 60.2 cm^2, IMT 1.46 ± 0.82 mm, urinary protein excretion 0.49 ± 0.79 g/day, and eGFR 57.9 ± 22.8 mL/min/1.73 m^2. The concomitant drug data showed that 80 subjects were being treated with an antihypertensive agent, 41 with a urate-lowering agent, 15 with an antidiabetic agent, 14 with a corticosteroid, 3 with an immunosuppressive agent, and 32 with a diuretic. The comorbidity data showed that 80 patients had hypertension, 55 had hyperuricemia, 41 had high TC, 33 had high LDL-C, 40 had hypertriglyceridemia, and 23 had diabetes mellitus. The median duration of follow-up was 112.8 months (interquartile range 64.6–115.6 months), during which 4 patients died, 17 were lost to follow-up, and 33 reached the end point (≥ 30% eGFR decline or ESRD). The characteristics of the subcohorts at baseline are shown in Tables 1b and S1.

Serum HDL-C cutoff value as a predictor of kidney disease progression

We performed ROC analyses to identify the optimal serum HDL-C cutoff value for discriminating a ≥ 30% eGFR decline or ESRD during the follow-up examination. The results revealed an optimal cutoff value of ≤ 43 mg/dL for male patients (area under the curve = 0.65, sensitivity = 52.4%, specificity = 63.0%, Fig. 2a) and ≤ 48 mg/dL for female patients (area under the curve = 0.60, sensitivity = 41.7%, specificity = 75.0%, Fig. 2b).

Comparison between clinical findings according to serum HDL-C values in the total cohort

We compared the clinical characteristics of the two groups established according to serum HDL-C values at baseline (Table 1). The baseline serum HDL-C (39.6 ± 5.6 vs. 62.3 ± 12.8 mg/dL, $P < 0.0001$), serum albumin (4.01 ± 0.33 vs. 4.26 ± 0.31, $P = 0.0002$), hemoglobin (12.6 ± 2.1 vs. 13.5 ± 1.6, $P = 0.0081$), eGFR (47.4 ± 25.6 vs. 61.4 ± 21.8, $P = 0.0043$), and serum TC (191.7 ± 37.0 vs. 210.9 ± 33.5, $P = 0.0101$) values of the low HDL-C group were significantly lower than those of the high HDL-C group. Conversely, the VFA (143.3 ± 65.9 vs. 111.7 ± 58.2 cm^2, $P = 0.0143$), TG (160.1 ± 78.4 vs. 127.7 ± 60.9, $P = 0.0207$), and urinary protein excretion [0.48 (0.12–1.77) vs. 0.05 (0.00–0.39) g/day, $P = 0.0005$] values of the low HDL-C group were significantly higher than those of the high HDL-C group.

Low HDL-C as a prognostic indicator in CKD patients

We performed a Kaplan–Meier analysis to assess kidney survival, using a ≥ 30% eGFR decline or ESRD as the end point. The analysis showed that the kidney survival rate in the low HDL-C group was significantly lower than that in the high HDL-C group (Fig. 3a). At the 100-month follow-up examination, a decrease in eGFR value of at least a 30% was observed in 45.8% of the low HDL-C group. However, the results showed a marked difference in the age-stratified analyses. Although the analysis in the cohort of patients < 70 years old showed a significantly lower kidney survival rate in the low HDL-C group than in the high HDL-C group, the results of analysis in the cohort of patients ≥ 70 years old showed no differences between the groups (Fig. 3b, c). The Kaplan–Meier analyses also showed that in the male, female, male < 70 years, and female < 70 years subcohort, the kidney survival rate of the CKD patients in the low HDL-C group was significantly lower than of those in the high HDL-C group (Fig. 4).

To determine whether a low HDL-C value was an independent predictor of a decline in renal function, we performed univariate and multivariate regression analyses on the basis of the Cox hazard model for associations between the clinical findings and a ≥ 30% eGFR decline or ESRD during the follow-up period (Table 2; Appendix, Table S2). The multivariate Cox regression analyses showed significant associations between eGFR (10 mL/min/1.73 m^2 increase) [hazard ratio (HR) 0.64, 95% CI (0.46–0.86), $P = 0.0045$], low HDL-C [HR 4.80, 95% CI (1.44–15.46), $P = 0.0090$], male sex [HR 3.14, 95% CI (1.15–8.83), $P = 0.0265$], and serum albumin (1 g/dL increase) [HR 0.19, 95% CI (0.04–0.92), $p = 0.0403$] and a ≥ 30% eGFR decline or ESRD (Table 2a).

Table 1 Patient characteristics according to baseline serum HDL cholesterol levels. (a) Total cohort, $n=120$. (b) Cohort of patients < 70 years old, $n=90$

Variables	Total $n=120$	Low HDL-C group $n=30$	High HDL-C group $n=90$	*P* value	Standardized differences
(a) Total cohort, $n=120$					
Clinical findings					
Age (years)	58.6 ± 13.6	62.6 ± 11.2	57.3 ± 14.1	0.0622	0.416
Sex (Male; %)	50.0	56.7	47.8	0.3991	0.179
SBP (mmHg)	125.7 ± 7.4	127.7 ± 5.0	125.0 ± 8.0	0.0875	0.405
DBP (mmHg)	76.4 ± 6.4	75.8 ± 6.4	76.6 ± 6.4	0.5315	0.125
MBP (mmHg)	92.8 ± 6.5	93.1 ± 5.6	92.8 ± 6.8	0.8121	0.048
BMI (kg/m^2)	23.7 ± 3.6	24.2 ± 3.5	23.6 ± 3.6	0.3790	0.169
Visceral fat area (cm^2)	119.6 ± 61.5	143.3 ± 65.9	111.7 ± 58.2	0.0143	0.508
Subcutaneous fat area (cm^2)	174.9 ± 82.9	184.3 ± 92.5	171.8 ± 79.8	0.4755	0.145
IMT (mm)	1.46 ± 0.82	1.52 ± 0.79	1.44 ± 0.83	0.6498	0.099
Laboratory findings					
Serum albumin (g/dL)	4.19 ± 0.33	4.01 ± 0.33	4.26 ± 0.31	0.0002	0.781
Hemoglobin (g/dL)	13.3 ± 1.7	12.6 ± 2.1	13.5 ± 1.6	0.0081	0.482
Serum creatinine (mg/dL)	1.20 ± 0.90	1.66 ± 1.34	1.04 ± 0.64	0.0010	0.590
eGFR (mL/min/1.73 m^2)	57.9 ± 23.5	47.4 ± 25.6	61.4 ± 21.8	0.0043	0.589
Uric acid (mg/dL)	5.67 ± 1.50	6.05 ± 1.43	5.55 ± 1.50	0.1142	0.341
Triglyceride (mg/dL)	135.8 ± 66.8	160.1 ± 78.4	127.7 ± 60.9	0.0207	0.462
Total cholesterol (mg/dL)	206.2 ± 35.2	191.7 ± 37.0	210.9 ± 33.5	0.0101	0.544
LDL cholesterol (mg/dL)	122.4 ± 32.1	119.6 ± 31.8	123.2 ± 32.3	0.6013	0.112
HDL cholesterol (mg/dL)	56.7 ± 15.1	39.6 ± 5.6	62.3 ± 12.8	< 0.0001	2.298
L/H ratio	2.27 ± 0.80	2.92 ± 0.84	2.05 ± 0.66	< 0.0001	1.152
TC/HDL-C ratio	3.83 ± 0.98	4.89 ± 0.86	3.49 ± 0.75	< 0.0001	1.735
TG/HDL-C ratio	2.70 ± 1.82	4.24 ± 2.41	2.19 ± 1.21	< 0.0001	1.075
RLP cholesterol (mg/dL)	6.01 ± 3.45	7.67 ± 4.80	5.53 ± 2.81	0.0084	0.544
Hemoglobin A1c (NGSP) (%)	6.08 ± 1.02	6.36 ± 1.26	5.98 ± 0.93	0.1442	0.343
Hs-CRP (ng/mL)	1032.4 ± 2537.1	965.5 ± 1172.6	1054.7 ± 2856.0	0.8683	0.041
U-Prot (g/day)	0.13 (0.00–0.58)	0.48 (0.12–1.77)	0.05 (0.00–0.39)	0.0005	0.702
Primary cause of CKD					
Diabetic nephropathy (%)	10.8	16.7	8.9	0.3072	0.235
CGN (%)	50.8	36.7	55.6	0.0731	0.386
Nephrosclerosis (%)	15.8	23.3	13.3	0.2475	0.261
Others (%)	22.5	23.3	22.2	0.8996	0.026
Concomitant drugs					
Antihypertensive agents (%)	66.7	63.3	67.8	0.6547	0.095
ARB and or ACEI	51.7	56.7	50.0	0.5269	0.135
Ca blockade	31.7	40.0	28.9	0.2663	0.235
Antihyperuricemic agents (%)	34.2	33.3	34.4	0.9115	0.023
Antidiabetic agents (%)	12.5	23.3	8.9	0.0383	0.400
Corticosteroids (%)	11.7	0.0	15.6	0.0215	0.608
Immunosuppressants (%)	2.5	0.0	3.3	0.5722	0.261
Diuretics (%)	26.7	30.0	25.6	0.6336	0.098
Comorbidities					
Hypertension (%)	66.7	63.3	67.8	0.6547	0.095
Hyperuricemia (%)	45.8	60.0	41.1	0.0721	0.385
Hypertriglyceridemia (%)	33.3	46.7	28.9	0.0736	0.373
High total cholesterol (%)	34.2	23.3	37.8	0.1486	0.319
High LDL cholesterol (%)	27.5	23.3	28.9	0.5551	0.128
Diabetes mellitus (%)	19.2	33.3	14.4	0.0228	0.455

