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Original Article

ORIGINAL ARTICLE

Low BMI and high waist-to-hip ratio are associated with mortality risk among hemodialysis patients: a multicenter prospective cohort study

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ABSTRACT

Background. Data are limited on the relationship between waist-to-hip ratio (WHR) and mortality risk among maintenance hemodialysis (MHD) patients. Moreover, the combined association of body mass index (BMI) and WHR with mortality remains uncertain. Therefore, we aimed to explore the individual and combined association of BMI and WHR with the all-cause and cardiovascular disease (CVD) mortality.

Methods. In this multicenter prospective cohort study, we enrolled 1034 MHD patients. The primary outcome was all-cause mortality and secondary outcome was CVD mortality. Multivariable Cox proportional hazards models were used to evaluate the individual and combined association of BMI and WHR with the risk of mortality.

Results. A nonlinear inverse relationship was found between BMI and risk of all-cause mortality (P for nonlinearity $<.05$). Being underweight (<18.5 kg/m^2) was associated with higher all-cause mortality risk (HR 1.45; 95% CI 1.08–1.94) compared with normal weight (18.5–23.9 kg/m^2), while being overweight (24–27.9 kg/m^2; HR 0.96; 95% CI 0.70–1.31) and obese ($\geq$28 kg/m^2; HR 1.19; 95% CI 0.62–2.26) showed no significant differences. Of note, WHR was independently and positively associated with all-cause mortality (per standard deviation increase, HR 1.13; 95% CI 1.00–1.27). When

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analyzed jointly, patients with low BMI (<18.5 kg/m^2) and high WHR (≥0.95) had the highest risk of all-cause mortality. Similar results were obtained for CVD mortality.

Conclusions. In patients undergoing hemodialysis from China, low BMI and high WHR were individually and jointly associated with higher risk of mortality. Our results emphasize that BMI and WHR may jointly affect the prognosis of MHD patients.

LAY SUMMARY

Several studies have reported that a high body mass index (BMI) is related to better survival in maintenance hemodialysis (MHD) patients. However, BMI fails to reflect the distribution of body fat, especially the abdominal fat, which can be measured by waist-to-hip ratio (WHR). The relationship of BMI and mortality risk may hide the detrimental effects of abdominal fat. As such, we aimed to explore the individual and combined relationship of BMI and WHR with mortality risk in MHD patients. We enrolled 1034 MHD patients in this multicenter prospective cohort study. During a median follow-up of 45.6 months, we found that low BMI (<18.5 kg/m^2) and high WHR (≥0.95) were individually and jointly associated with higher mortality risk in MHD patients. Our findings highlight that comprehensive consideration of BMI and WHR is of great significance to the assessment and improvement of the prognosis of patients undergoing MHD.

Keywords: all-cause mortality, body mass index, cardiovascular mortality, hemodialysis, waist-to-hip ratio

INTRODUCTION

Patients with end-stage renal disease (ESRD) receiving maintenance dialysis (MHD) are at high risk of developing cardiovascular disease (CVD) and death. Approximately 50% of deaths are attributed to CVD [1, 2]. Thus, it is important to investigate the modifiable risk factors associated with mortality in dialysis-dependent patients for which strategies for early identification and prevention can be formulated.

General obesity, as defined by body mass index (BMI) ≥30 kg/m^2, is a conventional risk factor for CVD and mortality in the general population [3]. By contrast, several studies have reported that a high BMI is related to better survival in MHD patients [4–7]. Although BMI is strongly correlated with percentage of body fat, it does not give a reliable assessment of body composition, and in particular does not reflect the distribution of body fat. Thus, the relationship between BMI and mortality risk does not reflect the detrimental effects of abdominal fat. Existing evidence has suggested that abdominal obesity [measured by waist-to-hip ratio (WHR)/waist circumference (WC)] may be better predicator of the risk of mortality than general obesity in the general population [8, 9]. However, studies are sparse that evaluate the association between abdominal obesity and the mortality risk in MHD patients. To our knowledge, only two cohort studies have assessed WHR with mortality risk in hemodialysis patients [10, 11]. Most cohort studies of BMI and WHR with mortality were conducted in European and American populations, which had a higher BMI (25–29 kg/m^2) than patients from Asian populations (21–22 kg/m^2), so their applicability to other populations is unclear [12, 13]. Besides, it has been suggested that the association of BMI and body fat differs in Asian populations compared with Western populations [14]. Therefore, there is an urgent need to investigate the association of WHR/WC with the risk of all-cause mortality and CVD mortality risk in Asian MHD patients. Furthermore, few studies have investigated the combined association of BMI and WHR with mortality risk in MHD patients. This question is especially meaningful to Asian populations where abdominal obesity may exist without general obesity [15, 16]. More importantly, the potential modifiers of the relationship between WHR and all-cause mortality have not been comprehensively investigated in previous studies.

