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The Prognostic Significance of Body Mass Index in Patients Undergoing Nephrectomy for Nonmetastatic Renal Cell Carcinoma

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Purpose: The aim of this study was to evaluate the impact of body mass index (BMI) on survival in patients with nonmetastatic renal cell carcinoma (RCC) treated with radical or partial nephrectomy.

Materials and Methods: Between June 1994 and December 2021, 482 patients with RCC underwent radical or partial nephrectomy. Among those patients, 21 patients with lymph node or distant metastasis were excluded. The medical records of the remaining 461 patients were retrospectively reviewed. The prognostic significance of various clinicopathological variables, including BMI, was evaluated in univariate and multivariate analyses.

Results: Of the total 461 patients, 171 (37.1%) were categorized as normal-weight, 118 (25.6%) as overweight, and 172 (37.3%) as obese. Forty-eight patients (10.4%) developed local recurrence or distant metastasis, and 26 patients (5.6%) died from the disease during the follow-up period. In the multivariate analysis, BMI (p=0.017), tumor size (p<0.001), T stage (p<0.001), Fuhrman nuclear grade (p=0.016), and lymphovascular invasion (p=0.012) were independent predictors of recurrence-free survival. Furthermore, BMI (p=0.025), tumor size (p<0.001), T stage (p<0.001), Fuhrman nuclear grade (p=0.047), and lymphovascular invasion (p=0.033) were independent predictors of cancer-specific survival.

Conclusions: Our results suggest that overweight and obese patients with nonmetastatic RCC treated with radical or partial nephrectomy have a more favorable prognosis. These findings indicate that BMI could be an important factor for predicting recurrence or survival in patients undergoing nephrectomy for nonmetastatic RCC.

Key Words: Body mass index, Recurrence, Renal cell carcinoma, Survival

INTRODUCTION

Renal cell carcinoma (RCC) is the most common malignant tumor of the kidney, and its incidence has been steadily increasing in recent decades [1]. Although several clinical, anatomical, and histological risk factors are associated with the disease prognosis in patients with RCC, only a handful of factors, such as tumor size, pathological stage, and nuclear grade, are recommended for use in routine clinical practice [2].

The relationship between body mass index (BMI) and the prognosis of various cancers is not well established. Previous studies have reported that a high BMI was associated with a favorable prognosis for a variety of cancers, including esophageal, colorectal, and head and neck cancers [3-5]. In contrast, similar analyses have found that higher BMI was

associated with poorer prognoses of breast and prostate cancer [6, 7].

Among the most common risk factors, tobacco smoke exposure, obesity, and hypertension have all been consistently associated with RCC [8]. This apparent link between obesity and RCC has been attributed to a combination of factors, including increased expression of insulin-like growth factor-1, higher circulating estrogen levels, arteriolar nephrosclerosis, and local inflammation [9]. However, although these factors have all been linked to RCC, whether there is an association between obesity and disease prognosis is not known. To address this apparent discrepancy in clinical findings, we evaluated the impact of BMI on survival in patients with nonmetastatic RCC treated with radical or partial nephrectomy.

MATERIALS AND METHODS

1. BMI and Patient Data

This study was approved by the Institutional Review Boards of Ajou University Hospital and Bundang Jesaeng Hospital (AJIRB-MED-MBD-21-558, DMC 2021-02-003). Between June 1994 and December 2021, radical or partial nephrectomy was performed in 482 patients with RCC at these 2 hospitals. Lymph node dissection was limited to patients with either palpable enlarged lymph nodes identified during surgery or abnormal findings on preoperative imaging studies. Follow-up examinations were performed every 3 months during the first 2 years after surgery, every 6 months during the next 2 years, and annually thereafter. Routine checkups, such as physical examinations, basic laboratory examinations, and chest x-ray examinations, were performed at each follow-up visit. Abdominopelvic computed tomography was performed every 6 months for the first 2 years and annually during follow-up or when clinically indicated. Disease recurrence was defined as a local mass in the tumor bed, regional lymph node involvement, or distant metastasis. Tumor staging was reassessed according to the 2010 TNM classification system, and the nuclear grade was assigned according to Fuhrman's nuclear grading system [10].

