Distinct Effect of Body Mass Index by Sex as a Prognostic Factor in Localized Renal Cell Carcinoma Treated with Nephrectomy ~ A Data from Multi-Institutional Study ~

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| Takeshi Tsutsumi          | Osaka Medical College |
|---------------------------|-----------------------|
| Kazumasa Komura           |                       |
| uto051@osaka-med.ac.jp    | Corresponding Author   |
| ORCID: https://orcid.org/ |                       |
| Takeshi Hashimoto         | Tokyo Medical University|
| Ryu Muraoka               | Tokyo Medical University|
| Naoya Satake              | Tokyo Medical University|
| Tomohisa Matsunaga        | Osaka Medical College  |
| Takuya Tsujino            | Osaka Medical College  |
| Yuki Yoshikawa            | Osaka Medical College  |
| Tomoaki Takai             | Osaka Medical College  |
| Koichiro Minami           | Osaka Medical College  |
| Kohei Taniguchi           |                       |
Osaka Medical College

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Osaka Medical College

Hirofumi Uehara
Osaka Medical College

Hajime Hirano
Osaka Medical College

Hayahito Nomi
Osaka Medical College

Naokazu Ibuki
Osaka Medical College

Kiyoshi Takahara
Fujita-Health University School of Medicine

Teruo Inamoto
Osaka Medical College

Yoshio Ohno
Tokyo Medical University

Haruhito Azuma
Osaka Medical College

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**SUBJECT AREAS**

Cancer Biology  Oncology

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Abstract

Purpose

We assessed the prognostic value of body mass index (BMI) in Asian patients with localized RCC who underwent nephrectomy.

Material and Methods

A total of 665 patients who underwent nephrectomy for localized RCC were enrolled in the present study and divided into the two BMI groups: i.e., BMI <25 in 463 (69.6%) and BMI ≥25 in 202 (30.4%) patients.

Results

There were 482 (72.5%) and 183 (27.5%) patients in male and female, respectively. No significant difference in the distribution of sex was seen between BMI groups (p=0.498). Five-year cancer-specific survival (CSS) and recurrence-free survival (RFS) rate were significantly higher in higher BMI (97.1 and 91.1%) compared to lower BMI group (92.5 and 82.7%) (P = 0.007 for CSS, and p=0.019 for RFS). When stratified by sex, significantly longer CSS in higher BMI was confirmed in male (5-year CSS of 92.7% in BMI <25 and 98.1% in BMI >25, p=0.005), while there was no difference in CSS between BMI groups for female patients (5-year CSS of 91.9% in BMI <25 and 93.7% in BMI >25, p=0.738). Multivariate analysis revealed that BMI was an independent predictor for CSS in male (HR: 0.4, 95%CI: 0.14 - 0.95, p=0.036), but not in female (HR: 0.73, 95%CI: 0.20 - 2.10, p=0.576).

Conclusion

Our findings collected from the multi-institutional Japanese dataset demonstrated the longer survival in patients with higher BMI compared to lower BMI for non-metastatic RCC treated with nephrectomy. Intriguingly, this finding was restricted to males, but not to females.

Introduction

Renal cell carcinoma (RCC) is the most common kidney cancer, and expected numbers in the United States account for 65,340 of new cases and 14,970 deaths in 2018 [1]. A number of risk factors of developing RCC have been reported, including smoking, hypertension, sex, and obesity [2]. Although obesity is a well-known factor of developing RCC, several studies have indicated that obese patients
treated with surgery for RCC may have a more favorable prognosis [3-7]. Recently, Albíges et al. further demonstrated that a multicenter cohort involving 1,975 patients from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and an external validation cohort of 4,657 patients revealed an improved survival in patients with higher body mass index (BMI) treated with molecular targeted agents for metastatic RCC [8]. However, whether these findings from the Caucasian population consistently can be applied in all races/ethnicity is still unknown. For example, a recent study suggested that RCC in Hispanic Americans and Native Americans have different clinical characteristics compared with European American patients [9, 10]. With regard to the Asian patients, the incidence of RCC seems to be less frequent in the Asian population than Caucasian, and treatment outcomes may differ between these ethnicities suggesting that the role of prognostic factors including BMI varies between ethnicities [11, 12]. In addition, several recent studies indicated that sex might affect the prognostic value of BMI in RCC [13, 14]. We previously reported the value of BMI as a prognostic factor in RCC treated with nephrectomy in the Asian patient cohort [15]. In the present study, we further assess the prognostic value of BMI using the multicenter-cohort dataset for the clinically localized RCC in Japanese patients who underwent nephrectomy with curative intent.

