Synergistic association of hyperuricemia and hyperhomocysteinemia with chronic kidney disease in middle-aged adults and the elderly population

Peng-Tzu Liu, MDa, Jong-Dar Chen, MD, MSca,b,*

Abstract
Chronic kidney disease (CKD) is a major global public health issue. Both hyperhomocysteinemia (HHcy) and hyperuricemia are independent risk factors for CKD. In this study, we evaluated the association of HHcy and hyperuricemia with CKD in the middle-aged and elderly populations in Taiwan.

In this cross-sectional study, we collected the data of 5910 patients aged ≥50 years after their self-paid health examination at a single medical center. Homocysteine (Hcy) levels were divided into 4 quartiles (Q1, <8.2; Q2, 8.2–9.8; Q3, 9.9–11.7; and Q4, >11.7 μM/L). Renal function was determined using the Chronic Kidney Disease Epidemiology Collaboration equation. Patients were considered to have CKD if their estimated glomerular filtration rate was <60 mL/min/1.73 m².

The prevalence of CKD significantly increased with the quartiles of uric acid (UA) and Hcy. In multiple logistic regression analysis, the odds ratios (ORs) of CKD increased with the quartiles of Hcy, independent of UA. There was 22.9% in Q4 in the normal serum UA group and 18.3% in the hyperuricemia group compared with Q1 of Hcy. Both hyperuricemia (OR 2.9) and Q4 of Hcy (OR 8.1) were significant independent risk factors for CKD. Furthermore, hyperuricemia and HHcy had significant synergistic association (synergy index, 1.7) with CKD.

The ORs of CKD increased with the quartiles of Hcy, independent of hyperuricemia. Hyperuricemia and HHcy had synergistic association with CKD.

Abbreviations: CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, Hcy = homocysteine, HHcy = hyperhomocysteinemia, OR = odds ratio, UA = uric acid

Keywords: chronic kidney disease, homocysteine, uric acid

1. Introduction
Chronic kidney disease (CKD) is a major global public health issue that can lead to end-stage renal disease (ESRD). CKD is associated with increased all-cause and cardiovascular mortality, acute kidney injury, cognitive decline, anemia, and mineral and bone disorders.[1–3] The prevalence of CKD is estimated to be 8% to 16% worldwide.[4–6] Wen et al.[11] reported an overall prevalence of 11.9% for CKD stages 1 to 5 (n = 462,293) based on a large database derived from a cohort who underwent commercial health examination in Taiwan with 13-year follow-up. Because of the high morbidity and mortality in patients with CKD the risk factors that significantly affect renal function must be identified. CKD cannot be fully explained by conventional factors, such as age, hypertension, diabetes, and dyslipidemia.

Numerous studies have demonstrated that hyperhomocysteinemia (HHcy) increases the risk of a low estimated glomerular filtration rate (eGFR) and cardiovascular disease.[7–12] The kidney is a major site of homocysteine (Hcy) metabolism. Patients with CKD have higher serum Hcy levels than patients with normal renal function. In a prospective study, Ninomiya et al.[8] revealed that patients with the highest tertile of plasma Hcy levels had an increased incidence of CKD compared with patients with lower tertiles.

Several epidemiological studies have demonstrated that hyperuricemia is associated with metabolic syndrome, renal
disease, hypertension, and cardiovascular disease.\textsuperscript{[2,13–17]} Researchers have suggested uric acid (UA) as a key biochemical marker of renal dysfunction and a pathogenic factor in CKD development.\textsuperscript{[16,18–22]}

Previous studies have discussed the association of Hcy and UA with CKD separately, but the synergistic association of HHcy and hyperuricemia with CKD are not well understood. In the present study, we investigated the synergistic effects of HHcy and hyperuricemia on CKD in the middle-aged and elderly populations in Taiwan.

2. Materials and methods

2.1. Participants

A total of 5910 patients aged $\geq$50 years (3844 men and 2066 women; mean age, 58 $\pm$ 7 years) who underwent self-paid health examination at Shin Kong Wu Ho-Su Memorial Hospital in Taiwan between January 2006 and May 2016 were included in this cross-sectional study. All patients were interviewed by physicians. Data in their age, body weight, body height, body mass index, waist circumference, and blood pressure were obtained during physical examination. This study was approved by the Institutional Review Board of Shin Kong Wu Ho-Su Memorial Hospital, and written informed consent was obtained from the study patients, who agreed to their data being stored as big data in the hospital database for retrospective medical research purposes.

