ORIGINAL ARTICLE

DOI: 10.37047/jos.galenos.2025.2025-11-10

J Oncol Sci 2025;11(3):269-275



# Body Mass Index as an Independent Prognostic Factor in Second-Line Nivolumab Therapy for Metastatic Clear Cell Renal Cell Carcinoma

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## ABSTRACT

**Objective:** Metastatic renal cell carcinoma (RCC) remains a therapeutic challenge despite significant advances with immune checkpoint inhibitors (ICIs). Nivolumab has demonstrated durable responses in pretreated metastatic clear cell RCC; however, prognostic and predictive biomarkers of response remain limited. Recent data suggest that increased body mass index (BMI) may correlate with improved survival outcomes in patients receiving ICIs, a phenomenon referred to as the "obesity paradox".

**Material and Methods:** This multicenter retrospective study evaluated the prognostic impact of BMI in 117 patients with metastatic clear cell RCC who received second-line nivolumab monotherapy following progression on prior tyrosine kinase inhibitor therapy.

**Results:** The median BMI was 26.0 kg/m.; 40.3% were classified as underweight or normal, and 59.7% as overweight or obese. The median progression-free survival was 8.1 months [95% confidence interval (CI) 6.1-10.1], and the median overall survival (OS) was 24.7 months (95% CI 17.6-31.7). Overweight or obese (BMI ≥25 kg/m.) patients had longer OS than underweight or normal-weight patients (31.2 vs. 20.9 months, p=0.039). In the multivariate Cox regression analysis, higher Eastern Cooperative Oncology Group performance status (≥2), sarcomatoid differentiation, and liver and bone metastases were independent adverse prognostic factors, whereas higher BMI remained an independent favorable prognostic factor (HR=0.60, 95% CI 0.36-0.99, p=0.045).

**Conclusion:** These results suggest that BMI may serve as a simple and clinically relevant prognostic marker in this population. Further large-scale prospective studies incorporating body composition and biomarker analyses are warranted to clarify the underlying mechanisms of this association.

**Keywords:** Renal cell carcinoma; nivolumab; body mass index; obesity; prognosis

## INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common urinary system malignancies in adults, and nearly half of patients initially diagnosed with localized disease eventually develop metastatic disease.[1,2] Over the past three decades, treatment strategies for metastatic RCC have evolved remarkably, from cytokine-based therapies in the 1990s to targeted agents in the 2000s, and more recently to the immuno-oncology era driven by immune checkpoint inhibitors (ICIs).[3-5] Reflecting these advances, the anti-programmed cell death protein-1 monoclonal antibody, nivolumab, has been shown to improve overall survival (OS) in patients previously treated with tyrosine kinase inhibitors (TKIs) and has become a standard option in clinical practice.[4]

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**Received:** 01.12.2025 **Accepted:** 19.12.2025 **Publication Date:** 23.12.2025

**Cite this article as:** Ön S, İçli MC, Ulaşlı T, et al. Body mass index as an independent prognostic factor in second-line nivolumab therapy for metastatic clear cell renal cell carcinoma. J Oncol Sci. 2025;11(3):269-275

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However, despite these therapeutic improvements, long-term outcomes remain suboptimal, with 5-year OS rates of approximately 26% among patients treated with nivolumab.[4] This highlights the ongoing need to identify reliable prognostic and predictive biomarkers to better determine which patients derive the greatest benefit from immunotherapy. Currently, the International Metastatic RCC Database Consortium (IMDC) and the Memorial Sloan Kettering Cancer Center scores are the most widely used prognostic models for risk stratification and treatment decision-making.[6,7] Nevertheless, these models may not fully capture the evolving clinical dynamics associated with modern immunotherapy.

