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RESEARCH ARTICLE

# High risk of renal outcome of metabolic syndrome independent of diabetes in patients with CKD stage 1–4: The ICKD database

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## Abstract

**Aims:** To investigate whether metabolic syndrome (MetS) could predict renal outcome in patients with established chronic kidney disease (CKD).

**Materials and Methods:** We enroled 2500 patients with CKD stage 1–4 from the Integrated CKD care programme, Kaohsiung for delaying Dialysis (ICKD) prospective observational study. 66.9% and 49.2% patients had MetS and diabetes (DM), respectively. We accessed three clinical outcomes, including all-cause mortality, RRT, and 50% decline in estimated glomerular filtration rate events.

**Results:** The MetS score was positively associated with proteinuria, inflammation, and nutrition markers. In fully adjusted Cox regression, the hazard ratio (HR) (95% confidence interval) of MetS for composite renal outcome (renal replacement therapy, and 50% decline of renal function) in the DM and non-DM subgroups was 1.56 (1.15–2.12) and 1.31 (1.02–1.70), respectively, while that for all-cause mortality was 1.00 (0.71–1.40) and 1.27 (0.92–1.74). Blood pressure is the most important component of MetS for renal outcomes. In the 2 by 2 matrix, compared with the non-DM/non-MetS group, the DM/MetS group (HR: 1.62 (1.31–2.02)) and the non-DM/MetS group (HR: 1.33 (1.05–1.69)) had higher risks for composite renal outcome, whereas the DM/MetS group had higher risk for all-cause mortality (HR: 1.43 (1.09–1.88)).

**Conclusions:** MetS could predict renal outcome in patients with CKD stage 1–4 independent of DM.

KEYWORDS
chronic kidney disease, diabetes mellitus, metabolic syndrome, renal outcomes

## 1 | INTRODUCTION

Metabolic syndrome (MetS) is a cluster of medical conditions, including hypertension (HTN), impaired glucose tolerance, central obesity, and dyslipidaemia.[1] MetS increments the risk of diabetes (DM), cardiovascular disease, and chronic kidney disease (CKD)[2] and is the trigger of cardiorenal metabolic disease. Patients with MetS may progress from normoglycaemia to overt DM resulting from a gradual β-cell function decline. DM is one of the most relevant risk factors for both heart failure and end-stage renal disease (ESRD) and

  

is also an important cause of CKD. Under the shadow of diabetic kidney disease (DKD), MetS-related CKD is less studied.

MetS itself is associated with early CKD.[3,4] The mechanisms of MetS-related kidney diseases are related to insulin resistance, oxidative stress, and activation of proinflammatory cytokines and renin–angiotensin–aldosterone.[5,6] The risks of CKD (estimated GFR [eGFR] < 60 ml/min/1.73 $m^2$) and albuminuria were 2–3 times higher in subjects with MetS in a cross-section study with or without diabetes (National Health and Nutrition Examination Survey [NHANES III]).[5] Meta-analysis reported that MetS was associated with the development of CKD and albuminuria.[7] MetS was also associated with rapid eGFR decline in a community-based study.[8]

The role of MetS in established CKD is not clearly studied. MetS was associated with ESRD or worse composite renal outcome in patients with CKD in some studies[9,10]; the effect of MetS was attenuated after the adjustment of proteinuria, late CKD stage, or diabetes in other studies.[11,12] MetS was also associated with mortality in CKD patients in some studies.[13] Components of MetS, especially HTN and hyperglycemia, are important risk factors for ESRD and should be controlled.[14,15] Many statistic models in these studies did not fully adjust the individual components.[9,10] Thus, whether we need MetS to summarise a cluster of risk factors for clinical outcome is still questioned.

Obesity or central obesity is the main component of MetS. Recently, we demonstrated that obesity paradox is not only for mortality but also for renal outcome.[16,17] High body mass index or high waist circumference was not associated with renal outcome in patients with advanced CKD.[17] One study also suggested that MetS was not a risk factor for CKD progression in patients with CKD stage 4 and 5.[12] Thus, whether there is a MetS paradox should be carefully studied.

We hypothesised that MetS is associated with worse renal outcome even after considering the traditional risks of cardiorenal metabolic disease in patients with CKD. We further hypothesised that CKD stage and DM could modify this association. After the initial analysis, we found that MetS was not associated with renal outcome in patients with CKD stage 5. We presented the association of MetS or DM with clinical outcomes in patients with CKD stage 1–4.