Patients were classified into 3 BMI groups on the basis of the World Health Organization recommendation for Asians [11], with <23.5, 23.5–25, and >25 kg/m^2 representing normal-weight, overweight, and obese, respectively. Clinicopathological data were collected and analyzed for each group.

2. Statistical Analysis

The chi-square test was used to assess the relationship between BMI and clinicopathological variables, including age, sex, smoking history, diabetes mellitus, hypertension, tumor histology, tumor size, T stage, Fuhrman nuclear grade, coagulative tumor necrosis, lymphovascular invasion, and nephrectomy type. Recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were estimated using the Kaplan-Meier method, stratified by BMI, and the log-rank test was used to compare the groups. The prognostic significance of BMI was calculated using a Cox proportional hazards model. All tests were 2-sided, with p-values <0.05 considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Among the 482 patients with RCC who underwent radical or partial nephrectomy, 21 were excluded due to lymph node involvement or distant metastasis. The medical records of the remaining 461 patients with nonmetastatic RCC (307 men and 154 women) were retrospectively reviewed and analyzed. The mean age of the patients was 55.9 years (range, 18–83 years), and the median follow-up duration was 71 months (mean, 73.5 months; range: 4–272 months). The clinicopathological data of the entire cohort are summarized in Table 1.

Of the 461 patients included in this study, 171 (37.1%) were categorized as normal-weight, 118 (25.6%) as overweight, and 172 (37.3%) as obese (Table 1). The associations of BMI with the clinicopathological characteristics of the 461 patients included in this study are shown in Table 2. Obesity was significantly associated with younger age (p=0.002), hypertension (p=0.003), small tumor size (p=0.021), lower T stage (p=0.008), and the absence of lymphovascular invasion

Table 1. Clinicopathological data of 461 patients with renal cell carcinoma

Characteristic	No. of patients (%)
Age (yr)	
≤60	283 (61.4)
>60	178 (38.6)
Sex	
Male	307 (66.6)
Female	154 (33.4)
Smoking history	
Never	189 (41.0)
Ever	272 (59.0)
Diabetes mellitus	
No	384 (83.3)
Yes	77 (16.7)
Hypertension	
No	292 (63.3)
Yes	169 (36.7)
Body mass index (kg/m^2)	
<23	171 (37.1)
23–24.9	118 (25.6)
≥25	172 (37.3)
Histology	
Clear cell	400 (86.8)
Papillary	23 (5.0)
Chromophobe	31 (6.7)
Collecting duct	2 (0.4)
Unclassified	5 (1.1)
Tumor size (cm)	
≤7	381 (82.6)
>7	80 (17.4)
T stage	
T1	320 (69.4)
T2	42 (9.1)
T3	95 (20.5)
T4	4 (0.9)
Grade	
1	31 (6.7)
2	148 (32.1)
3	239 (51.8)
4	43 (9.3)
Coagulative tumor necrosis	
No	389 (84.4)
Yes	72 (15.6)
Lymphovascular invasion	
No	432 (93.7)
Yes	29 (6.3)
Nephrectomy type	
Partial	37 (8.0)
Radical	424 (92.0)

(p=0.014). No associations were seen for sex, smoking history, diabetes mellitus, tumor histology, Fuhrman nuclear grade, coagulative tumor necrosis, or nephrectomy type (Table 2). Local recurrence or distant metastasis developed in 48 patients (10.4%), and 26 patients (5.6%) died from the disease during the follow-up period.