Material And Methods
Between 1987 and 2017, 760 RCC patients underwent either radical or partial nephrectomy in our multi-center cohort. Of them, clinicopathological data in 665 localized RCC patients with pT1-4 tumors without nodal and distant metastases at surgery were collected. Patients who did not undergo nephrectomy or had any missing clinicopathological/laboratory information were excluded from the study. The study design was approved in the institutional review board (IRB approval number: RIN-750-2571) and performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki [16].

Clinical stage in each patient was evaluated by computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and chest-X ray, and other patient information including performance status (Eastern Cooperative Oncology Group, ECOG-PS), BMI was preoperatively recorded within one month before surgery. BMI was calculated as the patient's weight at admission (in kilograms) divided
by the patient's height squared (in meters) and categorized based on WHO recommendations for Asians [17]. Pathological review, including Fuhrman nuclear grade [18] was examined in all patients as well as the 7th TNM classification of the UICC and AJCC guidelines of renal tumors. After discharge, follow up CT and Chest X-ray were performed to detect any findings suspected to disease progression every three months in the first year. Thereafter, patients were followed up every six months. Overall survival (OS) and cancer-specific survival (CSS) after nephrectomy were evaluated in all 665 patients. Follow-up was calculated from the day of surgery to the day of death or the last visit. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of disease recurrence or metastasis or the last follow-up in localized RCC patients.

The distribution of each factor was assessed by a contingency table with a Chi-square analysis. Kolmogorov-Smirnov normality was examined to check normal distribution in continuous variables followed by conducting a student's t-test, or one-way ANOVA was examined to assess the difference between the variables. For variables with non-normal distribution, Wilcoxon or Kruskal-Wallis test was performed to assess the difference. A Kaplan-Meier analysis was carried out to estimate survival free ratio, and a log-rank test was performed to compare the difference between assigned patient groups. On univariate and multivariate analysis, Cox proportional-hazard regression models were utilized to estimate crude hazard ratios (HR) followed by calculating covariate-adjusted HR. In all statistical analyses, a 2-sided p value of < 0.05 was considered significant. All analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

Results
Table 1 summarizes the clinical and pathologic characteristics of 665 patients according to BMI subgroups (< 25 kg/m2 and ≥ 25 kg/m2). There were 482 (72.5%) and 183 (27.5%) in male and female, respectively. Mean age in all patients was 62.2 ± 12.0 years (range: 21–91). The median follow-up time was 78.0 and 52 months for patients who survived (n = 561) and deceased (n = 104) during follow-up, respectively. Of the patients who deceased during follow-up, 62 (9.3%) patients died of RCC, 42 (6.3%) had died of other causes. During follow-up, 126 (18.9%) patients developed disease recurrence. The ECOG performance status was 0 in 612 patients (92.0%), 1 in 37 (5.6%), 2 in 13
(2.0%) and > 3 in 3 (0.4%). The histologic subtype of RCC was clear cell in 560 patients (84.2%), papillary in 73 (11.0%), chromophobe in 11 (1.7%) and others in 21 (3.1%). Pathological stage included pT1 in 520 patients (78.2%), pT2 in 61 (9.2%), pT3 in 80 (12.0%), pT4 in 4 (0.6%). Median tumor size was 4 cm (range: 0.9–18). The mean BMI (± SD) was 23.6 ± 3.2 kg/m² (range: 13-39.8) in the total cohort. There were 463 (69.6%) and 202 (30.4%) patients with BMI of < 25 kg/m² and ≥ 25 kg/m², respectively. No significant difference in the distribution of patient characteristics was seen between BMI groups in sex, histological subtypes, pathological stage, and tumor size, but age (< 65 vs > 65, p = 0.015) and ECOG-PS (0 vs > 1, p = 0.012).
Kaplan-Meier curves showed significantly longer OS in patients with higher BMI, in which the 5-year OS rates in BMI < 25 kg/m² and ≥ 25 kg/m² groups were 87.3% and 92.6%, respectively (P = 0.021) (Fig. 1). We also assessed CSS. As expected, the 5-year CSS and RFS rate was more favorable in