## 2 | METHODS

### 2.1 | Patients and measurements

From 11 November 2002 to 31 May 2009, we conducted a prospective observational study in the southern Taiwan. The study was followed up until 31 May 2010.[18] Three thousand three hundred and three patients with CKD were recruited from the nephrology outpatient departments of two affiliated hospitals of Kaohsiung Medical University (KMU). CKD was defined according to the Kidney Disease: Improving Global Outcome guidelines.[19] The definition of DM was consistent with the World Health Organization criteria,[20] with the absence of significant ketonuria and insulin treatment started at least 1 year after diagnosis. Patients with urological cancer and renal stones with haematuria were excluded. This study protocol was approved by the Institutional Review Board of the KMU Hospital and all of the patients were provided informed written consent.

The demographic features, baseline comorbidities, clinical data, and biochemical parameters of these patients were recorded on their first visit. Their medical history was reviewed by chart. The MetS score was defined according to the NHANES study.[21] HTN was outlined as systolic blood pressure of >140 mmHg, diastolic BP of >90 mmHg, or the use of antihypertensive medication. The characterisation of cardiovascular diseases was the clinical diagnoses of heart failure, acute or chronic ischaemic heart disease, or cerebrovascular disease. Laboratory data (haemoglobin, albumin, blood glucose, cholesterol, C-reactive protein [CRP], sodium, potassium, phosphorus, calcium, bicarbonate, and uric acid levels) were obtained during the outpatient department visit.

### 2.2 | Outcomes

We accessed three clinical outcomes, including all-cause mortality, RRT, and 50% decline in eGFR events. RRT was defined as the initiation of haemodialysis, peritoneal dialysis, or renal transplantation. We ascertained RRT initiation by chart reviewing and a catastrophic illness certificate, which is formally reviewed and approved by the National Health Insurance of Taiwan.[22] Renal function was examined using the CKD–EPI equation.[23] We validated the survival status and cause of death of patients by checking death certificates, patient charts, and the National Death Index.[22]

### 2.3 | Statistical analysis

The expression of the summarised statistical results of the baseline characteristics of the patients are means with standard deviation (SD), counts, and percentages for categorical data and medians with interquartile ranges determined for continuous variables with approximately normal distributions. Competing risk Cox proportional hazards analysis was used to assess the association between MetS and ESRD. Covariates were selected on the basis of the observations in our previous studies, and we log-transformed the continuous variables to obtain normal distributions.[18] The model was adjusted for age, gender, eGFR, log-transformed urine protein-to-creatinine ratio (UPCR), hypertension, cardiovascular diseases, mean BP (MBP), body mass index, haemoglobin, albumin, log-transformed cholesterol, log-transformed CRP, calcium, and phosphorus.

A $p$ value of <0.05 was considered statistically significant. Statistical analysis was performed using R 3.3.0 (R Foundation for Statistical Computing) and Statistical Package for Social Sciences Version 21.0 for Windows (SPSS Inc.).

## 3 | RESULTS

### 3.1 | Baseline characteristics of patients with CKD stage 1–4 divided by DM and MetS

Two thousand five hundred patients with stage 1–4 CKD were enroled in this cohort (Table 1). The mean ages were significantly higher in patients with MetS both in the non-DM CKD and DKD subgroups. In viewing renal function, there were significantly lower levels of eGFR, higher proportion of CKD stage 4, and higher levels of proteinuria in patients with MetS both in non-DM CKD and DKD. In the serum biochemistry profile, the serum uric acid level was significantly higher in patients with MetS both in non-DM CKD and DKD. There were significantly higher proportions of females (40.3%) and higher comorbidities (Charlson score 4.2 ± 2.1 vs. 3.8 ± 2.2, $p = 0.008$) in patients with MetS only in DKD (Table 1).

After a median follow-up of 8.21 years, patients with MetS had a higher proportion of receiving RRT and composite renal outcome (RRT + 50% decline eGFR) both in non-DM CKD and DKD. However, patients with MetS had significant higher all-cause mortality only in non-DM CKD and not in DKD (Table 1).