Table 2. Clinicopathological characteristics of patients grouped by body mass index (BMI) category

Variable	BMI category			p-value†
	Normal	Overweight	Obese	
Age (yr)				0.002*
≤60	94 (33.2)	67 (23.7)	122 (43.1)	
>60	77 (43.3)	51 (28.7)	50 (28.1)	
Sex				0.939
Male	117 (38.1)	73(23.8)	117 (38.1)	
Female	54 (35.1)	45(29.2)	55 (35.7)	
Smoking history				0.470
Never	62 (32.8)	58 (30.7)	69 (36.5)	
Ever	109 (40.1)	60 (22.1)	103 (37.9)	
Diabetes mellitus				0.485
No	147 (38.3)	94 (24.5)	143 (37.2)	
Yes	24 (31.2)	24 (31.2)	29 (37.7)	
Hypertension				0.003*
No	126 (43.2)	66 (22.6)	100 (34.2)	
Yes	45 (26.6)	52 (30.8)	72 (42.6)	
Tumor histology				0.983
Clear cell	148 (37.0)	103 (25.8)	149 (37.3)	
Nonclear cell	23 (37.7)	15 (24.6)	23 (37.7)	
Tumor size (cm)				0.021*
≤7	132 (34.6)	100 (26.2)	149 (39.1)	
>7	39 (48.8)	18 (22.5)	23 (28.8)	
T stage				0.008
Low (T1+T2)	123 (34.0)	95 (26.2)	144 (39.8)	
High (T3+T4)	48 (48.5)	23 (23.2)	28 (28.3)	
Grade				0.051
Low (G1+G2)	57 (31.8)	47 (26.3)	75 (41.9)	
High (G3+G4)	114 (40.4)	71 (25.2)	97 (34.4)	
Coagulative tumor necrosis				0.444
No	144 (37.0)	95 (24.4)	150 (38.6)	
Yes	27 (37.5)	23 (31.9)	22 (30.6)	
Lymphovascular invasion				0.014*
No	154 (35.6)	112 (25.9)	166 (38.4)	
Yes	17 (58.6)	6 (20.7)	6 (20.7)	
Nephrectomy type				0.987
Partial	14 (37.8)	9 (24.3)	14 (37.8)	
Radical	157 (37.0)	109 (25.7)	158 (37.3)	

Values are presented as number of patients (%).
*p<0.05, statistically significant differences. †Analyzed by chi-square test.

Kaplan-Meier curves for RFS, CSS, and OS according to the BMI category showed lower RFS, CSS and OS rates in the normal-weight group (Figs. 1–3). In the univariate analysis, obesity, tumor size, T stage, Fuhrman nuclear grade, coagulative tumor necrosis, and lymphovascular invasion were all significant prognostic factors for RFS. Meanwhile, obesity, tumor size, T stage, Fuhrman nuclear grade, and lymphovascular invasion were significant prognostic factors for CSS and OS. In the multivariate analysis, the independent prognostic factors for RFS, CSS, and OS were obesity, tumor size, T stage, Fuhrman nuclear grade, and lymphovascular

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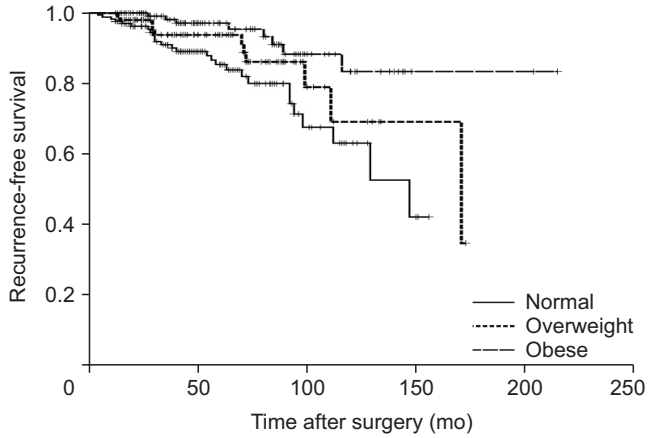

Fig. 1. Kaplan-Meier recurrence-free survival curves according to body mass index category.

