Body Mass Index, Mortality, and Gender Difference in Advanced Chronic Kidney Disease

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Abstract

Background and Aim
A higher body mass index (BMI) appears to be reversely associated with mortality in dialysis patients. Moreover, although women have better survival in chronic kidney disease (CKD), this survival advantage is cancelled in dialysis. The association between BMI and mortality and the gender difference remain controversial in advanced CKD.

Methods
This study enrolled 3,320 patients (1,938 men and 1,382 women) from southern Taiwan who had CKD stages 3–5 with a BMI of 15.0–35.0 kg/m².

Results
During a median 2.9-year follow-up, there were 328 (16.9%) all-cause mortality and 319 (16.5%) cardiovascular (CV) events and death in male patients, 213 (15.4%) all-cause mortality and 224 (16.2%) CV events and death in female patients. Compared with the reference BMI of 27.6–30.0 kg/m² in an adjusted Cox model, lower-BMI groups in men, BMI 15.0–20.0 kg/m² and 20.1–22.5 kg/m², were associated with higher risks of all-cause mortality: hazard ratios (HRs) 3.19 (95% confidence interval [CI], 1.97–5.18) and 2.01 (95% CI, 1.29–3.14), respectively. Higher-BMI group in men, BMI 30.1–35.0 kg/m², was associated with a higher risk of all-cause mortality: HR 1.72 (95% CI, 1.02–2.96). Likewise, lower- and higher-BMI groups in men were associated with a higher risk of CV events and death. In women, these associations between BMI and poor outcomes were not observed.
Conclusions
In advanced CKD, there was a reverse J-shaped association between BMI and all-cause mortality, and a U-shaped association between BMI and CV outcomes in men. Neutral associations between BMI and poor outcomes were detected in women. Gender could modify the effect of BMI on mortality in patients with CKD.

Introduction
Obesity and overweight have been a rapid-growing and pandemic problem worldwide over the past few decades [1]. Excess weight is associated with increased mortality in the general population, primarily because of the increased risk of cardiovascular disease (CVD) [2]. Accumulating evidence has shown either a J- or U-shaped association between body mass index (BMI) and mortality [3–5]. The lowest risk of death is observed at a BMI of 20.0–27.5 kg/m² [4,5], suggesting a survival advantage in individuals with a normal BMI. However, in certain disease groups, such as patients with heart failure [6], chronic obstructive pulmonary disease [7], and dialysis patients [8–10], the relationship between excess weight and death appears to be reversed.

In contrast to the general population and patients on dialysis, the relationship between BMI and mortality in patients with chronic kidney disease (CKD) remains contradictory. Some earlier studies suggested that a lower BMI was associated with an increased risk of death in CKD [11–13], whereas some investigations found no association between BMI and adverse outcomes in CKD [14–16]. Patients with advanced CKD are different from the general population and patients with earlier stages of CKD regarding the burden of cardiovascular (CV) events and mortality [17]. The risk nadir BMI and the association between BMI and mortality are not well understood in advanced CKD. Furthermore, men and women exhibit differences in the pathogenesis and clinical prognosis of many diseases [18]. In CKD, the female gender was associated with a slower decline in renal function and better renal and patient survival [11,19]; however, this survival advantage is cancelled in dialysis [20,21]. The gender difference in the relationship between BMI and mortality in advanced CKD remains unclear.

Therefore, the aims of our study were to investigate the association between BMI, CV events, and mortality and to explore gender differences in these associations in patients with CKD stages 3–5.

Methods
Ethics statement
The study protocol was approved by the institutional review board of the Kaohsiung Medical University Hospital (KMUH-IRB-20140076). Written informed consents were obtained from each patient, and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The patients gave consent for the publication of the clinical details.

Study design and participants
Integrated CKD care program Kaohsiung for delaying dialysis (ICKD) study was designed as a prospective cohort study to investigate the impact of an integrated CKD care program on clinical outcomes in patients with CKD stages 1–5. Exclusion criteria were acute kidney injury, which is defined as more than 50% decrease in the estimated glomerular filtration rate (eGFR).
in 3 months, and long-term dialysis. 3,749 patients participated in the study from the nephrology out-patient departments of two hospitals located in southern Taiwan between November 11, 2002 and May 31, 2009, and were followed-up until July 31, 2010. Thirty patients with missing BMI data, and 356 patients with CKD stages 1 or 2 were excluded. The definition of CKD was by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, and CKD stage was classified based on the participants’ baseline eGFR. Study participants were divided into six BMI categories as follows: 15.0–20.0, 20.1–22.5, 22.6–25.0, 25.1–27.5, 27.6–30.0 and 30.1–35.0 kg/m², according to previous Asian BMI studies [5]. The extreme-BMI groups, which represented less than 1% of participants, including five subjects with a BMI lower than 14.9 kg/m² and thirty-eight subjects with a BMI greater than 35.1 kg/m², were excluded from the study. A total 3,320 subjects with CKD stages 3–5 and a BMI of 15.0–35.0 kg/m² were enrolled and analyzed.

