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ORIGINAL ARTICLE

Clinical significance of single and persistent elevation of serum high-sensitivity C-reactive protein levels for prediction of kidney outcomes in patients with impaired fasting glucose or diabetes mellitus

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Abstract

Background The association between high-sensitivity C-reactive protein (hs-CRP) and chronic kidney disease remains controversial and long-term longitudinal studies are limited. We aim to investigate the impact of single and persistent elevation of hs-CRP on kidney outcomes.

Methods Our study was based on a subgroup of patients with hyperglycemia from the Kailuan cohort. Patients were divided into three groups according to two consecutive hs-CRP levels: (1) no elevation (twice hs-CRP < 3 mg/L); (2) single elevation (once hs-CRP ≥ 3 mg/L); (3) persistent elevation (twice hs-CRP ≥ 3 mg/L). Kidney outcomes include kidney function decline (glomerular filtration rate [GFR] decline ≥ 30% within two years or doubling of serum c reatinine or development of end stage kidney disease [ESKD]), development and progression of proteinuria.

Results Regarding the outcomes of kidney function decline, development and progression of proteinuria, we included 18,665, 11,754 and 1710 patients into analyses, respectively. After 5 years of follow-up, the number of incident cases of kidney function decline, development and progression of proteinuria were 1891, 1337 and 171, respectively. Compared to patients with no elevation of hs-CRP levels, those with persistent but not single elevation of hs-CRP were at higher risk of kidney function decline (hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.23–1.64) and development of proteinuria (1.49, 1.26–1.76), but not progression of proteinuria. The results were consistent with propensity score analysis.

Conclusion Persistent but not single elevation of hs-CRP was independently associated with increased risk of kidney function decline, and development of proteinuria but not progression in patients with impaired fasting glucose or diabetes.

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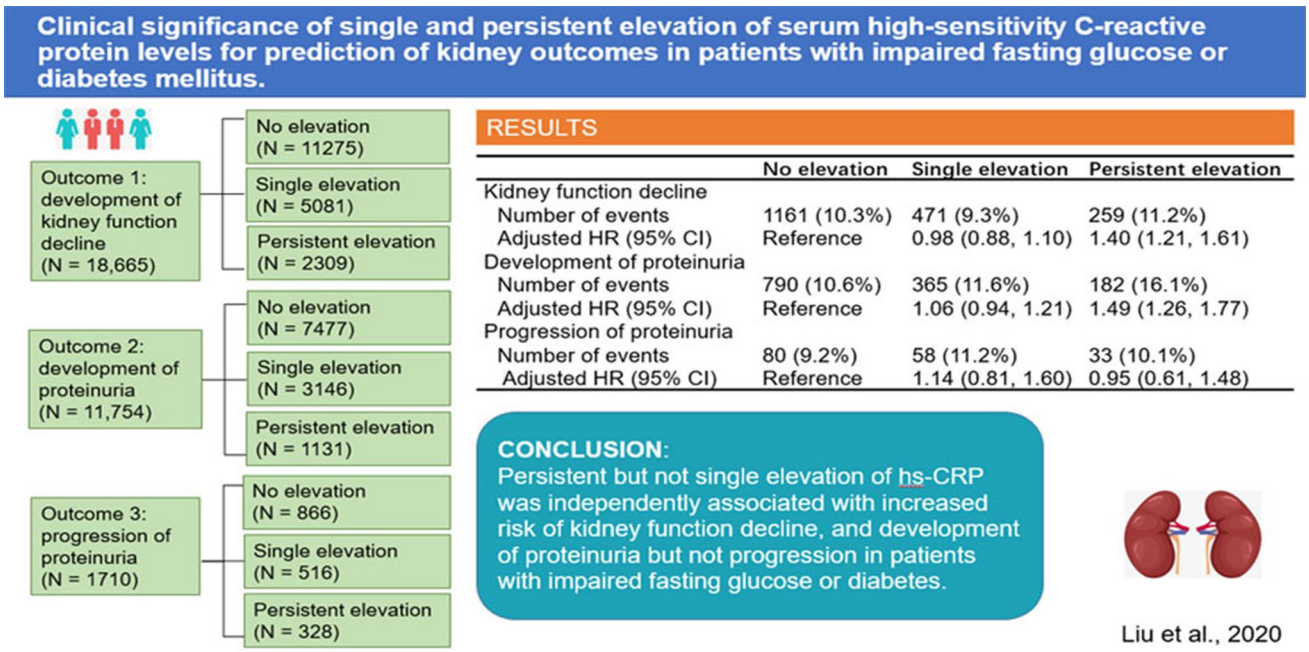
Graphic abstract



Keywords High-sensitivity C-reactive protein · Glomerular filtration rate · Kidney function decline · Proteinuria

Introduction

Chronic kidney disease (CKD) is an increasing public health issue with a prevalence of 8–16% worldwide [1]. The majority of patients with CKD are at risk of accelerated cardiovascular disease and death. For those who progress to end-stage kidney disease (ESKD), the limited accessibility to kidney replacement therapy is a problem in many parts of the world [2]. Thus, it is important to identify potential eliciting factors of the development and progression of CKD.