Recent studies have reported that a higher body mass index (BMI) may be associated with improved clinical outcomes in patients with metastatic RCC treated with ICIs.[8-10] This observation has been described as the "obesity paradox", because obesity is also a well-established risk factor for the development of RCC.[11] Most existing studies, however, include heterogeneous patient populations encompassing different treatment lines and histologic subtypes. In addition, ICI monotherapy and various combination regimens (ICI-TKI or ICI-ICI) are often analyzed together, which makes it difficult to interpret the specific impact of BMI within more homogeneous settings. This methodological variability particularly limits the ability to clarify the association between BMI and survival in patients with clear-cell histology receiving second-line nivolumab monotherapy.

To address this gap, a multicenter retrospective study was conducted to evaluate the impact of BMI on treatment outcomes and survival in patients with metastatic clear cell RCC who received nivolumab monotherapy as second-line therapy.

## MATERIAL AND METHODS

This multicenter, retrospective study included patients with metastatic RCC who received nivolumab as second-line treatment following progression on a TKI at three tertiary oncology centers in Türkiye between 2016 and 2025. Eligible patients were adults aged 18 years or older with histologically confirmed clear-cell RCC and measurable disease according to RECIST 1.1 criteria. Patients with non-clear-cell histology or those who received nivolumab in the first-line or beyond the second-line setting were excluded. Baseline demographics, disease characteristics, treatment exposure, and outcomes were collected from institutional databases and harmonized across centers using a standardized data form. BMI was calculated at the initiation of nivolumab as body weight (kg) divided by height squared ($m^2$), in accordance with World Health Organization recommendations. Patients were categorized into two groups: <25 $kg/m^2$ (underweight/normal) and ≥25 $kg/m^2$ (overweight/obese). Clinical variables included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, IMDC risk category, and metastatic sites. Treatment efficacy was assessed based on objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and OS. ORR was defined as the proportion of patients achieving complete response or partial response; DCR was defined as the proportion of patients whose best overall response was complete response, partial response, or stable disease. PFS was measured from the initiation of nivolumab to radiologic or clinical progression, or death, whichever occurred first. OS was defined as the time from nivolumab initiation to death from any cause; patients who were still alive were censored at last follow-up.

### Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as medians and interquartile ranges (IQR), and categorical variables as counts and percentages. Differences between BMI groups were assessed using the Mann-Whitney U test and the chi-square test, as appropriate. Cox proportional hazards models were used to evaluate predictors of PFS and OS. Only variables with a p-value <0.10 in univariate Cox analysis were included in the multivariate models. All tests were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ege University Faculty of Medicine Ethics Committee (approval number: 25-10T/43, date: 02.10.2025).

## RESULTS

A total of 117 patients with metastatic RCC treated with nivolumab were included. The median age was 59 years (IQR, 52-67), and 71.8% of the participants were male. ECOG performance status was 0-1 in 82.1% of patients. According to the IMDC classification, 22.2% were in the favorable-risk group, 51.3% in the intermediate-risk group, and 20.5% in the poor-risk group. The median BMI was 26.0 $kg/m^2$ (IQR, 23.0-28.9). According to BMI classification, 2.6% of patients were underweight (<18.5 $kg/m^2$), 37.6% were of normal weight (18.5-24.9 $kg/m^2$), 40.2% were overweight (25-29.9 $kg/m^2$), and 19.7% were obese (≥30 $kg/m^2$). Overall, 40.3% of patients were categorized as underweight/normal and 59.7% as overweight/obese. The most common metastatic sites were the lungs (70.6%) and bones (43.5%); liver metastases were present in 21.8% of patients. Sarcomatoid differentiation was observed in 9.2% of patients and was

not reported for 30% of patients. A prior nephrectomy had been performed in 48.7% of patients. Baseline characteristics were comparable between BMI groups (Table 1). The most common first-line therapy before nivolumab was pazopanib (61.5%), followed by sunitinib (30.8%) and cabozantinib (7.7%). The distribution of first-line agents did not differ significantly between BMI groups (p=0.33). The median PFS with first-line therapy was 12.6 months [95% confidence interval (CI): 8.9-16.4].