Collection of demographic, medical and laboratory data
Baseline variables were collected at the baseline visit and included demographic features (age and gender), medical history (diabetes mellitus, hypertension, CVD, current smoking status, and cancer), examination findings [BMI and mean arterial pressure (MAP)], renal function status [eGFR, CKD stage, and urine protein-to-creatinine ratio (Upcr)]. Laboratory data obtained at the baseline visit and within 3 months before the baseline visit were averaged and analyzed [albumin, hemoglobin, total cholesterol, C-reactive protein (CRP), glycated hemoglobin (HbA1c), bicarbonate, and phosphorus]. Demographic features were baseline records, and medical history was obtained by a review of physician’s charts and interviews with patients. BMI was calculated as the weight in kilograms divided by the square of height in meters. Mean MAP was calculated by the mean of repeated measured MAP 3 months before study enrollment. Upcr was calculated as urine protein (mg) divided by urine creatinine (g) in a random spot urine sample. Biochemistry measurements were performed during the screening visit, the baseline visit, and every 3 months thereafter, as the protocol.

Quantification of renal function
Kidney function was quantified using eGFR calculated by the four-variable equation in the Modification of Diet in Renal Disease (MDRD) Study [22]: eGFR mL/min/1.73 m² = 186 × serum creatinine⁻¹.154 × age⁻⁰.²⁰³ × 0.⁷⁴² (if female) × 1.²¹² (if black patient). We classified our patients according to evidence of kidney damage lasting for more than 3 months into CKD stage 3, 4, and 5 based on eGFR levels (mL/min/1.73 m²) of 30–59, 15–29, and <15, respectively.

Outcomes
Clinical outcomes, including all-cause mortality and CV events and death, were accessed. Survival status and cause of death were ascertained by reviewing death certificates using charts or the National Death Index. CV events were ascertained by reviewing charts and were defined as hospitalization for acute coronary syndrome (Deyo-modified Charlson score, ICD-9-CM: 410. x–412.x), acute cerebrovascular disease (430.x–438.x), congestive heart failure (428.x), and peripheral arterial occlusion disease (443.9, 441.x, 785.4, V43.4, procedure 38.48), followed by death by one of the aforementioned causes. Patients were not censored because of dialysis.
Statistical analysis

Summary statistical results regarding baseline characteristics of all subjects and stratification according to BMI are expressed as percentages for categorical data, mean standard ± deviation for continuous variables with an approximately normal distribution, and median and interquartile range for continuous variables with a skewed distribution. Differences between groups were assessed by the Pearson chi-square test for categorical variables or by the one way ANOVA for continuous variables. Cox proportional hazards analysis was used to investigate the relationship of BMI with all-cause mortality and CV events. The proportional hazards assumption was tested by the Schoenfeld goodness-of-fit procedures, which did not show meaningful violations. Study participants with a BMI of 27.6–30.0 kg/m² were used as the reference group because this group had the lowest all-cause mortality and CV events and death. All clinically relevant covariates were selected according to our previous publications and literature and continuous variables with a skewed distribution were log transformed to attain normal distribution. Adjusted covariates included age, gender, hypertension, CVD, diabetes mellitus, current smoking status, MAP, eGFR, log-transformed Ucr, albumin, hemoglobin, HbA1C, log-transformed total cholesterol, log-transformed CRP, and phosphorus [23–25]. Cox survival analyses with pre-specified subgroups were also performed by adding appropriate cross-product interaction terms including age, gender, CVD, CKD stages, Ucr, hemoglobin, albumin, and CRP. Statistical analysis was performed using the R 2.15.2 software (R Foundation for Statistical Computing, Vienna, Austria) and the SPSS, version 18.0 (SPSS Inc., Chicago, IL) for Windows.

Results

Baseline characteristics of study participants

A total of 3,320 non-dialyzed patients (1,938 men and 1,382 women) with CKD stages 3–5 were included in the study and analyzed. Baseline characteristics of study participants divided according to the categories of BMI are summarized in Tables 1 and 2.