High-sensitivity C-reactive protein (hs-CRP), an acute-phase protein of systemic inflammatory response, is a potent risk indicator of cardiovascular disease [3]. However, the association between hs-CRP and progression of CKD remains controversial and the long-term longitudinal studies are limited. It is worth noting that a study has found an association between hs-CRP and development of proteinuria rather than progression in patients with type 2 diabetes [4]. The possible reason may be a short follow-up period of only 1 year. Furthermore, some studies have reported the association between hs-CRP and development or progression of CKD in diabetic or non-diabetic patients [5–7], while certain studies reached opposite conclusions [4, 8–10]. However, previous studies used a single measurement of serum hs-CRP level, which may not appropriately reflect chronic inflammatory state because hs-CRP levels show extreme fluctuations over time [11].

Nowadays, diabetes has become the leading cause of CKD [12], even people with prediabetes are at high risk for development or progression of CKD [13]. Therefore, we aim to investigate the clinical significance of single and persistent elevation of serum hs-CRP levels for prediction of kidney outcomes including kidney function decline, development and progression of proteinuria in a large longitudinal cohort among patients with impaired fasting glucose (IFG) or diabetes.

Materials and methods

Study population

Our study was based on a subgroup of patients with IFG or diabetes from the Kailuan cohort. Detailed information of the Kailuan cohort have been described elsewhere [14]. Briefly, from June 2006 through October 2007, 101,510 employees (81,110 (80%) men) aged ≥ 18 years including the retired in the Kailuan Group participated in a biennial health examination which was conducted in Kailuan General Hospital and its ten affiliated hospitals.

IFG was defined as fasting blood glucose (FBG) between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L)

according to American Diabetes Association (ADA) criterion [15], without self-reported history of diabetes and taking hypoglycemic agents. Diabetes was defined as FBG ≥ 126 mg/dL (7.0 mmol/L), and/or self-reported history of diabetes, and/or taking hypoglycemic agents. Data of 30,016 individuals with IFG or diabetes were available. The detailed flow chart of the study population is shown in Fig. 1.

The protocol was approved by the Ethics Committee of Kailuan General Hospital in accordance with the Declaration of Helsinki and written informed consent was obtained from each participant.

Data collection

All individuals completed a questionnaire documenting their socio-demographic status (e.g., age, sex, education and economic status), health history (e.g., hypertension, diabetes and cardiovascular disease), and lifestyle habits (smoking status, alcohol consumption, and physical activity). During the in-person visits, anthropometric measurements including height, weight, waist circumference (WC), and blood pressure (BP) were collected according to a standard protocol [16]. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. BP was measured using a standardized mercury sphygmomanometer. Systolic BP and diastolic BP were taken at a 5-min interval for two times after participants had been sitting for at least 5 min. The average of the two readings was used for analysis. If the two measurements differed by > 5 mmHg, then the third measurement was conducted and the average of the three readings was used.

Serum samples were collected in the morning after an overnight fast and serum creatinine, FBG, lipid profile (including total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) were tested using a Hitachi 7600 auto-analyzer (Hitachi; Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated using the two-race CKD Epidemiological Collaboration equation [17]. A single mid-stream morning urine sample was collected from each participant. Urine protein concentration was assessed by dry chemistry method