| Variables                  | Total (%) | <25    | ≥25    | P value |
|----------------------------|-----------|--------|--------|---------|
| No. of patients            | 665       | 463 (69.6) | 202 (30.4) |         |
| Sex                        |           |        |        |         |
| Male                       | 482 (72.5) | 332 (71.7) | 150 (74.3) | 0.498   |
| Female                     | 183 (27.5) | 131 (28.3) | 52 (25.7)  |         |
| Age                        |           |        |        |         |
| <85                        | 354 (53.2) | 232 (60.1) | 122 (60.4) | 0.015   |
| ≥85                        | 311 (46.8) | 231 (49.9) | 80 (39.6)  |         |
| ECOG-PS                    |           |        |        |         |
| 0                          | 612 (92.0) | 418 (90.3) | 194 (96.0) | 0.012   |
| ≥1                         | 53 (8.0)   | 45 (9.7)   | 8 (4.0)     |         |
| Histological type          |           |        |        |         |
| clear cell                 | 560 (84.2) | 380 (82.1) | 180 (89.1) | 0.116   |
| papillary                  | 57 (11.0)  | 57 (2.3)   | 16 (7.9)    |         |
| chromophobe                | 11 (1.7)   | 8 (1.7)    | 3 (1.5)     |         |
| others                     | 21 (3.2)   | 18 (3.9)   | 3 (1.5)     |         |
| Pathological stage         |           |        |        |         |
| 1                          | 520 (78.2) | 357 (77.1) | 163 (80.7) | 0.378   |
| 2                          | 61 (9.2)   | 42 (9.1)   | 19 (9.4)    |         |
| 3                          | 80 (12.0)  | 80 (13.0)  | 20 (9.9)    |         |
| 4                          | 4          | 4 (0.9)    | 0 (0)       |         |
| Tumor size                 |           |        |        |         |
| <4cm                       | 366 (55.1) | 252 (54.4) | 114 (56.7) | 0.588   |
| ≥4cm                       | 208 (44.9) | 211 (45.6) | 87 (43.3)  |         |

RCC: renal cell carcinoma, BMI: body mass index, ECOG-PS: eastern cooperative oncology group - performance status,
higher BMI (97.1 and 91.1%) compared to lower BMI group (92.5 and 82.7%) (P = 0.007 for CSS, and 
p = 0.019 for RFS) suggesting the prognostic value of BMI in patients with RCC treated with 
nephrectomy. Of note, when stratified by sex as shown in Fig. 2, significantly longer CSS in higher BMI 
was confirmed in male (5-year CSS of 92.7% in BMI < 25 and 98.1% in BMI ≥ 25, p = 0.005), while 
there was no difference in CSS between BMI groups for female patients (5-year CSS of 91.9% in BMI < 
25 and 93.7% in BMI ≥ 25, p = 0.738). Longer RFS in higher BMI group was also observed in male 
patients (5-year RFS of 82.1% in BMI < 25 and 92.4% in BMI ≥ 25, p = 0.009), but not in female (5-year 
RFS of 84.2% in BMI < 25 and 86.9% in BMI ≥ 25, p = 0.954). To further interrogate the prognostic 
value of putative variables affecting CSS, including BMI, univariate, and multivariate analysis was 
conducted (Table 2). In univariable analysis, ECOG-PS (HR: 4.42, 95%CI: 2.34–7.85, p < 0.001), 
histological subtype (HR: 8.63, 95%CI: 5.23–14.40, p < 0.001), pathological stage (HR: 7.06, 95%CI: 
4.23–11.68, p < 0.001), tumor size (HR: 8.84, 95%CI: 4.31–21.33, p < 0.001), and BMI (HR: 0.38, 
95%CI: 0.17–0.79, p = 0.003) were significantly correlated with CSS. On multivariate analysis to adjust 
the effect of those prognostic factors, increased BMI still remained as an independent prognostic 
factor of longer CSS (HR: 0.45, 95%CI: 0.21–0.87, p = 0.017). Finally, to assess whether the prognostic 
value of BMI is associated with sex, we separately examined the regression model analysis for the 
prediction of CSS according to sex (Table 3). Multivariate analysis revealed that BMI was an 
independent predictor for CSS in male (HR: 0.4, 95%CI: 0.14–0.95, p = 0.036), but not in female (HR: 
0.73, 95%CI: 0.20–2.10, p = 0.576).
Discussion