In male patients, the mean age was 63.5 ± 13.4 years, 43.7% had a history of diabetes, and 26.7% had CKD stage 5. The overall mean BMI and eGFR were 24.8 ± 3.4 kg/m² and 29.2 ± 16.2 mL/min/1.73 m², respectively. Compared with those with a lower BMI, male patients with a higher BMI were more likely to have a younger age, a higher prevalence of diabetes and hypertension, as well as higher levels of MAP, eGFR, albumin, hemoglobin, and HbA1C.

In female patients, the mean age was 63.3 ± 13.7 years, 44.9% had a history of diabetes, and 45.6% had CKD stage 5. The overall mean BMI and eGFR were 24.3 ± 3.9 kg/m² and 20.2 ± 13.6 mL/min/1.73 m², respectively. Compared with those with a lower BMI, female patients with a higher BMI were tend to have an older age, a higher prevalence of diabetes, hypertension and CVD, higher levels of MAP, eGFR, hemoglobin, CRP, and HbA1C.

Associations between BMI and all-cause mortality

There were 328 deaths (16.9%) during a median follow-up period of 2.9 (1.8–4.7) years in male patients, and 213 deaths (15.4%) during the follow-up period in female patients. We generated Kaplan-Meier curves to illustrate cumulative probability of all-cause mortality. It demonstrated that male patients with a low BMI of 15.0–20.0 kg/m² had the highest cumulative probability of all-cause mortality. But such phenomenon was not observed in female patients (Fig 1).

Table 3 shows the results of Cox proportional hazards regression analysis for all-cause mortality, CV events and death in male patients. The low-BMI groups, i.e., male patients with a BMI of 15.0–20.0 and 20.1–22.5 kg/m², had significantly increased risks of all-cause mortality, with a hazard ratio (HR) (95% confidence interval [CI]) of 3.19 (1.97–5.18), P < 0.001; and
Table 1. Comparison of baseline characteristics among male patients stratified on BMI categories.