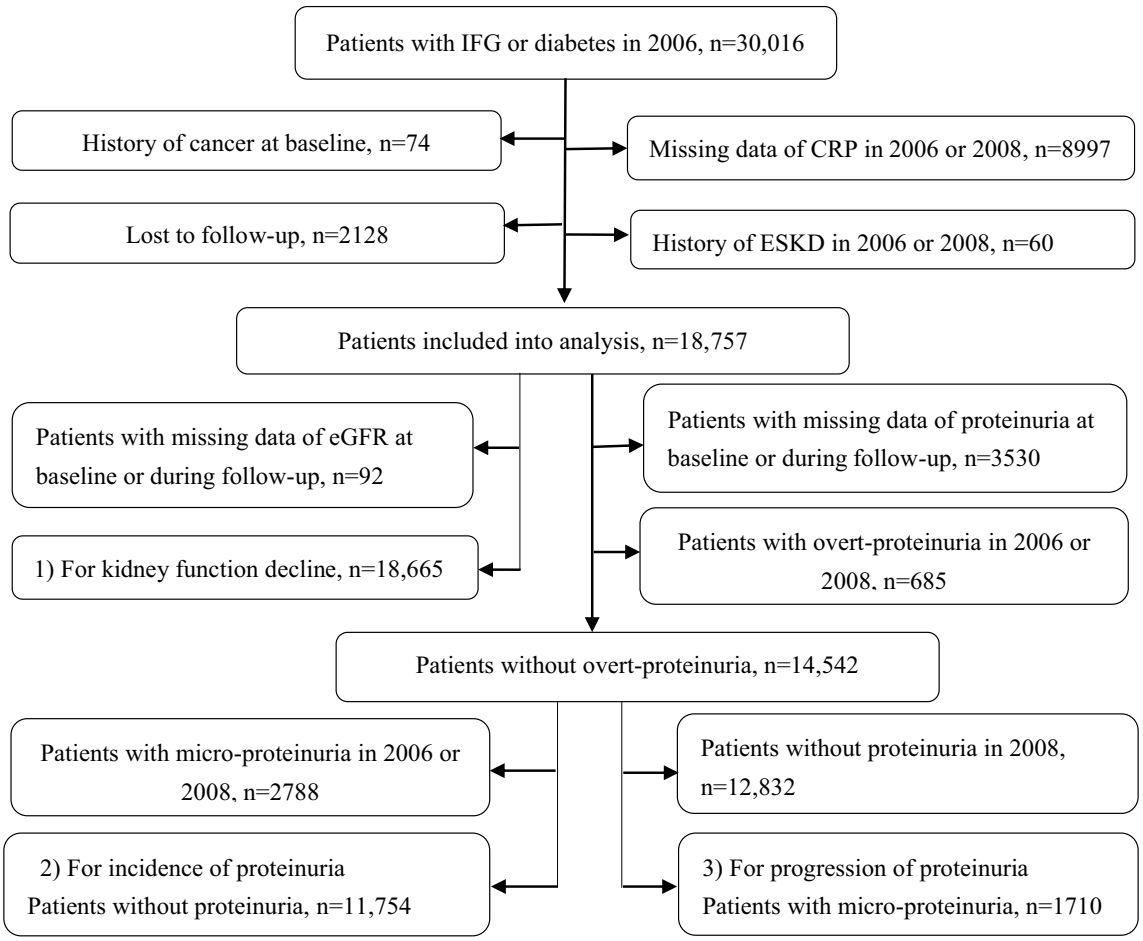


Fig. 1 Flow chart of the study population

with the test assay of H12-MA (Changchun Dirui Medical Technology Co., Ltd. Changchun, China). All the urine samples were measured using a urine analyzer (N-600, Dirui, Changchun, China) at the central laboratory of the Kailuan Hospital. The levels of the semi-quantitative dipstick test were recorded as negative, trace, 1+, 2+, or 3+. We further defined micro-proteinuria as urine dipstick reading trace or 1+ and overt-proteinuria as urine dipstick reading ≥ 2+ [18].

Measurement of hs-CRP and definition of exposure

Hs-CRP was measured by an immunoturbidimetry assay (Kanto Chemical Co Inc, Tokyo, Japan), with a lower limit of detection of 0.1 mg/L. Patients were divided into three groups according to two consecutive hs-CRP levels in 2006 and 2008. Group 1: no elevation of hs-CRP levels; group 2: single elevation of hs-CRP levels; group 3: persistent elevation of hs-CRP levels. In our study, we defined hs-CRP ≥ 3 mg/L as an elevated level of hs-CRP, which is a common cut-off for identifying high-risk groups [19].

Kidney outcomes

Our study included three kidney outcomes: (1) kidney function decline, defined as eGFR decline ≥ 30% within two years or doubling of serum creatinine or development of ESKD [20]; (2) development of proteinuria, defined as the transition from normal-proteinuria to micro-proteinuria or overt-proteinuria; (3) progression of proteinuria, defined as the transition from micro-proteinuria to overt-proteinuria.