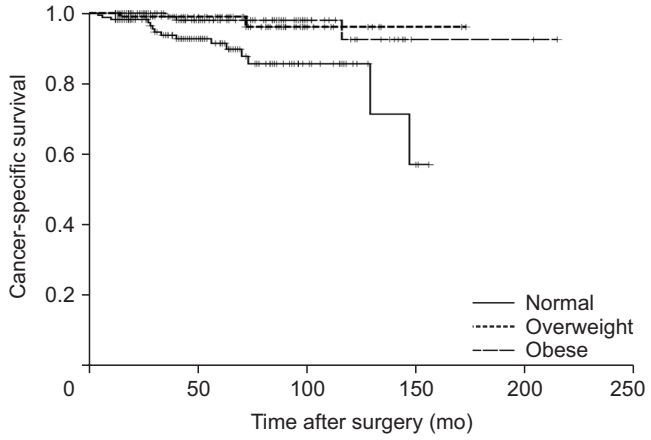

Fig. 2. Kaplan-Meier cancer-specific survival curves according to body mass index category.

invasion (Tables 3–5).

DISCUSSION

Several studies have suggested that obesity is a risk factor for the development of RCC [8, 9]. Obesity is also generally considered to be a major risk factor for complications during and after surgery due to the high rate of comorbidities [12]. However, there is considerable debate regarding whether obesity is a risk factor for disease progression and shorter survival in RCC. The initial findings of Yu et al. [13], who reported an apparently paradoxical association between obesity and both overall and disease-free survival in RCC, prompted several other studies to examine this relationship. The most extensive of these studies was a retrospective review

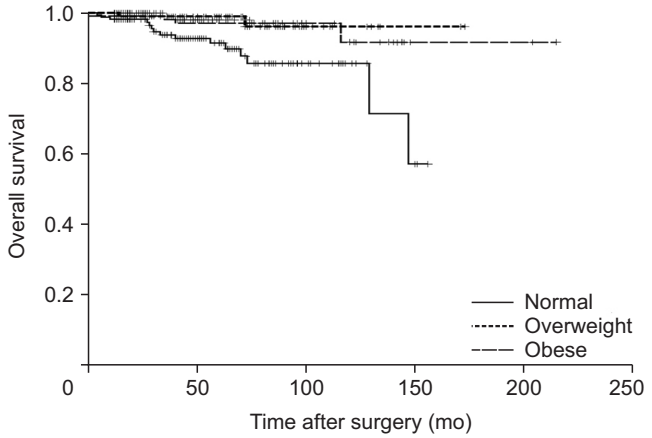

Fig. 3. Kaplan-Meier overall survival curves according to body mass index category.

Table 3. Univariate and multivariate analysis of recurrence-free survival in 461 patients with renal cell carcinoma

Variable	Univariate	Multivariate	
	p-value†	Hazards ratio (95% CI)	p-value‡
Age, ≤60 yr vs. >60 yr	0.187	1.299 (0.700–2.413)	0.407
Sex, male vs. female	0.851	1.652 (0.620–4.398)	0.315
Smoking history, never vs. ever	0.469	1.465 (0.571–3.758)	0.427
Diabetes mellitus, no vs. yes	0.851	0.963 (0.397–2.338)	0.934
Hypertension, no vs. yes	0.325	0.605 (0.288–1.269)	0.183
BMI (kg/m^2)			
Obesity, ≥25	Reference	Reference	
Overweight, 23–24.9	0.135	2.276 (0.890–5.819)	0.086
Normal, <23	0.001*	2.926 (1.298–6.600)	0.010*
Tumor histology, conventional vs. nonconventional	0.827	1.130 (0.456–2.802)	0.791
Tumor size, ≤7 cm vs. >7 cm	<0.001*	3.730 (1.941–7.172)	<0.001*
T stage, T1+T2 vs. T3+T4	<0.001*	5.592 (2.796–11.186)	<0.001*
Grade, G1+G2 vs. G3+G4	<0.001*	3.163 (1.299–7.701)	0.011*
Coagulative tumor necrosis	0.005*	1.153 (0.563–2.358)	0.697
Lymphovascular invasion	<0.001*	2.296 (1.113–4.740)	0.025*
Nephrectomy type, partial vs. radical	0.430	0.471 (0.102–2.178)	0.335