**TABLE 1** Characteristics of CKD stage 1–4 patients by diabetes and metabolic syndrome.

| | Non-DM | | | DM | | |
|---|---|---|---|---|---|---|
| Variable | Non-MetS | MetS | *p* Value | Non-MetS | MetS | *p* Value |
| No. of patients | 628 (49.4%) | 642 (50.6%) | | 199 (16.2%) | 1031 (83.8%) | |
| Demographics and medical history | | | | | | |
| Age (year) | 58.0 (17.3) | 62.8 (14.2) | <0.001 | 62.0 (13.5) | 64.9 (12.2) | 0.003 |
| Sex (female) | 202 (32.2%) | 231 (36.0%) | 0.152 | 51 (25.6%) | 415 (40.3%) | <0.001 |
| Cardiovascular disease | 84 (13.4%) | 126 (19.6%) | 0.003 | 39 (19.6%) | 304 (29.5%) | 0.004 |
| Ischaemic heart disease | 52 (8.3%) | 88 (13.7%) | 0.002 | 21 (10.6%) | 175 (17.0%) | 0.024 |
| Congestive heart disease | 29 (4.6%) | 57 (8.9%) | 0.003 | 19 (9.5%) | 116 (11.3%) | 0.482 |
| Cerebrovascular disease | 62 (9.9%) | 84 (13.1%) | 0.073 | 25 (12.6%) | 224 (21.7%) | 0.003 |
| Hypertension | 263 (41.9%) | 405 (63.1%) | <0.001 | 96 (48.2%) | 749 (72.6%) | <0.001 |
| Hyperuricaemia | 106 (16.9%) | 165 (25.7%) | <0.001 | 20 (10.1%) | 157 (15.2%) | 0.057 |
| Charlson score | 2.6 (1.6) | 2.5 (1.5) | 0.379 | 3.8 (2.2) | 4.2 (2.1) | 0.008 |
| Renal function status | | | | | | |
| eGFR (ml/min/1.73 $m^2$) | 40.1 (26.5–56.2) | 35.1 (24.5–47.9) | <0.001 | 36.3 (26.1–50.5) | 32.4 (23.4–44.7) | 0.003 |
| UPCR (mg/g) | 451 (162–1171) | 608 (218–1368) | 0.004 | 645 (208–2847) | 1065 (344–2720) | 0.01 |
| CKD stage 4 | 195 (31.1%) | 242 (37.7%) | 0.011 | 69 (34.7%) | 455 (44.1%) | 0.005 |
| Laboratory data | | | | | | |
| Haemoglobin (g/dl) | 12.4 (2.1) | 12.6 (2.2) | 0.087 | 11.8 (2.3) | 11.9 (2.2) | 0.769 |
| Albumin (g/dl) | 4.0 (0.5) | 4.0 (0.5) | 0.084 | 3.7 (0.7) | 3.8 (0.6) | 0.139 |
| ALT (mg/dl) | 23.6 (17.2) | 26.7 (23.3) | 0.007 | 26.5 (19.0) | 28.8 (29.0) | 0.16 |
| WBC (×1000 cells/μl) | 6.7 (2.3) | 7.1 (2.1) | 0.002 | 7.3 (2.4) | 7.5 (2.3) | 0.115 |
| CRP (mg/l) | 0.7 (0.2–2.8) | 1.0 (0.4–4.0) | <0.001 | 1.2 (0.4–6.9) | 1.2 (0.4–5.6) | 0.632 |
| Phosphorus (mg/dl) | 3.7 (0.8) | 3.8 (0.8) | 0.034 | 4.0 (0.9) | 4.0 (0.9) | 0.613 |
| Calcium (mg/dl) | 9.2 (0.6) | 9.2 (0.7) | 0.552 | 9.3 (0.7) | 9.3 (0.7) | 0.575 |
| Uric acid (mg/dl) | 7.2 (1.9) | 7.9 (2.0) | <0.001 | 7.3 (2.3) | 7.7 (1.9) | 0.022 |
| Outcomes | | | | | | |
| RRT | 88 (14.0%) | 122 (19.0%) | 0.031 | 42 (21.1%) | 295 (28.6%) | 0.034 |
| RRT + 50% decline of eGFR | 141 (22.5%) | 182 (28.3%) | 0.009 | 57 (28.6%) | 401 (38.9%) | 0.011 |
| All-cause mortality | 84 (13.4%) | 112 (17.4%) | 0.045 | 47 (23.6%) | 281 (27.3%) | 0.288 |

*Note*: Data are presented as mean (standard error), median (interquartile range), or count (percentage %). $p < 0.05$ indicates a significant difference.
Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MS, metabolic syndrome; RRT, renal replacement therapy; UPCR, urine protein-to-creatinine ratio; WBC, white blood cell.