Other potential covariates

BMI was classified as underweight (< 18.5 kg/m^2), normal (18.5–23.9 kg/m^2), overweight (24.0–27.9 kg/m^2) and obesity (≥ 28 kg/m^2). Central obesity was defined as WC ≥ 90 cm for men and ≥ 80 cm for women. Hypertension was defined as average systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, or self-reported history of hypertension, or use of antihypertensive medication. Dyslipidemia was defined by the presence of at least one of the following: serum total cholesterol level ≥ 200 mg/dL (5.2 mmol/L), triglycerides ≥ 150 mg/dL (1.7 mmol/L), low density lipoprotein cholesterol ≥ 130 mg/dL (3.4 mmol/L), high density lipoprotein cholesterol < 40 mg/dL (1.0 mmol/L), or use of lipid-lowering drugs [21]. Hyperuricemia was defined as serum uric acid concentration greater than 420 μmol/L in males and 360 μmol/L in females. "Inactive" physical activity was defined as "no physical activity" or "occasional (once or twice a week)", and "active" physical activity was defined as "frequent (more than three times a week and each time lasting more than 30 min)". Current smokers were defined as regular when smoking at least one cigarette a day in the past 12 months; and current drinkers were identified by average wine consumption of 100 mL or more a day for more than a year.

Statistical analysis

The baseline characteristics were described and compared among different groups. Continuous variables were expressed as mean ± SD when normally distributed, or median (interquartile range) when skewed distributed. Categorical variables were presented as number (percentage). Baseline characteristics of all participants were compared using the analysis of variance or Kruskal–Wallis test for continuous variables depending on data distribution and the χ^2 test for categorical variables. Incidence rates were expressed as per 100,000 person-years. The time to event was calculated from visit time in 2008 until a record of kidney outcome, or was censored because the follow-up was lost or the end of visit in 2015, whichever came first.

Before the Cox regression analysis, we conducted a series of scatterplots (Supplementary Figs. 1–7) to assess the association between hs-CRP and eGFR or proteinuria at baseline or endpoint, between FBG and eGFR or proteinuria at endpoint or hs-CRP, as well as multiple correlation analysis with stepwise regression (*SLE* and *SLS* = 0.15). To examine the association between single and persistent elevation of hs-CRP levels and the risk of kidney outcomes, Cox regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). In all three outcomes, model 1 was adjusted for age and sex. Model 2 was further adjusted for BMI (underweight vs. normal vs. overweight vs. obesity), central obesity (yes vs. no), FBG (continuous), leukocyte count (continuous), platelet count (continuous), dyslipidemia (yes vs. no), hypertension (yes vs. no), hypotensive agents (yes vs. no), hyperuricemia (yes vs. no), smoking (current yes vs. no), drinking (current yes vs. no), physical activity (active vs. inactive), and baseline eGFR (continuous) as potential confounders. In addition, we also adjusted for proteinuria (yes vs. no) in model 2 regarding the outcome of kidney function decline. We further conducted a subgroup analysis according to IFG or diabetes, as well as a sensitivity analysis by removing patients with urinary leukocyte ≥ 1+ (N = 404) to exclude infections of the urinary tract, which were adjusted for the same potential confounders in model 2. Proportional Hazards assumption was tested by Schoenfeld residuals and it was held for all the variables in Cox models ($P > 0.05$).

Given the non-randomized nature of these data (Table 1), we conducted an inverse probability of treatment weighted (IPTW) propensity score analysis to obtain optimal balance across groups by using population average treatment effects and generalized boosted models. Details on the methodology of propensity score weighting with

Table 1 Baseline characteristics of patients as a whole and stratified as different hs-CRP groups as well as comparability of balance before and after propensity score weighting