2.2. Definition of CKD, quartiles of Hcy and hyperuricemia, and laboratory measurements

Plasma Hcy levels were measured using the Architect i2000SR analyzer (Abbott, IL). We divided Hcy levels into 4 quartiles: Q1, $<8.2 \mu M/L$; Q2, 8.2 to 9.8 $\mu M/L$; Q3, 9.9 to 11.7 $\mu M/L$; and Q4, $>11.7 \mu M/L$. Patients with a plasma Hcy level of $>11.7 \mu M/L$ were defined as having HHcy. Renal function was evaluated by measuring the eGFR, which was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation as follows:

- **Female**
  \[ \text{Cr} \leq 0.7, \text{eGFR} (\text{mL/min/1.73 m}^2) = 144 \times \left[ \text{serum creatinine (mg/dL/0.7)}^{-0.329} \times (0.993)^{\text{age (years)}} \right] \]
- **Male**
  \[ \text{Cr} > 0.7, \text{eGFR} (\text{mL/min/1.73 m}^2) = 144 \times \left[ \text{serum creatinine (mg/dL/0.7)}^{-1.209} \times (0.993)^{\text{age (years)}} \right] \]

Patients were considered to have CKD if their eGFR was $<60 \text{mL/min/1.73 m}^2$. Blood samples were collected after at least an 8-hour overnight fast. The biochemical markers of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, UA, creatinine, and fasting blood glucose in the serum were analyzed using an automated clinical analyzer (Hitachi 7600, Hitachi Ltd., Tokyo, Japan). We defined the abnormal serum UA level as $>7.6 \text{mg/dL}$ in male patients and $>6.6 \text{mg/dL}$ in female patients according to the reference range at our hospital.

2.3. Statistical analysis

Continuous variables were compared using Student $t$ test. The chi-squared test was used to analyze categorical variables, which are presented as frequencies and percentages. A univariate comparison was made between the quartiles of Hcy using ANOVA. The association between UA, Hcy, and CKD was established through multiple logistic regression analysis. $P < .05$ was considered significant. All statistical analyses were performed using the SAS statistical software package (SAS, Institute, Cary, NC).

3. Results

We divided patients into 2 groups based on whether they had CKD (Table 1). Elderly patients and male patients had a higher prevalence of CKD. The CKD group had higher blood pressure and higher levels of serum fasting blood glucose, lipid, and UA and plasma Hcy. The mean plasma Hcy level was 14.9 $\mu M/L$ in patients with CKD and 10.1 $\mu M/L$ in patients with normal kidney function.

Table 2 presents the basic data of metabolic parameters and the eGFR obtained according to Hcy quartiles. Based on ANOVA, waist circumference, body mass index, blood pressure, and serum levels of triglyceride and UA were significantly higher in patients with Q2 to Q4 of Hcy than in patients with Q1 of Hcy. The eGFR and serum level of high-density lipoprotein cholesterol were significantly lower in patients with Q2 to Q4 of Hcy than in patients with Q1 of Hcy. The prevalence of CKD was significantly higher among patients with hyperuricemia than among patients with normal UA level in Q1 to Q4 of Hcy (Fig. 1). The highest prevalence of patients with hyperuricemia (19%) was observed in Q4 of Hcy.

Table 3 presents the association between the quartiles of Hcy and CKD among patients with or without hyperuricemia. The adjusted odds ratios (ORs) of CKD increased with the quartiles of Hcy in the normal UA group (Q2, 2.6; Q3,
6.6; Q4, 22.9) and the hyperuricemic group (Q2, 2.1; Q3, 5.1; Q4, 18.3) (Table 3). The magnitude of increased ORs of CKD appeared to be more prominent in the normal UA group.

Table 4 displays that both hyperuricemia (OR 2.9) and Q4 of Hcy (OR 8.1) were significant risk factors for CKD. Moreover, UA and Hcy had significant synergistic association (synergy index, 1.7, 95% confidence interval 1.1–2.5) with CKD.

### 4. Discussion

In this cross-sectional study, we examined the associations among Hcy, UA, and CKD in the middle-aged and elderly populations. Higher serum UA and Hcy levels were associated with higher ORs of CKD. The ORs of CKD increased with the quartiles of Hcy. Furthermore, hyperuricemia and HHcy had significant synergistic association with CKD.