### 3.2 | Metabolic components of patients with MetS in non-DM CKD and DKD

To examine the association of metabolic profiles of MetS with DKD, we analysed the proportion of metabolic components in patients with MetS in non-DM CKD and DKD. The percentages of waist and BP components of MetS were both higher in patients with MetS in non-DM CKD and DKD. In viewing lipid profiles, patients with MetS had higher serum triglyceride and lower high-density lipoprotein (HDL) in non-DM CKD and DKD. The serum glucose level and glycated haemoglobin (HbA1c) were higher in patients with MetS in non-DM CKD (fasting glucose 103.8 mg/dl vs. 94.7 mg/dl, HbA1c 5.7% vs. 5.5%; both $p < 0.001$). However, both parameters were not higher in patients with MetS in DKD (fasting glucose 139.4 mg/dl vs. 137.7 mg/dl, HbA1c 7.7% vs. 7.7%, both $p > 0.05$) (Table 2).

### 3.3 | The association of clinical factors with MetS score in CKD

To examine the association of MetS score with clinical factors, we executed the multivariate linear regression analysis. Age, female versus male, proteinuria, haemoglobin, albumin, CRP, phosphorus, and BMI were positively correlated with MetS score, whereas eGFR was negatively correlated (Table 3). With the logistic regression analysis, age, gender, eGFR, proteinuria, severe liver disease, BMI, albumin, and phosphorus were correlated with MetS (MetS score ≧3) (Table S1).

### 3.4 | The association of MetS with clinical outcomes in non-DM CKD and DKD

Two hundred and ten patients entered ESRD in non-DM CKD, and 337 patients entered ESRD in DKD. There were 202 patients with non-DM CKD and 328 deceased patients with DM CKD. To clarify the associations of MetS components and clinical outcomes in non-DM CKD and DKD, we accomplished the Cox proportional hazards analysis. Patients with the BP component of MetS had a higher risk of renal outcome in non-DM CKD (HR of 1.50, 95% CI: 1.08–2.08, $p < 0.001$) and marginally higher in DKD (Table 4). Patients with the HDL component of MetS also had a marginally higher risk of renal outcome in non-DM CKD. Other MetS components were not significant and there was a trend of lower risk of renal outcome in patients with waist component of MetS.

To investigate the association of MetS with clinical outcomes, we performed a competing risk Cox proportional hazards analysis. In the fully adjusted model, patients with MetS had a higher risk of renal outcome in both non-DM CKD (HR of 1.31, 95% CI: 1.02–1.70, $p < 0.001$) and DKD (HR of 1.56, 95% CI: 1.15–2.12, $p < 0.001$).

**TABLE 2** Components of metabolic syndrome by diabetes and metabolic syndrome.

| | Non-DM | | | DM | | |
|---|---|---|---|---|---|---|
| Variable | Non-MetS | MetS | *p* Value | Non-MetS | MetS | *p* Value |
| Components of metabolic syndrome | | | | | | |
| MetS scores | 1.5 (0.7) | 3.6 (0.7) | <0.001 | 1.8 (0.4) | 3.9 (0.8) | <0.001 |
| Waist[a] | 133 (21.2%) | 500 (77.9%) | <0.001 | 20 (10.1%) | 767 (74.4%) | <0.001 |
| Blood pressure[a] | 425 (67.7%) | 589 (91.7%) | <0.001 | 133 (66.8%) | 968 (93.9%) | <0.001 |
| HDL cholesterol[a] | 167 (26.6%) | 489 (76.2%) | <0.001 | 20 (10.1%) | 723 (70.1%) | <0.001 |
| Blood sugar[a] | 130 (20.7%) | 375 (58.4%) | <0.001 | 174 (87.4%) | 1010 (98.0%) | <0.001 |
| Triglyceride[a] | 69 (11.0%) | 342 (53.3%) | <0.001 | 18 (9.0%) | 535 (51.9%) | <0.001 |
| Associated data | | | | | | |
| Waist (cm) | 80.8 (11.1) | 92.5 (10.9) | <0.001 | 79.4 (10.7) | 92.5 (12.1) | <0.001 |
| Systolic BP (mmHg) | 131.1 (18.9) | 138.6 (18.2) | <0.001 | 132.2 (20.0) | 142.6 (20.5) | <0.001 |
| Diastolic BP (mmHg) | 79.3 (12.6) | 82.5 (12.5) | <0.001 | 75.5 (11.1) | 80.1 (13.0) | <0.001 |
| Total cholesterol (mg/dl) | 194 (168–222) | 192 (168–223) | 0.656 | 198 (163–225) | 194 (165–226) | 0.937 |
| Triglyceride (mg/dl) | 98 (71–125) | 155 (109–211) | <0.001 | 100 (69–123) | 155 (109–221) | <0.001 |
| HDL cholesterol (mg/d) | 50.9 (15.2) | 38.8 (11.1) | <0.001 | 53.4 (14.3) | 40.0 (11.5) | <0.001 |
| Blood glucose (mg/dl) | 94.7 (16.0) | 103.8 (18.7) | <0.001 | 137.7 (72.0) | 139.4 (54.3) | 0.075 |
| HbA1c (%) | 5.5 (0.6) | 5.7 (0.6) | <0.001 | 7.7 (1.8) | 7.7 (1.9) | 0.858 |