Characteristics	Total (n = 18,757)	No elevation of hs-CRP (n = 11,333)	Single elevation of hs-CRP (n = 5104)	Persistent elevation of hs-CRP (n = 2320)	*P*	Max ASMD	
						Before	After
Age, years	51.5 ± 10.7	51.2 ± 10.4	52.2 ± 10.8	56.9 ± 10.3	< 0.001	0.62	0.04
Male	15,564 (83.0)	9693 (85.5)	4169 (81.7)	1702 (73.4)	< 0.001	0.32	0.02
BMI categories							
Underweight	148 (0.8)	87 (0.8)	40 (0.8)	21 (0.9)	< 0.001	0.02	0.02
Normal	5304 (28.3)	3517 (31.0)	1288 (25.2)	499 (21.5)		0.21	0.04
Overweight	8628 (46.0)	5284 (46.6)	2321 (45.5)	1023 (44.1)		0.05	0.01
Obesity	4677 (24.9)	2445 (21.6)	1455 (28.5)	777 (33.5)		0.28	0.05
Central obesity	9767 (52.1)	5175 (45.7)	2849 (55.8)	1743 (75.1)	< 0.001	0.37	0.01
FBG, mmol/L	6.2 (5.8, 7.1)	6.1 (5.8, 7.9)	6.2 (5.8, 7.2)	6.4 (5.9, 7.8)	< 0.001	0.28	0.01
Dyslipidemia	12,659 (67.5)	7426 (65.5)	3521 (69.0)	1712 (73.8)	< 0.001	0.18	0.05
Hyperuricemia	1420 (7.6)	749 (6.6)	442 (8.7)	229 (9.9)	< 0.001	0.12	0.04
eGFR, ml/min/1.73 m^2	83.6 ± 20.6	84.4 ± 19.9	81.9 ± 20.4	82.8 ± 19.9	< 0.001	0.10	0.02
Current smoker	6966 (37.8)	4638 (41.0)	1771 (35.1)	557 (26.9)	< 0.001	0.22	0.02
Current drinker	7898 (42.9)	5345 (47.3)	1965 (38.9)	588 (28.5)	< 0.001	0.44	0.03
Physical exercise	3229 (17.6)	2026 (17.9)	873 (17.3)	330 (16.1)	0.127	0.10	0.01
Hypertension	9598 (51.2)	5430 (47.9)	2696 (52.8)	1472 (63.5)	< 0.001	0.40	0.01
Hypotensive drugs	2730 (30.4)	1524 (29.4)	794 (31.3)	412 (32.6)	0.04	0.12	0.01
Leukocyte count, 10^9/L	6.5 (5.6, 7.6)	6.5 (5.6, 7.5)	6.5 (5.7, 7.7)	6.7 (5.7, 8.1)	< 0.001	0.26	0.01
Platelet count, 10^9/L	201 (172, 234)	201 (175, 235)	201 (171, 235)	194 (164, 229)	< 0.001	0.25	0.01

Data are given as mean ± SD, median (IQR) or absolute number n (percentage); *P* values for differences between different hs-CRP groups were obtained using the analysis of variance for normal distribution data, Kruskal–Wallis rank test for skewed distribution data, and using the χ^2 test for categorical variables

ASMD absolute standardized mean difference before and after inverse probability of treatment weighting

more than two treatment groups are described by McCaffrey et al. [22]. Weights were estimated using the twang package in R. The underlying propensity models included 18 pretreatment covariates in Table 1, including demographics and factors relating to kidney outcomes. To describe the comparability of the three groups after propensity score weighting, covariate balance among groups was estimated by using the max absolute standardized mean difference (ASMD). ASMD < 0.10 is considered as good balance across groups. Weighted Cox regression models were used to estimate the impact of single or persistent elevation of hs-CRP levels on kidney outcomes. Regarding the outcomes of kidney function, we used doubly robust models of combining propensity score weights and baseline proteinuria.

All statistical analyses were performed with SAS System version 9.4 (SAS Institute; Cary, NC, USA) except for propensity score weighting and non-linear fitting which were performed with Stata version 14 (StataCorp) and R version 3.6.3 (R Foundation for Statistical Computing). *P* value < 0.05 was considered to be of statistical significance.

Results

Comparability of groups before and after propensity score weighting

As shown in Fig. 1, there were 18,757 eligible patients initially. Mean age was 51.5 ± 10.7 years, and 83.0% (N = 15,564) were male. Before propensity score weighting, patients with elevated hs-CRP levels tended to be of older age, to include more females, and to have higher levels of FBG, a higher proportion of obesity, dyslipidemia, hyperuricemia and hypertension, and a lower proportion of smoking, drinking and frequent physical activity (Table 1). However, propensity score weighting successfully balanced groups with regard to all baseline covariates included in the propensity score model, as shown in Table 1 (all ASMD < 0.10).

Incidence rates of kidney outcomes

Regarding the outcome of kidney function decline, we included 18,665 patients (51.5 ± 10.7 years, 15,483 males)

in the analysis after further excluding 92 patients without measurement of eGFR at baseline or during follow-up. Mean follow-up time was 5.3 ± 1.6 years with a total of 98,323 person-years of follow-up. During the follow-up, we observed 1891 (10.1%) cases of kidney function decline (incidence ratio: 1923/100,000 person-years).

Regarding the development of proteinuria, we included 11,754 patients without proteinuria (51.7 ± 10.2 years, 9592 male) at baseline in the analysis. Mean follow-up time was 5.2 ± 1.5 years with a total of 60,946 person-years of follow-up. During the follow-up, we observed 1337 (11.4%) cases who developed proteinuria (incidence ratio: 2194/100,000 person-years).