Table 1 (continued)

Variables	Total $n=90$	Male $n=44$	Female $n=46$	P value
(b) Cohort of patients < 70 years old, $n = 90$				
Clinical findings				
Age (years)	53.1 ± 10.9	53.3 ± 11.0	53.0 ± 11.0	0.9220
SBP (mmHg)	125.5 ± 8.2	127.2 ± 8.2	123.8 ± 7.9	0.0485
DBP (mmHg)	76.5 ± 6.8	77.8 ± 7.1	75.3 ± 6.2	0.0793
MBP (mmHg)	92.8 ± 7.1	94.3 ± 7.3	91.5 ± 6.6	0.0605
BMI (kg/m^2)	23.8 ± 3.7	24.5 ± 3.5	23.1 ± 3.8	0.0772
Visceral fat area (cm^2)	112.5 ± 58.2	138.2 ± 60.1	88.0 ± 48.2	< 0.0001
Subcutaneous fat area (cm^2)	178.4 ± 85.2	153.0 ± 63.9	202.8 ± 95.6	0.0048
IMT (mm)	1.33 ± 0.70	1.66 ± 0.84	1.02 ± 0.35	< 0.0001
Laboratory findings				
Serum albumin (g/dL)	4.25 ± 0.30	4.21 ± 0.39	4.28 ± 0.24	0.2829
Hemoglobin (g/dL)	13.6 ± 1.7	14.1 ± 2.0	13.1 ± 1.2	0.0047
Serum creatinine (mg/dL)	1.16 ± 0.82	1.39 ± 0.99	0.95 ± 0.76	0.0188
eGFR (mL/min/1.73 m^2)	61.0 ± 22.3	57.8 ± 23.8	64.0 ± 23.1	0.2100
Uric acid (mg/dL)	5.61 ± 1.45	6.40 ± 1.11	4.85 ± 1.41	< 0.0001
Triglyceride (mg/dL)	135.7 ± 65.0	150.0 ± 67.8	121.9 ± 62.6	0.0437
Total cholesterol (mg/dL)	209.5 ± 34.1	202.6 ± 30.4	216.0 ± 36.8	0.0621
LDL cholesterol (mg/dL)	124.0 ± 32.3	121.7 ± 30.1	126.3 ± 34.1	0.4988
HDL cholesterol (mg/dL)	58.3 ± 12.1	50.9 ± 11.4	65.3 ± 15.2	< 0.0001
L/H ratio	2.27 ± 0.69	2.51 ± 0.81	2.04 ± 0.76	0.0062
TC/HDL-C ratio	3.80 ± 0.80	4.15 ± 1.00	3.46 ± 0.89	0.0007
TG/HDL-C ratio	2.60 ± 1.48	3.21 ± 1.92	2.02 ± 1.21	0.0007
RLP cholesterol (mg/dL)	5.97 ± 3.54	6.48 ± 3.82	5.49 ± 3.40	0.2220
Hemoglobin A1c (NGSP) (%)	6.01 ± 0.93	6.15 ± 1.09	5.83 ± 0.73	0.1809
Hs-CRP (ng/mL)	670 ± 973.0	825.3 ± 1195.8	521.4 ± 685.0	0.1405
U-Prot (g/day)	0.22 (0.01–0.63)	0.27 (0.01–0.82)	0.14 (0.00–0.50)	0.1204
Primary cause of CKD				
Diabetic nephropathy (%)	11.1	26.3	7.0	0.0316
CGN (%)	53.3	36.8	57.8	0.1255
Nephrosclerosis (%)	14.4	21.1	12.7	0.4613
Others (%)	21.1	15.8	22.5	0.7531
Concomitant drugs				
Antihypertensive agents (%)	63.3	70.5	56.5	0.1703
ARB and or ACEI	52.2	57.9	50.7	0.6147
Ca blockade	26.7	31.6	25.4	0.5723
Antihyperuricemic agents (%)	36.7	54.6	19.6	0.0006
Antidiabetic agents (%)	8.9	6.5	11.4	0.4198
Corticosteroids (%)	12.2	11.4	13.0	0.8078
Immunosuppressants (%)	2.2	2.3	2.2	1.0000
Diuretics (%)	27.8	31.8	23.9	0.4026
Comorbidities				
Hypertension (%)	63.3	70.5	56.5	0.1703
Hyperuricemia (%)	46.7	70.5	23.9	< 0.0001
Hypertriglyceridemia (%)	31.1	38.6	23.9	0.1315
High total cholesterol (%)	37.8	27.3	47.8	0.0444
High LDL cholesterol (%)	28.9	22.7	34.8	0.2072
Low HDL cholesterol (%)	21.1	27.3	15.2	0.2072

Table 1 (continued)

Variables	Total $n=90$	Male $n=44$	Female $n=46$	*P* value
Diabetes mellitus (%)	16.7	20.5	13.0	0.1613

n number, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *BMI* body mass index, *IMT* maximum carotid intima-media thickness, *eGFR* estimated glomerular filtration rate, *L/H ratio* LDL cholesterol-to-HDL cholesterol ratio, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *RLP* remnant lipoprotein, *Hs-CRP* high-sensitivity C-reactive protein, *U-Prot* Urinary protein excretion, *CGN* chronic glomerulonephritis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as percentages

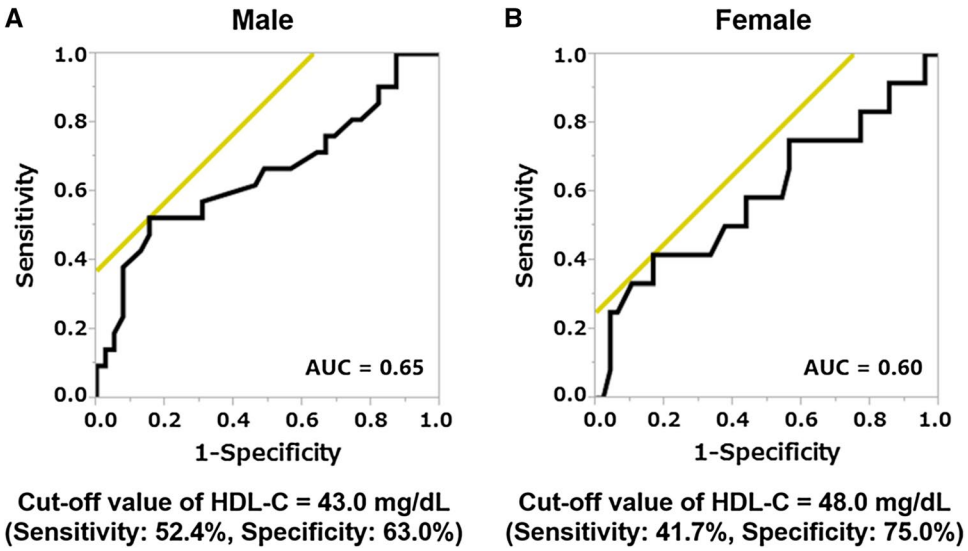

Fig. 2 Receiver operating characteristic analysis to identify the optimal serum HDL-C cutoff value for predicting an eGFR decline by ≥ 30% from baseline or ESRD during the follow-up examination period. (**a** male; **b** female). *ESRD* end-stage renal disease, *eGFR* estimated glomerular filtration rate, *vs.* versus, *HDL-C* high-density lipoprotein cholesterol

