ORIGINAL RESEARCH

The influence of sex on the prognostic value of body mass index in non-metastasis renal cell carcinoma

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Purpose: The prognostic value of obesity in patients with renal cell carcinoma (RCC) remains controversial. This study aimed to assess the sex-dependent prognostic role of body mass index (BMI) in patients with nonmetastatic RCC who underwent radical or partial nephrectomy.

Patients and methods: We retrospectively analyzed 643 consecutive patients with nonmetastatic RCC who underwent curative nephrectomy in our center between 2004 and 2014. Associations among BMI, sex, overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS) were analyzed.

Results: Males were more likely to have a higher BMI than females (BMI as a categorical variable: $P<0.001$; BMI as a continuous variable: $P=0.002$). In men, a high BMI was significantly correlated with better 5-year OS, CSS, and MFS rates ($P=0.001$, 0.014, and 0.001, respectively), and multivariate analysis identified that a high BMI was independently associated with greater OS, CSS, and MFS (OS: hazard ratio [HR]=0.207, $P=0.011$; CSS: HR=0.225, $P=0.005$; MFS: HR=0.243, $P=0.004$). However, in women, there was no significant difference in 5-year OS, CSS, and MFS rates according to BMI ($P=0.781$, 0.812, and 0.538, respectively). Moreover, a high BMI was no longer independently associated with OS, CSS, or MFS ($P=0.821$, 0.832, and 0.801, respectively). Among patients with clear cell RCC, BMI was significantly associated with OS, CSS, and MFS only among men (all $P<0.05$) and not among women (all $P>0.05$).

Conclusion: Among patients with nonmetastatic RCC, a high BMI was a favorable prognostic factor in males rather than females. Therefore, sex might influence the correlation between obesity and urological outcomes in nonmetastatic RCC.

Keywords: renal cell carcinoma, body mass index, prognosis, sex

Introduction

Renal cell carcinoma (RCC) is one of most common malignant tumors of the kidney; its global incidence has increased by about 2% in the last two decades.[1–3] In 2008, the numbers of new cases and kidney-cancer related deaths worldwide were approximately 27,400 and 117,000, respectively.[4] In Asia, the number of cases of kidney cancer per 100,000 person years in Japan, Singapore, Hong Kong, Shanghai (China), and India was 6.5, 4.3, 3.8, 2.9, and 2.0, respectively, showing Japan as having the highest incidence.[5] Furthermore, the urological outcomes of RCC patients who underwent curative surgery were not favorable, with approximately 30% of patients experiencing local or distant recurrence.[3] Therefore, an increasing number of researchers focus on identifying and evaluating prognostic factors to categorize patients with worse prognosis at early time-points.

Obesity, as characterized by body mass index (BMI), is a well-known risk factor for RCC,[6] and the relative risks of RCC increase consistently with obesity in a dose-response manner.[7] However, the prognostic value of obesity in RCC patients remains a controversy, with some studies even demonstrating contradictory findings. Some researchers reported no significant relationship between obesity and urological outcomes in RCC,[8–10] while some others argued that obesity is an independent predictor of prognosis.[11,12] Furthermore, a previous study demonstrated a nonlinear association between obesity and RCC prognosis.[13] This phenomenon was called the "obesity paradox".[14] Therefore, we hypothesized that the significance of obesity in RCC prognosis might be influenced by some factor(s).

A recent study found that a higher BMI is significantly associated with increased risk of RCC among men, but not among women,[15] suggesting that the relationship between obesity and urological outcomes in RCC might be sex-specific. However, to date, only few studies have reported the prognostic role of obesity in RCC patients according to sex, and the results were conflicting.[10,16,17] Therefore, this present study aimed to evaluate the sex-dependent role of BMI in predicting the survival outcomes of patients with nonmetastatic RCC who underwent radical or partial nephrectomy.

Patients and methods
Patients

After obtaining institutional review board approval, we retrospectively reviewed 803 consecutive patients with nonmetastatic RCC (pathological T1-4N0M0) following radical or partial nephrectomy between January 2004 and July 2014 at the First Affiliated Hospital of Wenzhou Medical University. The following were excluded from the study: patients with kidney transplantation before surgery, with only one kidney, or with hemodialysis therapy (n=29); patients with a history of any cancer, bilateral RCC, or prior surgery for RCC (n=51); and patients with BMI<18.5 kg/m^2 (n=29). Patients with incomplete preoperative medical information were also excluded (n=51) (Figure 1). In addition, neoadjuvant chemotherapy was not performed in any patients preoperatively. Finally, 643 patients were included for analysis.

Variables

The clinicopathological characteristics of patients according to sex are shown in Table 1. These variables were
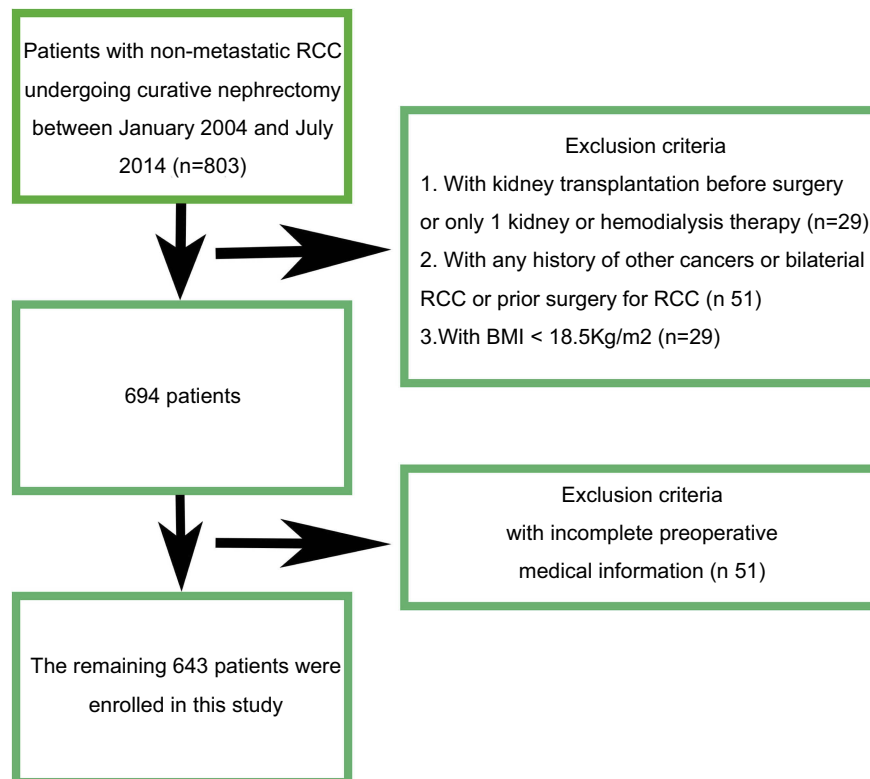

Figure 1 The patient selection flowchart.
Abbreviations: BMI, body mass index; RCC, renal cell carcinoma.