Abbreviations: BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; MS, metabolic syndrome.

[a]Criteria of MS components: 1. waist circumference ≧90 cm in men or ≧80 cm in women; 2. systolic blood pressure ≧130 mmHg or diastolic blood pressure ≧85 mmHg or hypertension; 3. HDL cholesterol >40 mg/dl in men or >50 mg/dl in women; 4. fasting blood glucose ≧100 mg/dl or diabetes mellitus; and 5. triglycerides ≧150 mg/dl.

**TABLE 3** Linear regression for MetS score.

| Variables | Beta coefficient | 95% CI beta coefficient | *p* |
|---|---|---|---|
| Age (years) | 0.013 | 0.010 to 0.016 | <0.001 |
| Gender (female vs. male) | 0.317 | 0.220 to 0.414 | <0.001 |
| eGFR (ml/min/1.73 $m^2$) | −0.004 | −0.006 to −0.002 | <0.001 |
| UPCR log | 0.385 | 0.301 to 0.470 | <0.001 |
| Cardiovascular disease | 0.056 | −0.050 to 0.162 | 0.299 |
| Cancer | −0.005 | −0.161 to 0.152 | 0.954 |
| Severe liver disease | −0.186 | −0.377 to 0.004 | 0.055 |
| Body mass index (kg/$m^2$) | 0.126 | 0.116 to 0.137 | <0.001 |
| Haemoglobin (g/dl) | 0.034 | 0.009 to 0.060 | 0.008 |
| Albumin (g/dl) | 0.171 | 0.077 to 0.264 | <0.001 |
| Total cholesterol log | −0.052 | −0.448 to 0.345 | 0.798 |
| C-reactive protein log | 0.080 | 0.033 to 0.126 | 0.001 |
| Phosphorus (mg/dl) | 0.062 | 0.006 to 0.117 | 0.030 |

Abbreviations: eGFR, estimated glomerular filtration rate; UPCR, urine protein-to-creatinine ratio.

**TABLE 4** Associations between components of metabolic syndrome and clinical outcomes by diabetes.

| | Non-DM | | DM | |
|---|---|---|---|---|
| | MetS component (−) | MetS component (+) | MetS component (−) | MetS component (+) |
| HR for RRT + 50% decline of eGFR | | | | |
| Waist | 1 (reference) | 0.84 (0.64–1.12) | 1 (reference) | 0.90 (0.71–1.14) |
| Blood pressure | 1 (reference) | 1.50 (1.08–2.08)* | 1 (reference) | 1.45 (0.98–2.15) |
| HDL cholesterol | 1 (reference) | 1.25 (0.99–1.58) | 1 (reference) | 1.16 (0.95–1.42) |
| Blood sugar | 1 (reference) | 1.16 (0.91–1.47) | - | - |
| Triglyceride | 1 (reference) | 0.93 (0.73–1.19) | 1 (reference) | 1.08 (0.90–1.31) |
| HR for all-cause mortality | | | | |
| Waist | 1 (reference) | 0.95 (0.67–1.34) | 1 (reference) | 1.08 (0.82–1.42) |
| Blood pressure | 1 (reference) | 1.33 (0.85–2.09) | 1 (reference) | 0.93 (0.61–1.42) |
| HDL cholesterol | 1 (reference) | 1.19 (0.88–1.59) | 1 (reference) | 1.09 (0.87–1.38) |
| Blood sugar | 1 (reference) | 1.19 (0.89–1.59) | - | - |
| Triglyceride | 1 (reference) | 0.94 (0.68–1.32) | 1 (reference) | 0.83 (0.65–1.05) |

*Note*: Criteria of MS components: 1. waist circumference ≧90 cm in men or ≧80 cm in women; 2. systolic blood pressure ≧130 mmHg or diastolic blood pressure ≧85 mmHg or hypertension; 3. HDL cholesterol >40 mg/dl in men or >50 mg/dl in women; 4. fasting blood glucose ≧100 mg/dl or diabetes mellitus; and 5. triglycerides ≧150 mg/dl.