Among evaluable patients who received nivolumab as second-line therapy, the ORR was 23.1% and the DCR was 57.3%. ORR was 14.9% in the underweight/normal BMI group and 28.6% in the overweight/obese group (p=0.08), while DCR was 48.9% in the underweight/normal BMI group and 62.9% in the overweight/obese group (p=0.13) (Table 2). The median PFS among patients receiving nivolumab was 8.1 months (95% CI: 6.1-10.1). When stratified by BMI, the median PFS was 6.7 months (95% CI: 4.2-9.2) in the underweight/normal BMI group and 8.3 months (95% CI: 3.2-13.5) in the overweight/obese group, indicating a numerically longer, but not statistically significant, PFS among patients with higher BMI (log-rank p=0.138; Figure 1). In univariate Cox analysis, higher ECOG performance status [hazard ratio (HR)=10.83; 95% CI: 4.34-27.03; p<0.001] and poor IMDC risk (HR=2.80; 95% CI: 1.49-5.22; p<0.001) were significantly associated with shorter PFS. The presence of liver metastases (HR=2.05; 95% CI: 1.29-3.27; p=0.003) or bone metastases (HR=1.65; 95% CI: 1.10-2.49; p=0.016) was also associated with an increased risk of disease progression.

The median OS for the entire cohort was 24.7 months (95% CI: 17.7-31.7). When patients were stratified by BMI, median OS was 21.0 months (95% CI: 15.5-26.4) in the underweight/normal group and 31.2 months (95% CI: 11.7-50.6) in the overweight/obese group (Figure 2). Patients with higher BMI had significantly longer OS (log-rank test, p=0.039). As presented in Table 3, the multivariate Cox regression analysis identified several independent prognostic factors for overall survival. A higher ECOG performance status (≥2) emerged as the strongest predictor of poor prognosis (HR=24.83, 95% CI: 6.16-100.17, p<0.001). The presence of sarcomatoid differentiation (HR=4.27, 95% CI: 1.89-9.64, p<0.001), liver metastasis (HR=1.92, 95% CI: 1.06-3.47, p=0.032), and bone metastasis (HR=1.65, 95% CI: 1.00-2.82, p=0.046) was also independently associated with worse overall survival. In contrast, patients categorized as overweight or obese demonstrated significantly better survival compared with those with normal or low BMI (HR=0.60; 95% CI: 0.36-0.99; p=0.045).

**TABLE 1: Baseline patient characteristics according to BMI group.**

| Variable | All patients (n=117) | Underweight/normal (n=47) | Overweight/obese (n=70) | p-value |
|---|---|---|---|---|
| Age, median (IQR), years | 59.0 (52.0-66.5) | 60.5 (53.0-68.0) | 58.0 (50.0-65.0) | 0.44 |
| Male sex, n (%) | 84 (71.4) | 33 (70.2) | 51 (72.9) | 0.63 |
| ECOG 0-1, n (%) | 96 (82.1) | 37 (78.7) | 59 (84.3) | 0.52 |
| IMDC n (%) | | | | |
| Favorable | 26 (22.2) | 12 (25.5) | 14 (20) | 0.78 |
| Intermediate | 60 (51.3) | 22 (46.8) | 38 (54.3) | |
| Poor | 24 (20.5) | 10 (21.3) | 14 (20) | |
| Unknown | 7 (6) | 3 (6.4) | 4 (5.7) | |
| Sarcomatoid differentiation n (%) | 11 (9.2) | 4 (8.5) | 7 (10) | 0.85 |
| Prior nephrectomy n (%) | 57 (48.7) | 28 (58.6) | 29 (41.4) | 0.06 |
| First-line TKI n (%) | | | | |
| Sunitinib | 36 (30.8) | 14 (29.8) | 22 (31.4) | 0.33 |
| Pazopanib | 72 (61.5) | 28 (59.6) | 44 (62.9) | |
| Cabozantinib | 9 (7.7) | 5 (10.6) | 4 (5.7) | |
| Lung metastasis, n (%) | 82 (71.3) | 35 (77.8) | 47 (67.1) | 0.22 |
| Liver metastasis, n (%) | 26 (22.6) | 14 (31.1) | 12 (17.1) | 0.08 |
| Bone metastasis, n (%) | 50 (43.5) | 17 (37.8) | 33 (47.1) | 0.32 |
| Brain metastasis, n (%) | 11 (9.6) | 3 (6.8) | 8 (11.4) | 0.14 |