To address the aforementioned knowledge gaps, we aimed to investigate the individual and combined association of BMI and WHR with the risk of all-cause and CVD mortality in Chinese adults undergoing hemodialysis. We also explored the potential modifiers of the association between WHR and mortality risk.

MATERIALS AND METHODS

Study population

The design of the study and some of the results have been reported elsewhere [17, 18]. Briefly, this was a multicenter prospective cohort study conducted from January 2014 to December 2015 in eight hemodialysis centers in Guangdong province in China. The study was established to assess nutritional status and its impact on the prognosis of patients receiving MHD. The study showed that dietary energy, protein and fiber intake are associated with mortality risk among MHD patients [17–19]. Inclusion criteria were as follows: male or female patients receiving MHD for more than 3 months, aged more than 18 years and with a normal oral dietary intake. Exclusion criteria included hyperthyroidism, acute infection, liver cirrhosis, multiple organ failure, serious gastrointestinal disease, cognitive disorder and advanced malignant tumor.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Medical Ethics Committee of Nanfang Hospital. Written informed consent was obtained from all patients.

Data collection and measurements

Baseline data were collected by trained research staff following a standard operating procedure. A standardized questionnaire designed for the present study was used to collect the following data: age, sex, occupation, education level, marital status, smoke status, alcohol use and medical history. Diabetes mellitus was defined as use of insulin, oral hypoglycemics agents or

medical history. Hypertension was defined as use of antihypertensive drugs or medical history. Cardiovascular disease was defined as history of myocardial infarction, congestive heart failure, transient ischemic attack, cerebrovascular accident or peripheral arterial disease.

Physical examination

Physical examination was conducted to measure body weight, height, and waist and hip circumference after a hemodialysis session when the patients were at dry weight according to the Kidney Disease Outcomes Quality Initiative guideline recommendations [20]. Waist and hip circumferences were measured with a nonstretchable tape according to the World Health Organization recommendations. Waist circumference was measured over the unclothed abdomen at the midpoint of the lower ribs and iliac crest in the midaxillary line and hip circumference was measured around the buttocks where the diameter is widest. All measurements were recorded to the nearest 0.1 cm. WHR was defined as waist circumference/hip circumference. BMI was calculated with the formula: BMI = weight/height squared (kg/m^2).

Laboratory evaluation

Blood samples were obtained prior to the hemodialysis session at baseline. Biochemical parameters, including serum albumin, blood urea nitrogen (BUN), C-reactive protein (CRP), triglyceride, total cholesterol (TC), calcium and phosphate, were measured at each local dialysis center following the same standard protocol. Kt/V were calculated using urea kinetic modeling formula: Kt/V = –ln (post-BUN/pre-BUN – 0.008 × t) + (4–3.5 × post-BUN/pre-BUN) × UF/post-weight, where t is effective dialysis time, BUN is blood urea nitrogen and UF is ultrafiltration.

Study outcomes

The primary outcome of interest was all-cause mortality and the secondary outcome was CVD mortality. CVD events contributing to CVD death included sudden cardiac death, myocardial infarction, heart failure, stroke, cardiovascular hemorrhage and death due to other known vascular causes. Evidence for death included the death certificates from hospitals or consensus from experts' comprehensive consideration if death occurred outside hospitals. Participants were followed up at each routine dialysis visit until July 2019, where vital signs and possible endpoint events were documented by trained research staff and physicians. All patients were followed until death, transfer to kidney transplantation, peritoneal dialysis, loss to follow-up or the end of study on June 2019.

Statistical analysis

Baseline characteristics were presented as means ± standard deviations (SDs) or medians (25th–75th) for continuous variables and frequencies (percentages) for categorical variables according to the classification of BMI [underweight (<18.5 kg/m^2), normal weight (18.5–23.9 kg/m^2), overweight (24–27.9 kg/m^2) and obesity (≥28 kg/m^2)] [21] and quartiles of WHR. Differences between the groups were tested using Chi-square tests or Fischer's exact test for categorical variables, ANOVA tests or Kruskal–Wallis tests for continuous variables as appropriate.