Table 1 Patient characteristics

Variables	All (n=643)	Male (n=414)	Female (n=229)	*P*-value
Age (>65 vs ≤65 years)	270/373	178/236	92/137	0.488
ASA grade (≥3 vs <3)	44/599	28/386	16/213	0.914
BMI, Kg/m^2				
(1) Mean ± SD, Kg/m^2	23.4(2.8)	23.8(2.7)	22.8(2.9)	**<0.001***
(2) High vs normal BMI	160/483	119/295	41/188	**0.002***
DM (Yes vs No)	218/425	144/270	74/155	0.527
Hypertension (Yes vs No)	271/372	185/229	86/143	0.079
Anemia (Yes vs No)	93/550	51/363	42/187	**0.038***
Surgical approach				0.193
Partial nephrectomy	139	96	43	
Radical nephrectomy	504	318	186	
CKD stage				0.147
CKD 1	424	265	159	
CKD 2	174	124	50	
CKD 3	31	17	14	
CKD 4	5	2	3	
CKD 5	9	6	3	
Pathologic stage				0.075
pT1	499	324	175	
pT2	75	40	35	
pT3	61	43	18	
pT4	8	7	1	
Fuhrman grade				0.851
1	201	130	71	
2	277	174	103	
3	146	98	48	
4	19	12	7	
Histologic subtype				**<0.001***
Clear cell	562	367	195	
Papillary	40	30	10	
Chromophobe	37	13	24	
Collecting duct	1	1	0	
Unclassified	3	3	0	
Clear cell vs non-clear cell	562/81	47/367	34/195	0.201
Tumor necrosis (Yes vs No)	22/621	15/399	7/222	0.705
Tumor size (≥7 vs <7 cm)	112/531	67/347	45/184	0.267
Follow-up duration, months, median (IQR)	51.2(30.5–86.4)	48.2(30.1–82.9)	56.3(31.2–92.7)	0.088
All –cause death, n(%)	57 (8.9)	43(10.4)	14(6.1)	0.093
Cancer-specific death, n(%)	39(6.1)	25(6.0)	14(6.1)	0.970
Metastasis, n(%)	71(11.0)	54(13.0)	17(7.4)	**0.029***

Note: *Statistically significant.
Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range; DM, diabetes mellitus; CKD, chronic kidney disease.

Table 2 Multivariate analysis of variables for the prediction of OS in all patients

Variables	BMI as categorical variable			BMI as continuous variable		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (>65 vs ≤65 years)	3.359	1.716–6.575	**<0.001***	4.781	2.303–9.931	**<0.001***
Gender (men vs women)	1.935	1.026–3.649	**0.042***	2.066	1.023–4.173	**0.043***
ASA grade (≥3 vs <3)	1.577	0.778–3.199	0.207	1.955	0.813–4.702	0.134

BMI, Kg/m^2
  (1) Category: ≥25 vs <25
  (2) Continuous
	0.326
	
	-
		0.126–0.842
		
		-
			0.021*	
				
				0.857
					-
					
					0.747–982
						
						0.027*

Anemia (Yes vs No)	1.806	1.004–3.246	**0.048***	2.341	1.146–4.784	**0.020***
Surgical approach (partial vs radical)	0.831	0.318–2.175	0.706	0.600	0.214–1.678	0.330

CKD stage
  CKD 1
  CKD 2–3 vs CKD 1
  CKD 4–5 vs CKD 1
	1.000
	1.572
	5.544
		Reference
		0.889–2.782
		1.746–17.605
			1.000
			0.120
			0.004*
				1.000
				1.639
				1.695
					Reference
					0.854–3.147
					0.386–7.446
						1.000
						0.138
						0.485

Pathologic stage
  pT1
  pT2 vs pT1
  pT3 vs pT1
  pT4 vs pT1
	1.000
	1.793
	2.211
	3.789
		Reference
		0.710–4.531
		0.997–4.900
		0.686–20.926
			1.000
			0.217
			0.051
			0.006*
				1.000
				2.200
				1.988
				2.847
					Reference
					0.723–6.691
					0.780–5.067
					0.333–24.305
						1.000
						0.165
						0.150
						0.009*

Fuhrman grade (≥3 vs <3)	1.953	1.112–3.431	**0.020***	2.312	1.232–4.336	**0.009***
Tumor necrosis (yes vs no)	1.916	0.670–5.486	0.225	1.728	0.467–6.398	0.413
Tumor size (≥7 vs <7)	1.593	0.703–3.608	0.265	1.457	0.552–3.849	0.448

Note: *Statistically significant.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; OS, overall survival.

retrospectively obtained from a prospectively maintained computer database at our center. BMI was measured before surgery and categorized as normal BMI (<25 kg/m^2) and high BMI (≥25 kg/m^2; obesity).[18–20] The T stage and histological subtype of tumors were determined based on the seventh edition of the TNM classification by the Union for International Cancer Control, the guidelines by the American Joint Committee on Cancer, and the Heidelberg recommendations. Nuclear grade was evaluated using the Fuhrman grading system. Tumor size was defined as the largest diameter of the tumor according to the pathological report. The pathological features of tumors were evaluated by urological pathologists. Postoperative follow-up care consisted of blood and urine tests, and chest and abdominal computed tomography or magnetic resonance imaging every 3 to 6 months for the first 2 years and annually thereafter. The follow-up cutoff was September 1, 2016. Overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS) were calculated from the date of surgery to the (a) date of death from any cause, (b) date of cause-specific death, and (c) date of the last follow-up of recurrence of radiologically or histologically confirmed distant metastasis, respectively.

Statistical analysis

All statistical analyses were performed using SPSS software package version 25.0 (IBM, Armonk, NY). All *P*-values were two-tailed, and *P*<0.05 was considered statistically significant. Relationships between patients' clinicopathological characteristics and sex were compared using Student's test for continuous variables and Pearson's chi-square test for categorical variables. Trends of variables for different BMIs were analyzed using the Cochran-Armitage test. OS, CSS, and MFS rates were estimated using the Kaplan-Meier method stratified according to BMI for all patients, men, and women. The prognostic values of BMIs as categorical and continuous variables were evaluated using univariate

analysis and multivariate Cox regression analysis. Other variables were also analyzed, including age, American Society of Anesthesiologists (ASA) grade, diabetes mellitus (DM), hypertension, anemia, surgical approach, chronic kidney disease (CKD) stage, pathological stage, Fuhrman grade, histological subtype, tumor necrosis, and tumor size. Additionally, variables with $P<0.1$ in the univariate analysis were included in the multivariate model.

Results

Associations between BMI, sex, and clinical and pathological characteristics

Table 1 shows the associations of clinical and pathological factors with sex. Overall, there were 414 (64.4%) males and 229 (35.6%) females, with a male-to female ratio of 1.81:1. The mean age of this cohort was 61.59 (standard deviation, 12.67) years, and the median follow-up duration was 51.2 (interquartile range, 30.5–86.4) months. There were no significant differences between men and women according to age and follow-up duration ($P=0.488$ and $P=0.088$, respectively). Men were more likely to have significantly higher BMI than women ($P<0.05$). Furthermore, the BMI in men significantly decreased with ageing ($r=-0.028$, $P=0.006$) (Figure 2A); however, BMI in women tended to increase with age ($r=0.007$, $P=0.656$) (Figure 2B). In addition, men were more likely to be anemia and had higher risk of metastasis ($P=0.038$ and $P=0.029$, respectively).

Overall survival according to BMI and sex

During the follow-up, 57 (8.9%) patients died (Table 1). In all population, the 5-year OS rates were 88.7% and 97.8% in patients with normal BMI and high BMI, respectively ($P=0.004$) (Figure 3A). BMI was identified as an independent favorable factor of OS (BMI as a categorical variable: HR=0.326, $P=0.021$; BMI as a continuous variable: HR=0.857, $P=0.027$) through univariate analysis and multivariate analysis (Tables S1–S3, Table 2, and Figure 4A and B). In men, the 5-year OS rates were 85.5% and 98.1% in patients with normal BMI and high BMI, respectively ($P=0.001$) (Figure 3B). BMI was also identified as an independent favorable factor of OS in men (BMI as a categorical variable: HR=0.207, $P=0.011$; BMI as a continuous variable: HR=0.805, $P=0.012$) according to univariate analysis and multivariate analysis (Table 3, and Figure 4). However, in women, there was no significant difference between normal BMI patients and high BMI patients with 93.3% and 91.8% 5-year OS rates, respectively ($P=0.781$) (Figure 3C). Furthermore, BMI was not an independent predictor of OS in women (BMI as a categorical variable: HR=1.201, $P=0.821$; BMI as a continuous variable: HR=0.990, $P=0.934$) (Table 3, and Figure 4).