Abbreviations: DM, diabetes mellitus; HDL, high-density lipoprotein; MS, metabolic syndrome.

*$p < 0.05$.

However, patients with MetS were not associated with all-cause mortality in non-DM CKD and DKD (Table 5).

## 3.5 | The association of MetS × DM with clinical outcomes

To further elucidate the associations of MetS and DM with clinical outcomes, we performed 2 by 2 matrix analysis. Patients with MetS and DM had the highest risk of renal outcome (HR of 1.62, 95% CI: 1.31–2.02, $p < 0.001$) and patients with MetS and non-DM had secondarily high risk of renal outcome (HR of 1.33, 95% CI: 1.05–1.69, $p < 0.001$) compared with patients with non-MetS and non-DM. Patients with MetS and DM had a higher risk of all-cause mortality (HR of 1.43, 95% CI: 1.09–1.88, $p < 0.001$) and patients with non-MetS and DM had a marginally higher risk (Table 6).

To inspect the associations between the DM-MetS matrix and clinical outcomes in patients with CKD stage 1–4 and CKD stage 5,

**TABLE 5** Associations between metabolic syndrome and clinical outcomes in patients with diabetes and non-diabetes.

| | Non-DM | | DM | |
|---|---|---|---|---|
| | Non-MetS | MetS | Non-MetS | MetS |
| HR for RRT + 50% decline of eGFR | | | | |
| Unadjusted | 1 (reference) | 1.34 (1.07–1.67)* | 1 (reference) | 1.49 (1.13–1.97)* |
| Fully adjusted | 1 (reference) | 1.31 (1.02–1.70)* | 1 (reference) | 1.56 (1.15–2.12)* |
| HR for all-cause mortality | | | | |
| Unadjusted | 1 (reference) | 1.40 (1.05–1.88)* | 1 (reference) | 1.12 (0.82–1.52) |
| Fully adjusted | 1 (reference) | 1.27 (0.92–1.74) | 1 (reference) | 1.00 (0.71–1.40) |

*Note*: Fully adjusted model: adjusted for age, sex, eGFR, UPCR log, cardiovascular disease, cancer, severe liver disease, smoker, haemoglobin, albumin, C-reactive protein log, phosphorus, and body mass index.

Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MS, metabolic syndrome; RRT, renal replacement therapy.

*Indicates $p < 0.05$.

**TABLE 6** Associations between diabetes–metabolic syndrome matrix and clinical outcomes.

| | Non-DM/Non-MetS | Non-DM/MetS | DM/Non-MetS | DM/MetS |
|---|---|---|---|---|
| HR for RRT + 50% decline of eGFR | | | | |
| Unadjusted | 1 (reference) | 1.34 (1.07–1.67)* | 1.49 (1.09–2.03)* | 2.25 (1.86–2.73)* |
| Fully-adjusted | 1 (reference) | 1.33 (1.05–1.69)* | 1.12 (0.82–1.54) | 1.62 (1.31–2.02)* |
| HR for all-cause mortality | | | | |
| Unadjusted | 1 (reference) | 1.33 (1.00–1.77)* | 1.95 (1.37–2.79)* | 2.25 (1.76–2.87)* |
| Fully-adjusted | 1 (reference) | 1.23 (0.91–1.66) | 1.40 (0.97–2.01) | 1.43 (1.09–1.88)* |

Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MS, metabolic syndrome; RRT, renal replacement therapy.

*$p < 0.05$.

we accomplished 2 by 2 matrix analysis. Patients with MetS and DM did not have higher risk of renal outcome and a marginally higher risk of all-cause mortality (Table S2).

## 4 | DISCUSSION

Our study demonstrated that MetS was prevalent in CKD, especially in those with DM. MetS was associated with obesity, inflammation, and proteinuria but also with better nutritional markers. We found that BP and metabolic component of MetS were marginally associated with renal outcome, whereas waist component was not. We illustrated for the first time that CKD stage 1–4 patients with MetS had higher risks of renal outcome in both DM and non-DM, even after considering traditional risks of cardiorenal metabolic disease.