The results of the age-stratified analyses in the cohort of patients < 70 years old showed significant associations between eGFR (10 mL/min/1.73 m^2 increase) [HR 0.71, 95% CI (0.50–0.98), $P=0.0396$] and low HDL-C (vs. no) [HR 4.96, 95% CI (1.34–19.41), $P=0.0165$] and a ≥ 30% eGFR decline or ESRD (Table 2b). The analysis in the cohort of patients ≥ 70 years old showed an association between male sex [HR 16.83, 95% CI (2.70–189.99), $P=0.0015$] and a ≥ 30% eGFR decline or ESRD (Appendix, Table S2A). The other subgroup analyses using a multivariate Cox regression model showed that the serum HDL-C value was a prognostic indicator for CKD progression in the female [HR 4.19, 95% CI (1.05–16.42), $P=0.0423$] (Table 2c) and female < 70-year-old subcohorts [HR 13.86, 95% CI (2.43–114.41), $P=0.0033$] (Table 2d) but not the male subcohort (Table 2e).

Correlations between serum HDL-C levels and other parameters

As the serum HDL-C levels may have been affected by confounders, the baseline serum HDL-C levels were tested for correlations with the clinical and laboratory parameters at baseline. As shown in Table 3, the serum HDL-C levels were significantly correlated with the SBP ($r=-0.34$, $P=0.0002$), MBP ($r=-0.21$, $p=0.0192$), VFA ($r=-0.43$, $P<0.0001$, Fig. 5c), IMT ($r=0.32$, $P=0.0003$, Fig. 5d), serum albumin ($r=0.29$, $P=0.0012$), serum creatinine ($r=-0.32$, $P=0.0003$), eGFR ($r=0.26$, $P=0.0037$, Fig. 5a), serum UA ($r=-0.35$, $P<0.0001$), serum TG ($r=-0.36$, $P<0.0001$), serum TC ($r=0.34$, $P=0.0002$), serum remnant lipoprotein cholesterol (RLP) ($r=-0.29$, $P=0.0034$), and urinary protein excretion ($r=-0.33$, $P=0.0003$). There was no correlation between serum HDL-C and age.

We also conducted sex- and age-stratified correlation analyses (Table 3; Appendix, Table S3). The sex-stratified univariate correlation analyses showed that serum HDL-C levels were negatively correlated with SBP and MBP in female patients and with urine protein excretion in male patients. VFA was also negatively correlated with the serum HDL-C levels in both male patients and female patients, and SFA was correlated with the serum HDL-C levels only in female patients (Table 3). The multivariate correlation

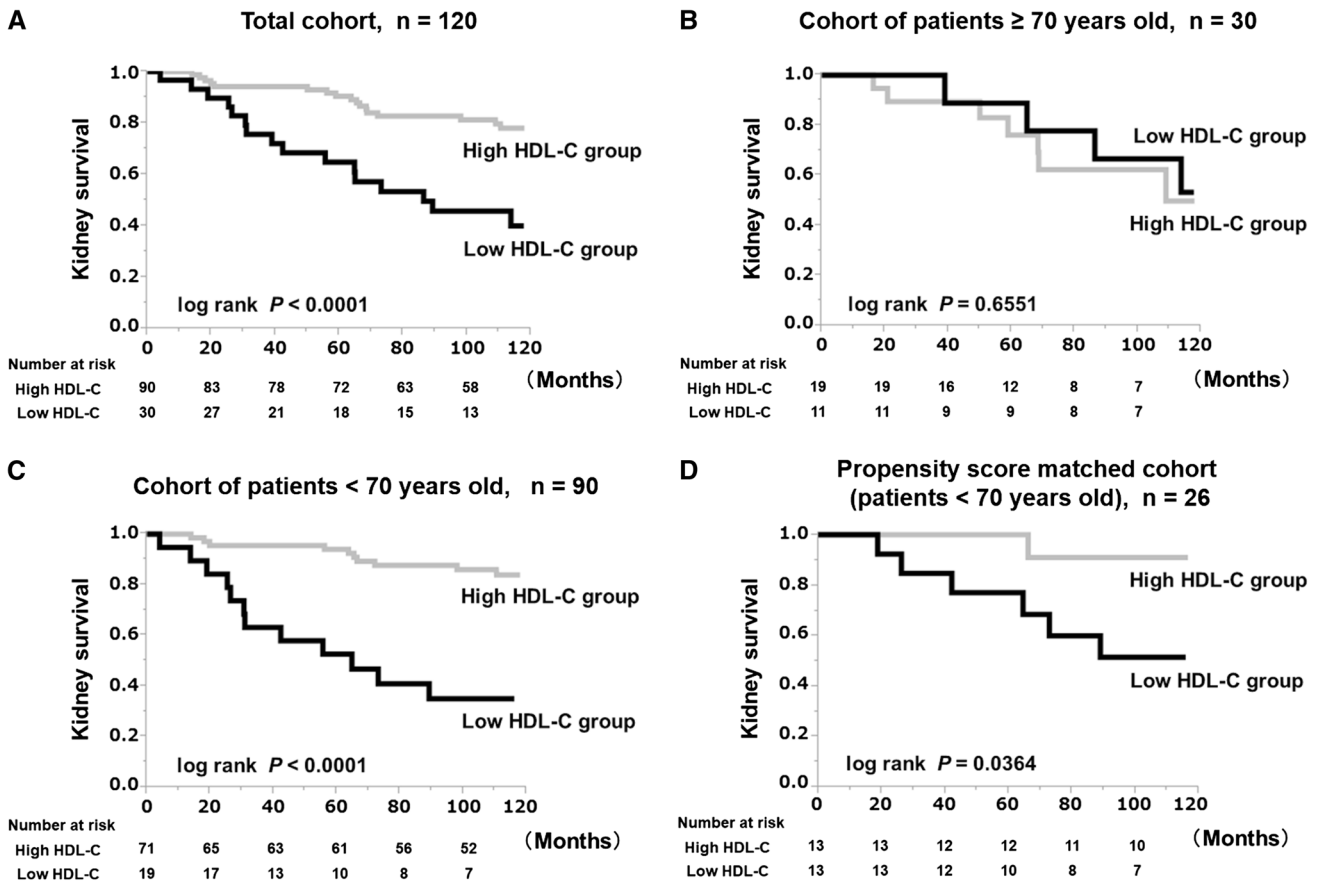

Fig. 3 Kidney survival rate of the low HDL-C group and the high HDL-C group in the total cohort (**a**), the cohort of patients ≥ 70 years old (**b**), the cohort of patients < 70 years old (**c**), and the propensity score-matched cohort (patients < 70 years old) (**d**). *HDL-C* high-density lipoprotein cholesterol

analyses showed that there were significant correlations between VFA and the serum HDL-C levels in both male patients and female patients (Table 4). In the age-stratified univariate analyses based on the cutoff age of 70 years, the correlation coefficients of patients under 70 years old were almost the same as those of the total cohort (Appendix, Table S3). In contrast, because of the small number of patients (number = 30), there were few significant correlations in the cohort older than 70 years (Appendix, Table S3). The multivariate correlation analyses in the under 70-year-old cohort showed that male sex, VFA, and serum albumin levels were significantly correlated with the serum HDL-C levels (Appendix, Table S4).

Comparisons between clinical and laboratory findings according to HDL-C levels in the propensity score-matched cohorts

To assess whether the associations between serum HDL-C levels and eGFR decline were consistent across the clinically matched subgroups, we created propensity score-matched models that included potential modifying variables (age, sex, eGFR, MBP) and performed subgroup analyses. We created a propensity score-matched cohort of the low HDL-C and high HDL-C groups, and the comparisons between the clinical and laboratory findings in the two groups at baseline are summarized in Table 5. In the propensity score-matched cohort (patients < 70 years old), the kidney survival rate of the CKD patients in the low HDL-C group was significantly lower than of those in the high HDL-C group (Fig. 3d).