CSS according to BMI and sex

During the follow-up, 39 (6.1%) patients died due to RCC (Table 1). In all population, the 5-year CSS rates were 91.6% and 97.3% in patients with normal BMI and high BMI, respectively ($P=0.029$) (Figure 5A). BMI was identified as an independent favorable factor of CSS (BMI as a categorical variable: HR=0.425, $P=0.019$; BMI as a continuous variable: HR=0.891, $P=0.047$) using univariate analysis and multivariate analysis (Table S2, Tables 4 and 5, and Figure 6). In men, the 5-year CSS rates were 90.4% and 99.1% in patients with normal BMI and high BMI, respectively ($P=0.014$) (Figure 5B). BMI was also identified as an independent favorable factor of CSS in men (BMI as a categorical variable: HR=0.225, $P=0.005$; BMI as a continuous variable:
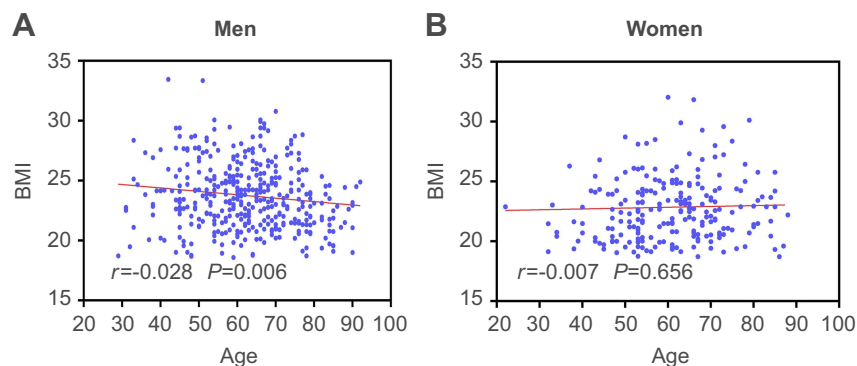

Figure 2 Correlation between age and BMI. The BMI in men significantly decreased when they were ageing (**A**); however, the BMI in women increased with increasing age while the relationship was not significant (**B**).
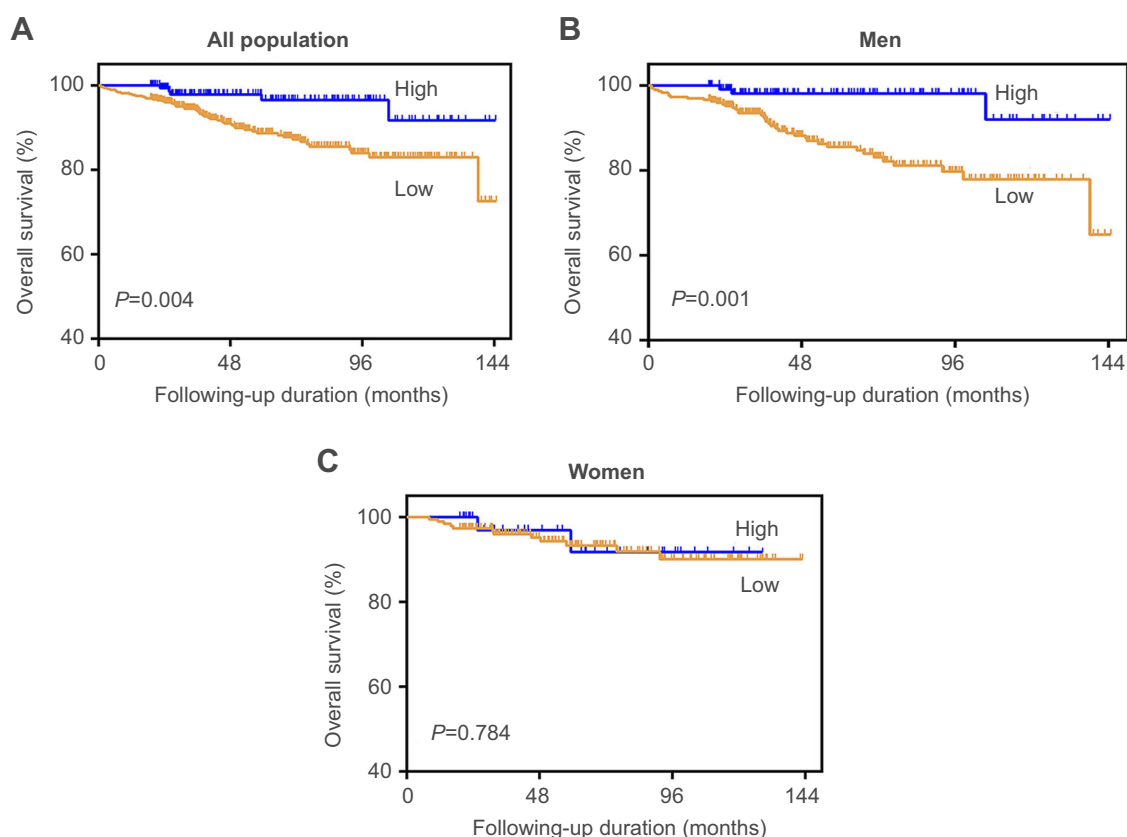**Abbreviation:** BMI, Body mass index.

Figure 3 Kaplan-Meier curves for overall survival stratified by BMI in all patients (**A**), male patients (**B**), and female patients (**C**) with non-metastasis RCC.
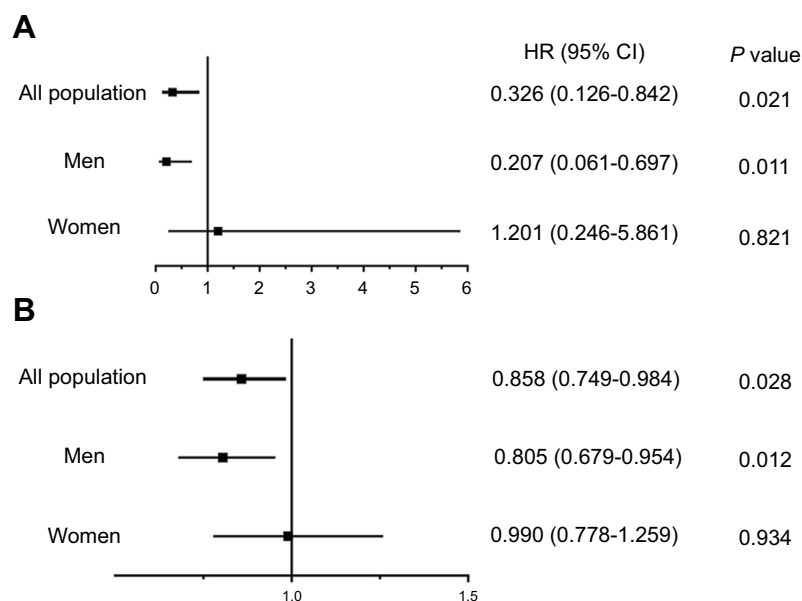**Abbreviations:** BMI, body mass index; RCC, renal cell carcinoma.