BMI: Body mass index; ECOG: Eastern cooperative oncology group; IMDC: International metastatic renal cell carcinoma database consortium; IQR: Interquartile ranges; TKI: Tyrosine kinase inhibitor.

| TABLE 2: Treatment efficacy according to BMI group. | | | | |
|---|---|---|---|---|
| **Outcome** | **All patients (n=117)** | **Underweight/normal** | **Overweight/obese** | **p-value** |
| ORR (CR+PR), n (%) | 27 (23.1) | 7 (14.9) | 20 (28.6) | 0.08 |
| DCR (CR+PR+SD), n (%) | 67 (57.3) | 23 (48.9) | 44 (62.9) | 0.13 |

BMI: Body mass index; ORR: Objective response rate; DCR: Disease control rate; CR: Complete response; PR: Partial response; SD: Stable disease.

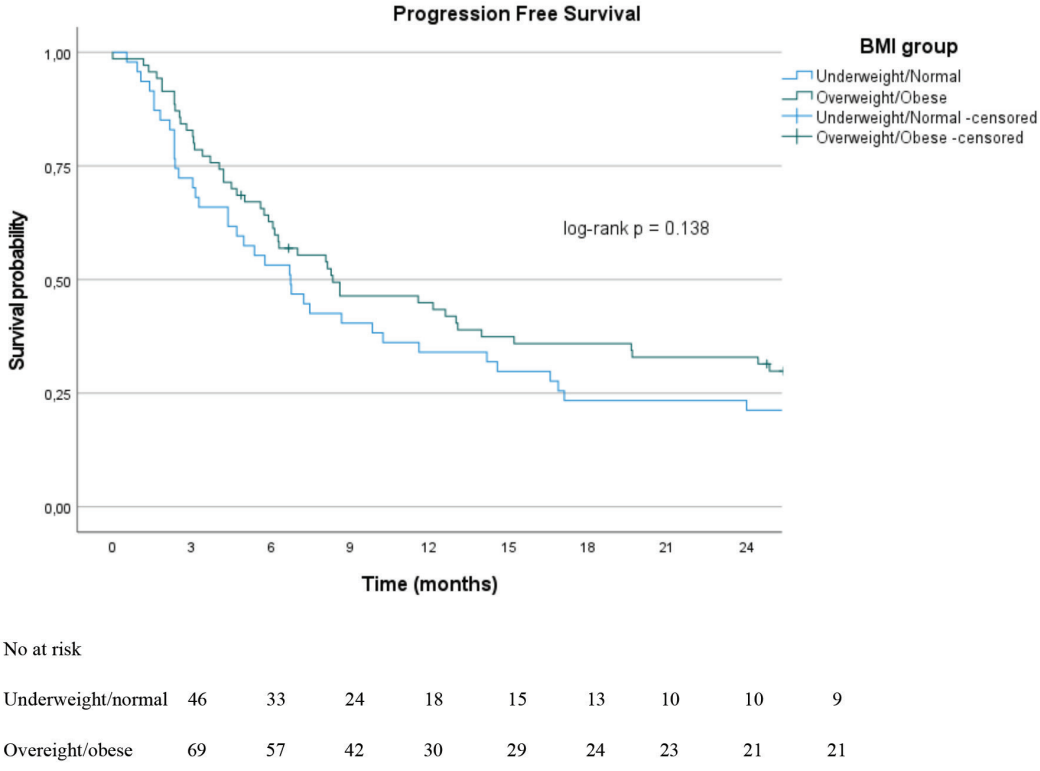


**FIGURE 1.** Kaplan-Meier curves for progression-free survival (PFS according to body mass index (BMI) group in patients treated with second-line nivolumab. Median PFS was 6.7 months [95% confidence interval (CI): 4.2-9.2] in the underweight/normal group and 8.3 months (95% CI: 3.2-13.5) in the overweight/obese group. The difference between groups was not statistically significant (log-rank p=0.138). Numbers at risk for each BMI category are shown below the x-axis.

## DISCUSSION

In this multicenter retrospective study, overweight and obese patients treated with second-line nivolumab for metastatic clear cell RCC demonstrated improved OS compared with patients with normal or low BMI; median survival increased from approximately 21 to 31 months (nearly one year). In the pivotal prospective trial that established nivolumab for metastatic RCC, the median OS was 26 months, which closely matched the outcome observed in our cohort.[4]

In a retrospective cohort of 203 patients, obesity was associated with longer OS in the unadjusted analysis (HR=0.54, 95% CI: 0.31-0.95), but this association attenuated after adjustment for the IMDC risk score (HR=0.72, 95% CI: 0.40-1.30).[12] Similarly, a recent meta-analysis of over 2,000 ICI-treated metastatic RCC patients confirmed improved OS among those with higher BMI (HR=0.77, 95% CI: 0.65-0.91).[13] However, these analyses included patients treated at various lines of therapy and with non-clear-cell histologies, thereby limiting the specificity of the analyses. Our study confirms this favorable prognostic effect of higher BMI in a more homogeneous cohort, demonstrating that increased BMI independently predicts survival regardless of other prognostic variables.

Two major studies, the IMDC-based multicenter analysis and the ARON-1 trial, also reported prolonged OS among overweight and obese patients with metastatic RCC. In the IMDC cohort (n=735), higher BMI was associated with better OS (HR=0.75, 95% CI: 0.57-0.97), but was not associated with significant differences in PFS or ORR.[14] Likewise, the ARON-1 study (n=675) found longer OS among overweight/obese patients (55.7 vs. 28.4 months; p=0.001), while PFS and ORR