Regarding the progression of proteinuria, we included 1710 patients with micro-proteinuria at baseline (52.3 ± 11.1 years, 1475 males) into the analysis. Mean follow-up time was 5.0 ± 1.6 years with a total of 8614 person-years of follow-up. During the follow-up, we observed 171 (10.0%) cases with progression of proteinuria (incidence ratio: 1985/100,000 person-years).

In addition, the incidence rates of kidney outcomes according to different groups of hs-CRP are shown in Table 2.

Scatterplots and multiple correlation analysis

The scatterplots and the fitted lines (linear or non-linear) are shown in Supplementary Figs. 1–7. The linear relationship between FBG and hs-CRP seems to be valid only for hs-CRP levels above 20 mg/L as shown in Supplementary Fig. 7a, so we focused on the hs-CRP levels below 20 mg/L and reran the linear relation between them (Supplementary Fig. 7b), the correlation coefficient still implicated a weak positive correlation ($r = 0.09$, $p < 0.001$). Furthermore, we modeled this using a piecewise linear relationship (Supplementary Fig. 7c) and cubic spline (Supplementary Fig. 7d), and both methods showed a positive relationship between FBG and hs-CRP. Multiple correlation analysis (Supplementary Tables 1–7) indicated that a single baseline hs-CRP has no association with eGFR at baseline or eGFR at endpoint, while FBG has a weak association with proteinuria or eGFR at endpoint, and has a weak association with hs-CRP.

Table 2 Traditional and weighted Cox regression analysis (IPTW) for kidney outcomes in different hs-CRP groups

	No elevation of hs-CRP levels	Single elevation of hs-CRP levels	Persistent elevation of hs-CRP levels
Kidney function decline			
Number of events	1161 (10.3%)	471 (9.3%)	259 (11.2%)
Per 100,000 person-years	1921	1765	2308
Model 1, HR (95% CI)	Reference	0.96 (0.86, 1.07)	1.42 (1.24, 1.63)
Model 2, HR (95% CI)	Reference	0.98 (0.88, 1.10)	1.40 (1.21, 1.61)
Sensitivity analysis	Reference	0.99 (0.89, 1.10)	1.44 (1.24, 1.67)
IPTW, HR (95% CI)	Reference	0.99 (0.89, 1.11)	1.29 (1.06, 1.56)
Development of proteinuria			
Number of events	790 (10.6%)	365 (11.6%)	182 (16.1%)
Per 100,000 person-years	2025	2228	3278
Model 1, HR (95% CI)	Reference	1.12 (0.99, 1.27)	1.70 (1.44, 2.01)
Model 2, HR (95% CI)	Reference	1.06 (0.94, 1.21)	1.49 (1.26, 1.77)
Sensitivity analysis	Reference	1.06 (0.93, 1.20)	1.50 (1.27, 1.78)
IPTW, HR (95% CI)	Reference	1.05 (0.92, 1.19)	1.47 (1.20, 1.85)
Progression of proteinuria			
Number of events	80 (9.2%)	58 (11.2%)	33 (10.1%)
Per 100,000 person-years	1801	2198	2154
Model 1, HR (95% CI)	Reference	1.20 (0.86, 1.68)	1.08 (0.71, 1.65)
Model 2, HR (95% CI)	Reference	1.14 (0.81, 1.60)	0.95 (0.61, 1.48)
Sensitivity analysis	Reference	1.16 (0.82, 1.63)	0.95 (0.60, 1.49)
IPTW, HR (95% CI)	Reference	1.01 (0.72, 1.44)	1.01 (0.62, 1.65)

These models were adjusted for age, sex, BMI, waist circumference, fasting blood glucose, leukocyte count, platelet count, dyslipidemia, hypertension, hypotensive agents, hyperuricemia, smoking, drinking, physical activity and baseline eGFR. Regarding the outcome of kidney function decline, plus proteinuria

IPTW inverse probability of treatment weighted

Single and persistent elevation of hs-CRP levels and kidney outcomes

The HRs and 95% CIs for the associations between different groups of hs-CRP and the risk of kidney outcomes are also shown in Table 2. Compared to patients with no elevation of hs-CRP levels, those with persistent elevation of hs-CRP levels were associated with higher risk of kidney function decline (HR 1.42, 95% CI 1.24–1.63) and development of proteinuria (HR 1.70, 95% CI 1.44–2.01) after adjusting for age and sex (model 1), but not the progression of proteinuria (HR 1.08, 95% CI 0.71–1.65), whereas those with single elevation of hs-CRP levels were not significantly associated with any increased risk of kidney outcomes. These results did not change substantially in the fully adjusted models, in the sensitivity analysis or in the IPTW propensity score analysis (Table 2).