MetS is a constellation of metabolic derangements of insulin resistance and obesity, which could aggravate the progression of CKD.[1] Insulin resistance impairs complete removal of carbohydrates and free fatty acids from circulation, which leads to excess accumulation in whole body organs. The overspill of glucose and adipocytes produce multiple proinflammatory cytokines, recruit inflammatory cells, and increase oxidative stress of the whole body, especially heart and kidney, in MetS.[24,25] The renin-angiotensin- aldosterone system is also activated in patients with MetS. This not only increases sodium retention but also alters haemodynamics leading to kidney failure.[26,27] These pathophysiological mechanisms will ultimately lead to cardiorenal metabolic syndrome. Recurrent inflammatory conditions that occur in both CKD and heart failure trigger reactive oxygen species (ROS) production by activating leucocytes to release oxidative components.[28] Ang II has been ascertained to be involved in a myriad of inflammatory and oxidative responses. Ang II infusion increased renal tumour necrosis factor α (TNF-?) production, augmented renal synthesis of interleukin (IL)-6, monocyte chemotactic protein-1 (MCP-1), and enhanced tissue levels of activated NF-?B.[29] Moreover, Ang II stimulates superoxide production by activating NADH and NADPH oxidases.[30] These will ultimately lead to glomerulosclerosis, tubulointerstitial fibrosis, and arteriosclerosis.[31,32]

MetS is associated with CKD.[33–36] In the general population, MetS is a risk factor for the development of CKD with an OR of 2.08.[35] In the study of The Third National Health and Nutrition Examination Survey (NHANES III), which recruited 7800 patients with CKD or microalbuminuria, patients with MetS were found to have an OR of 2.6 for CKD and an OR of 1.89 for microalbuminuria, respectively.[36] These studies excluded those with DM, which is not only a prospective element of MetS but also one of the major risk factors of CKD. In the study by Lucove et al., MetS was associated

with an increasing risk of developing CKD in American Indians without DM. Moreover, the relationship between MetS and renal outcomes was stronger in those who developed DM during follow-up.[34] In a meta-analysis study of 30,146 participants, MetS was not only associated with CKD (OR 1.55) but the components of MetS were also associated with CKD.[7] Our study showing the association between MetS and proteinuria is in accord with these studies and further demonstrated that MetS is associated with renal outcome in patients with CKD stage 1–4.

The studies investigating MetS in patients with advanced CKD (stage 3–4) are sparse and inconsistent.[11,33,37] Proteinuria is one of the explanations of this inconsistency. The largest study by Navaneethan et al. is an electronic health record-based CKD registry with 25,868 patients in stages 3 and 4 for a mean follow-up period of 2.3 years.[33] There were 52% missing data of proteinuria in that cohort. They observed an association of MetS with progression to ESRD with HR 1.33 (95% CI: 1.08, 1.64) but no association with all-cause mortality. In the African–American Study of Hypertension and Kidney Disease, which recruited 842 patients with hypertension and non-diabetic CKD with a mean eGFR of 45.7 $\pm$ 13 ml/min/1.73 $m^2$, they found an association between MetS and proteinuria but not an independent association between MetS and CKD progression.[11] Another study from Japan also demonstrated that the association between MetS and CKD progression was confounded by albuminuria.[10] In our study, we adjusted not only proteinuria but also traditional risks such as mean blood pressure and glycated haemoglobin. MetS was still associated with poor renal outcomes in CKD stage 1–4 patients with or without DM. Our results suggested that proteinuria could not explain the inconsistency between studies. Besides proteinuria, there are other mediators that cause CKD progression in MetS.

The study conducted by Pammer et al.,[13] which comprised a cohort of patients with moderate CKD (mean eGFR of 49.4 $\pm$ 18.2 ml/min/1.73 $m^2$), suggests that hyperglycemia is associated with the highest increase in the risk of all-cause mortality. However, in the present study, hypertension was identified as the most significant component or factor in the development of renal outcomes of MetS in CKD. The mean eGFR of our patients with CKD was 40.1 ml/min/1.73 $m^2$, indicating that the patients in our study were in more advanced stages of the disease. As the renal function declines, the role of hypertension in conjunction with MetS in renal outcomes may become increasingly pronounced.