Obesity has been recognized as a risk factor for various diseases. To date, a number of epidemiological and clinical studies have suggested that obesity is a significant risk factor for developing RCC. Renehan et al. reported a systematic review of 221 databases to uncover the association between obesity and the occurrence of cancer [2]. They demonstrated that a 5 kg/m² increase in BMI was strongly associated with the risk of RCC in both men (HR: 1.24, p < 0.0001) and women (HR: 1.34, p < 0.0001). Intriguingly, there have also been a number of studies that showed a favorable clinical outcome in RCC patients with increased BMI compared to decreased BMI, which is known as the "obesity paradox", namely higher incidence and improved clinical outcome of RCC in higher BMI population [3, 6, 19]. In 1991, Yu et al. firstly investigated the prognosis of 360 RCC patients at 29 hospitals in Oklahoma between 1981 and 1987, and the disease-free survival and OS
were significantly longer in patients who were obese than in non-obese patients [19]. Thereafter, the finding of improved clinical outcome in higher BMI patients for RCC have been supported in considerable data from retrospective studies. In 2016, Donin and colleagues showed the data from a prospective randomized trial reporting an association between obesity and improved overall survival for patients with clear cell RCC [20]. These data were further supported in metastatic RCC in the recent large cohort study, which concludes that high BMI is a prognostic factor for improved survival and progression-free survival in patients with metastatic RCC treated with targeted therapy [8]. However, these findings were mainly derived from Caucasian population, which raise a question that BMI can also be applied in all race/ethnicity. In the Asian population, reports from Korean cohort studies consistently demonstrated the improved clinical outcomes in higher BMI patients [6, 21]. Recently, Byun et al. reported a large multicenter retrospective analysis of non-metastatic RCC in Korean cohort [22]. They demonstrated that higher BMI was associated with a favorable RFS and CSS among older patients (> 45 years) but not among young patients (< 45 years) concluding that association between obesity and prognosis in RCC might vary according to age. Interestingly, they also demonstrated that higher BMI is a favorable prognostic indicator in males, but not in female patients [13]. In Japanese RCC patients, several articles interrogating the prognostic value of BMI have been reported, all of which were conducted as single-institute cohort study [14, 15, 23]. In the current study, we conducted a multi-institutional cohort study for localized RCC patients who were treated with radical or partial nephrectomy. Consistent with the data from previous studies, increased BMI was significantly correlated with improved clinical outcomes compared to decreased BMI and remained as an independent predictor for longer CSS (p = 0.017) in patients with non-metastatic RCC treated with nephrectomy. Of note, our data also support the hypothesis that the prognostic value of BMI is male-specific as suggested by Byun et al. [13]. Of note, in their study, male patients had a higher BMI ratio than female patients (P = 0.03), whereas, in the present study, there was no significant difference in the distribution between BMI groups and sex, which allowed us to assess the crude effect of BMI on prognosis according to sex difference. Although several studies have sought to elucidate the biological underpinnings, a mechanism by
which obesity may improve clinical outcomes in RCC still remains unclear. Adipose tissue produces a variety of inflammatory factors, including leptin, adiponectin, and cytokines. Of them, leptin has been shown to upregulate expression of phosphorylated-STAT3 (signal transducers and activators of transcription 3), phosphorylated-ERK (extracellular signal-regulated kinase), and AP-1 (transcript activator protein 1), which might confer the proliferative effect on tumor cells [24]. On the other hands, there was a conflicting study showing that serum leptin level was positively correlated with BMI and inversely related to tumor stage and grade [25]. Given the multiple roles of leptin in chronic inflammation and autoimmunity [26], further experiments are required to answer the question. Ito and colleagues recently assessed the impact of BMI, serum adiponectin level, total adiponectin secretion from perinephric adipose tissue, and intratumor expression of adiponectin receptors in RCC [27]. In their study, secreted adiponectin levels in perinephric adipose tissue and intratumor adiponectin receptors (AdipoR1/R2) expression were not correlated with RCC aggressiveness or survival, whereas decreased BMI and increased serum adiponectin level was significantly associated with poor overall survival in patients with non-metastatic RCC, which might offer new molecular insight of ‘obese paradox’. Finally, The Cancer Genome Atlas (TCGA) data set revealed the downregulation of fatty acid synthase (FASN) in obese RCC patients by transcriptome analysis without specific DNA alternation [28]. They demonstrated that increased FASN mRNA expression level was associated with lower BMI and shorter OS. Furthermore, in the IMDC biospecimen cohort, FASN immunohistochemistry positivity was significantly more detected in IMDC poor (48%) and intermediate (34%) risk groups than in the favorable risk group (17%) indicating the potential role of FASN regulating lipid homeostasis in RCC [8].