Discussion

A recent Mendelian randomization study suggested a robust causal association between HDL cholesterol concentration and GFR but not LDL cholesterol concentration [27]. In our study, low HDL cholesterol was an independent risk factor for CKD progression on multivariate Cox analysis, and there was no association between eGFR decline and LDL-C or TG. Of interest, our data indicated that low serum

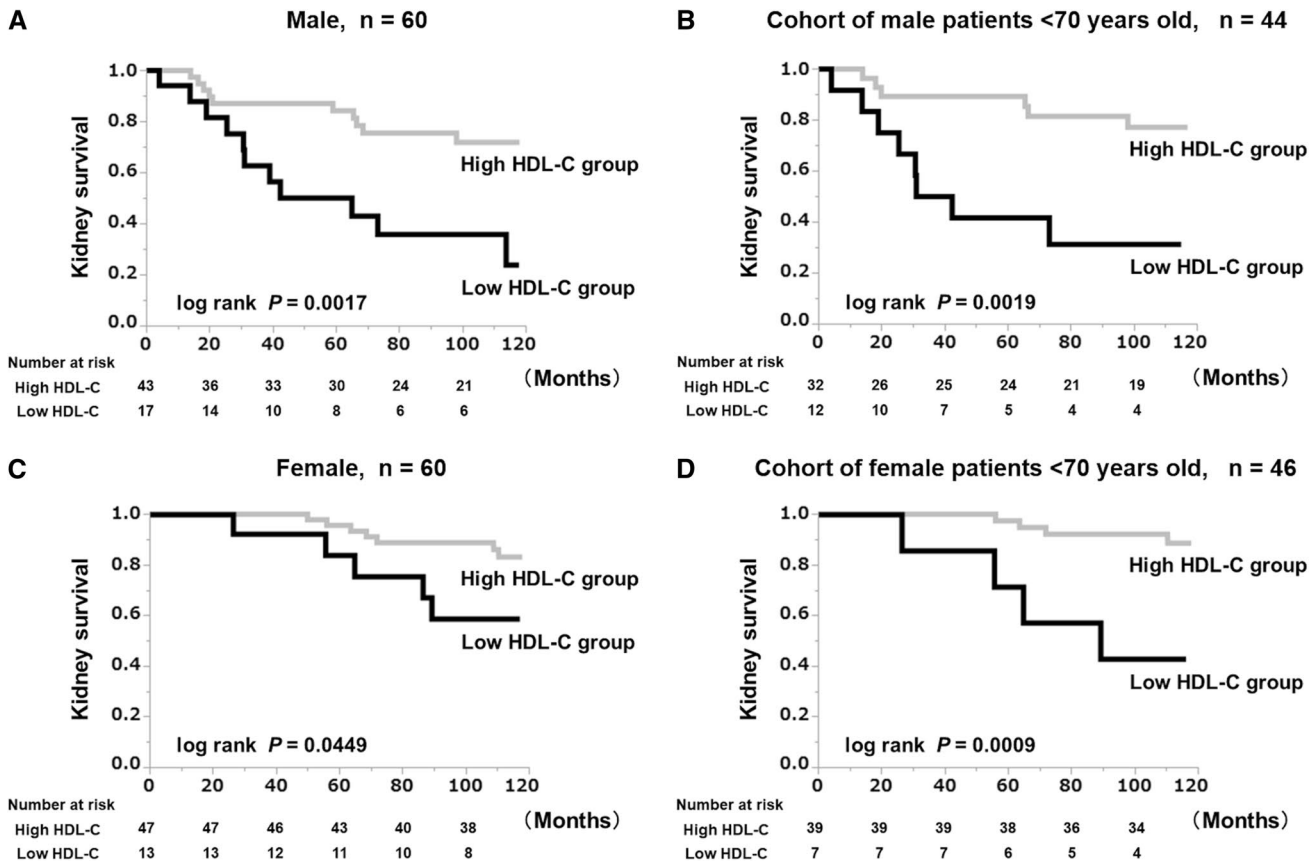

Fig. 4 Kidney survival rate of the low HDL-C group and the high HDL-C group in the male cohort (**a**), the cohort of male patients < 70 years old (**b**), the female cohort (**c**), and the cohort of female patients < 70 years old (**d**). *HDL-C* high-density lipoprotein cholesterol

HDL cholesterol had the strongest association with decline in eGFR among lipid factors, such as hypertriglyceridemia, high TC, high LDL-C, LDL cholesterol-to-HDL cholesterol ratio (*L*/*H* ratio), TC/HDL-C ratio, TG/HDL-C ratio, and RLP cholesterol (Table 2A). The TG/HDL-C ratio is thought to be an indicator of insulin resistance, and an association between TG/HDL-C and albuminuria has been reported [28]. In 2015, Tsuruya et al. [29] reported that higher quartile TG/HDL-C ratios were significantly associated with a decline in eGFR and an increase in urinary protein excretion over a 2-year study period. In their study, serum HDL cholesterol level, which was correlated with the TG/HDL-C ratio, was also an independent risk factor for a decline in eGFR. Our longer follow-up study (median duration was 112.8 months) showed that low serum HDL cholesterol had a stronger association with a decline in eGFR than with the TG/HDL-C ratio. The reasons for these differences are not clear; however, we believe that the antioxidant and anti-inflammatory properties of HDL cholesterol themselves play crucial roles in the progression of CKD [30].

Dyslipidemia in CKD is characterized by a diminished plasma HDL concentration; impaired HDL antioxidant and anti-inflammatory activities; and elevated plasma triglyceride, very low-density lipoprotein, intermediate density lipoprotein, chylomicron remnant, and oxidized lipid and lipoprotein levels [31]. It is considered that a vicious cycle is formed between the progression of renal dysfunction and dyslipidemia [32], and an atherogenic profile may exist behind this cycle [1].

Hwang et al. [33] recently reported that baseline VFA was an independent predictor of the future development of atherogenic dyslipidemia. Visceral fat is a key regulator of numerous adipokines and cytokines and has been found to be associated with insulin resistance, metabolic syndrome, and diabetes [34]. Increased visceral fat causes a decrease in adiponectin and promotes arteriosclerosis owing to increased secretion of adipocytokines, such as tumor necrosis factor-α, resistin, and plasminogen activator inhibitor-1. In addition, visceral fat promotes insulin resistance and contributes to dyslipidemia, including low HDL-C; has higher metabolic activity than subcutaneous fat; accelerates fat synthesis and decomposition; and releases metabolite free fatty acids (FFAs) to the portal vein. FFAs flow into the liver through the portal vein, promote TG and cholesterol syntheses, suppress insulin catabolism, and cause hyperinsulinemia. In visceral fat obesity, production of sex hormone

Table 2 Univariate and multivariate analysis of risk factors associated with a ≥ 30% eGFR decline or ESRD. (a) Total cohort, $n = 120$. (b) Cohort of patients < 70 years old, $n = 90$. (c) Female, $n = 60$. (d) Female cohort of patients < 70 years old, $n = 46$. (e) Male, $n = 60$