CI, confidence interval; BMI, body mass index.
*p<0.05, statistically significant differences. †Analyzed by log-rank test. ‡Analyzed by Cox proportional hazards regression model.

of 400 patients undergoing nephrectomy for RCC, in which Kamat et al. [14] confirmed a more favorable prognosis and disease-specific survival in overweight and obese patients than in normal-weight patients.

Many studies have since reported an inverse linear correlation between obesity and RCC prognosis, commonly referred to as the "obesity paradox," although the mechanism underlying this phenomenon remains poorly understood. One hypothesis is that obese patients are less likely to have

Table 4. Univariate and multivariate analysis of cancer-specific survival in 461 patients with renal cell carcinoma

Variable	Univariate	Multivariate	
	p-value†	Hazards ratio (95% CI)	p-value‡
Age, ≤60 yr vs. >60 yr	0.036*	2.120 (0.782–5.744)	0.140
Sex, male vs. female	0.888	0.690 (0.191–2.489)	0.571
Smoking history, never vs. ever	0.786	0.927 (0.271–3.171)	0.904
Diabetes mellitus, no vs. yes	0.575	0.875 (0.229–3.339)	0.845
Hypertension, no vs. yes	0.970	0.857 (0.284–2.588)	0.785
BMI (kg/m^2)			
Obesity, ≥25	Reference	Reference	
Overweight, 23–24.9	0.355	0.608 (0.113–3.273)	0.563
Normal, <23	0.014*	2.760 (1.003–7.592)	0.049
Tumor histology, conventional vs. nonconventional	0.392	0.501 (0.108–2.327)	0.377
Tumor size, ≤7 cm vs. >7 cm	<0.001*	6.955 (2.696–17.947)	<0.001*
T stage, T1+T2 vs. T3+T4	<0.001*	6.198 (2.248–17.088)	<0.001*
Grade, G1+G2 vs. G3+G4	0.004*	3.340 (1.023–10.906)	0.046*
Coagulative tumor necrosis	0.503	0.603 (0.199–1.827)	0.371
Lymphovascular invasion	<0.001*	2.997 (1.071–8.384)	0.037*
Nephrectomy type, partial vs. radical	0.648	0.286 (0.031–2.602)	0.266

CI, confidence interval; BMI, body mass index.
*p<0.05, statistically significant differences. †Analyzed by log-rank test. ‡Analyzed by Cox proportional hazards regression model.

Table 5. Univariate and multivariate analysis of overall survival in 461 patients with renal cell carcinoma

Variable	Univariate	Multivariate	
	p-value†	Hazards ratio (95% CI)	p-value‡
Age, ≤60 yr vs. >60 yr	0.138	1.370 (0.563–3.331)	0.488
Sex, male vs. female	0.737	0.668 (0.201–2.216)	0.509
Smoking history, never vs. ever	0.411	1.195 (0.383–3.727)	0.759
Diabetes mellitus, no vs. yes	0.737	1.042 (0.329–3.301)	0.945
Hypertension, no vs. yes	0.767	1.260 (0.475–3.343)	0.643
BMI (kg/m^2)			
Obesity, ≥25	Reference	Reference	
Overweight, 23–24.9	0.407	0.557 (0.166–2.978)	0.489
Normal, <23	0.013*	2.884 (1.112–8.780)	0.047*
Tumor histology, conventional vs. nonconventional	0.456	0.376 (0.085–1.662)	0.197
Tumor size, ≤7 cm vs. >7 cm	<0.001*	6.100 (2.557–14.547)	<0.001*
T stage, T1+T2 vs. T3+T4	<0.001*	5.710 (1.582–13.702)	0.003*
Grade, G1+G2 vs. G3+G4	0.005*	2.981 (1.220–8.803)	0.048*
Coagulative tumor necrosis	0.615	0.526 (0.181–1.527)	0.238
Lymphovascular invasion	<0.001*	3.626 (1.380–9.525)	0.015*
Nephrectomy type, partial vs. radical	0.725	0.271 (0.055–1.341)	0.220