Multivariable Cox proportional hazards models were used to assess the association of BMI, WC and WHR with all-cause and CVD mortality. WHR and WC were analyzed as continuous variables (per SD increment) and quartiles variables. In Model 1, dialysis center, age, sex, smoke, alcohol intake, comorbidities (diabetes, hypertension, history of CVD) and BMI/WHR were adjusted. Model 2 included the same variables as Model 1 and prespecified factors including albumin, CRP, triglycerides, TC, calcium, phosphorus, hemoglobin, dialysis duration and Kt/V. In further analysis, we performed restricted cubic spline Cox regression, with four knots (20th, 40th, 60th and 80th percentiles of BMI or WHR), to test for linearity and explore the shape of the dose–response relationship between BMI or WHR and risk of all-cause and CVD mortality.

Possible modifiers of the association between BMI and WHR with the risk of all-cause and CVD mortality were assessed for variables including sex (male versus female), age (<60 versus ≥60 years), diabetes (yes versus no), history of CVD (yes versus no), albumin (<38 versus ≥38 g/L) and CRP (<8 versus ≥8 mg/L) levels at baseline.

In all analyses, a two-tailed $P < .05$ was considered statistically significant. All analyses were conducted using R software, version 4.0.2 (http://www.R-project.org).

RESULTS

Patient characteristics

The present study enrolled 1034 MHD patients with complete data of WHR and BMI (shown in Supplementary data, Fig. S1). Baseline characteristics by BMI levels are summarized in Table 1. Of the 1034 patients, 57.9% were male and the mean age was 54.1 years (SD 15.1). The mean values of BMI, WC and WHR were 21.2 ± 3.4 kg/m^2, 80.3 ± 10.4 cm and 0.90 ± 0.07, respectively. The percentages of underweight, normal weight, overweight and obese were 21.2%, 60.3%, 15.1% and 3.4%, respectively. Underweight patients had lower prevalence of diabetes, lower waist circumference and WHR, lower triglycerides, TC, phosphate and CRP levels, and tended to be younger and female (Table 1). Baseline WHR was positively associated with age, male gender, prevalence of diabetes and CVD, BMI, WHR, triglycerides, TC and CRP, and was inversely associated with serum albumin levels (Supplementary data, Table S1).

Relationship between BMI and the risk of outcomes

During the median follow-up period of 45.6 months, all-cause death occurred in 351 (33.9%) patients, of which 209 (20.2%) were due to CVD events.

Overall, a significant nonlinear inverse relationship was found between BMI and the risk of all-cause mortality (shown in Fig. 1A) (P for nonlinearity <.05). The risk of all-cause mortality was higher only in patients with relatively lower BMI. Compared with normal weight (18.5–23.9 kg/m^2), being underweight (BMI <18.5 kg/m^2) was associated with increased risk of all-cause mortality (HR 1.45; 95% CI 1.08–1.94). As no significant differences were found for the risk of all-cause mortality when comparing the overweight and obesity with the normal weight group, we redefined BMI as a binary variable with BMI ≥18.5 kg/m^2 as the reference group, and found similar results. Similarly, when compared with BMI ≥18.5 kg/m^2, those underweight had a significantly higher risk of CVD mortality (HR 1.46; 95% CI 1.00–2.14) (Fig. 1B; Table 2).

Relationship between waist circumference and the risk of outcomes

Overall, there was a positive association between WC and the risk of all-cause mortality (per SD increment, HR 1.43; 95% CI

Table 1: Baseline characteristics of the study participants according to BMI levels.