| Characteristics          | BMI (kg/m²) | **All** (n = 1938) | **15.0–20.0** (n = 140) | **20.1–22.5** (n = 319) | **22.6–25.0** (n = 601) | **25.1–27.5** (n = 482) | **27.6–30.0** (n = 252) | **30.1–35.0** (n = 144) | **P (ANOVA)** |
|--------------------------|-------------|--------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------|
| **Demographic and medical history** |             |                    |                          |                          |                          |                          |                          |                          | <0.001                |
| Age (year)               |             | 63.5±13.4          | 65.3±16.2                | 65.1±13.7                | 64.1±12.7                | 62.7±13.0                | 63.2±13.2                | 59.3±13.5                | <0.001                |
| Hypertension (%)         |             | 65.2               | 52.1                     | 64.6                     | 65.0                     | 66.0                     | 70.2                     | 68.8                     | 0.003                 |
| Diabetes mellitus (%)    |             | 43.7               | 37.9                     | 39.8                     | 43.1                     | 45.2                     | 47.2                     | 48.6                     | 0.008                 |
| Cardiovascular disease (%) |           | 26.1               | 25.7                     | 23.2                     | 27.1                     | 24.3                     | 29.8                     | 27.8                     | 0.275                 |
| Current smoking status (%) |           | 17.5               | 15.7                     | 16.3                     | 18.1                     | 17.2                     | 18.3                     | 19.4                     | 0.213                 |
| Cancer (%)               |             | 8.8                | 13.6                     | 13.2                     | 8.3                      | 7.7                      | 5.6                      | 6.3                      | <0.001                |
| **Examination findings** |             |                    |                          |                          |                          |                          |                          |                          | <0.001                |
| BMI (kg/m²)              |             | 24.8±3.4           | 18.5±1.2                 | 21.4±0.7                 | 23.8±0.7                 | 26.2±0.7                 | 28.6±0.7                 | 31.8±1.4                 | <0.001                |
| MAP (mmHg)               |             | 100.3±13.9         | 94.8±12.8                | 98.1±13.7                | 99.9±13.5                | 101.2±13.2               | 103.3±15.2               | 103.2±14.2               | <0.001                |
| **Renal function status** |             |                    |                          |                          |                          |                          |                          |                          | <0.001                |
| eGFR (ml/min/1.73 m²)    |             | 29.2±16.2          | 23.7±15.2                | 27.7±16.2                | 28.4±16.0                | 30.1±16.1                | 30.9±15.6                | 34.8±16.7                | <0.001                |
| CKD stage                |             |                    |                          |                          |                          |                          |                          |                          | <0.001                |
| Stage 3 (%)              |             | 46.4               | 33.6                     | 40.7                     | 45.1                     | 49.8                     | 51.2                     | 56.9                     | <0.001                |
| Stage 4 (%)              |             | 26.9               | 27.8                     | 30.1                     | 25.8                     | 24.7                     | 27.4                     | 29.9                     | <0.001                |
| Stage 5 (%)              |             | 26.7               | 38.6                     | 29.2                     | 29.1                     | 25.5                     | 21.4                     | 13.2                     | <0.001                |
| Uprc (mg/g)              |             | 863 (292–2080)     | 972 (404–2188)           | 937 (299–2116)           | 892 (287–2375)           | 886 (329–1942)           | 728 (227–1829)           | 690 (230–1792)           | 0.011                 |
| **Laboratory data**      |             |                    |                          |                          |                          |                          |                          |                          | <0.001                |
| Albumin (g/dL)           |             | 3.8±0.6            | 3.7±0.6                  | 3.8±0.6                  | 3.8±0.6                  | 3.9±0.5                  | 3.9±0.5                  | 3.9±0.6                  | 0.002                 |
| Hemoglobin (g/dL)        |             | 11.7±2.4           | 10.3±2.0                 | 11.0±2.2                 | 11.7±2.4                 | 12.0±2.5                 | 12.3±2.4                 | 12.9±2.3                 | <0.001                |
| Total cholesterol (mg/dL)|             | 185 (157–213)      | 175 (141–201)            | 181 (155–213)            | 190 (162–215)            | 184 (158–212)            | 183 (156–213)            | 190 (164–216)            | 0.066                 |
| CRP (mg/L)               |             | 1.3 (0.4–5.5)      | 2.2 (0.5–9.1)            | 1.0 (0.3–5.0)            | 1.1 (0.4–4.5)            | 1.2 (0.4–5.6)            | 1.6 (0.4–6.7)            | 1.9 (0.5–6.4)            | 0.265                 |
| HbA1C (%)                |             | 6.5±1.6            | 6.3±1.6                  | 6.4±1.6                  | 6.4±1.6                  | 6.7±1.6                  | 6.5±1.4                  | 6.9±1.6                  | <0.001                |
| Bicarbonate (mEq/L)      |             | 22.6±4.2           | 21.5±4.7                 | 22.3±4.5                 | 22.5±4.1                 | 22.8±3.9                 | 22.7±4.1                 | 23.9±4.1                 | <0.001                |
| Phosphorus (mg/dL)       |             | 4.2±1.2            | 4.4±1.4                  | 4.3±1.4                  | 4.1±1.2                  | 4.1±1.1                  | 4.0±1.1                  | 4.0±1.0                  | <0.001                |
| **Outcomes**             |             |                    |                          |                          |                          |                          |                          |                          | <0.001                |
| All-cause mortality (%)  |             | 16.9               | 32.1                     | 21.3                     | 15.0                     | 15.1                     | 11.5                     | 16.0                     | 0.002                 |
| CV events and death (%)  |             | 16.5               | 18.6                     | 18.8                     | 15.3                     | 17.6                     | 13.1                     | 16.0                     | 0.095                 |

Data expressed as mean ± standard deviation, median (interquartile range) or percentage.

Abbreviations: BMI, body mass index; MAP, mean arterial pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Uprc, urine protein-to-creatinine ratio; CRP, C-reactive protein; HbA1C, glycated hemoglobin; CV, cardiovascular.

2.01 (1.29–3.14), P = 0.002, respectively, compared with a BMI of 27.6–30.0 kg/m² in the fully adjusted model. The high-BMI group (BMI of 30.1–35.0 kg/m²) also had an increased risk of all-cause mortality, with a HR (95% CI) of 1.72 (1.02–2.96), P = 0.042, compared with a BMI of 27.6–30.0 kg/m² in the fully adjusted model. It showed a reverse J-shaped association between BMI and all-cause mortality in male patients (Fig 2).

Compared with those with a BMI of 27.6–30.0 kg/m², female patients with a lower BMI did not show significantly increased risk of all-cause mortality in the fully-adjusted model.

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However, the high-BMI group (BMI of 30.1–35.0 kg/m²) exhibited a trend of decreased risk of all-cause mortality, with a HR (95% CI) of 0.52 (0.26–1.02), P = 0.057 (Table 4). The relationship between BMI and all-cause mortality in female patients showed a nearly flat curve (Fig 2).