CI, confidence interval; BMI, body mass index.
*p<0.05, statistically significant differences. †Analyzed by log-rank test. ‡Analyzed by Cox proportional hazards regression model.

aggressive tumor biology. A genomic study of 2,119 patients with clear cell RCC revealed that obese patients had tumors with downregulated expression of the metabolic and fatty acid genes essential for tumor growth [15]. Other hypotheses propose a role of excessive perirenal fat as a protective barrier, or that high nutritional status can protect against treatment-related stress [16]. However, studies of the obesity paradox have been criticized due to various methodological problems, including the limitations of BMI, confounding factors, detection and selection bias, and reverse causation; nonetheless, the consistency with which the obesity paradox has been observed in clinical studies renders it virtually undeniable.

Several proteins and signaling factors capable of attenuating RCC progression have been reported in adipose tissue. For example, adipose tissue synthesizes leptin, the circulating levels of which are strongly related to obesity. Leptin has also been shown to play an important role in stimulating pro-inflammatory T helper (Th) 1 immune responses [17]. In contrast, a change in the predominant immunologic response from Th1 to Th2 is strongly correlated with higher RCC stages [18]. Therefore, leptin expression may play a pivotal role in delaying RCC progression.

To better understand the obesity paradox, several studies have conducted subgroup analyses given the high degree of heterogeneity seen among RCC cases. An epidemiological study of 2,769 patients with nonmetastatic RCC indicated that higher BMI was associated with a good prognosis for clear cell RCC, an unclear prognosis for papillary RCC, and a poor prognosis for chromophobe RCC [19]. Another study of 2,097 patients with nonmetastatic clear cell RCC revealed significant inverse correlations of obesity with RFS and CSS in men, but not in women [20]. The present study evaluated the association of BMI with the prognosis of patients with RCC, and found that obese and overweight patients had superior survival outcomes compared to normal-weight and underweight patients. However, significant relationships were not observed in subgroup analyses based on factors such as age, sex, and histologic subtype.

Our study had several limitations. First, it used a retrospective design, which is known to pose a risk of bias. In particular, as shown in Table 2, obese patients had smaller tumors, lower rates of tumors with a high T stage, and a lower frequency of lymphovascular invasion. Therefore, these disparities in the distribution between the patient groups might have resulted in a higher survival rate in

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obese patients. Second, we were unable to adjust for several potential confounding factors, such as RCC-associated molecular markers and nutritional status, although we did include the most widely accepted prognostic factors of nonmetastatic clear cell RCC. Third, we were unable to assess other indices of obesity, such as waist circumference, waist-to-hip ratio, and visceral adiposity. While BMI remains the most commonly used obesity index in clinical studies and real practice, the use of these other factors might improve our understanding of the prognostic value of obesity for RCC. Finally, our study included only Korean patients, such that our findings may not be generalizable to other ethnic groups, particularly Western populations.

CONCLUSIONS

Our results suggest that overweight and obese patients with nonmetastatic RCC, treated with radical or partial nephrectomy, have a more favorable prognosis than normal-weight patients. Thus, BMI could be an effective tool for predicting recurrence or survival in patients undergoing nephrectomy for nonmetastatic RCC.

NOTES

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