The present study had some limitations. Firstly, the patient selection was biased as the cohort in the study was retrospectively designed. Secondly, we could not assess potential prognostic factors, such as smoking, molecular markers, and peripheral blood measurement at surgery [29–31]. Nevertheless, our findings collected from multi-institutional Japanese data set further confirmed the improved survival in patients with higher BMI compared to lower BMI for non-metastatic RCC treated with nephrectomy, and intriguingly, this finding was restricted to male, but not to female. These findings
might help physicians to make decision making in daily practice. Further research is warranted to unveil the biological mechanisms, which is responsible for the benefit of high BMI on improved RCC survival in males.

Conclusion

Our findings collected from the multi-institutional Japanese dataset demonstrated the longer survival in patients with higher BMI compared to lower BMI for non-metastatic RCC treated with nephrectomy. Intriguingly, this finding was restricted to males, but not to females.

Declarations

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Conflict of interest statement

The authors have no conflict of interest.

Conflict of interest statement:

The authors have declared that no conflict of interest exists.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.

2. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569-78.

3. Waalkes S, Merseburger AS, Kramer MW, Herrmann TR, Wegener G, Rustemeier J, Hofmann R, Schrader M, Kuczyk MA, Schrader AJ. Obesity is associated with improved survival in patients with organ-confined clear-cell kidney cancer. Cancer Causes Control. 2010;21(11):1905-10.

4. Donat SM, Salzhauer EW, Mitra N, Yanke BV, Snyder ME, Russo P. Impact of body
mass index on survival of patients with surgically treated renal cell carcinoma. J Urol. 2006;175(1):46-52.

5. van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA. Relation of height, body mass, energy intake, and physical activity to risk of renal cell carcinoma: results from the Netherlands Cohort Study. Am J Epidemiol. 2004;160(12):1159-67.

6. Jeon HG, Jeong IG, Lee JH, Lee CJ, Kwak C, Kim HH, Lee SE, Lee E. Prognostic value of body mass index in Korean patients with renal cell carcinoma. J Urol. 2010;183(2):448-54.

7. Kamat AM, Shock RP, Naya Y, Rosser CJ, Slaton JW, Pisters LL. Prognostic value of body mass index in patients undergoing nephrectomy for localized renal tumors. Urology. 2004;63(1):46-50.

8. Albiges L, Hakimi AA, Xie W, McKay RR, Simantov R, Lin X, Lee JL, Rini BI, Srinivas S, Bjarnason GA, et al. Body Mass Index and Metastatic Renal Cell Carcinoma: Clinical and Biological Correlations. J Clin Oncol. 2016;34(30):3655-63.

9. Batai K, Harb-De la Rosa A, Lwin A, Chaus F, Gachupin FC, Price E, Lee BR. Racial and Ethnic Disparities in Renal Cell Carcinoma: An Analysis of Clinical Characteristics. Clin Genitourin Cancer. 2019;17(1):e195-202.

10. Suarez-Sarmiento A, Yao X, Hofmann JN, Syed JS, Zhao WK, Purdue MP, Chow WH, Corley D, Shuch B. Ethnic disparities in renal cell carcinoma: An analysis of Hispanic patients in a single-payer healthcare system. Int J Urol. 2017;24(10):765-70.

11. Naito S, Tomita Y, Rha SY, Uemura H, Oya M, Song HZ, Zhong LH, Wahid MI. Kidney Cancer Working Group report. Jpn J Clin Oncol. 2010;40(Suppl 1):i51-6.

12. Naito S, Yamamoto N, Takayama T, Muramoto M, Shinohara N, Nishiyama K, Takahashi A, Maruyama R, Saika T, Hoshi S, et al. Prognosis of Japanese metastatic...
renal cell carcinoma patients in the cytokine era: a cooperative group report of 1463 patients. Eur Urol. 2010;57(2):317-25.

13. Byun SS, Hwang EC, Kang SH, Hong SH, Chung J, Kwon TG, Kim HH, Kwak C, Kim YJ, Lee WK. Sex-Specific Prognostic Significance of Obesity in Nonmetastatic Clear-Cell Renal-Cell Carcinoma in Korea: A Large Multicenter Cohort Analysis. Clin Genitourin Cancer 2017.