Subgroup analysis

As shown in Table 3, we conducted subgroup analysis and weighted Cox regression analysis according to patients with IFG and diabetes. In the fully adjusted models, the results did not change substantially in patients with IFG for kidney function decline (HR 1.43, 95% CI 1.18–1.73), development of proteinuria (HR 1.50, 95% CI 1.19–1.89) and progression of proteinuria (HR 1.47, 95% CI 0.80–2.70) as compared to those with no elevation. Similarly, the results did not change substantially in patients with diabetes for kidney function decline (HR 1.36, 95% CI 1.06–1.74), development of proteinuria (HR 1.53, 95% CI 1.19–1.96) and progression of proteinuria (HR 0.65, 95% CI 0.34–1.24). The results derived from IPTW propensity score weighting were consistent with traditional multivariate Cox regression analysis.

Discussion

Based on a large cohort of patients with IFG or diabetes, we found that a single elevation of hs-CRP level was not associated with the increased risk of kidney outcomes. In contrast, persistent elevation of hs-CRP levels was independently associated with increased risk of kidney function decline and development of proteinuria, but not progression of proteinuria in patients with IFG or diabetes.

Association between hs-CRP and kidney outcomes in patients with IFG and diabetes

To the best of our knowledge, this is the first study to evaluate the association between hs-CRP and kidney outcomes among patients with IFG. It is known that both IFG and hs-CRP are risk factors for diabetes and cardiovascular disease [3, 23–25], whereas the association between IFG and kidney outcomes was unclear [26, 27]. We hypothesized that other confounding factors may exist in their association. Our study found that combined IFG and persistent elevation of hs-CRP levels could contribute to the increased risk of deterioration of kidney disease.

Table 3 Traditional and weighted Cox regression analysis (IPTW) for kidney outcomes in different hs-CRP groups according to IFG and diabetes

	No elevation of hs-CRP levels	Single elevation of hs-CRP levels	Persistent elevation of hs-CRP levels
Kidney function decline			
IFG (N = 13,121)	Reference	1.00 (0.88, 1.14)	1.43 (1.18, 1.73)
IPTW, HR (95% CI)	Reference	1.00 (0.88, 1.13)	1.29 (1.03, 1.60)
Diabetes (N = 5544)	Reference	0.95 (0.77, 1.17)	1.36 (1.06, 1.74)
IPTW, HR (95% CI)	Reference	0.98 (0.80, 1.21)	1.39 (1.05, 1.84)
Development of proteinuria			
IFG (N = 8498)	Reference	1.02 (0.87, 1.19)	1.50 (1.19, 1.89)
IPTW, HR (95% CI)	Reference	1.02 (0.87, 1.20)	1.53 (1.14, 2.05)
Diabetes (N = 3256)	Reference	1.10 (0.90, 1.35)	1.53 (1.19, 1.96)
IPTW, HR (95% CI)	Reference	1.12 (0.91, 1.37)	1.35 (1.01, 1.87)
Progression of proteinuria			
IFG (N = 1090)	Reference	1.07 (0.64, 1.80)	1.47 (0.80, 2.70)
IPTW, HR (95% CI)	Reference	0.96 (0.57, 1.63)	1.35 (0.68, 2.69)
Diabetes (N = 620)	Reference	1.12 (0.70, 1.78)	0.65 (0.34, 1.24)
IPTW, HR (95% CI)	Reference	1.02 (0.64, 1.63)	0.74 (0.39, 1.39)

These models were adjusted for age, sex, BMI, waist circumference, fasting blood glucose, leukocyte count, platelet count, dyslipidemia, hypertension, hypotensive agents, hyperuricemia, smoking, drinking, physical activity and baseline eGFR. Regarding the outcome of kidney function decline, plus proteinuria