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
(a) Total cohort, $n = 120$				
Age (1-year increase)	1.03 (1.01–1.07)	0.02	1.00 (0.96–1.03)	0.8740
Male (vs. female)	2.44 (1.22–5.13)	0.01	3.14 (1.15–8.83)	0.0265
BMI (kg/m^2)	0.99 (0.90–1.09)	0.9	–	–
eGFR (10 mL/min/1.73 m^2 increase)	0.56 (0.46–0.67)	< 0.0001	0.64 (0.46–0.86)	0.0045
Hemoglobin (1 g/dL increase)	0.58 (0.47–0.71)	< 0.0001	0.91 (0.65–1.29)	0.6098
Serum albumin (1 g/dL increase)	0.04 (0.01–0.17)	< 0.0001	0.19 (0.04–0.92)	0.0403
Hypertriglyceridemia (vs. no)	1.18 (0.60–2.38)	0.6	–	–
High total cholesterol (vs. no)	0.73 (0.33–1.49)	0.4	–	–
High LDL cholesterol (vs. no)	1.09 (0.49–2.22)	0.8	–	–
Low HDL cholesterol (vs. no)	3.63 (1.81–7.23)	0.0004	4.80 (1.44–15.46)	0.0090
L/*H* ratio	1.54 (1.01–2.32)	0.05	0.04 (0.00–4.81)	0.1331
TC/HDL-C ratio	1.48 (1.06–2.03)	0.02	22.84 (0.18–1385.59)	0.1551
TG/HDL-C ratio	1.16 (0.98–1.32)	0.08	0.41 (0.17–1.11)	0.0521
RLP cholesterol (mg/dL)	0.73 (0.19–12.46)	0.2	–	–
Hypertension (vs. no)	1.86 (0.87–4.40)	0.2	–	–
Diabetes mellitus (vs. no)	3.04 (1.45–6.11)	0.004	2.07 (0.69–6.06)	0.1815
Hyperuricemia (vs. no)	5.00 (2.40–11.40)	< 0.0001	1.75 (0.63–5.11)	0.2868
(b) Cohort of patients < 70 years old, $n = 90$				
Age (1-year increase)	1.05 (1.00–1.10)	0.0548	1.01 (0.95–1.07)	0.7926
Male (vs. female)	2.51 (1.07–6.30)	0.0334	1.53 (0.51–4.72)	0.4491
BMI (kg/m^2)	0.98 (0.87–1.11)	0.7547	–	–
eGFR (10 mL/min/1.73 m^2 increase)	0.53 (0.41–0.65)	< 0.0001	0.71 (0.50–0.98)	0.0396
Hemoglobin (1 g/dL increase)	0.55 (0.42–0.71)	< 0.0001	0.96 (0.65–1.42)	0.0856
Serum albumin (1 g/dL increase)	0.04 (0.01–0.13)	< 0.0001	0.48 (0.07–3.33)	0.4531
Low HDL cholesterol (vs. no)	6.52 (2.79–15.58)	< 0.0001	4.96 (1.34–19.41)	0.0165
Hypertension (vs. no)	3.04 (1.13–10.53)	0.0256	2.80 (0.71–14.53)	0.1489
Diabetes mellitus (vs. no)	3.67 (1.34–7.88)	0.0113	1.24 (0.31–4.30)	0.7528
Hyperuricemia (vs. no)	11.85 (4.01–50.57)	< 0.0001	3.69 (0.87–20.05)	0.0773
(c) Female, $n = 60$				
Age (1-year increase)	1.04 (0.99–1.10)	0.0900	1.00 (0.95–1.06)	0.9713
BMI (kg/m^2)	1.01 (0.87–1.18)	0.8559	–	–
eGFR (10 mL/min/1.73 m^2 increase)	0.58 (0.41–0.77)	0.0001	0.67 (0.44–0.99)	0.0444
Hemoglobin (1 g/dL increase)	0.59 (0.40–0.89)	0.0115	0.84 (0.53–1.34)	0.4533
Serum albumin (1 g/dL increase)	0.42 (0.05–3.60)	0.4255	–	–
Low HDL cholesterol (vs. no)	3.05 (0.90–9.57)	0.0707	4.19 (1.05–16.42)	0.0423
Hypertension (vs. no)	1.04 (0.33–3.52)	0.9448	–	–
Diabetes mellitus (vs. no)	2.73 (0.60–9.20)	0.1701	–	–
Hyperuricemia (vs. no)	5.83 (1.85–19.72)	0.0030	2.66 (0.51–12.57)	0.2360
(d) Female cohort of patients < 70 years old				
Age (1-year increase)	1.07 (0.99–1.20)	0.0966	1.03 (0.94–1.15)	0.5290
BMI (kg/m^2)	0.98 (0.81–1.17)	0.8281	–	–
eGFR (10 mL/min/1.73 m^2 increase)	0.53 (0.35–0.75)	0.0002	0.51 (0.27–0.85)	0.0084
Hemoglobin (1 g/dL increase)	0.65 (0.36–1.16)	0.1458	–	–
Serum albumin (1 g/dL increase)	2.08 (0.12–56.20)	0.6263	–	–
Low HDL cholesterol (vs. no)	7.48 (1.76–31.74)	0.0082	13.86 (2.43–114.41)	0.0033
Hypertension (vs. no)	2.33 (0.54–15.89)	0. 2729	–	–
Diabetes mellitus (vs. no)	2.18 (0.32–9.50)	0. 3734	–	–
Hyperuricemia (vs. no)	12.51 (2.87–85.57)	0. 0007	2.76 (0.44–23.57)	0.2844

Table 2 (continued)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
(e) Male, $n=60$				
Age (1-year increase)	1.03 (0.99–1.07)	0.1483	0.98 (0.94–1.03)	0.5214
BMI (kg/m^2)	0.93 (0.80–1.07)	0.3079	–	–
eGFR (10 mL/min/1.73 m^2 increase)	0.55 (0.42–0.69)	< 0.0001	0.68 (0.44–1.01)	0.0579
Hemoglobin (1 g/dL increase)	0.52 (0.40–0.65)	< 0.0001	0.97 (0.57–1.55)	0.9054
Serum albumin (1 g/dL increase)	0.02 (0.01–0.08)	< 0.0001	0.07 (0.01–0.44)	0.0050
Low HDL cholesterol (vs. no)	3.65 (1.53–8.82)	0.0032	1.57 (0.43–5.59)	0.4892
Hypertension (vs. no)	2.50 (0.85–10.79)	0.0994	1.59 (0.39–8.33)	0.5352
Diabetes mellitus (vs. no)	2.64 (1.07–6.25)	0.0353	0.89 (0.20–3.34)	0.8643
Hyperuricemia (vs. no)	3.31 (1.22–11.53)	0.0169	1.22 (0.34–5.00)	0.7618

ESRD end-stage renal disease, *n* number, *CI* confidence interval, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *vs.* versus, *L/H ratio* LDL cholesterol-to-HDL cholesterol ratio, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *RLP* remnant lipoprotein

Variables with *P* values < 0.1 in the univariate model, such as age, sex, and eGFR were included in the multivariate model

Table 3 Coefficients of the correlation between serum HDL cholesterol levels and continuous variables (cohort of total, male, and female)

Variables	Total, $n=120$		Male, $n=60$		Female, $n=60$	
	r	*P* value	*r*	*P* value	*r*	*P* value
Clinical findings						
Age (years)	−0.14	0.1189	−0.08	0.5388	−0.18	0.1576
SBP (mmHg)	−0.34	0.0002	−0.12	0.3500	−0.40	0.0017
DBP (mmHg)	−0.13	0.1589	0.09	0.4876	−0.24	0.0643
MBP (mmHg)	−0.21	0.0192	0.02	0.8919	−0.31	0.0164
BMI (kg/m^2)	−0.25	0.0061	−0.08	0.5588	−0.28	0.0002
Visceral fat area (cm^2)	−0.43	< 0.0001	−0.33	0.0094	−0.32	0.0137
Subcutaneous fat area (cm^2)	−0.06	0.5191	−0.06	0.6708	−0.30	0.0215
IMT (mm)	−0.32	0.0003	−0.22	0.0888	−0.12	0.3663
Laboratory findings						
Serum albumin (g/dL)	0.29	0.0012	0.37	0.0033	0.27	0.0345
Hemoglobin (g/dL)	0.03	0.7730	0.25	0.0527	0.10	0.4653
Serum creatinine (mg/dL)	−0.32	0.0003	−0.31	0.0168	−0.18	0.1729
eGFR (mL/min/1.73 m^2)	0.26	0.0037	0.23	0.0709	0.24	0.0685
Uric acid (mg/dL)	−0.35	< 0.0001	−0.30	0.0216	−0.14	0.3004
Triglyceride (mg/dL)	−0.36	< 0.0001	−0.38	0.0031	−0.29	0.0272
Total cholesterol (mg/dL)	0.34	0.0002	0.23	0.0722	0.29	0.0251
LDL cholesterol (mg/dL)	0.06	0.5333	0.04	0.7522	0.03	0.8466
L/H ratio	−0.61	< 0.0001	−0.62	< 0.0001	−0.55	< 0.0001
TC/HDL-C ratio	−0.75	< 0.0001	−0.75	< 0.0001	−0.73	< 0.0001
TG/HDL-C ratio	−0.63	< 0.0001	−0.64	< 0.0001	−0.59	< 0.0001
RLP cholesterol (mg/dL)	−0.29	0.0034	−0.46	0.0008	−0.17	0.4092
Hemoglobin A1c (NGSP) (%)	−0.17	0.1150	−0.28	0.0668	−0.10	0.5262
Hs-CRP (ng/mL)	−0.04	0.6989	−0.05	0.7008	−0.01	0.9223
U-Prot (g/day)	−0.33	0.0003	−0.33	0.0096	−0.19	0.1501

n number, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *BMI* body mass index, *IMT* maximum carotid intima-media thickness, *eGFR* estimated glomerular filtration rate, *L/H ratio* LDL cholesterol-to-HDL cholesterol ratio, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *RLP* remnant lipoprotein, *Hs-CRP* high-sensitivity C-reactive protein, *U-Prot* urinary protein excretion