Hyperuricemia was previously identified as an independent risk factor for CKD. In a meta-analysis of 15 cohort studies, each 1 mg/dL serum UA increment was significantly associated with a 1.22-fold increase in CKD risk in middle-aged patients. Serum UA may induce oxidative stress and endothelial dysfunction, resulting in the development of both systemic and glomerular hypertension, which would reduce renal blood flow and elevate renal vascular resistance.

Serum UA may stimulate vascular smooth muscle cell proliferation through the activation of the renin–angiotensin system, and serum UA may induce the epithelial-to-mesenchymal transition, with direct effects on renal tubular cells. Animal studies have indicated that an elevated serum UA level may be directly

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**Table 2**

| Quartiles of plasma homocysteine level | Q1 (n = 1516) | Q2 (n = 1425) | Q3 (n = 1460) | Q4 (n = 1509) |
|--------------------------------------|---------------|---------------|---------------|---------------|
| Age (yr)                             | 57 ± 6        | 58 ± 7*       | 58 ± 7*       | 59 ± 7*       |
| BMI (kg/m²)                          | 24 ± 4        | 25 ± 3*       | 25 ± 6*       | 26 ± 4*       |
| WC (cm)                              | 82 ± 9        | 86 ± 25*      | 87 ± 9*       | 88 ± 9*       |
| Systolic BP (mm Hg)                  | 119 ± 19      | 122 ± 19*     | 123 ± 18*     | 126 ± 19*     |
| Diastolic BP (mm Hg)                 | 71 ± 11       | 74 ± 11*      | 76 ± 10*      | 77 ± 11*      |
| FBG (mg/dL)                          | 100 ± 26      | 103 ± 29      | 103 ± 28      | 104 ± 31*     |
| TC (mg/dL)                           | 209 ± 36      | 205 ± 38      | 203 ± 37*     | 199 ± 38*     |
| TG (mg/dL)                           | 133 ± 76*     | 138 ± 76*     | 149 ± 92*     | 154 ± 99*     |
| LDL-C (mg/dL)                        | 133 ± 32      | 133 ± 33      | 133 ± 33      | 131 ± 34      |
| HDL-C (mg/dL)                        | 57 ± 16*      | 53 ± 15*      | 50 ± 14*      | 48 ± 14*      |
| UA (mg/dL)                           | 5.3 ± 1.2     | 6.1 ± 1.3*    | 6.4 ± 1.3*    | 6.8 ± 1.5*    |
| eGFR (mL/min/1.73 m²)                | 98 ± 13       | 94 ± 16*      | 91 ± 17*      | 83 ± 20*      |

Data are presented as mean ± standard deviation. BMI = body mass index, BP = blood pressure, eGFR = estimated glomerular filtration rate, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride, UA = uric acid, WC = waist circumference. *P < .05, compared with Q1 in ANOVA.

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**Figure 1.** Prevalence of CKD among patients with and without hyperuricemia according to quartiles of homocysteine. CKD = chronic kidney disease, UA = uric acid. *P* value of the chi-square test <.01.
toxic to the kidney, which manifests as renal vasoconstriction, systemic hypertension, and tubulointerstitial injury through a crystal-independent mechanism.[29,31–33]

Previous studies have demonstrated that in renal injury, Hcy damages cells or induces sclerotic changes.[34–37] Several major cellular and molecular mechanisms have been noted, including oxidative stress, inflammation, endoplasmic reticulum stress, and DNA hypomethylation.[37–39] Tyagi et al.[38] demonstrated that Hcy increases the mRNA level of NADPH oxidase in a dose- and time-dependent manner, which is accompanied by an increase in hydrogen peroxide and a decrease in NO production in endothelial cells. Various studies have demonstrated that NADPH oxidase is involved in progressive glomerular injury and leads to ESRD, which is associated with HHcy.[38,40,41] In a rat model, Hcy-induced local oxidative stress, resulting in mesangial expansion, podocyte dysfunction, and fibrosis, and extracellular matrix metabolism in glomerular cells are associated with an enhanced NADPH oxidase activity.[37,41–43] Moreover, inflammatory responses and impaired endothelial function may be elicited by the activation of transcription factors such as nuclear factor-κB.[35] Endothelial dysfunction alters endothelial properties, and endothelium within the glomerular basement membrane may modify glomerular barrier permeability, leading to a decreased eGFR.[44]

Because the kidney plays a prominent role in Hcy metabolism, a reduction in renal Hcy clearance and metabolism is one of the causes of HHcy.[45,46] Hcy levels increase as renal function declines, which gradually leads to ESRD development, and more than 85% of patients undergoing dialysis have mild-to-moderate HHcy.[47,48] An alternative theory is that currently unidentified uremic substances that inhibit normal extrarenal Hcy metabolism. Some studies have confirmed the strong inverse relationship between Hcy levels and renal function, even in the normal range of GFR (>60 mL/min).[49,50] Our study also revealed that the ORs of CKD increased with the quartiles of Hcy.