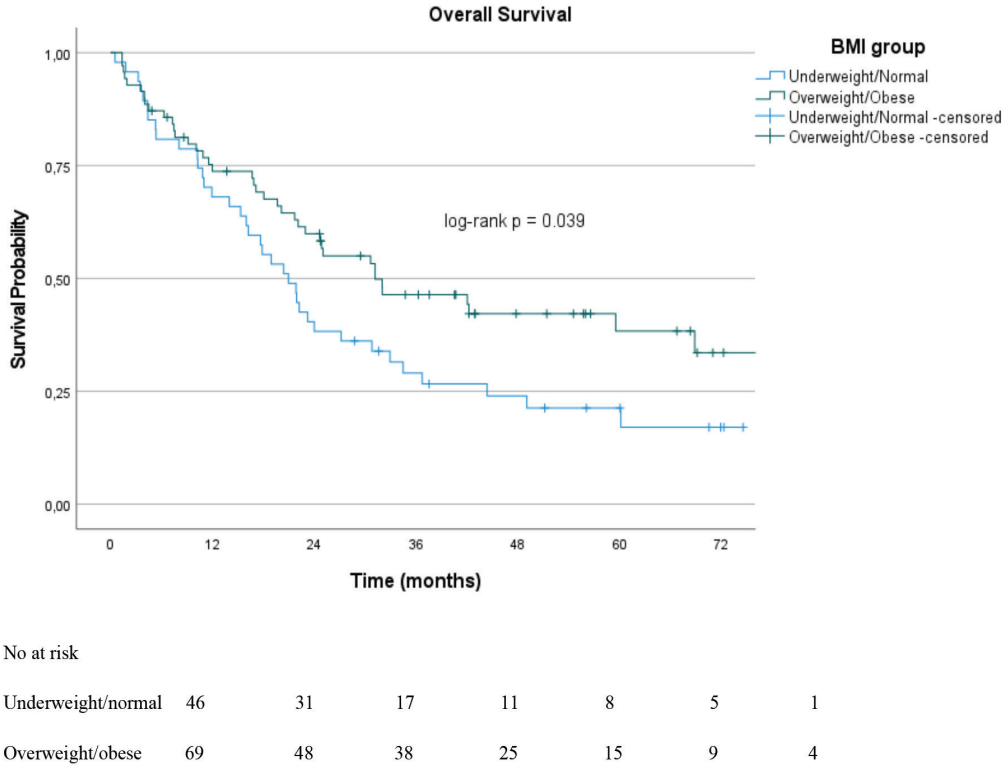


**FIGURE 2.** Kaplan-Meier curves for overall survival (OS) according to body mass index (BMI) group in patients treated with second-line nivolumab. Median OS was 21.0 months [95% confidence interval (CI): 15.5-26.4] in the underweight/normal group and 31.2 months (95% CI: 11.7-50.6) in the overweight/obese group (log-rank p=0.039). Numbers at risk for each BMI group are shown below the x-axis.

**TABLE 3: Univariate and multivariate cox regression analysis for overall survival.**

| Variable | Univariate HR (95% CI) | p-value | Multivariate HR (95% CI) | p-value |
|---|---|---|---|---|
| ECOG ≥2 | 10.83 (4.34-27.03) | **<0.001** | 24.83 (6.16-100.17) | **<0.001** |
| IMDC (intermediate vs. favorable) | 1.40 (0.74-2.62) | 0.29 | 1.36 (0.79-3.07) | 0.155 |
| IMDC (poor vs. favorable) | 3.15 (1.56-6.37) | **0.001** | 3.01 (1.15-7.89) | **0.02** |
| Sarcomatoid differentiation | 2.11 (1.09-4.08) | **0.026** | 4.27 (1.89-9.64) | **<0.001** |
| Liver metastasis | 2.05 (1.29-3.27) | **0.003** | 1.92 (1.06-3.47) | **0.032** |
| Bone metastasis | 1.65 (1.10-2.49) | **0.016** | 1.65 (1.00-2.82) | **0.046** |
| BMI (overweight/obese vs. normal) | 0.63 (0.40-0.98) | **0.041** | 0.60 (0.36-0.99) | **0.045** |
| Brain metastasis | 1.96 (0.97-3.95) | 0.061 | 1.43 (0.67-3.03) | 0.35 |
| Lung metastasis | 1.47 (0.85-2.53) | 0.164 | – | |
| Age | 1.02 (0.99-1.04) | 0.152 | – | – |
| Sex (male) | 1.23 (0.73-2.07) | 0.436 | – | – |
| Prior nephrectomy | 1.05 (0.67-1.64) | 0.848 | – | – |

BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; IMDC: International metastatic renal cell carcinoma database consortium; HR: Hazard ratio; CI: Confidence interval; Significant p-values are highlighted in bold.

remained similar between groups (PFS: 15.9 vs. 14.1 months; p=0.07).[15] Similar findings have been reported in patients receiving ICIs across various cancer types, not limited to renal cell carcinoma.[16] Consistent with these findings, our results showed improved OS but no enhancement in short-term efficacy measures, suggesting that the benefit of ICIs stems from a longer duration of response rather than higher initial response rates.[17]

The biological mechanisms underlying the association between obesity and improved ICI outcomes remain unclear.

Preclinical data suggest that obesity alters the tumor microenvironment via metabolic and immune modulation, affecting oxidative phosphorylation, angiogenesis, and immune infiltration-changes that may enhance antitumor responses.[18,19] Furthermore, increased adipose-derived leptin signaling and modified T-cell metabolism have been proposed to contribute to prolonged immune activation and to sustained response duration.[20,21] However, as our study was retrospective and lacked translational analyses, these mechanisms could not be directly evaluated. Prospective studies integrating metabolic, immune, and molecular profiling are needed to clarify this association.

In our study, the lungs were the most common metastatic site; liver and bone metastases were observed in 22% and 43% of patients, respectively. These findings are consistent with previous reports, which documented liver and bone metastasis rates of 12-20% and 25-35%, respectively.[22] The negative prognostic impact of liver and bone metastases was also confirmed in our analysis.[23] Sarcomatoid differentiation is observed in approximately 20% of metastatic RCC cases and is associated with poor prognosis.[24] However, ICIs have demonstrated greater efficacy than TKIs in this subgroup.[25] In our study, sarcomatoid differentiation was identified as a negative prognostic factor. Nonetheless, it (sarcomatoid differentiation) was not reported in one-third of patients; this limits the reliability of the findings and underscores the importance of consistent reporting of sarcomatoid differentiation in pathology reports. The prognostic impact of performance status and IMDC risk score was also consistent with previous literature.[6]

### Study Limitations

This study has several limitations. First, due to its retrospective design, potential biases, such as patient selection and missing data, could not be eliminated. Second, certain pathological parameters, including sarcomatoid differentiation, were not available for all patients, which may have limited the robustness of the multivariate analyses. Third, only patients who received second-line nivolumab monotherapy were included; therefore, the findings may not be generalizable to other treatment combinations or lines of therapy. Additionally, BMI was calculated using baseline measurements obtained before nivolumab initiation; longitudinal changes in body weight or body composition (e.g., muscle mass) were not assessed. Because the number of patients with an underweight BMI was very small, they were not analyzed as a separate subgroup; consequently, no specific conclusions could be drawn for this population. Consequently, prospective studies with larger cohorts and comprehensive biomarker analyses are needed to validate and expand upon these findings.

## CONCLUSION

This multicenter retrospective study evaluated the prognostic impact of BMI on patients with metastatic clear-cell RCC who were treated with second-line nivolumab monotherapy. Our findings demonstrated that patients with higher BMI had significantly longer OS; this association remained independent of other established prognostic factors. These results suggest that the efficacy of ICIs may be influenced not only by tumor biology but also by the patient's metabolic status. However, given the retrospective nature of the study and limited sample size, prospective large-scale investigations incorporating biomarker analyses are warranted to validate the prognostic value of BMI in this setting.

### Ethics

**Ethics Committee Approval:** The study adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ege University Faculty of Medicine Ethics Committee (approval number: 25-10T/43, date: 02.10.2025).

**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: S.Ö., G.Ş., A.G., M.E., E.G.; Concept: S.Ö., G.Ş., A.G., H.Ç.Y., H.S.S., M.E., E.G.; Design: S.Ö., G.Ş., A.G., H.Ç.Y., M.E., E.G.; Data Collection or Processing: S.Ö., M.C.İ., T.U., G.Ş., A.G., B.Ç.Q., Y.E.S., H.Ç.Y., H.S.S.; Analysis or Interpretation: S.Ö., M.C.İ., T.U., B.Ç.Q., Y.E.S., H.Ç.Y., E.G.; Literature Search: S.Ö., T.U., B.Ç.Q., Y.E.S., H.Ç.Y.; Writing: S.Ö., M.C.İ., T.U., H.Ç.Y., H.S.S., M.E., E.G.

**Conflict of Interest:** Hüseyin Salih Semiz MD is section chief in Journal of Oncological Sciences. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

**Financial Disclosure:** The authors declared that this study received no financial support.

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