**Associations between BMI and CV outcomes**

During the follow-up period, there were 319 CV events and death (16.5%) in male patients, and 224 CV events and death (16.2%) in female patients. The Kaplan-Meier curves illustrating...
cumulative probability of CV events and death showed that male patients with a low BMI of

Table 3. Association between BMI and clinical outcomes in male patients.

| BMI (kg/m²) | 15.0–20.0 | 20.1–22.5 | 22.6–25.0 | 25.1–27.5 | 27.6–30.0 | 30.1–35.0 |
|------------|----------------|----------------|----------------|----------------|----------------|----------------|
| All-cause mortality | | | | | | |
| Unadjusted HR (95% CI) | 3.54 (2.22–5.65)† | 2.08 (1.35–3.21)† | 1.34 (0.88–2.04) | 1.35 (0.88–2.07) | 1 (Reference) | 1.54 (0.89–2.66) |
| Adjusted HR (95% CI) | 3.19 (1.97–5.18)† | 2.01 (1.29–3.14)* | 1.24 (0.81–1.89) | 1.28 (0.83–1.97) | 1 (Reference) | 1.72 (1.02–2.96)* |
| CV events and death | | | | | | |
| Unadjusted HR (95% CI) | 2.39 (1.63–3.51)† | 1.65 (1.17–2.33)* | 1.20 (0.87–1.65) | 1.29 (0.92–1.79) | 1 (Reference) | 1.38 (0.90–2.12) |
| Adjusted HR (95% CI) | 1.95 (1.31–2.90)† | 1.61 (1.13–2.29)* | 1.07 (0.77–1.48) | 1.25 (0.89–1.74) | 1 (Reference) | 1.54 (1.00–2.37)* |

Values expressed as hazard ratio (HR) and 95% confidence interval (CI).
Full-adjusted model: adjusted for age, hypertension, cardiovascular disease, diabetes mellitus, MAP, HbA1C, log-transformed total cholesterol, current smoker, log-transformed CRP, eGFR, log-transformed Upcr, albumin, hemoglobin and phosphorus.
Abbreviations are the same as in Table 1.
*P < 0.05 compared with reference BMI category.
†P < 0.001 compared with reference BMI category.
15.0–20.0 kg/m² had the highest cumulative probability of poor CV outcomes. But this relationship was not found in female patients (Fig 3).

The low-BMI groups in male patients with a BMI of 15.0–20.0 and 20.1–22.5 kg/m², had significantly increased risks of CV events and death, with a hazard ratio (HR) (95% CI) of 1.95 (1.31–2.90), \( P < 0.001 \); and 1.61 (1.13–2.29), \( P = 0.008 \), respectively, compared with a BMI of 27.6–30.0 kg/m² in the fully adjusted model. The high-BMI group in male patients (BMI of 30.1–35.0 kg/m²) also demonstrated an increased risk of CV events and death, with a HR (95% CI) of 1.54(1.00–2.37), \( P = 0.049 \), compared with a BMI of 27.6–30.0 kg/m² in the fully adjusted

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**Table 4. Association between BMI and clinical outcomes in female patients.**

| BMI (kg/m²) | 15.0–20.0 | 20.1–22.5 | 22.6–25.0 | 25.1–27.5 | 27.6–30.0 | 30.1–35.0 |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|
| **All-cause mortality** | | | | | | |
| Unadjusted HR (95% CI) | 0.95 (0.57–1.61) | 0.97 (0.61–1.56) | 1.00 (0.63–1.58) | 0.96 (0.59–1.57) | 1 (Reference) | 0.62 (0.31–1.22) |
| Adjusted HR (95% CI) | 0.84 (0.48–1.46) | 1.14 (0.70–1.86) | 0.98 (0.62–1.57) | 0.93 (0.57–1.53) | 1 (Reference) | 0.52 (0.26–1.02) |
| **CV events and death** | | | | | | |
| Unadjusted HR (95% CI) | 0.89 (0.59–1.34) | 0.94 (0.65–1.35) | 0.94 (0.66–1.34) | 0.84 (0.57–1.24) | 1 (Reference) | 1.15 (0.74–1.79) |
| Adjusted HR (95% CI) | 0.78 (0.51–1.20) | 1.08 (0.74–1.58) | 0.97 (0.68–1.40) | 0.79 (0.53–1.17) | 1 (Reference) | 1.03 (0.66–1.60) |

Values expressed as hazard ratio (HR) and 95% confidence interval (CI).

Full-adjusted model: adjusted for age, hypertension, cardiovascular disease, diabetes mellitus, MAP, HbA1C, log-transformed total cholesterol, current smoker, log-transformed CRP, eGFR, log-transformed Upcr, albumin, hemoglobin and phosphorus.

Abbreviations are the same as in Table 1.

\*\( P < 0.05 \) compared with reference BMI category.