Figure 4 HRs and 95% CIs for overall survival by BMI as categorical variable (**A**) or continuous variable (**B**).
Abbreviation: BMI, body mass index.

HR=0.817, *P*=0.027) according to univariate analysis and multivariate analysis (Table 5, and Figure 6). Nevertheless, in women, the 5-year CSS rates were 93.3% and 91.8% in patients with normal BMI and high BMI, respectively. There was no significant difference between the two groups (*P*=0.812) (Figure 5C), and BMI was not an independent

Table 3 The significance of BMI for the prediction of OS using multivariate analysis by sex

Sex	BMI as categorical variable				BMI as continuous variable		
		HR	95%CI	*P*-value	HR	95%CI	*P*-value
All	High vs normal BMI	0.326	0.126–0.842	**0.021***	0.858	0.749–0.984	**0.028***
Men	High vs normal BMI	0.207	0.061–0.697	**0.011***	0.805	0.679–0.954	**0.012***
Women	High vs normal BMI	1.201	0.246–5.861	0.821	0.990	0.778–1.259	0.934

Note: *Statistically significant.
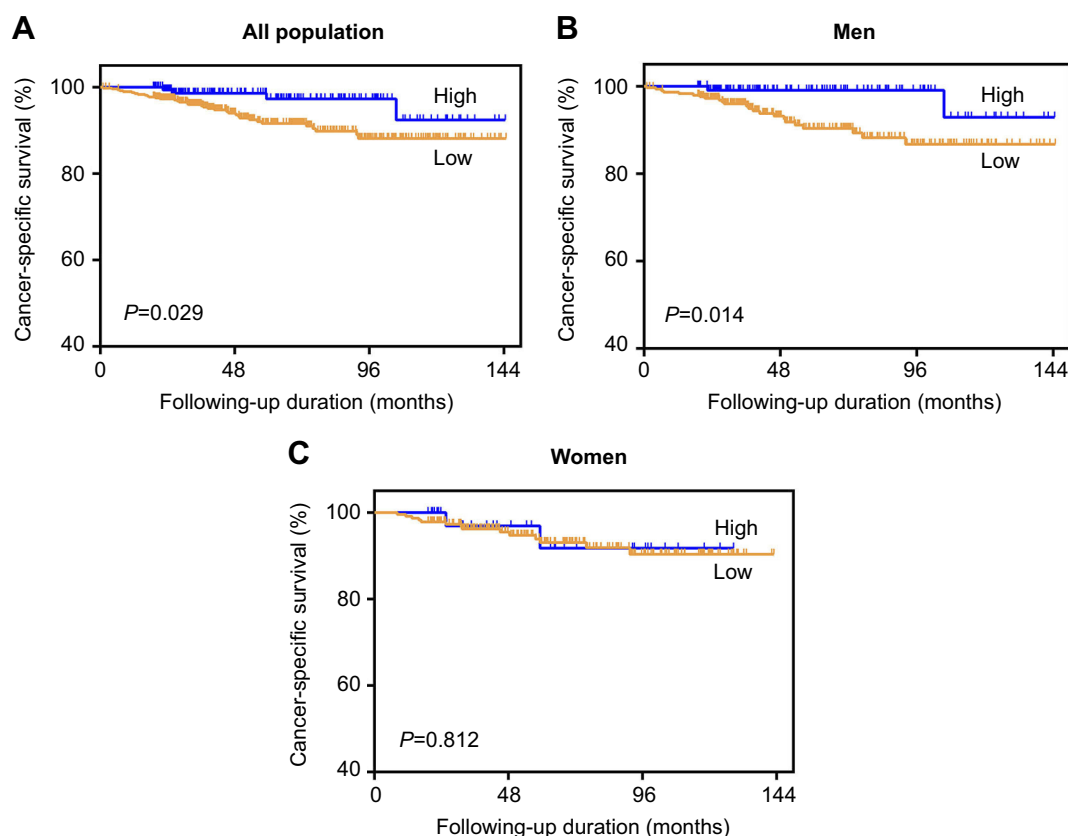**Abbreviations:** BMI, body mass index; OS, overall survival.

Figure 5 Kaplan-Meier curves for cancer-specific survival stratified by BMI in all patients (**A**), male patients (**B**), and female patients (**C**) with non-metastasis RCC.
Abbreviations: BMI, body mass index; RCC, renal cell carcinoma.

factor of CSS in women (BMI as a categorical variable: HR=1.193, *P*=0.832; BMI as a continuous variable: HR=0.990, *P*=0.934) (Table 5 and Figure 6A and B).

MFS according to BMI and sex

During the follow-up, 71 (11.0%) patients experienced metastasis (Table 1). In all population, the 5-year MFS rates were 85.7% and 96.6% in patients with normal BMI and high BMI, respectively (*P*=0.002) (Figure 7A). BMI was identified as an independent favorable factor of MFS (BMI as a categorical variable: HR=0.331, *P*=0.007; BMI as a continuous variable: HR=0.895, *P*=0.047) using univariate analysis and

multivariate analysis (Table S3, Tables 6 and 7, and Figure 8). In men, the 5-year MFS rates were 90.4% and 99.1% in patients with normal BMI and high BMI, respectively (*P*=0.001) (Figure 7B). BMI was also identified as an independent favorable factor of MFS in men (BMI as a categorical variable: HR=0.243, *P*=0.004; BMI as a continuous variable: HR=0.865, *P*=0.044) according to univariate analysis and multivariate analysis (Table 7, and Figure 8). Nevertheless, in women, the 5-year MFS rates were 93.3% and 91.8% in patients with normal BMI and high BMI, respectively. There was no significant difference between the two groups (*P*=0.538) (Figure 7C), and BMI was not an independent

Table 4 Multivariate analysis of variables for the prediction of CSS in all patients

Variables	BMI as categorical variable			BMI as continuous variable		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (>65 vs ≤65 years)	3.191	1.460–6.977	**0.004***	4.121	1.767–9.610	**0.001***
ASA grade (≥3 vs <3)	1.649	0.698–3.896	0.255	2.031	0.735–5.611	0.172

BMI, Kg/m^2
  (1) Category: ≥25 vs <25
  (2) Continuous
	0.425	0.145–1.245
		-
			0.019*	0.891	-
					0.762–1.043
						0.047*

Anemia (yes vs no)	1.505	0.742–3.052	0.257	1.795	0.784–4.113	0.166
Surgical approach (partial vs radical)		-		0.599	0.166–2.168	0.435

CKD stage
  CKD 1
  CKD 2–3 vs CKD 1
  CKD 4–5 vs CKD 1
	1.000
	1.998
	2.033
		Reference
		1.013–3.943
		0.255–16.192
			1.000
			0.046*
			0.503
				1.000
				2.152
				0.518
					Reference
					0.998–4.639
					0.053–5.064
						1.000
						0.051
						0.571

Pathologic stage
  pT1
  pT2 vs pT1
  pT3 vs pT1
  pT4 vs pT1
	1.000
	1.610
	2.752
	6.593
		Reference
		0.542–4.778
		1.078–7.028
		1.102–39.426
			1.000
			0.391
			0.034*
			0.039*
				1.000
				1.693
				2.380
				4.507
					Reference
					0.497–5.764
					0.834–6.788
					0.521–38.995
						1.000
						0.399
						0.105
						0.171

Fuhrman grade (≥3 vs <3)	2.854	1.439–5.662	**0.003***	3.073	1.465–6.446	**0.003***
Tumor necrosis (yes vs no)	2.661	0.906–7.818	0.075	2.625	0.681–10.123	0.161
Tumor size (≥7 vs <7)	2.403	0.943–6.123	0.066	2.537	0.888–7.247	0.082

Note: *Statistically significant.
Abbreviations: BMI, body mass index; CSS, cancer-specific survival; CKD, chronic kidney disease.