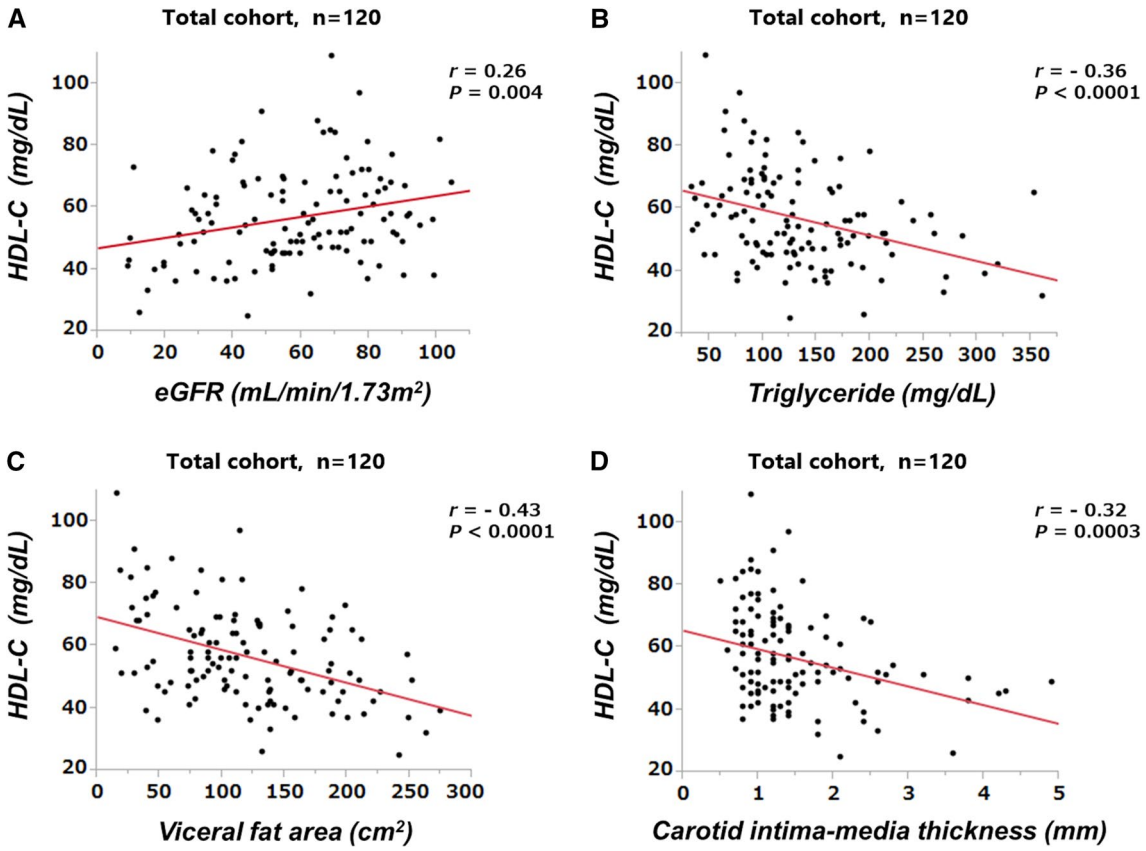

Fig. 5 Relationship between serum HDL-C levels and eGFR (**a**), triglyceride (**b**), visceral fat area (**c**), and maximum carotid intima-media thickness (**d**). *eGFR* estimated glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol

Table 4 Correlations between serum HDL cholesterol and continuous variables: multivariate regression analysis (cohort of total, male, and female)

Variables	Total, $n=120$		Male, $n=60$		Female, $n=60$	
	β	P value	β	P value	β	P value
Male (vs. female)	−0.26	0.0040	–	–	–	–
Age (years)	0.03	0.6853	0.04	0.7811	0.02	0.8787
Visceral fat area (cm^2)	−0.29	0.0013	−0.32	0.0129	−0.29	0.0369
Serum albumin (g/dL)	0.21	0.0164	0.25	0.0819	0.22	0.1067
eGFR (mL/min/1.73 m^2)	0.09	0.3490	0.13	0.4076	0.11	0.4234
Uric acid (mg/dL)	−0.11	0.2473	−0.20	0.1304	–	–

n number, *eGFR* estimated glomerular filtration rate

Variables with P values < 0.1 in the univariate model were included in the multivariate model. Factors related to blood pressure, lipid-related factors, urine protein excretion, and maximum carotid intima-media thickness were not included in consideration of causality

binding globulin (SHBG) in the liver is decreased, which causes an increase in free testosterone and estradiol in the blood and affects lipid metabolism. Low serum HDL-C levels have been identified as a risk factor for metabolic syndrome [14]. The present study showed that serum HDL-C was significantly correlated with VFA and IMT (Fig. 5c, d). This may suggest that increasing VFA leads to low serum HDL-C levels, which are a risk factor for CKD progression through an atherogenic mechanism. The adipokines secreted by adipose tissue have proinflammatory, atherogenic, and oxidative effects [35]. Overweightness and obesity induce glomerular hypertrophy and focal segmental glomerulosclerosis, which accelerate the progression of kidney disease [36, 37]. It has been reported that focal segmental glomerulosclerosis is associated with more severe proteinuria [38]. It has also been shown that low levels of serum HDL-C are

Table 5 Patient characteristics according to baseline serum HDL cholesterol levels (propensity score-matched cohort of patients < 70 years old, $n = 26$)

Variables	Total $n = 26$	Low HDL-C group $n = 13$	High HDL-C group $n = 13$	*P* value	Standardized differences
Clinical findings					
Age (years)	54.5 ± 10.5	55.2 ± 10.5	53.7 ± 10.6	0.7133	0.142
Sex (male; %)	50.0	53.9	46.2	1.0000	0.154
SBP (mmHg)	127.0 ± 5.7	128.4 ± 5.4	125.6 ± 6.0	0.2342	0.491
DBP (mmHg)	77.3 ± 4.1	78.0 ± 4.4	76.6 ± 3.7	0.3977	0.344
MBP (mmHg)	93.9 ± 4.5	94.8 ± 4.6	93.0 ± 4.3	0.3053	0.404
BMI (kg/m^2)	24.6 ± 3.8	25.3 ± 3.2	23.8 ± 4.3	0.3218	0.475
Visceral fat area (cm^2)	132.2 ± 57.3	152.4 ± 59.3	112.0 ± 55.4	0.0850	0.704
Subcutaneous fat area (cm^2)	199.3 ± 82.8	218.9 ± 91.6	179.7 ± 73.0	0.2387	0.473
IMT (mm)	1.27 ± 0.71	1.15 ± 0.44	1.38 ± 0.90	0.4283	0.325
Laboratory findings					
Serum albumin (g/dL)	4.21 ± 0.28	4.12 ± 0.32	4.29 ± 0.24	0.1395	0.601
Hemoglobin (g/dL)	13.9 ± 1.6	13.7 ± 1.7	14.2 ± 1.5	0.4521	0.312
Serum creatinine (mg/dL)	1.13 ± 0.80	1.23 ± 1.07	1.03 ± 0.38	0.5465	0.249
eGFR (mL/min/1.73 m^2)	58.2 ± 21.5	59.0 ± 23.5	57.3 ± 19.3	0.8412	0.079
Uric acid (mg/dL)	5.90 ± 1.41	6.18 ± 1.62	5.62 ± 1.16	0.3258	0.397
Triglyceride (mg/dL)	151.7 ± 72.7	152.8 ± 65.8	150.7 ± 79.1	0.9426	0.029
Total cholesterol (mg/dL)	217.8 ± 32.2	212.6 ± 29.8	222.9 ± 34.5	0.4230	0.320
LDL cholesterol (mg/dL)	134.1 ± 29.2	139.0 ± 27.0	129.2 ± 31.1	0.4013	0.337
HDL cholesterol (mg/dL)	52.6 ± 12.3	41.6 ± 3.6	63.6 ± 17.0	0.0001	1.790
L/H ratio	2.76 ± 0.72	3.35 ± 0.65	2.16 ± 0.78	0.0003	1.658
TC/HDL-C ratio	4.41 ± 0.85	5.15 ± 0.81	3.67 ± 0.88	0.0002	1.750
TG/HDL-C ratio	3.13 ± 1.58	3.73 ± 1.79	2.53 ± 1.33	0.0639	0.761
RLP cholesterol (mg/dL)	7.11 ± 3.91	7.06 ± 4.07	7.16 ± 3.76	0.9481	0.026
Hemoglobin A1c (NGSP) (%)	6.00 ± 1.03	6.31 ± 1.46	5.77 ± 1.52	0.2458	0.362
Hs-CRP (ng/mL)	756.8 ± 895.8	734.0 ± 535.3	779.7 ± 1148.3	0.8976	0.051
U-Prot (g/day)	0.26 (0.00–0.72)	0.56 (0.21–1.13)	0.05 (0.00–0.45)	0.0198	0.574
Primary cause of CKD					
Diabetic nephropathy (%)	7.7	15.4	0	0.4800	0.603
Chronic glomerulonephritis (%)	53.9	46.2	61.5	0.4314	0.311
Nephrosclerosis (%)	23.1	23.1	23.1	1.0000	0.000
Others (%)	15.4	15.4	15.4	1.0000	0.000
Concomitant drugs					
Antihypertensive agents (%)	53.9	38.5	69.2	0.2377	0.647
ARB and or ACEI	52.2	57.9	50.7	0.6147	0.145
Ca blockade	26.7	31.6	25.4	0.5723	0.138
Antihyperuricemic agents (%)	23.1	7.7	38.5	0.1602	0.785
Antidiabetic agents (%)	7.7	15.4	0.0	0.4800	0.603
Corticosteroids (%)	7.7	0.0	15.4	0.4800	0.603
Immunosuppressants (%)	3.9	0.0	7.7	1.0000	0.408
Diuretics (%)	26.9	15.4	38.5	0.3783	0.539
Comorbidities					
Hypertension (%)	53.9	38.5	69.2	0.2377	0.647
Hyperuricemia (%)	50.0	53.9	46.2	1.0000	0.154
Hypertriglyceridemia (%)	34.6	30.8	38.5	1.0000	0.162