\^\( P < 0.001 \) compared with reference BMI category.
Fig 3. The cumulative probability of cardiovascular (CV) events and death using the Kaplan-Meier method in male (A) and female (B) patients according to the categories of body mass index (BMI).
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Fig 4. Multivariate-adjusted hazard ratios (HRs) of cardiovascular (CV) events and death according to the categories of body mass index (BMI) in male (■) and female (△) patients. Error bars indicate 95% confidence intervals. Multivariate-adjusted HRs were adjusted for age, gender, cardiovascular disease, diabetes mellitus, mean arterial pressure, glycated hemoglobin, log-transformed total cholesterol, current smoking status, log-transformed C-reactive protein, estimated glomerular filtration rate, log-transformed urine protein-to-creatinine ratio, albumin, hemoglobin, and phosphorus, using participants with a BMI of 27.6–30.0 kg/m² as the reference group.
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The multivariate-adjusted association between BMI and CV outcomes in male patients was U-shaped (Fig 4).

Compared with those with a BMI of 27.6–30.0 kg/m², female patients with a lower or a higher BMI did not show significantly increased risk of CV events and death in the fully-adjusted model (Table 4). The association between BMI and CV outcomes in female patients showed a nearly flat curve (Fig 4).

Discussion
In the present study, we investigated the relationship of BMI with mortality, CV events and death in Asian patients with CKD stages 3–5. We found gender differences in associations between BMI, all-cause mortality, and CV events and death. There was a reverse J-shaped association between BMI and all-cause mortality, and a U-shaped association between BMI and CV outcomes in male patients with advanced CKD. By contrast, the associations of BMI with all-cause mortality and CV outcomes in female patients were illustrated as nearly flat curves.

Although emerging evidence indicates a survival advantage for a high BMI in dialysis patients, the role of BMI in CKD patients and gender differences has not been described well. Kovesdy et al. [12] showed that a lower BMI (<22.2 kg/m²) was associated with mortality in 521 veterans mainly with CKD stage 3 or 4. Furthermore, Kwan et al. [13] found an association between increased BMI and lower mortality among 461 participants, the majority of whom had CKD stage 3, in the Atherosclerosis Risk in Communities (ARIC) study. An inverse relationship between excess weight and mortality appears to be evident in CKD. However, some studies did not support this paradoxical association [14,26]. These discrepancies may be explained by the effects of comorbid conditions, racial differences, and severity of CKD among the study cohorts. Despite a limited number of studies in advanced CKD, Evans et al. [11] reported an inverse relationship between BMI and mortality in patients with CKD stages 4–5. Our findings in male patients with advanced CKD were partly comparable with those reported by Kovesdy et al. and Evans et al., suggesting a low BMI increased mortality risk.

In the present study, we found a U-shaped association between BMI and CV outcomes in male patients, whereas previous studies of Caucasian cohorts showed no association between BMI and CV outcomes [14,15]. The reasons for these different associations are not clear but may be related to racial disparities. Investigations based on the US Renal Data System data showed that Asian-American ESRD patients do not have better survival at a high BMI and reported a U-shaped association in this population [27,28]. Obesity may exert race-specific effects on survival advantage in CKD and dialysis patients. The associations between BMI and health risks may differ between Asian and European populations [29]. Moreover, it has been shown that Asians develop a higher rate of diabetes than do white populations at a BMI of 30 kg/m² [30]. Given the impact of obesity and diabetes on CV risk, a stronger association between a high BMI and CVD in Asians compared with the Western population is expected, as in the present study.

In contrast to reverse J-shaped or U-shaped associations between BMI and poor outcomes in men, female patients displayed overall neutral associations. Sex hormone may contribute to the different severity of inflammation and wasting among men and women. A low BMI usually reflects malnutrition and inflammation, leading to endothelial dysfunction in pre-dialysis and dialysis patients [31,32]. Estrogen has anti-inflammatory and immunomodulatory effects, as it modulates proinflammatory cytokines, chemokines, and adhesion molecules and reduces oxidative stress [33–35]. Testosterone deficiency, which has been associated with muscle wasting and inflammation in men with CKD [36], may also play an important role. Previous reports showed that reduced muscle mass and elevated CRP were associated with a lower survival rate
in male, but not in female CKD patients close to the start of dialysis [37]. Loss of muscle mass in conjunction with presence of inflammation might be a much more detrimental sign in men. These hormonal and metabolic derangements might account for the positive association between low BMI with poor outcomes in men, but not in women with CKD.

Furthermore, gender differences in body composition might be another possible explanation, as women have a higher percentage of body fat compared with men at an equivalent BMI [38]. A higher fat mass was associated with a lower risk of mortality in dialysis patients [39,40]. The favorable effects of increased fat mass were presumably due to higher metabolic reserves and sequestration of uremic toxins, thus providing energy that is required for survival in ill conditions, such as those with advanced CKD and dialysis patients. Taken together, it appears to be an interaction between sex hormones and metabolic factors, regarding the gender differences in associations between BMI and poor outcomes in CKD.