Table 5 The significance of BMI for the prediction of CSS using multivariate analysis by sex

Sex	BMI as categorical variable				BMI as continuous variable		
		HR	95%CI	*P*-value	HR	95%CI	*P*-value
All	High vs normal BMI	0.425	0.145–1.245	**0.019***	0.891	0.762–1.043	**0.047***
Men	High vs normal BMI	0.225	0.049–1.034	**0.005***	0.817	0.658–1.014	**0.027***
Women	High vs normal BMI	1.193	0.234–6.071	0.832	0.990	0.778–1.259	0.934

Note: *Statistically significant.
Abbreviations: BMI, body mass index; CSS, cancer-specific survival.

factor of MFS in women (BMI as a categorical variable: HR=0.820, *P*=0.801; BMI as a continuous variable: HR=0.926, *P*=0.504) (Table 7 and Figure 8A and B).

Associations between BMI, sex, and urological outcomes in patients with clear cell RCC

As shown in Table 8, there were 367 (65.3%) males and 195 (34.7%) females, with a male-to-female ratio of 1.88:1. Men were more likely to have significantly higher BMI than women (*P*<0.05). There were no

significant differences between men and women in terms of other factors. As shown in Table 9, the BMI of patients with clear cell RCC was significantly associated with OS (BMI as a categorical variable: HR=0.158, *P*=0.013; BMI as a continuous variable: HR=0.798, *P*=0.017), CSS (BMI as a categorical variable: HR=0.104, *P*=0.036; BMI as a continuous variable: HR=0.756, *P*=0.032), and MFS (BMI as a categorical variable: HR=0.229, *P*=0.007; BMI as a continuous variable: HR=0.869, *P*=0.003) only among men, and not among women (all *P*>0.05).
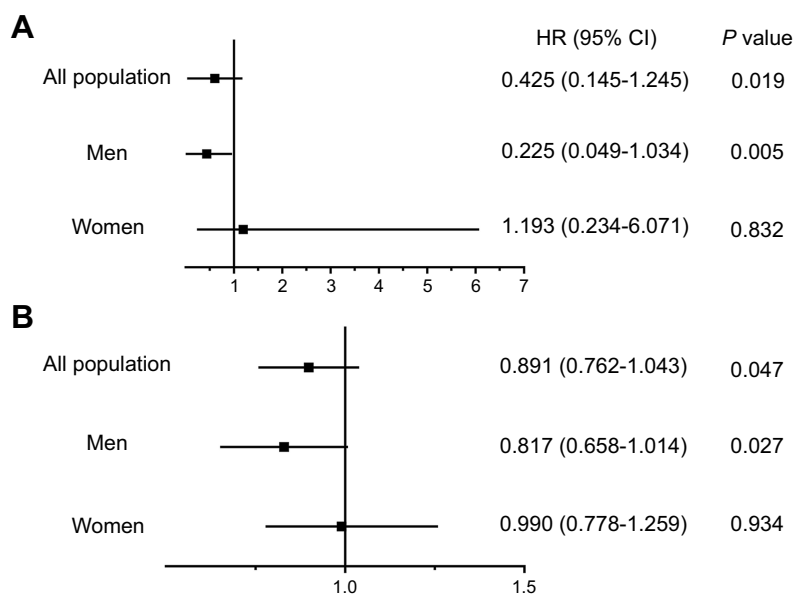
A

B

Figure 6 HRs and95% CIs for cancer-specific survival by BMI as categorical variable (**A**) or continuous variable (**B**).
Abbreviation: BMI, body mass index.
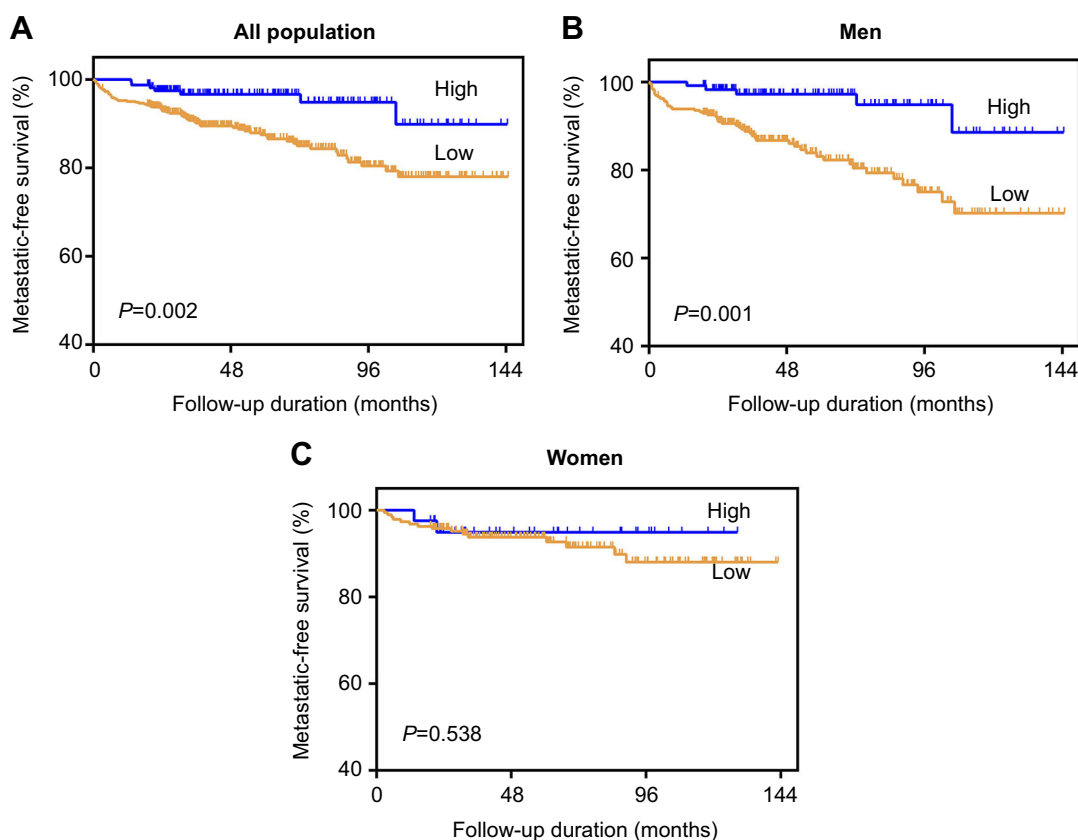
A

B

C

Figure 7 Kaplan-Meier curves for metastasis-free survival stratified by BMI in all patients (**A**), male patients (**B**), and female patients (**C**) with non-metastasis RCC.
Abbreviations: BMI, body mass index; RCC, renal cell carcinoma.