Table 5 (continued)

Variables	Total $n=26$	Low HDL-C group $n=13$	High HDL-C group $n=13$	*P* value	Standardized differences
High total cholesterol (%)	50.0	46.2	53.9	1.0000	0.154
High LDL cholesterol (%)	34.6	38.5	30.8	1.0000	0.162
Diabetes mellitus (%)	15.4	23.1	7.7	0.5930	0.437

n number, SBP, systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *BMI* body mass index, *IMT* maximum carotid intima-media thickness, *eGFR* estimated glomerular filtration rate, *L/H ratio* LDL cholesterol-to-HDL cholesterol ratio, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglyceride, *RLP* remnant lipoprotein, *Hs-CRP* high-sensitivity C-reactive protein, *U-Prot* urinary protein excretion

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as percentages

associated with microalbuminuria in patients with type 2 diabetes mellitus [39, 40]. Furthermore, low HDL-C levels have been shown to be an independent risk factor for the development of microalbuminuria and macroalbuminuria [5]. Although antioxidant and anti-inflammatory actions of HDL cholesterol have been reported [41], they are impaired in type 2 diabetes [42] and obesity [43]. The low HDL cholesterol group in the present study had higher proteinuria, which might indicate the severity of the inflammatory and oxidative stress described above and might have contributed to the eGFR decline.

While the serum HDL-C levels of male patients do not greatly fluctuate with age, those in female patients tend to decrease owing to a decrease in estrogen activity [44]. As the serum SHBG levels gradually decrease in the postmenopausal period [45], it becomes a free testosterone = dominant hormonal environment, and the prevalence of self-contained obesity increases irrespective of age. Thus, it is now recognized that the relationship between serum HDL-C levels and atherosclerosis is complex [46].

The complexity of HDL biology demands a different approach, such as the cross-classification approach. In general, patients have many attributes; however, previous reports had used a stratified-classification approach involving a single variable (e.g., male vs. female, old vs. young) [15]. One-variable-at-a-time comparisons fundamentally result in subcohorts being more similar to the total cohort because patients have multiple characteristics simultaneously [47]. Cross-classification enables effective classification according to two attributes at the same time. Subgroup analysis by cross-classification facilitates determination of positive findings that can identify which subcohort will benefit from a treatment intervention as well as negative findings that can identify which sub-cohort does not require treatment. In this study, the positive findings were that a low serum HDL-C level was a risk factor for CKD progression in female patients under 70 years old, whereas the negative finding was that a low serum HDL-C level was not a risk factor for CKD progression in female patients over 70 years old. Furthermore, the analysis in the propensity score-matched cohort of patients < 70 years old showed a significantly lower kidney survival rate in the low HDL-C group than in the high HDL-C group, and the analysis in the cohort of patients ≥ 70 years old showed no differences in the kidney survival rate between the low HDL-C group and high HDL-C group. There are sex differences (male > female) in the incidence and prevalence of chronic renal failure, the transition to ESRD in CKD patients [48], the risk of cardiovascular disease [49], and the mortality risk is lower for female patients than for male patients [48]. Although there are few renal prognostic factors strongly related to female patients compared with male patients, our results suggest that a low serum HDL-C level is a useful renal prognostic factor in female patients under 70 years old. The significant association between low serum HDL-C level and renal dysfunction in CKD patients under 70 years old suggests that the association between serum HDL-C levels and renal function may vary with age. As Fassett has noted in his review, there are no specific evidence-based guidelines available for the treatment of CKD in elderly individuals, particularly those over 70 years of age, and the guidelines are based on evidence obtained from younger populations [24]. Considering that there is a lack of evidence on how to treat elderly individuals with CKD because clinical trials usually have an exclusion criterion of > 70 years and elderly individuals require special consideration because of their frequent comorbidities, it is reasonable to use the cross-classification approach in a clinical setting.

This study has several limitations. First, as all subjects were Japanese CKD patients, the association between serum HDL-C levels and kidney survival may not be generalizable to other populations. Second, because only the baseline laboratory data were used in the analysis and the impact of the changes in HDL-C on the patients' outcomes was difficult to demonstrate. Third, there may have been selection bias because only CKD patients who had agreed to undergo abdominal CT and carotid ultrasonography

were enrolled in this study. Another limitation of this study was that the serum HDL-C and creatinine levels were analyzed using single measurements and may have been affected by comorbidities at the time.

In conclusion, the findings of this study indicate that low serum HDL-C levels are significantly associated with CKD progression, especially in female patients with CKD younger than 70 years.