Variables	BMI (kg/m^2)				P
	<18.5	18.5–23.9	24–27.9	≥28	
N	219	624	156	35	
Age, years	48.8 ± 17.8	55.4 ± 14.2	56.4 ± 13.2	53.3 ± 13.7	<.001
Male, *n* (%)	98 (44.7)	383 (61.4)	99 (63.5)	19 (54.3)	<.001
Current smoking, *n* (%)	24 (11.0)	94 (15.1)	26 (16.7)	6 (17.1)	.367
Current alcohol drinking, n(%)	6 (2.7)	24 (3.8)	8 (5.1)	0 (0.0)	.414
Married, *n* (%)	180 (82.2)	578 (92.6)	150 (96.2)	33 (94.3)	<.001
Occupation, *n* (%)					.005
Farmer	1 (0.5)	17 (2.7)	3 (1.9)	0 (0.0)	
Worker	8 (3.7)	26 (4.2)	9 (5.8)	0 (0.0)	
Unemployed	123 (56.2)	272 (43.6)	57 (36.5)	13 (37.1)	
Other	87 (39.7)	309 (49.5)	87 (55.8)	22 (62.9)	
Education, *n* (%)					.180
Primary or below	55 (25.1)	188 (30.1)	56 (35.9)	7 (20.0)	
Middle school	72 (32.9)	192 (30.8)	50 (32.1)	10 (28.6)	
High school or above	92 (42.0)	244 (39.1)	50 (32.1)	18 (51.4)	
Comorbidities					
Diabetes, *n* (%)	26 (11.9)	175 (28.0)	59 (37.8)	17 (48.6)	<.001
Hypertension, *n* (%)	182 (83.1)	541 (86.7)	133 (85.3)	33 (94.3)	.279
History of CVD, n(%)	47 (21.5)	121 (19.4)	21 (13.5)	11 (31.4)	.061
Physical examination					
BMI, kg/m^2	17.1 ± 1.1	21.1 ± 1.5	25.5 ± 1.1	30.6 ± 2.0	<.001
WC, cm	69.5 ± 6.1	80.2 ± 7.4	91.3 ± 6.8	102.1 ± 8.4	<.001
WHR	0.86 ± 0.06	0.90 ± 0.06	0.95 ± 0.06	0.96 ± 0.07	<.001
Laboratory results					
Albumin, g/L	38.1 ± 3.9	38.0 ± 3.8	38.1 ± 3.8	38.8 ± 3.1	.681
Triglycerides, mmol/L	1.4 ± 0.8	1.8 ± 1.2	2.5 ± 1.6	3.6 ± 2.7	<.001
TC, mmol/L	4.0 ± 1.1	4.1 ± 1.1	4.3 ± 1.2	4.8 ± 1.6	<.001
Calcium, mmol/L	2.2 ± 0.3	2.2 ± 0.3	2.2 ± 0.3	2.2 ± 0.2	.393
Phosphate, mmol/L	2.0 ± 0.6	2.1 ± 0.7	2.2 ± 0.6	2.4 ± 0.6	.002
Uric acid, mg/dL	8.3 ± 2.0	8.5 ± 1.9	8.8 ± 1.7	8.8 ± 1.9	.072
Hemoglobin, g/L	108.6 ± 22.0	106.7 ± 21.0	108.0 ± 18.8	105.8 ± 17.2	.629
CRP, mg/L	1.8 (0.5–6.1)	2.3 (1.0–6.2)	5.0 (2.0–13.7)	7.2 (3.9–9.7)	<.001
Dialysis vintage, months	26.3 (12.4–55.1)	24.3 (12.3–49.6)	24.1 (12.4–52.2)	16.4 (10.5–38.9)	.378

Continuous variables are presented as mean (SD) or median (interquartile range); categorical variables are presented as number (percentage).

1.18–1.72) in male participants (Supplementary data, Table S2). Consistently, when WC was assessed as quartiles, a significantly higher risk of all-cause mortality (HR 2.13; 95% CI 1.43–3.17) was found in male participants in quartile 4 (≥88 cm) compared with those in quartiles 1–3 (<87.9 cm). Similar associations were found between WC and CVD mortality in male participants. However, among female participants, no significant associations were found between WC and all-cause mortality and CVD mortality.

Relationship between WHR and the risk of outcomes

WHR was positively associated with all-cause mortality in MHD patients (per SD increment, HR 1.13; 95% CI 1.00–1.27; Fig. 1C; Table 3). Consistently, analysis of WHR across quartiles showed that patients in quartile 4 (≥0.95) had a 1.31-fold higher risk of all-cause mortality compared with patients in quartiles 1–3 (<0.95: HR 1.31; 95% CI 1.03–1.67) (Table 3). Similarly, for per-SD increase in WHR, there was a 25% increase in CVD mortality (HR 1.25; 95% CI 1.09–1.43) (Fig. 1D; Table 3).

Moreover, additional analyses were performed separately in males and females to verify the association between WHR and all-cause and CVD mortality. The adjusted HRs of all-cause and CVD mortality for per-SD increase in WHR were 1.14 (95% CI 0.97–1.34) and 1.25 (95% CI 1.04–1.49) in males, and 1.11 (95% CI 0.92–1.32) and 1.24 (95% CI 0.97–1.57) in females, respectively. Similar results were obtained when WHR was analyzed as quartiles (Supplementary data, Table S3).