IPTW inverse probability of treatment weighted

The associations between hs-CRP and kidney outcomes have been repeatedly reported in both cross-sectional and longitudinal studies among patients with diabetes, and the results are inconsistent. Previous studies were all based on one measure of baseline hs-CRP, while the levels of hs-CRP might fluctuate substantially. Unlike previous studies, our analyses used single and two consecutive elevations of hs-CRP levels to assess their associations with kidney outcomes. A recent study from the United States involving 12,310 patients with type 2 diabetes observed an association between hs-CRP and changes in eGFR or deterioration of albuminuria after 2.1 years of follow-up [6]. In addition, the Finnish Diabetic Nephropathy Study found a borderline significant association between hs-CRP and the development of albuminuria in patients with type 1 diabetes [5]. However, the associations between high hs-CRP levels and kidney outcomes have not always been consistent. An analysis based on the Diabetes Control and Complications Trial (DCCT) suggested that an elevated hs-CRP level was not associated with the changes in urinary albumin creatinine ratio (uACR) after 9 years of follow-up in patients with type 1 diabetes [9]. In 2014, Yasuaki Hayashino et al. analyzed the associations between hs-CRP level and the risk of development and progression of albuminuria separately for the first time in 2518 patients with type 2 diabetes, and revealed that high levels of hs-CRP were associated with a high risk of development, but not of progression of albuminuria [4], but the short follow-up time of only 1 year could be a possible reason. Similarly, our study, which was based on a long-term follow-up period, also found no association between hs-CRP and the progression of proteinuria in patients with IFG or diabetes. However, the reason might be a lack of statistical effectiveness as relatively small numbers of patients (N = 1710) were enrolled in the outcome of proteinuria progression as compared with kidney function decline (N = 18,665) and development of proteinuria (N = 11,754).

Potential explanations for the association between hs-CRP and kidney disease

There are several potential mechanisms behind the association between hs-CRP and kidney disease. Firstly, recent research revealed that hs-CRP may promote CD32b-NF-κB signaling to mediate kidney inflammation in type 2 diabetes [28]. Secondly, a high level of hs-CRP is associated with insulin resistance and hyperglycemia [29], which in turn could induce the production of hs-CRP and thus promote kidney inflammation. Finally, other biomarkers of inflammation, such as necrosis factor receptor 1, IL-6, monocyte chemoattractant protein 1, intercellular and vascular cellular adhesion molecules are associated with progression of kidney disease [30, 31]. Therefore, the mechanisms behind the results could be complex and further studies are needed to clarify whether avoiding inflammatory states could be a therapeutic target to prevent the development and progression of kidney disease. A longitudinal randomized clinical trial showed that serum CRP levels were significantly reduced by soy protein intake, and significant improvements were also seen in proteinuria and urinary creatinine [32]. Another study also indicated that following a plant-based diet was associated with higher glucose disposal rate and insulin sensitivity as well as lower inflammation among elderly men with pre-dialysis CKD [33].

Strengths and limitations

Our study has several limitations. Firstly, the majority of participants in the current study were male, which may limit the generalizability of our results. Secondly, the possibility of residual confounders may exist as we did not have any information regarding the use of hs-CRP-lowering drugs such as statins or uACR-lowering drugs such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in our study. Thirdly, we did not distinguish between type 1 and type 2 diabetes in this study. However, type 2 diabetes is the predominant form of diabetes in adults [34, 35]. In addition, accumulating evidence has demonstrated that acute kidney injury is a robust predictor of subsequent decline in kidney function [36] and is associated with inflammation. In our study, we did not have information on acute kidney injury. However, this will not affect our conclusions substantially since acute kidney injury might be an intermediate link between inflammation and subsequent kidney function decline. Finally, like most observational studies, kidney outcomes were identified by only one measurement of eGFR and uACR, which may have resulted in misclassification of outcomes. Although IPTW propensity score analysis was used, it is likely that some unmeasured residual confounding factors were still present. The cause-effect relationship between hs-CRP and kidney disease is unclear, and other proteins of similar weight but not involved in inflammation may also be involved in kidney disease. Unfortunately, we did not have the relevant information. Despite these limitations, ours is a large prospective study with a long-term follow-up period using both single and persistent elevation of hs-CRP levels to assess the kidney outcomes in order to provide more reliable results.

Conclusions

In conclusion, persistent but not single elevation of hs-CRP levels was independently associated with increased risk of kidney function decline and development of proteinuria in patients with IFG or diabetes, which supports the underlying

mechanisms between chronic systemic inflammation and kidney disease.

Author contributions LL designed the study, interpreted the results, and drafted the manuscript. LL, JW and CY analyzed the data. SW, SC, QL, HZ and GW were involved in data collection and data cleaning. BG, MC, MZ and LZ made critical revision of the manuscript for important intellectual content. MZ, LZ and MC obtained the funding. All authors had read and approved the final manuscript. LZ is the study guarantor.

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Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest associated with this manuscript.

Ethical approval This study was approved by the Ethics Committee of Kailuan General Hospital in accordance with the Declaration of Helsinki.

Consent to participate The written informed consent was obtained from each participant.

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