14. Ohno Y, Nakashima J, Nakagami Y, Satake N, Gondo T, Ohori M, Hatano T, Tachibana M. Sex and the clinical value of body mass index in patients with clear cell renal cell carcinoma. Br J Cancer. 2013;109(7):1899-903.

15. Komura K, Inamoto T, Black PC, Koyama K, Katsuoka Y, Watsuji T, Azuma H. Prognostic significance of body mass index in Asian patients with localized renal cell carcinoma. Nutr Cancer. 2011;63(6):908-15.

16. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

17. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157-63.

18. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6(7):655-63.

19. Yu ML, Asal NR, Geyer JR. Later recurrence and longer survival among obese patients with renal cell carcinoma. Cancer. 1991;68(7):1648-55.

20. Donin NM, Pantuck A, Klopfer P, Bevan P, Fall B, Said J, Beldegrun AS, Chaimie K. Body Mass Index and Survival in a Prospective Randomized Trial of Localized High-Risk Renal Cell Carcinoma. Cancer Epidemiol Biomarkers Prev. 2016;25(9):1326-32.

21. Choi Y, Park B, Jeong BC, Seo SI, Jeon SS, Choi HY, Adami HO, Lee JE, Lee HM. Body mass index and survival in patients with renal cell carcinoma: a clinical-based cohort
and meta-analysis. Int J Cancer. 2013;132(3):625–34.

22. Byun SS, Hwang EC, Kang SH, Hong SH, Chung J, Kwon TG, Kim HH, Kwak C, Kim YJ, Lee WK. Age-dependent prognostic value of body mass index for non-metastatic clear cell renal cell carcinoma: A large multicenter retrospective analysis. J Surg Oncol. 2018;118(1):199–205.

23. Awakura Y, Nakamura E, Ito N, Yamasaki T, Kamba T, Kamoto T, Ogawa O. Influence of body mass index on prognosis of Japanese patients with renal cell carcinoma. Urology. 2007;70(1):50–4.

24. Hu X, Juneja SC, Maihle NJ, Cleary MP. Leptin—a growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst. 2002;94(22):1704–11.

25. Rasmuson T, Grankvist K, Jacobsen J, Olsson T, Ljungberg B. Serum insulin-like growth factor-1 is an independent predictor of prognosis in patients with renal cell carcinoma. Acta Oncol. 2004;43(8):744–8.

26. La Cava A, Alviggi C, Mataire G. Unraveling the multiple roles of leptin in inflammation and autoimmunity. J Mol Med (Berl). 2004;82(1):4–11.

27. Ito R, Narita S, Huang M, Nara T, Numakura K, Takayama K, Tsuruta H, Maeno A, Saito M, Inoue T, et al. The impact of obesity and adiponectin signaling in patients with renal cell carcinoma: A potential mechanism for the "obesity paradox". PLoS One. 2017;12(2):e0171615.

28. Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G, Mikklineni N, Fiegoli B, Kim PH, Voss MH, et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. J Natl Cancer Inst. 2013;105(24):1862–70.

29. Tsujino T, Komura K, Hashimoto T, Muraoka R, Satake N, Matsunaga T, Tsutsumi T,
Yoshikawa Y, Takai T, Minami K, et al: C-reactive protein-albumin ratio as a prognostic factor in renal cell carcinoma - A data from multi-institutional study in Japan. *Urol Oncol* 2019.

30. Tsujino T, Komura K, Ichihashi A, Tsutsumi T, Matsunaga T, Yoshikawa Y, Maenosono R, Okita K, Takai T, Oide R, et al. The combination of preoperative platelet count and neutrophil lymphocyte ratio as a prognostic indicator in localized renal cell carcinoma. *Oncotarget*. 2017;8(66):110311–25.

31. Tsujino T, Komura K, Matsunaga T, Yoshikawa Y, Takai T, Uchimoto T, Saito K, Tanda N, Oide R, Minami K, et al. Preoperative Measurement of the Modified Glasgow Prognostic Score Predicts Patient Survival in Non-Metastatic Renal Cell Carcinoma Prior to Nephrectomy. *Ann Surg Oncol*. 2017;24(9):2787–93.

**Figures**

![Kaplan-Meier curves of OS, CSS, and RFS in 655 localized RCC patients according to BMI subgroups.](image)

**Figure 1**

Kaplan-Meier curves of OS, CSS, and RFS in 655 localized RCC patients according to BMI subgroups.
Figure 2

Kaplan-Meier curves of CSS, and RFS in localized RCC patients according to BMI subgroups with the stratification by sex.