Combined association of BMI and WHR with outcomes

Compared with patients with higher BMI (≥18.5 kg/m^2) and lower WHR (quartiles 1–3: <0.95), those with higher BMI and higher WHR (HR 1.28; 95% CI 0.99–1.64), lower BMI and lower WHR (HR 1.40; 95% CI 1.03–1.90), and lower BMI and higher WHR (HR 2.05; 95% CI 1.09–3.86) had higher risk of all-cause mortality (Fig. 2A). Similar results were obtained for CVD mortality (Fig. 2B).

Stratified analyses

Stratified analyses were performed to further assess the relationship of WHR as a continuous variable (per-SD increment) and BMI as a binary variable (<18.5 kg/m^2 versus ≥18.5 kg/m^2) with the risk of all-cause in various subgroups.

None of the variables, including sex (male versus female), age (<60 versus ≥60 years), history of CVD (yes versus no), diabetes (yes versus no), CRP (<8 versus ≥8 mg/L) and albumin (<38 versus ≥38 g/L), significantly modified the association between BMI

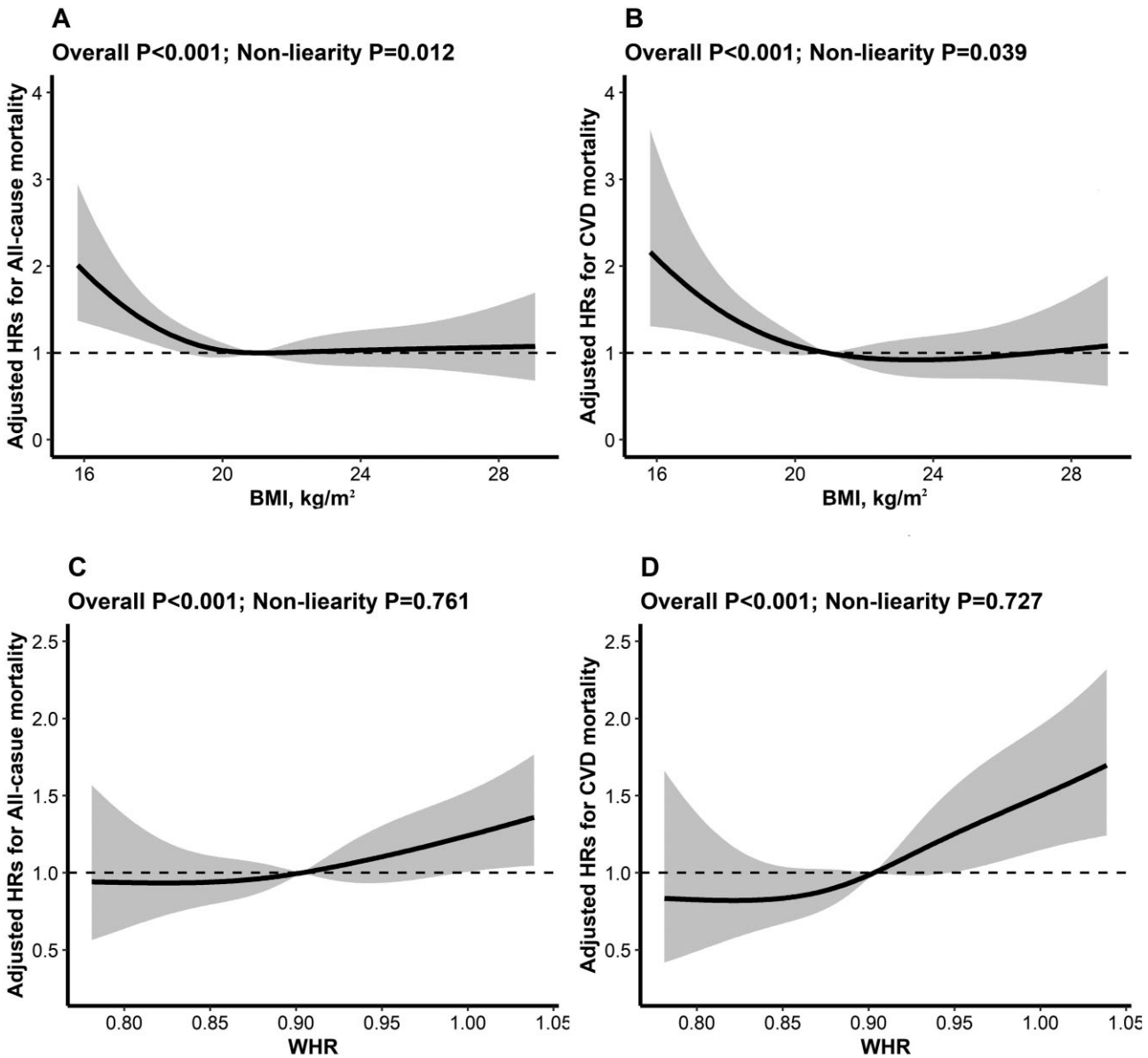

Figure 1: Relationship of BMI (**A**, **B**) and WHR (**C**, **D**) with risk of all-cause and CVD mortality based on restricted cubic splines*. *Adjusted for centers, age, sex, smoke, alcohol intake, diabetes, history of CD, hypertension, albumin, CRP, triglycerides, TC, calcium, phosphorus, hemoglobin, dialysis duration, Kt/V, and WHR or BMI.

and all-cause mortality (P for interaction >.05) (Supplementary data, Fig. S2).

None of these variables significantly modified the relationship between WHR and all-cause mortality (Supplementary data, Fig. S3).

DISCUSSION

Our study is the first prospective study to evaluate the individual and combined association of BMI and WHR on mortality risk in MHD patients with relatively low BMI levels. We observed that there was a nonlinear inverse relationship between BMI with all-cause and CVD mortality, and the risk of mortality was higher only in the underweight patients; WHR was positively and independently associated with increased all-cause and CVD mortality risk. Moreover, when BMI and WHR were considered together, the patients with higher BMI (≥18.5 kg/m^2) and lower WHR (<0.95) had the lowest risk of all-cause and CVD mortality, while the patients with lower BMI (<18.5 kg/m^2) and higher WHR (≥0.95) had the highest risk of all-cause mortality. Thus, measurement of both general and central obesity provides a better assessment of the mortality risk.

Several studies have assessed the relationship of BMI and mortality risk in MHD patients. A recent meta-analysis reported a linear and inverse relationship of BMI with all-cause mortality (per 1 kg/m^2 increase, HR 0.97; 95% CI 0.96–0.98) and CVD mortality (per 1 kg/m^2 increase, HR 0.96; 95% CI 0.92–1.00) in ESRD patients [4]. A large retrospective cohort study revealed that BMI exceeding 30 kg/m^2 was associated with better survival (HR 0.89; 95% CI 0.81–0.99) [22]. However, we found a nonlinear inverse relationship of BMI with the risk of all-cause and CVD mortality in MHD patients. There was a strong association of mortality risk

Table 2: The relationship between BMI and outcomes in MHD patients.

		Adjusted 1[a]		Adjusted 2[b]	
BMI (kg/m^2)	No. of events (%)	HR (95% CI)	P	HR (95% CI)	P
All-cause mortality					
Clinical cut-off categories					
<18.5	72 (32.9)	1.47 (1.10–1.96)	.008	1.45 (1.08–1.94)	.012
18.5–23.9	212 (34.0)	Ref		Ref	
24–27.9	56 (35.9)	0.93 (0.69–1.27)	.662	0.96 (0.70–1.31)	.778
≥28	11 (31.4)	0.93 (0.50–1.73)	.822	1.19 (0.62–2.26)	.603
Clinical cut-off categories					
<18.5	72 (32.9)	1.49 (1.12–1.97)	.006	1.45 (1.09–1.94)	.011
≥18.5	279 (34.2)	Ref		Ref	
CVD mortality					
Clinical cut-off categories					
<18.5	41 (18.7)	1.44 (0.99–2.10)	.055	1.41 (0.96–2.07)	.076
18.5–23.9	128 (20.5)	Ref		Ref	
24–27.9	33 (21.2)	0.88 (0.59–1.30)	.508	0.91 (0.61–1.37)	.655
≥28	7 (20.0)	0.91 (0.42–1.98)	.805	1.20 (0.54–2.67)	.661
Clinical cut-off categories					
<18.5	41 (18.7)	1.47 (1.02–2.13)	.041	1.46 (1.00–2.14)	.049
≥18.5	168 (20.6)	Ref		Ref	

[a]Adjusted for centers, age, sex, smoke, alcohol intake, marital status, occupation, education level, diabetes, history of CVD, hypertension and WHR.
[b]Adjusted for Model 1 + albumin, CRP, triglycerides, TC, calcium, phosphorus, hemoglobin, dialysis duration and Kt/V.

Table 3: The relationship between WHR and outcomes in MHD patients.

			Adjusted 1[a]		Adjusted 2[b]	
WHR	N	No. of events (%)	HR (95% CI)	P	HR (95% CI)	P
All-cause mortality						
Continuous (per SD increment)	1034	351 (33.9)	1.16 (1.03–1.30)	.015	1.13 (1.00–1.27)	.043
Quartiles						
Q1 (<0.86)	259	57(22.0)	Ref		Ref	
Q2 (0.86–0.90)	258	79 (30.6)	1.15 (0.81–1.64)	.421	1.06 (0.74–1.51)	.748
Q3 (0.90–0.95)	259	94 (36.3)	1.09 (0.78–1.56)	.623	1.06 (0.74–1.52)	.730
Q4 (≥0.95)	258	121 (46.9)	1.45 (1.02–2.08)	.041	1.38 (0.96–1.98)	.081
Categories						
Q1–Q3 (<0.95)	776	230 (29.6)	Ref		Ref	
Q4 (≥0.95)	258	121 (46.9)	1.33 (1.04–1.69)	.022	1.31 (1.03–1.67)	.028
CVD mortality						
Continuous (per SD increment)	1034	209 (20.2)	1.27 (1.11–1.46)	<.001	1.25 (1.09–1.43)	.001
Quartiles						
Q1 (<0.86)	259	29 (11.2)	Ref		Ref	
Q2 (0.86–0.90)	258	48 (18.6)	1.45 (0.90–2.33)	.124	1.34 (0.83–2.16)	.235
Q3 (0.90–0.95)	259	50 (19.3)	1.22 (0.74–1.99)	.434	1.20 (0.73–1.97)	.469
Q4 (0.95–1.40)	258	82 (31.8)	2.11 (1.30–3.40)	.002	2.09 (1.29–3.39)	.003
Categories						
Q1–Q3 (<0.95)	776	127 (16.4)	Ref		Ref	
Q4 (0.95–1.40)	258	82 (31.8)	1.69 (1.24–2.29)	<.001	1.73 (1.27–2.36)	<.001

[a]Adjusted for centers, age, sex, smoke, alcohol intake, marital status, occupation, education level, diabetes, history of CVD, hypertension and BMI.
[b]Adjusted for Model 1 + albumin, CRP, triglycerides, TC, calcium, phosphorus, hemoglobin, dialysis duration and Kt/V.

with low BMI but no association with extreme weight. This discrepancy may be partly explained by the racial differences in the association of BMI and mortality [23]. Studies have suggested that the obesity paradox is more consistent in African American patients receiving hemodialysis compared with other racial-ethnic groups [24]. Consistently, Johansen *et al.* found that high BMI was associated with increased survival in Whites, African Americans and Hispanics, but not in Asians [25].

Few studies have examined the association of WC/WHR with all-cause and CVD mortality in MHD patients. A prospective cohort study including 537 ESRD patients found that WC and WHR were related to all-cause mortality (WC: per 10 cm increase, HR 1.23; 95% CI 1.02–1.47; WHR: per 0.1 increase, HR 1.24; 95% CI 1.06–1.46) and CVD mortality (WC: HR 1.37; 95% CI 1.09–1.73; WHR: HR 1.21; 95% CI 0.98–1.50) [10]. In a study covering 379 incident hemodialysis participants (<6 months), Fitzpatrick *et al.* demonstrated that WHR was significantly associated with CVD mortality (every 0.1 increase, HR 1.75; 95% CI 1.06–2.86) [11]. However, these two studies were conducted in Western populations with higher BMI than Asian populations, so the association of

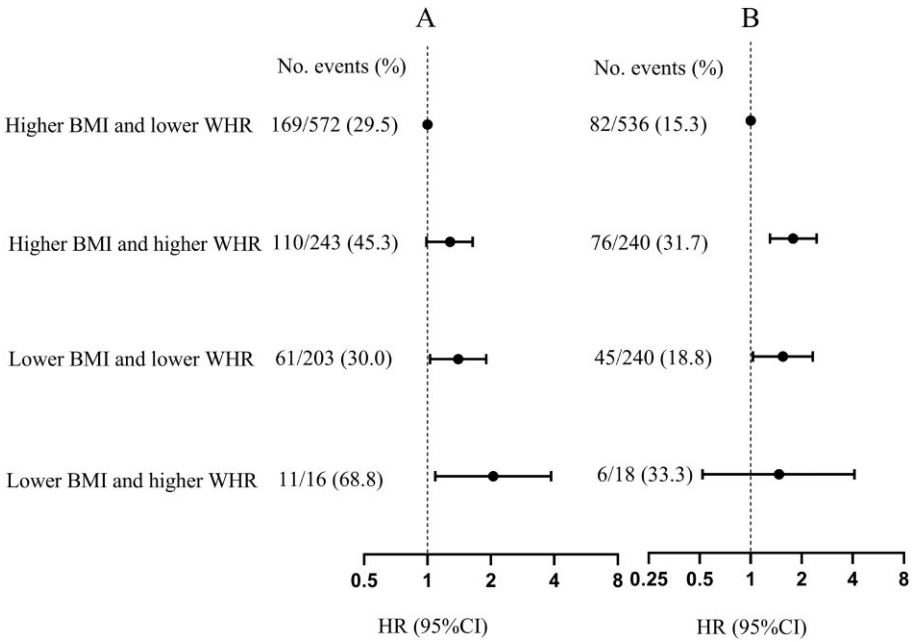

Figure 2: Joint association of BMI and WHR with all-cause (**A**) and CVD mortality (**B**)*. *Adjusted for centers, age, sex, smoke, alcohol intake, diabetes, history of CVD, hypertension, albumin, CRP, triglycerides, TC, calcium, phosphorus, hemoglobin, dialysis duration and Kt/V.

WC/WHR with mortality in Asian MHD patients with relatively low BMI remained uncertain. In our current study, we reported a positive relationship between WHR and all-cause and CVD mortality in Chinese MHD patients. Mechanistically, higher WHR is associated with higher visceral adipose tissue, which is more pathogenic than subcutaneous tissue [25]. Multiple studies have demonstrated that visceral adipose tissue is metabolically active, secreting some mediators such as adipocytokins, markers of hemostasis and fibrinolysis, and growth factors, which may contribute to the development of cardiometabolic diseases and increase the risk of death [26]. In addition, increased abdominal adiposity has been linked to systemic inflammation [27, 28], oxidative stress [29], insulin resistance [30], metabolic syndrome [31] and endothelial dysfunction [32], all of which contribute to poor outcomes.

According to our study, there was a gender difference in the association between WC and the risk of mortality. We found that WC was associated with all-cause and CVD mortality risk in males but not in females, which may be due to the sex difference in body fat distribution [33]. Women have larger stores of subcutaneous fat, while men are more likely to deposit visceral fat, which is associated with adverse outcomes [33]. It has been reported that women have more subcutaneous abdominal fat than men for a given WC [34]. However, more studies are needed to verify our results and further examine the detailed mechanisms.

Furthermore, the present study evaluated the combined association of BMI and WHR with all-cause and CVD mortality in MHD patients. A previous study found that the incidence rate of overall and CVD death was highest in patients with relatively lower BMI (less than median) and higher waist circumferences (at least median) and lowest in patients with higher BMI (at least median) and small waist circumferences (less than median) [10]. However, this study only reported the crude incidence rate of mortality and did not provide HRs of mortality after adjustment for major traditional risk factors. Our study also confirmed that MHD patients with low BMI and high WHR had the highest all-cause and CVD mortality risk. These findings suggest that both general and abdominal fat measurements provide a better assessment of the risk of adverse outcomes in MHD patients.

Our study has several strengths. First, it is a multicenter prospective cohort with long observational period and full adjustment for multiple CVD factors. Second, it is the first study to evaluate the individual and combined association of BMI and WHR with all-cause and CVD mortality risk in MHD patients with relatively low BMI. However, there are also some limitations that should be considered. First, we did not perform machine-based assessments of abdominal fat such as magnetic resonance imaging, computed tomography or dual energy X-ray absorptiometry. Given that these tools are extremely costly and complicated, they are not feasible for large-scale epidemiological studies and for routine clinical use. WHR is a simple, cheap and easy anthropometric index for evaluating abdominal fat, and has been validated in several populations. Second, only baseline data were collected, hence we did not take into consideration the changes in WHR during follow-up. Third, this study was conducted in the south of China, where the population has a relatively lower BMI level. Therefore, the effects of extremely high BMI on survival remained to be studied.

CONCLUSIONS

In summary, our results suggest that BMI is inversely related to all-cause and CVD mortality, whereas a higher WHR, reflecting abdominal obesity, is associated with increased all-cause and CVD mortality risk in patients receiving MHD. Moreover, patients with higher BMI and lower WHR had the lowest risk of all-cause and CVD mortality. Thus, comprehensive consideration of BMI and WHR is of great significance to the assessment and improvement of the prognosis of patients undergoing MHD.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be available from the corresponding author upon request, after the request is submitted and formally reviewed and approved by the Medical Ethics Committee of Nanfang Hospital.

CONFLICT OF INTEREST STATEMENT

None declared.

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