Acknowledgements We express our gratitude to Dr. Takahiro Mochizuki(†Deceased 25 June 2017) for his advice on this work and for his contribution to medical care and medical research in Japan. We want to specially thank Dr. Yukako Sawara, Mrs. Naomi Iwasa, and Mrs. Rie Yoshida for contributing to this article by collecting clinical data.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Mikolasevic I, Zutelija M, Mavrinac V, Orlic L (2017) Dyslipidemia in patients with chronic kidney disease: etiology and management. Int J Nephrol Renovasc Dis 10:35–45
2. Cases A, Coll E (2005) Dyslipidemia and the progression of renal disease in chronic renal failure patients. Kidney Int Suppl 99:S87–S93
3. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ (2000) Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kidney Int 58:293–301
4. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, Buring JE, Gaziano JM (2003) Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol 14:2084–2091
5. Morton J, Zoungas S, Li Q, Patel AA, Chalmers J, Woodward M, Celermajer DS, Beulens JW, Stolk RP, Glasziou P, Ng MK, Group AC (2012) Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study. Diabetes Care 35:2201–2206
6. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D (2004) Predictors of new-onset kidney disease in a community-based population. JAMA 291(7):844–850
7. Kronenberg F (2018) HDL in CKD—the devil is in the detail. J Am Soc Nephrol 29:1356–1371
8. Kronenberg F (2016) High-density lipoprotein cholesterol on a roller coaster: where will the ride end? Kidney Int 89:747–749
9. Coassin S, Friedel S, Kottgen A, Lamina C, Kronenberg F (2016) Is high-density lipoprotein cholesterol causally related to kidney function? Evidence from genetic epidemiological studies. Arterioscler Thromb Vasc Biol 36:2252–2258
10. Rahman M, Yang W, Akkina S, Alper A, Anderson AH, Appel LJ, He J, Raj DS, Schelling J, Strauss L, Teal V, Rader DJ (2014) Relation of serum lipids and lipoproteins with progression of CKD: the CRIC study. Clin J Am Soc Nephrol 9:1190–1198
11. Bowe B, Xie Y, Xian H, Balasubramanian S, Al-Aly Z (2016) Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression. Kidney Int 89:886–896
12. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM (2012) Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 157:251–262
13. Burgess S, Scott RA, Timpson NJ, Davey Smith G, Thompson SG (2015) Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol 30:543–552
14. Lanktree MB, Theriault S, Walsh M, Pare G (2018) HDL cholesterol, LDL cholesterol, and triglycerides as risk factors for CKD: a mendelian randomization study. Am J Kidney Dis 71:166–172
15. Sacristan JA (2013) Patient-centered medicine and patient-oriented research: improving health outcomes for individual patients. BMC Med Inform Decis Mak 13:6
16. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G (2005) Definition and classification of chronic kidney disease: a position statement from kidney disease—improving global outcomes (KDIGO). Kidney Int 67:2089–2100
17. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A (2009) Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53:982–992
18. Ording AG, Sorensen HT (2013) Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. Clin Epidemiol 5:199–203
19. Sawara Y, Takei T, Uchida K, Tsuchiya K, Nitta K (2009) Metabolic syndrome and anthropometric factors in Japanese patients with chronic kidney disease. Heart Vessels 24:199–203
20. Tamei N, Ogawa T, Ishida H, Ando Y, Nitta K (2010) Relationship of high-molecular-weight adiponectin levels to visceral fat accumulation in hemodialysis patients. Intern Med 49:299–305
21. Ogawa T, Shimada M, Ishida H, Matsuda N, Fujiu A, Ando Y, Nitta K (2009) Relation of stiffness parameter beta to carotid arteriosclerosis and silent cerebral infarction in patients on chronic hemodialysis. Int Urol Nephrol 41:739–745
22. Sato M, Ogawa T, Sugimoto H, Otsuka K, Nitta K (2012) Relation of carotid intima-media thickness and silent cerebral infarction to cardiovascular events and all-cause mortality in chronic hemodialysis patients. Intern Med 51:2111–2117
23. de Bray JM, Baud JM, Delanoy P, Camuzat JP, Dehans V, Descamp-Le Chevoir J, Launay JR, Luizy F, Sentou Y, Cales P (1998) Reproducibility in ultrasonic characterization of carotid plaques. Cerebrovasc Dis 8:273–277
24. Fassett RG (2014) Current and emerging treatment options for the elderly patient with chronic kidney disease. Clin Interv Aging 9:191–199
25. Carrero JJ (2010) Gender differences in chronic kidney disease: underpinnings and therapeutic implications. Kidney Blood Press Res 33:383–392
26. Matsushita K, Chen J, Sang Y, Ballew SH, Shimazaki R, Fukagawa M, Imai E, Coresh J, Hishida A (2016) Risk of end-stage renal disease in Japanese patients with chronic kidney disease increases proportionately to decline in estimated glomerular filtration rate. Kidney Int 90:1109–1114
27. Lanktree MB, Theriault S, Walsh M, Pare G (2017) HDL cholesterol, LDL cholesterol, and triglycerides as risk factors for CKD: a Mendelian randomization study. Am J Kidney Dis 71(2):166–172
28. Kang HT, Kim JK, Kim JY, Linton JA, Yoon JH, Koh SB (2012) Independent association of TG/HDL-C with urinary albumin excretion in normotensive subjects in a rural Korean population. Clin Chim Acta 413:319–324
29. Tsuruya K, Yoshida H, Nagata M, Kitazono T, Iseki K, Iseki C, Fujimoto S, Konta T, Moriyama T, Yamagata K, Narita I, Kimura K, Kondo M, Asahi K, Kurahashi I, Ohashi Y, Watanabe T (2015) Impact of the triglycerides to high-density lipoprotein

cholesterol ratio on the incidence and progression of CKD: a longitudinal study in a large Japanese population. Am J Kidney Dis 66:972–983
30. Streja E, Kovesdy CP, Streja DA, Moradi H, Kalantar-Zadeh K, Kashyap ML (2015) Niacin and progression of CKD. Am J Kidney Dis 65:785–798
31. Vaziri ND (2010) Lipotoxicity and impaired high density lipoprotein-mediated reverse cholesterol transport in chronic kidney disease. J Ren Nutr 20:S35–S43
32. Vaziri ND, Navab M, Fogelman AM (2010) HDL metabolism and activity in chronic kidney disease. Nat Rev Nephrol 6:287–296
33. Hwang YC, Fujimoto WY, Hayashi T, Kahn SE, Leonetti DL, Boyko EJ (2016) Increased visceral adipose tissue is an independent predictor for future development of atherogenic dyslipidemia. J Clin Endocrinol Metab 101:678–685
34. Wajchenberg BL (2000) Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 21:697–738
35. Kataoka H, Ariyama Y, Deushi M, Osaka M, Nitta K, Yoshida M (2016) Inhibitory effect of serotonin antagonist on leukocyte–endothelial interactions in vivo and in vitro. PLoS ONE 11:e0147929
36. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD (2001) Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 59:1498–1509
37. Kataoka H, Ohara M, Shibui K, Sato M, Suzuki T, Amemiya N, Watanabe Y, Honda K, Mochizuki T, Nitta K (2012) Overweight and obesity accelerate the progression of IgA nephropathy: prognostic utility of a combination of BMI and histopathological parameters. Clin Exp Nephrol 16:706–712
38. Harvey JM, Howie AJ, Lee SJ, Newbold KM, Adu D, Michael J, Beevers DG (1992) Renal biopsy findings in hypertensive patients with proteinuria. Lancet 340:1435–1436
39. Sun X, Xiao Y, Li PM, Ma XY, Sun XJ, Lv WS, Wu YL, Liu P, Wang YG (2018) Association of serum high-density lipoprotein cholesterol with microalbuminuria in type 2 diabetes patients. Lipids Health Dis 17:229
40. Tu ST, Chang SJ, Chen JF, Tien KJ, Hsiao JY, Chen HC, Hsieh MC (2010) Prevention of diabetic nephropathy by tight target control in an asian population with type 2 diabetes mellitus: a 4-year prospective analysis. Arch Intern Med 170:155–161
41. Baldi S, Frascerra S, Ferrannini E, Natali A (2007) LDL resistance to oxidation: effects of lipid phenotype, autologous HDL and alanine. Clin Chim Acta 379:95–100
42. Morgantini C, Natali A, Boldrini B, Imaizumi S, Navab M, Fogelman AM, Ferrannini E, Reddy ST (2011) Anti-inflammatory and antioxidant properties of HDLs are impaired in type 2 diabetes. Diabetes 60:2617–2623
43. Zhang J, Zhang Y, Liu H, Bai H, Wang Y, Jiang C, Fan P (2015) Antioxidant properties of high-density lipoproteins are impaired in women with polycystic ovary syndrome. Fertil Steril 103:1346–1354
44. Stevenson JC, Crook D, Godsland IF (1993) Influence of age and menopause on serum lipids and lipoproteins in healthy women. Atherosclerosis 98:83–90
45. Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L (1995) A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas 21:103–113
46. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W (2011) Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 365:2255–2267
47. Hayward RA, Kent DM, Vijan S, Hofer TP (2006) Multivariable risk prediction can greatly enhance the statistical power of clinical trial subgroup analysis. BMC Med Res Methodol 6:18
48. van Dijk PC, Zwinderman AH, Dekker FW, Schon S, Stel VS, Finne P, Jager KJ (2007) Effect of general population mortality on the north–south mortality gradient in patients on replacement therapy in Europe. Kidney Int 71:53–59
49. Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, Rabi D, Tremblay J, Alamian A, Barnett T, Cox J, Ghali WA, Grace S, Hamet P, Ho T, Kirkland S, Lambert M, Libersan D, O'Loughlin J, Paradis G, Petrovich M, Tagalakis V (2007) A comprehensive view of sex-specific issues related to cardiovascular disease. CMAJ 176:S1–S44