Obesity was not associated with poor renal outcome in late CKD (stage 4–5). The late CKD stage might also attenuate the predictive value of MetS. In a national cohort of 453,946 United States veterans, Kovesdy et al. demonstrated that high BMI was associated with CKD progression in patients with CKD stage 3 but not in stage 4.[38] Our previous study also showed a similar result.[17] Thus, one study from Taiwan found that the impact of MetS in CKD progression became insignificant in patients with stage 4–5 CKD. They interpreted the result as a paradoxical phenomenon.[12] Our study is consistent with these findings that MetS was not associated with poor renal outcomes in patients with CKD stage 5.

There are several studies trying to investigate the associations of single MetS components with outcomes in patients with CKD. In the meta-analysis study of 30,146 participants, the ORs for CKD development for individual components of MetS were elevated blood pressure 1.61, elevated triglycerides 1.27, low HDL cholesterol 1.23, abdominal obesity 1.19, and impaired fasting glucose 1.14.[7] This is in line with our results that elevated blood pressure had the highest risk of renal outcome among the five MetS components. HTN with uncontrolled blood pressure is a strong risk factor for progression to ESRD.[39] However, the waist component was not associated with renal outcome in our cohort.

MetS triggers cardiometabolic disease. Whether MetS is still important after the development of DKD should need further study. DKD occurs in more than 30% of type 1 and 2 diabetic patients with more than a 15-year follow-up time after the onset of diabetes.[40,41] With the progression from prediabetes in MetS, turning to DM, and ultimately entering DKD, the cardiometabolic risk factors increase strikingly.[42] Patients with MetS and DM have the highest risk of cardiovascular disease and kidney disease compared to those with MetS alone or DM alone.[43,44] Previous literature either excluded diabetic patients or did not separate non-DM versus DM. The above-mentioned study from Taiwan found that the impact of MetS on CKD progression became insignificant in diabetic patients with CKD.[12] In our study, MetS was still associated with CKD progression in patients with stage 1–4 DKD but was not associated with all-cause mortality.

MetS and DM together might have a synergistic effect on clinical outcomes. In adults over 50 years old in the US, patients with MetS and DM had the highest risk of coronary heart disease, while MetS alone was second, compared to no-MetS/no-DM adults or patients with DM/no-MetS.[43] In patients with DM in Asia, patients with MetS had a HR of 1.31 for CKD compared with those without MetS.[44] The HRs of risk of CKD increased progressively with an increase in fulfiling each MetS component. Our study results are in accord with some of these studies that the DM/MetS had the highest risk of CKD progression and death. These results may indicate that the risk relationship between MetS, DM, cardiovascular disease, and CKD is not only an interactive influence but also synergistic.[36,45]

Our study has several limitations. First, this was an observational study, and causal relationships thus could not be delineated. Second, cardiovascular events were not precisely recorded and we could not further analyse cardiovascular risks. Third, as we have shown before, obesity paradox for renal outcome could be presented in advanced CKD. The waist component was not prognostic in this cohort but could be a risk factor in earlier patients with CKD. Fourth, the MetS definition of East Asia is a little bit different from other regions. Whether this definition is still good for CKD is not known. Fifth, although we considered many traditional risks in the regression model, residual confounding could not be completely eliminated.

In conclusion, our study in patients with CKD stage 1–4 demonstrated that MetS was not only associated with obesity, inflammation, and proteinuria but also with better nutritional

markers. BP and metabolic components were marginally associated with renal outcome. MetS, a cluster of risk factors, was associated with a higher risk for poor renal outcome in both patients with DM and non-DM, even after considering the traditional risks of cardiorenal metabolic disease. However, MetS was not associated with all-cause mortality.

## AUTHOR CONTRIBUTIONS

Hugo Y.-H. Lin and Chi-Chih Hung conceived the project and designed the experiments. Li-Yun Chang and Sheng-Wen Niu designed the statistical model. I-Ching Kuo and Chia-Hung Yen executed the computational framework. Feng-Ching Shen and Phang-Lang Chen contributed to data interpretation and modification of the experiment design. The manuscript was composed by Hugo Y.-H. Lin and Chi-Chih Hung, with inputs from all authors. Jer-Ming Chang provided overall supervision of the project.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

## ETHICS STATEMENT

The whole study process was approved by the Ethics Committees of the Institutional Review Board of the KMU Hospital under the guidelines of the Declaration of Helsinki. All patients gave written informed consent before being included in this study.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, CH. The data are not publicly available because they contain information that could compromise the privacy of research participants.

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## PEER REVIEW

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## SUPPORTING INFORMATION

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