Discussion

The results of this study revealed that BMI was an independent predictor of OS, CSS, and MFS in patients with nonmetastatic RCC following nephrectomy. Such findings were consistent with those of previous studies.[11,12,21] However, in the subgroup analysis, men had

Table 6 Multivariate analysis of variables for the prediction of MFS in all patients

Variables	BMI as categorical variable			BMI as continuous variable		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (>65 vs ≤65 years)	3.191	1.460–6.977	**0.004***	2.832	1.570–5.110	**0.001**
Gender (men vs women)	2.375	1.336–4.223	**0.003***	2.171	1.164–4.048	**0.015**
ASA grade (≥3 vs <3)	1.125	0.525–2.413	0.761	1.095	0.452–2.653	0.841

BMI, Kg/m^2
  (1) Category: ≥25 vs <25
  (2) Continuous
	0.331
	
	-
		0.147–0.744
		
		-
			0.007*
			
				0.895
					-
					
					0.799–1.003
						
						0.047*

Hypertension (yes vs no)	1.090	0.647–1.835	0.746		-	
Anemia (yes vs no)	1.505	0.742–3.052	0.257	1.797	0.924–3.492	0.084
Surgical approach (partial vs radical)	0.796	0.352–1.797	0.582	0.586	0.248–1.385	0.586

CKD stage
  CKD 1
  CKD 2–3 vs CKD 1
  CKD 4–5 vs CKD 1
	1.000
	1.429
	6.103
		Reference
		0.858–2.379
		2.097–17.764
			1.000
			0.170
			0.001*
				1.000
				1.654
				2.858
					Reference
					0.931–2.937
					0.737–11.081
						1.000
						0.086
						0.129

Pathologic stage
  pT1
  pT2 vs pT1
  pT3 vs pT1
  pT4 vs pT1
	1.000
	1.885
	2.112
	3.288
		Reference
		0.815–4.360
		1.017–4.384
		0.657–16.450
			1.000
			0.139
			0.045*
			0.147
				1.000
				1.927
				1.583
				1.976
					Reference
					0.722–5.143
					0.682–3.679
					0.290–13.460
						1.000
						0.191
						0.285
						0.486

Fuhrman grade (≥3 vs <3)	1.652	1.006–2.714	**0.047***	2.088	1.198–3.639	**0.009**
Tumor necrosis (yes vs no)	3.277	1.345–7.986	**0.009***		-	
Tumor size (≥7 vs <7)	1.480	0.708–3.093	0.298	1.550	0.655–3.668	0.319

Note: *Statistically significant.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; MFS, metastasis-free survival.

Table 7 The significance of BMI for the prediction of MFS using multivariate analysis by sex

Sex	BMI as categorical variable				BMI as continuous variable		
		HR	95%CI	*P*-value	HR	95%CI	*P*-value
All	High vs normal BMI	0.331	0.147–0.744	**0.007***	0.895	0.799–1.003	**0.047***
Men	High vs normal BMI	0.243	0.093–0.638	**0.004***	0.865	0.751–0.996	**0.044***
Women	High vs normal BMI	0.820	0.175–3.848	0.801	0.926	0.739–1.160	0.504

Note: *Statistically significant.
Abbreviations: BMI, body mass index; MFS, metastasis-free survival.

a significantly higher BMI than women. Moreover, a high BMI was significantly associated with favorable OS, CSS, and MFS in men, but not in women, with RCC. The same findings were observed among patients with clear cell RCC. To our knowledge, this is the first study to assess the prognostic influence of BMI on nonmetastatic RCC according to sex.

To date, four studies have assessed the associations between sex, BMI, and survival outcomes in RCC.[10,16,17,22] Donat et al (2006) retrospectively reviewed 1137 consecutive patients with RCC who underwent radical or partial nephrectomy between 1995 and 2003, to evaluate the influence of BMI on survival in RCC patients.[10] Their results did not show a significant difference in OS or progression-free
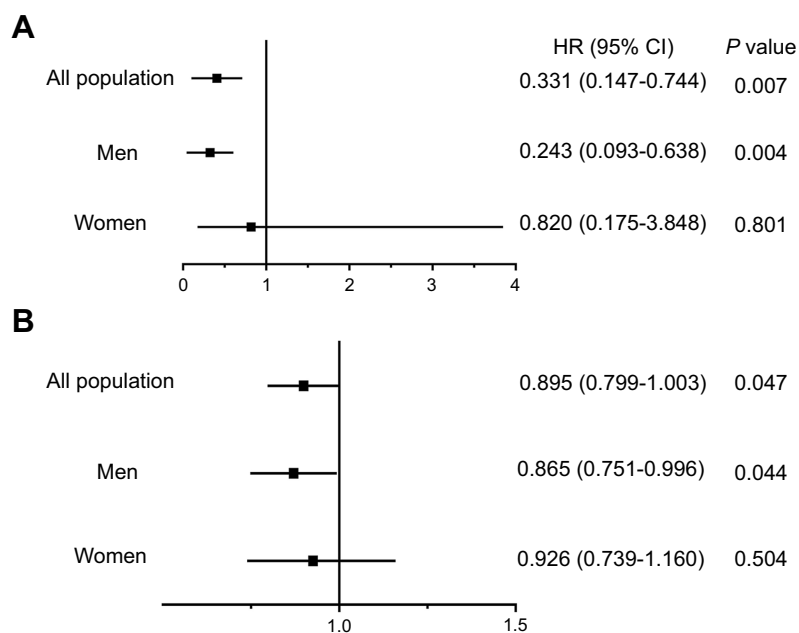
Figure 8 HRs and 95% CIs for metastasis-free survival by BMI as categorical variable (**A**) or continuous variable (**B**).
Abbreviation: BMI, body mas index.

survival based on BMI between males and females. Moreover, their study included all RCC patients but not exclude those with metastasis. Because the natural history, clinicopathological features, and subsequent treatment of metastatic RCC are commonly different from those of non-metastatic RCC,[3] such difference might have influenced the associations between sex, BMI, and RCC prognosis demonstrated in their study. Reeves et al (2007) also recruited 1.2 million women from the UK who were aged 50–64 years during 1996–2001, to examine the relationship between BMI and incidence of and mortality from cancer, including kidney cancer.[22] They reported that increased BMI is associated with increased incidence of and mortality from kidney cancer among women. Although their study had a large sample size, it did not include well-known prognostic factors of RCC, such as pathological stage and nuclear grade. Therefore, their conclusion about kidney cancer requires evaluation. Years after, Ohno et al (2013) retrospectively analyzed 435 patients with clear cell RCC.[17] Their results demonstrated that BMI is significantly associated with CSS among all patients and men, but not among women. Although their results were consistent with ours, their research had two limitations: First, the male-to-female ratio of 2.7:1 for RCC was much higher than the recommended ratio of 1.5:1 reported in the guidelines.[3] The sample size of females was only 117, which was relatively small for subgroup analysis. Second, their study also included patients with metastasis, with 44 (10.1%) patients of the whole

population having metastasis before surgery. Meanwhile, Byun et al analyzed 2097 patients with nonmetastatic clear-cell RCC who underwent surgery.[16] They also reported that a high BMI is associated with greater recurrence-free survival or CSS rates among all patients and men, but not among women. Although their study had a large sample size, there were 1524 males and only 573 females, resulting in a male-to-female ratio as high as 2.6:1. This finding might attenuate any putative associations between sex, BMI, and RCC prognosis.