Some studies have discussed the association of UA or Hcy with renal function, but our study demonstrated the synergistic association of hyperuricemia and HHcy with CKD. In molecular and cellular mechanisms, both UA and Hcy induce oxidative stress and inflammation in endothelial cells and the extracellular matrix, leading to glomerular hypertension and sclerosis. These mechanisms would reduce renal blood flow, elevate renal vascular resistance, and further decrease the eGFR. In addition, when renal function declines, the clearance and metabolism of UA and Hcy progressively reduce. Our study indicated that the presence of both hyperuricemia and HHcy might further exacerbate renal function, thus decreasing the eGFR.

This large population-based study demonstrated the synergistic association of hyperuricemia and HHcy with CKD in middle-aged and elderly patients. However, this study has some limitations. First, because this was a cross-sectional study, we cannot ensure the causal relationship between these 2 factors and CKD. Second, the history of diet and medication and their effect on UA, Hcy, and CKD cannot be estimated.

In conclusion, this study demonstrated the synergistic association of hyperuricemia and HHcy with CKD. The presence of both hyperuricemia and HHcy might further exacerbate renal function. The ORs of CKD increased with the quartiles of serum Hcy, independent of hyperuricemia. Additional studies should be conducted to investigate the association between Hcy, UA, and CKD and should consider the synergistic association of HHcy and hyperuricemia with CKD. In addition, the increased ORs of CKD with the quartiles of Hcy are more prominent in patients

### Table 3

| Quartiles of plasma homocysteine level | 01 | 02 | 03 | 04 |
|--------------------------------------|----|----|----|----|
| **Crude**†                           |    |    |    |    |
| Normal UA                           | Ref. | 3.4 (1.4–8.2) † | 9.7 (4.3–21.8) † | 31.7 (14.7–68.4) † |
| High UA                             | Ref. | 2.3 (0.5–11.0) | 4.3 (1.0–19.0) | 15.3 (3.7–64.2) |
| **Model 1 ‡**                       |    |    |    |    |
| Normal UA                           | Ref. | 2.6 (1.1–6.4) † | 6.6 (2.9–15.1) † | 22.9 (10.4–50.6) † |
| High UA                             | Ref. | 2.1 (0.4–11.3) | 5.1 (1.1–24.6) † | 18.3 (4.0–83.0) † |

Ref. = reference, UA = uric acid.

† P<.05, multiple logistic regression, Q1 as reference.

‡ Adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HbA1c, total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

### Table 4

| Hyperuricemia | HHcy | Patients in subgroup, n | Patients with CKD, n (% ) | OR of CKD | 95% CI | SI | 95% CI |
|---------------|------|-------------------------|--------------------------|-----------|-------|----|-------|
| (–) (-)       | 4188 | 63 (1.5)                | 1.0                      | Reference | No risk | –  | –     |
| (+) (-)       | 551  | 23 (4.1)                | 2.9*                     | 1.8 to 4.6 | Only 1 risk | –  | –     |
| (–) (+)       | 841  | 104 (12.4)              | 8.1*                     | 5.9 to 11.2 | Only 1 risk | –  | –     |
| (+) (+)       | 230  | 43 (19.0)               | 15.9*                    | 10.6 to 24.0 | 1.7 | 1.1 to 2.5* | –  | –     |

CI = confidence interval, HHcy = hyperhomocysteinemia, OR = odds ratio, SI, synergy index.

* P< .05.

† Serum uric acid level as >7.6 mg/dL in male patients and >6.6 mg/dL in female patients.

‡ Patients with plasma homocysteine level >11.7 μM/L.
with normal UA. Therefore, we should pay attention to the possibility of CKD in patients with high Hcy and normal UA.

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Author contributions
Conceptualization: Peng-Tzu Liu.
Formal analysis: Peng-Tzu Liu.
Investigation: Peng-Tzu Liu, Jong-Dar Chen.
Methodology: Jong-Dar Chen.
Software: Jong-Dar Chen.
Supervision: Jong-Dar Chen.
Writing – original draft: Peng-Tzu Liu.
Writing – review & editing: Jong-Dar Chen.

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