There were several limitations in the present study. First, we used the baseline BMI for analysis. Data of time-dependent changes in BMI were not obtained, and we were not able to investigate the association between weight variation and outcomes. Second, the study subjects had advanced CKD; thus, the results may not be generalizable to all CKD populations. Third, although premature death is often observed in CKD, the observation period was relatively short in the present study. Third, BMI is limited to differentiate the fat and lean mass. Therefore, body composition analysis using dual-energy X-ray absorption is of importance to elucidate in the future studies. Moreover, BMI may be misleading in the presence of edema, which occurs commonly in patients with advanced CKD. Waist-to-hip ratio or conicity index may be a more sensitive marker for risk stratification in CKD [41,42].

In conclusion, our findings suggest a reverse J-shaped association between BMI and all-cause mortality, and a U-shaped association between BMI and CV outcomes in male patients with advanced CKD. However, neutral associations were detected in female patients. Hormonal and metabolic derangements might play a role in gender differences in associations between BMI and poor outcomes in CKD.

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Author Contributions

Conceived and designed the experiments: J-CH J-CT C-CH. Performed the experiments: J-CH HY-HL L-ML S-CC J-MC J-CT C-CH. Analyzed the data: J-CH J-CT C-CH. Contributed reagents/materials/analysis tools: J-CH HY-HL L-ML S-CC J-MC S-JH J-CT C-CH H-CC. Wrote the paper: J-CH J-CT C-CH.

References

1. Abelson P, Kennedy D. The obesity epidemic. Science. 2004; 304: 1413. PMID: 15178768
2. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009; 373: 1083–1096. doi:10.1016/S0140-6736(09)60318-4 PMID: 19299006
3. Gu D, He J, Duan X, Reynolds K, Wu X, Chen J, et al. Body weight and mortality among men and women in China. JAMA. 2006; 295: 776–783. PMID: 16478900
4. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, Maclnnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010; 363: 2211–2219. doi: 10.1056/NEJMoa1000367 PMID: 21121834
5. Zheng W, McLerran DF, Rolland B, Zhang X, Inoue M, Matsuo K, et al. Association between body mass index and risk of death in more than 1 million Asians. N Engl J Med. 2011; 364: 719–729. doi: 10.1056/NEJMoa1010679 PMID: 21345101

6. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med. 2005; 165: 55–61. PMID: 15642875

7. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis. 1989; 139: 1435–1438. PMID: 2658702

8. Levey SF, Strawderman RL, Jones CA, Port FK, Held PJ. Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis. 1998; 31: 997–1006. PMID: 9631845

9. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK. Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. Kidney Int. 1999; 55: 1560–1567. PMID: 10201023

10. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. Am J Clin Nutr. 2005; 81: 543–554. PMID: 15755821

11. Evans M, Fryzek JP, Elinder CG, Cohen SS, McLaughlin JK, Nyren O, et al. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. Am J Kidney Dis. 2005; 46: 863–870. PMID: 16253726

12. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. Am J Kidney Dis. 2007; 49: 581–591. PMID: 17472839

13. Kwan BC, Murtaugh MA, Beddhu S. Associations of body size with metabolic syndrome and mortality in moderate chronic kidney disease. Clin J Am Soc Nephrol. 2007; 2: 992–998. PMID: 17702712

14. Madero M, Samak MJ, Wang X, Sceppa CC, Greene T, Beck GJ, et al. Body mass index and mortality in CKD. Am J Kidney Dis. 2007; 50: 404–411. PMID: 17720519

15. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, et al. The relationship between body mass index and risk of death in more than 1 million Asians. N Engl J Med. 2011; 364: 719–729. doi:10.1056/NEJMoa1010679 PMID: 21345101

16. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int. 2006; 69: 375–382. PMID: 16408129

17. Villar E, Remontet L, Labeuwe M, Ecchard R. Effect of age, gender, and diabetes on excess death in end-stage renal failure. J Am Soc Nephrol. 2007; 18: 2125–2134. PMID: 17582163

18. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004; 351: 1296–1305. PMID: 15385656

19. Carrero JJ. Gender differences in chronic kidney disease: underpinnings and therapeutic implications. Kidney Blood Press Res. 2010; 33: 363–392. doi:10.1186/0003203819 PMID: 20948227

20. Eriksson BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int. 2006; 69: 375–382. PMID: 16408129

21. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004; 351: 1296–1305. PMID: 15385656

22. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004; 351: 1296–1305. PMID: 15385656

23. Chen SC, Hung CC, Tsai YC, Huang JC, Kuo MC, Lee JJ, et al. Association of cholesterol levels with mortality and cardiovascular events among patients with CKD and different amounts of proteinuria. Clin J Am Soc Nephrol. 2013; 8: 1915–1926. doi: 10.2215/CJN.0350213PMID: 23929929

24. Chen SC, Hung CC, Kuo MC, Lee JJ, Chiu YW, Chang JM, et al. Association of dyslipidemia with renal outcomes in chronic kidney disease. PLoS One. 2013; 8: e55643. doi: 10.1371/journal.pone.0055643 PMID: 23930545

25. Liu WC, Hung CC, Chen SC, Yeh SM, Lin MY, Chiu YW, et al. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. Clin J Am Soc Nephrol. 2012; 7: 541–548. doi: 10.2215/CJN.09420911 PMID: 23007373

26. Hsu CY, McCulloch CE, Irribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006; 144: 21–28. PMID: 16389251

27. Wong JS, Port FK, Huibert-Shearon TE, Carroll CE, Wolfe RA, Agodoa LY, et al. Survival advantage in Asian American end-stage renal disease patients. Kidney Int. 1999; 55: 2515–2523. PMID: 10354301
28. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. Am J Clin Nutr. 2004; 80: 324–332. PMID: 15277152

29. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004; 363: 157–163. PMID: 14726171

30. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. Diabetes Care. 2011; 34: 1741–1748. doi: 10.2337/dc10-2300 PMID: 21680722

31. Annuk M, Lind L, Linde T, Fellaistrom B. Impaired endothelium-dependent vasodilatation in renal failure in humans. Nephrol Dial Transplant. 2001; 16: 302–306. PMID: 11158404

32. Stenvinkel P. Inflammatory and atherosclerotic interactions in the depleted uremic patient. Blood Purif. 2001; 19: 53–61. PMID: 11114578

33. Persky AM, Green PS, Stubley L, Howell CO, Zaulyanov L, Brazeau GA, et al. Protective effect of estrogens against oxidative damage to heart and skeletal muscle in vivo and in vitro. Proc Soc Exp Biol Med. 2000; 223: 59–66. PMID: 10632962

34. Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences. Science. 2005; 308: 1583–1587. PMID: 15947173

35. Caulin-Glaser T, Farrell WJ, Pfau SE, Zaret B, Bunger K, Setaro JF, et al. Modulation of circulating cellular adhesion molecules in postmenopausal women with coronary artery disease. J Am Coll Cardiol. 1998; 31: 1555–1560. PMID: 9626834

36. Cigarrán S, Pouma M, Castro MJ, González B, Martínez A, Barril G, et al. Endogenous testosterone, muscle strength, and fat-free mass in men with chronic kidney disease. J Ren Nutr. 2013; 23: e89–e95. doi: 10.1053/j.jrn.2012.08.007 PMID: 23046736

37. Stenvinkel P, Barany P, Chung SH, Lindholm B, Heimbürger O. A comparative analysis of nutritional parameters as predictors of outcome in male and female ESRD patients. Nephrol Dial Transplant. 2002; 17: 1266–1274. PMID: 12105251

38. Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J, et al. (2008) Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes (Lond). 2008; 32: 959–966. doi: 10.1038/ijo.2008.11 PMID: 18283284

39. Kakiya R, Shoji T, Tsujimoto Y, Tatsumi N, Hatsuda S, Shinohara K, et al. Body fat mass and lean mass as predictors of survival in hemodialysis patients. Kidney Int. 2006; 70: 549–556. PMID: 16798699

40. Kalantar-Zadeh K, Kuwae N, Wu DY, Shantouf RS, Fouque D, Anker SD, et al. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. Am J Clin Nutr. 2006; 83: 202–210. PMID: 16469976

41. Elsayed EF, Tighiouart H, Weiner DE, Griffith J, Salem D, Levey AS, et al. Waist-to-hip ratio and body mass index as risk factors for cardiovascular events in CKD. Am J Kidney Dis. 2008; 52: 49–57. doi: 10.1053/j.ajkd.2008.04.002 PMID: 18514990

42. Cordeiro AC, Qureshi AR, Stenvinkel P, Heimbürger O, Axelson J, Bárány P, et al. Abdominal fat deposition is associated with increased inflammation, protein-energy wasting and worse outcome in patients undergoing haemodialysis. Nephrol Dial Transplant. 2010; 25: 562–568. doi: 10.1093/ndt/gfp492 PMID: 19762603