Our study has several advantages over the four studies mentioned above.[10,16,17,22] First, we only included patients with nonmetastatic RCC (pathological T1-4N0M0) and excluded those with metastasis before surgery, because the presence of metastasis might influence the analysis of associations between sex, BMI, and survival outcomes in RCC. Second, our study included 414 males and 229 females, resulting in a male-to female ratio of 1.81:1, which is close to 1.5:1. Lastly, we included the majority of well-known accepted prognostic factors of nonmetastatic RCC, including age, nuclear grade, histological subtype, tumor necrosis, tumor size, and pathological stage.[3]

The obesity paradox has been observed in several studies,[23] but its cause remains unclear. Our findings suggest that sex should be considered when evaluating the prognostic value of obesity in RCC prognosis. However, it is unclear why the relationship between obesity and RCC prognosis may be sex-specific. One hypothesis is that

Table 8 Clear cell RCC patient characteristics*Statistically significant

Variables	All (n=562)	Male (n=367)	Female (n=195)	P-value
Age (>65 vs ≤65 years)	240/322	160/207	80/115	0.558
ASA grade (≥3 vs <3)	40/522	27/340	13/182	0.762

BMI, Kg/m^2
  (3) Mean ± SD, Kg/m^2
  (4) High vs normal BMI
	
	23.5(2.9)
	146/416
		
		23.6(2.8)
		110/257
			
			22.5(3.0)
			36/159
				
				<0.001*
				0.003*

DM (yes vs no)	218/425	127/240	66/129	0.857
Hypertension (yes vs no)	236/326	164/203	72/123	0.076
Anemia (yes vs no)	93/550	43/324	33/162	0.086

Surgical approach
  Partial nephrectomy
  Radical nephrectomy
	
	118
	444
		
		83
		284
			
			35
			160
				0.196

CKD stage
  CKD 1
  CKD 2
  CKD 3
  CKD 4
  CKD 5
	
	371
	153
	26
	3
	9
		
		233
		111
		15
		2
		6
			
			138
			42
			11
			1
			3
				0.253

Pathologic stage
  pT1
  pT2
  pT3
  pT4
	
	443
	65
	47
	7
		
		289
		37
		35
		6
			
			154
			28
			12
			1
				0.153

Fuhrman grade (≥3 vs <3)	125/437	85/282	40/155	0.472
Tumor necrosis (Yes vs No)	22/621	13/354	6/189	0.771
Tumor size (≥7 vs <7 cm)	97/465	58/309	39/156	0.210
Follow-up duration, months, median (IQR)	51.5(30.9–87.7)	49.3(30.2–84.4)	57.8(31.7–93.4)	0.065
All –cause death, n(%)	48 (8.5%)	35(9.5%)	13(6.7%)	0.247
Cancer-specific death, n(%)	33(5.9%)	20(5.4%)	13(6.7%)	0.559
Metastasis, n(%)	61(10.9%)	45(12.3%)	16(8.2%)	0.141

Abbreviations: BMI, body mass index; RCC, renal cell carcinoma; ASA, American Society of Anesthesiologists; DM, diabetes mellitus; CKD, chronic kidney disease; IQR, interquartile range.

changes in hormones and genetic expression, which are two sex-specific factors, may influence the magnitude of the prognostic role of obesity in RCC. A previous study revealed that the body weight of women would reach its maximum during menopause and their relative body fat and abdominal fatness would increase with advancing age.[24] In our study, there was a trend toward an increased BMI with increasing age in females, although the relationship was not significant (P=0.656). These physiological features are regulated by hormonal changes and may lead to significant differences in predicting the RCC prognosis according to BMI between men and women. Regarding to the genomic characteristics of RCC between men and women, Lucca et al reported that immune- or inflammation-associated genes are more likely to overexpress in males, while catabolic process-related genes tend to overexpress in females.[25] Brannon et al performed a meta-analysis of studies on gene expression in clear cell RCC. In their study of 366 autosomal genes, they identified 326 (89.1%) genes as differentially expressed between the

Table 9 The significance of BMI for the prediction of OS, CSS, and MFS using multivariate analysis by sex among clear cell RCC patients

OS	BMI as categorical variable				BMI as continuous variable		
		HR	**95%CI**	*P*-value	**HR**	**95%CI**	*P*-value
All	High vs normal BMI	0.320	0.112–0.918	**0.030***	0.877	0.760–1.011	**0.041***
Men	High vs normal BMI	0.158	0.037–0.683	**0.013***	0.798	0.663–0.961	**0.017***
Women	High vs normal BMI	1.358	0.274–6.741	0.708	1.023	0.823–1.271	0.837
CSS	**BMI as categorical variable**				**BMI as continuous variable**		
		HR	**95%CI**	*P*-value	**HR**	**95%CI**	*P*-value
All	High vs normal BMI	0.325	0.094–1.127	**0.046***	0.885	0.747–1.048	**0.045***
Men	High vs normal BMI	0.104	0.013–0.867	**0.036***	0.756	0.586–0.977	**0.032***
Women	High vs normal BMI	1.358	0.274–6.741	0.708	1.023	0.823–1.271	0.837
MFS	**BMI as categorical variable**				**BMI as continuous variable**		
		HR	**95%CI**	*P*-value	**HR**	**95%CI**	*P*-value
All	High vs normal BMI	0.312	0.130–0.749	**0.009***	0.913	0.811–1.029	**0.005***
Men	High vs normal BMI	0.229	0.078–0.668	**0.007***	0.869	0.745–1.013	**0.003***
Women	High vs normal BMI	0.865	0.189–3.956	0.851	0.956	0.777–1.177	0.675

Note: *Statistically significant.
Abbreviations: BMI, body mass index; CSS; cancer-specific survival; MFS, metastasis-free survival; RCC, renal cell carcinoma; OS, overall survival.

sexes. Furthermore, some of these gene participate in important biological processes, including DNA repair (*PARP8* and *ERCC5*), cell signaling (*MAPKSP1*, *SPAG1*, etc.) and cell motility (*VCAN* and *CYR61*).[26] A previous study also analyzed three large-scale clear cell RCC mutation sequencing projects. Their results revealed that mutation of the BAP1 gene was significantly associated with poorer OS in the whole population and among females, but not among males. Furthermore, they concluded that the combination of sex and mutation of a specific gene, such as BAP1, may be associated with OS in RCC patients.[27]

Our study has several limitations. First, it has a retrospective design and was conducted in a single institution, which might have led to selection bias. Nevertheless, our department is the largest urological center with the largest sample size for RCC patients in the south of Zhejiang Province; therefore, our data were representative and reliable. Second, we were unable to include some potential predictors, such as smoking history and nutritional status, due to lack of patient information. The antecedent weight loss, which might have influenced the outcomes, was also not reported. However, we had included the majority of well-known accepted prognostic factors of nonmetastatic RCC. Lastly, we were also unable to obtain information on

waist circumference, waist-to-hip ratio, and visceral adiposity that could further improve the understanding of the prognostic role of obesity in survival outcomes in RCC patients. Nevertheless, BMI is the most widely used index for obesity in clinical practice. Thus, further prospective studies and basic researches are required to investigate the sex-dependent prognostic value and mechanisms of BMI in RCC patients.

Conclusion

Our study showed that a high BMI was a favorable prognostic factor in patients with nonmetastatic RCC who underwent nephrectomy. However, when the patients were stratified according to sex, BMI was significantly associated with OS, CSS, and MFS only among men, and not among women. The same findings were observed among patients with clear cell RCC. Our results suggest that sex may influence the relationship between obesity and prognosis of nonmetastatic RCC.

Abbreviation list

RCC, renal cell carcinoma; BMI, body mass index; OS, overall survival; MFS, metastasis-free survival; CSS, cancer-specific survival; CKD, chronic kidney disease; DM, diabetes mellitus.

Ethics approval and informed consent

This study was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China). The study protocol is in accordance with the Declaration of Helsinki. All patients' informed consent from telephone interview had been obtained before their participation in this study, although none of them came to our center to give written informed consent. Furthermore, we stated that all data from patients was anonymized or maintained with confidentiality. The consent process has been approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China).

Author contributions

Xiaomin Gao conceived and designed the study, Yangqin Zheng, Lianmin Bao, and Jingfeng Chen acquired the data, Yue Pan analyzed and interpreted the data, and Lianguo Chen and Xiaomin Gao drafted the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Univariate analysis of variables for the prediction of overall survival in all patients

Variables	BMI as categorical variable			BMI as continuous variable		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (>65 vs ≤65 years)	4.597	2.428-8.705	**<0.001***	6.017	3.115-11.620	**<0.001***
ASA grade (≥3 vs <3)	3.731	1.963-7.092	**<0.001***	3.873	1.846-8.125	**<0.001***
Gender (men vs women)	1.807	0.988-3.307	0.055	1.780	0.952-3.329	0.071

BMI, Kg/m^2
  (1) Category: ≥25 vs <25
  (2) Continuous
	0.281	0.112-0.704	**0.007***	
				
				0.837
					
					0.745-0.939
						
						0.002*

DM (yes vs no)	1.091	0.628-1.895	0.756	0.972	0.546-1.731	0.924
Hypertension (yes vs no)	1.204	0.712-2.034	0.488	1.080	0.624-1.868	0.784
Anemia (yes vs no)	3.801	2.223-6.500	**<0.001***	4.559	2.532-8.210	**<0.001***
Surgical approach (partial vs radical)	0.435	0.173-1.091	0.076	0.324	0.127-0.828	**0.019***

CKD stage
  CKD 1
  CKD 2-3 vs CKD 1
  CKD 4-5 vs CKD 1
	1.000
	2.369
	7.691
		Reference
		1.374-4.085
		2.664-22.207
			1.000
			0.002*
			<0.001*
				1.000
				2.746
				6.667
					Reference
					1.554-4.852
					1.948-22.820
						1.000
						0.001*
						0.003*

Pathologic stage
  pT1
  pT2 vs pT1
  pT3 vs pT1
  pT4 vs pT1
	1.000
	2.810
	3.762
	5.906
		Reference
		1.469-5.375
		1.885-7.507
		1.409-24.746
			1.000
			0.002*
			<0.001*
			0.015*
				1.000
				3.165
				3.321
				5.032
					Reference
					1.572-6.373
					1.573-7.011
					0.975-25.970
						1.000
						0.001*
						0.002*
						0.014*

Fuhrman grade (≥3 vs <3)	2.753	1.635-4.634	**<0.001***	3.427	1.970-5.961	**<0.001***
Histologic subtype (Clear cell vs non-clear cell)	1.418	0.695-2.892	0.337	1.339	0.630-2.843	0.448
Tumor necrosis (Yes vs No)	2.388	0.863-6.607	0.094	2.382	0.778-7.295	0.129
Tumor size (≥7 vs <7)	2.733	1.585-4.713	**<0.001***	2.902	1.613-5.224	**<0.001***

Note: *Statistically significant.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus.

Table S2 Univariate analysis of variables for the prediction of cancer-specific survival in all patients

Variables	BMI as categorical variable			BMI as continuous variable		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (>65 vs ≤65 years)	4.196	1.990-8.845	**<0.001***	5.056	2.358-10.837	**<0.001***
ASA grade (≥3 vs <3)	3.773	1.733-8.215	**0.001***	4.072	1.745-9.499	**0.001***
Gender (men vs women)	1.069	0.555-2.058	0.842	0.987	0.502-1.939	0.970
BMI, Kg/m² (1) Category: ≥25 vs <25 (2) Continuous	0.333	0.118-0.938	**0.037***	0.843	0.735-0.967	**0.014***
DM (yes vs no)	0.851	0.423-1.710	0.650	0.753	0.368-1.544	0.439
Hypertension (yes vs no)	1.624	0.865-3.049	0.131	1.480	0.774-2.831	0.236
Anemia (yes vs no)	3.297	1.713-6.345	**<0.001***	3.722	1.856-7.462	**<0.001***
Surgical approach (partial vs radical)	0.372	0.114-1.211	0.101	0.287	0.087-0.946	**0.040***
CKD stage CKD 1 CKD 2-3 vs CKD 1 CKD 4-5 vs CKD 1	1.000 2.789 2.866	Reference 1.463-5.318 0.380-21.634	1.000 **0.002*** 0.307	1.000 3.066 1.962	Reference 1.573-5.974 0.242-15.929	1.000 **0.001*** 0.528
Pathologic stage pT1 pT2 vs pT1 pT3 vs pT1 pT4 vs pT1	1.000 3.714 5.419 10.264	Reference 1.712-8.055 2.429-12.087 2.372-44.411	1.000 **0.001*** **<0.001*** **0.002***	1.000 4.111 4.625 8.907	Reference 1.819-9.290 1.977-10.818 1.680-47.225	1.000 **0.001*** **<0.001*** **0.010***
Fuhrman grade (≥3 vs <3)	3.479	1.844-6.562	**<0.001***	4.172	2.156-8.073	**<0.001***
Histologic subtype (Clear cell vs non-clear cell)	1.377	0.577-3.289	0.471	1.282	0.520-3.163	0.589
Tumor necrosis (yes vsno)	3.506	1.245-9.873	**0.018***	3.721	1.195-11.585	**0.023***
Tumor size (≥7 vs <7)	4.282	2.281-8.039	**<0.001***	4.650	2.387-9.060	**<0.001***

Note: *Statistically significant.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus.

Table S3 Univariate analysis of variables for the prediction of metastasis-free survival in all patients

Variables	BMI as categorical variable			BMI as continuous variable		
	HR	**95%CI**	***P*-value**	**HR**	**95%CI**	***P*-value**
Age (>65 vs ≤65 years)	2.864	1.730-4.741	**<0.001***	3.537	2.081-6.012	**<0.001***
ASA grade (≥3 vs <3)	2.319	1.188-4.530	**0.014***	1.871	1.057-3.311	**0.032***
Gender (men vs women)	1.924	1.115-3.322	0.019	1.780	0.952-3.329	0.071
BMI, Kg/m²						
(1) Category: ≥25 vs <25	0.316	0.145-0.690	**0.004***			
(2) Continuous				0.300	0.134-0.668	**0.003***
DM (yes vs no)	0.833	0.496-1.399	0.490	0.741	0.429-1.278	0.281
Hypertension (yes vs no)	1.580	0.991-2.520	0.055	1.475	0.900-2.418	0.123
Anemia (yes vs no)	2.711	1.638-4.485	**<0.001***	2.711	1.638-4.485	**<0.001***
Surgical approach (partial vs radical)	0.452	0.207-0.988	0.047	0.365	0.163-0.815	**0.014***
CKD stage						
CKD 1	1.000	Reference	1.000	1.000	Reference	1.000
CKD 2-3 vs CKD 1	2.148	1.324-3.484	**0.002***	2.436	1.455-4.077	**0.001***
CKD 4-5 vs CKD 1	7.691	2.664-22.207	**<0.001***	6.806	2.153-21.518	**0.001***
Pathologic stage						
pT1	1.000	Reference	1.000	1.000	Reference	1.000
pT2 vs pT1	2.692	1.509-4.803	**0.001***	3.029	1.600-5.735	**0.001***
pT3 vs pT1	3.115	1.635-5.936	**0.001***	2.736	1.348-5.551	**0.005***
pT4 vs pT1	4.459	1.076-18.483	**0.009***	3.724	0.728-19.041	**0.014***
Fuhrman grade (≥3 vs <3)	2.371	1.485-3.785	**<0.001***	3.427	1.970-5.961	**<0.001***
Histologic subtype (clear cell vs non-clear cell)	1.240	0.635-2.422	0.528	1.339	0.630-2.843	0.448
Tumor necrosis (yes vs no)	3.210	1.390-7.417	**0.006***	2.382	0.778-7.295	0.129
Tumor size (≥7 vs <7)	2.604	1.592-4.260	**<0.001***	2.902	1.613-5.224	**<0.001***

Note: *Statistically significant.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus.