Acta Medica Alanya

RESEARCH ARTICLE

ARAŞTIRMA MAKALESİ

Acta Medica Alanya

2025;9(1):55-63

DOI: 10.30565/medalanya.1606884

Impact of Serum Sodium Levels on Treatment Efficacy and Prognosis in Advanced Renal Cell Carcinoma Patients Receiving Subsequent Line Nivolumab

İkinci Sıra veya Sonrasında Nivolumab ile Tedavi Edilen Metastatik Renal Hücreli Karsinom Hastalarında Serum Sodyum Düzeyinin Sağkalım Üzerine Etkisi

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ABSTRACT

Aim: We aimed to evaluate the effect of serum sodium levels on treatment efficacy and prognosis in metastatic renal cell cancer (RCC) patients receiving subsequent line Nivolumab.

Methods: This retrospective, single-center study include 55 patients (n=55). Clinicopathological factors and serum sodium levels were recorded before nivolumab (pre-ICI) initiation and at the eighth week of nivolumab (post-ICI). Patients were divided into two groups according to the median sodium levels for pre-ICI (138 mEq/L) and post-ICI 137 (mEq/L). Cox regression analysis was used to determine proportional hazards.

Results: The median age of the study population was 63 (33-90) and 44 (78.6%) patients were male. Progression-free survival (PFS) ans overall survial (OS) was similar for pre-ICI sodium low and high patients. However, post-ICI sodium-high patients had significantly longer PFS [30.9 months, 95% CI; (2.0-59.9) ve 3.4 months, %95 CI; (0.0-7.1); respectively (p<0.001)] and OS [NR vs 9.1 months, 95% CI; (0.0-22.6); (p<0.001)] than the patients with low post-ICI sodium levels. In the multivariate analyses, the only independent predictor was post-ICI sodium level for both PFS [HR: 0.288; 95% CI 0.149-0.559, (p<0.001)] and OS [HR: 0.239; 95% CI, 0.107-0.533, (p<0.001)].

Conclusion: Our results are consistent with those of previous studies showing the prognostic and predictive value of serum sodium levels. As serum sodium is an easy, fast, and affordable marker, it may be a feasible prognostic marker. More comprehensive studies are needed to highlight this topic.

Key Words: Renal cell carcinoma, Immunotherapy, Sodium, Prognosis

ÖZ

Amaç: Bu çalışmada, ikinci sıra ve ötesinde Nivolumab ile tedavi edilen metastatik renal hücreli karsinom (RCC) hastalarında serum sodyum düzeyinin tedavi etkinliği ve prognoz üzerindeki etkisini değerlendirmeyi amaçladık.

Yöntem: Tek merkezli retrospektif bir çalışma olarak tasarlanan bu araştırmaya 55 hasta (n=55) dahil edildi. Klinikopatolojik faktörler ve serum sodyum seviyeleri, Nivolumab başlamadan önce ve Nivolumab'ın sekizinci haftasında olmak üzere kaydedildi. Hastalar medyan sodyum değerline (Nivolumab öncesi için 138 mEq/L ve sekizinci hafta için 137 mEq/L) göre dikotomize edildi. Sodyum dahil progresyona etki eden faktörler cox-regresyon ile incelendi.

Bulgular: Çalışma popülasyonunun medyan yaşı 63 (33-90) olup, 44'ü (%78.6) erkekti. Tedavi öncesi düşük sodyum (≤138 mEq/L) ve yüksek sodyum (>138 mEq/L) değerine sahip hastalar arasında progresyonsuz sağkalım (PFS) açısından fark bulunmazken (p=0.507), sekizince hafta yüksek sodyum seviyesine (>137 mEq/L) sahip hastalarda PFS, düşük sodyum seviyesine (≤137 mEq/L) sahip hastalardan belirgin şekilde daha uzundu [30.9 ay, %95 GA; (2.0-59.9) ve 3.4 ay, %95 GA; (0.0-7.1); sırasıyla (p<0.001)]. Çok değişkenli analizlerde yalnızca sekizinci hafta sodyum seviyeleri anlamlı bulundu (p<0.001). Nivolumab öncesi düşük ve yüksek sodyum değerine sahip hastalar arasında genel sağkalım (OS) benzerdi (p=0.292). Ancak, sekizinci haftada yüksek sodyum değerine sahip hastalar, düşük değere sahip olanlardan anlamlı şekilde daha uzun OS'ye sahipti [Yüksek sodyum grubu için ulaşılmamış ve düşük sodyum hastalar için 9.1 ay, %95 GA; (0.0-22.6); (p<0.001)].

Sonuç: Bulgularımız, serum sodyum seviyelerinin prognostik ve prediktif değerine işaret eden eski çalışmalarla uyumluydu. Serum sodyumunun kolay, hızlı ve uygun maliyetli bir belirteç olması nedeniyle bu konuyu daha fazla vurgulamak için daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Renal kanser, İmmünoterapi, Sodyum, Prognoz

Received: 24/12/2024 Accepted: 21/02/2025 Published (Onlıne): 01/04/2025

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To cited: Guzel HG, Ozturk B. Impact of Serum Sodium Levels on Treatment Efficacy and Prognosis in Advanced Renal Cell Carcinoma Patients Receiving Subsequent Line Nivolumab. Acta Med. Alanya 2025;9(1): 55-63

doi: 10.30565/medalanya.1606884

Introduction

Renal cell carcinoma (RCC) is the fourteenth most commonly diagnosed malignancy globally, with 431,288 new cases reported in 2020 [1]. Between 20% and 40% of RCC cases present with metastatic disease at the time of diagnosis. The median overall survival is estimated to be approximately 4 years for advanced stage disease. The prognostic factors that influence survival outcomes include age, performance status, and comorbid conditions [2]. Recent analyses derived from the United States Surveillance, Epidemiology, and End Results (SEER) database have indicated a notable reduction in mortality associated with metastatic RCC since 2012, suggesting that advancements in therapeutic approaches have substantially improved survival rates [3].

Therapeutic strategies for metastatic RCC have progressed significantly over the past two decades. Initial treatments, centered on first-generation immunotherapies (e.g., interferon and interleukin-2), have evolved to include targeted therapies targeting vascular endothelial growth factor (VEGF), immune checkpoint inhibitors (ICI), and combination regimens.[4] Immune checkpoint inhibitors, originally approved as second-line or later therapies, are now incorporated into the first-line treatment protocols in combination regimens. Historically, RCC management was primarily palliative; however, the advent of checkpoint inhibitors has extended survival and created a potential for long-term complete response. Nonetheless, the benefits of ICIs are not universal; some patients may experience immune-related adverse effects without achieving therapeutic benefits. The IMDC risk score remains a critical instrument in clinical practice, although it primarily serves as a prognostic marker rather than a predictive marker of immunotherapy efficacy [5,6]. Although biomarkers such as PD-L1 expression, immune infiltration, and tumor mutation burden have predictive relevance across multiple malignancies, they remain inadequate for reliably predicting immunotherapy outcomes in RCC. Emerging studies suggest that genomic expression profiles and loss of pro-angiogenic proteins, including VHL and PBRM-1, may have predictive value, although their clinical applicability remains unclear [7].

Ongoing research efforts continue to explore biomarkers predictive of immunotherapy responses in RCC. Serum sodium (Na) levels have previously been investigated as potential markers, with hyponatremia (serum sodium ≤ 135 mEq/L) serving as an independent prognostic factor across various malignancies, including metastatic RCC [8,9]. Furthermore, serum sodium levels in the low-normal range have been associated with poor prognosis in patients with metastatic RCC receiving tyrosine kinase inhibitors and immunotherapy [10,11]. Moreover, hyponatremia occurs frequently in this population. Altered kidney functions, syndrome of inappropriate antidiuresis due to uncontrolled cancer, immune-related diarrhea, adrenalitis, or hypophysitis are possible causes of hyponatremia in RCC patients [12,13].

This study aimed to evaluate the impact of serum sodium levels measured before the initiation of nivolumab and at the eighth week of nivolumab treatment on the efficacy and prognosis of immunotherapy in patients with metastatic RCC undergoing nivolumab as second-line therapy or beyond.

Method

Study Population

This retrospective study examined patients diagnosed with metastatic RCC who were treated with single-agent nivolumab at Antalya Training and Research Hospital between January 2016 and July 2024. Eligible patients were aged 18 years or older. Patients who received immunotherapy as a first-line treatment or had incomplete follow-up or treatment data were excluded from the study. Data were obtained from the hospital records and electronic health information systems. This study complies with the Declaration of Helsinki, and ethical committee approval was obtained from Antalya Training and Research Hospital (Approval No: 10/37, 11.07.2024).

Management Policy and Data Collection

Patients with metastatic RCC were managed according to current clinical guidelines and best practices. Nivolumab was administered at a dose of 3 mg per kilogram of total body weight or 240 mg flat dose once every 2 weeks (Q2W) [14]. Staging

was conducted according to the American Joint Cancer Committee (AJCC) 8th Edition Criteria. Response evaluation criteria in solid tumors (version 1.1; RECIST v1.1) was the main guide used to determine treatment response in routine practice. Data collected included demographic and clinical variables as age, sex, Eastern Cooperative Oncology Group Performance Score (ECOG PS), body mass index, smoking history, primary tumor surgery, RCC histological subtype (grouped as clear cell and non-clear cell), histological grade (grouped as grade 1-2 and grade 3-4), presence of sarcomatoid differentiation, date of diagnosis for metastatic stage, IMDC risk classification, initial treatment regimen, nivolumab initiation date, baseline and post-treatment laboratory parameters such as sodium and glomerular filtration rate (GFR), best response to nivolumab, progression date if occurred, and date of death if occurred. Baseline (pre-ICI) sodium levels were defined as those recorded within two weeks before nivolumab initiation, and sodium levels at the eighth week of nivolumab (post-ICI) were recorded for each patient. The normal range of sodium was 135-145 mEq/L.

The data of this study are available upon request from the corresponding author.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 26.0. Continuous variables were reported as mean ± standard deviation (SD). Otherwise, the median value (min-max) was used. Progression-free survival (PFS) was defined as the time from the initiation of nivolumab to disease progression, death, or the last recorded follow-up for patients without progression. Overall survival (OS) was defined as the time from the initiation of nivolumab treatment to death or the latest control date. For statistical comparisons, patients were stratified based on the median values of baseline (pre-ICI) and eighth-week (post-ICI) sodium levels. Kaplan-Meier estimates were used for univariate survival analysis. Certain clinically relevant variables and variables with a $p<0.3$ in the univariate analysis were included in multivariate analysis. Multivariate analyses were performed using Cox regression analysis. Statistical significance was defined as $P<0.05$.

Results

Clinicopathological Characteristics of The Study Population

We retrospectively screened 85 patients diagnosed with metastatic RCC who received nivolumab (n=85). However, 27 (n=27) were excluded due to missing data, and 6 (n=6) were excluded because they had received first-line immunotherapy, resulting in a final cohort of 55 patients (n=55). The median age of the study population was 63 (33-90) and 44 (78.6%) patients were male. The clear cell subtype was the dominant histological subtype, accounting for 45 patients (81.8%). The median value of pre-ICI sodium was 138 (130-145) mEq/L, 29 patients (n=29) had pre-ICI Na≤138 mEq/L, and 26 patients (n=26) had pre-ICI sodium >138 mEq/L. The median value was 137 (127-144) for post-ICI sodium, and 28 patients (n=28) had post-ICI Na≤137 mEq/L, while 27 (n=27) had >137 mEq/L. Clinicopathological feature distributions per median pre-ICI and post-ICI sodium values are provided separately. (Table 1)

Efficacy Analyses

The median follow-up was 50.2 (38.6-61.9) months for the study population. During the follow-up period, 40 patients (71.4%) had disease progression and 30 patients (53.6%) died in the entire population. The pre-ICI low (≤138 mEq/L) and high (>138 mEq/L) sodium groups were similar in terms of objective response rates (ORR), [%44.8 and %50.0; respectively (p=0.701)] and disease control rates (DCR) [%72.4 and %73.1; respectively (p=0.956)]. The post-ICI low (≤137 mEq/L) and high (>137 mEq/L) sodium groups were similar in terms of ORR, [%35.7 and %59.3; respectively (p=0.08)] while DCR was significantly better in those with high post-ICI sodium levels [%60.2 and %85.7; respectively (p=0.042)].

Progression-Free Survival Analyses

According to the univariate Kaplan-Meier analyses, the median PFS did not differ significantly between the pre-ICI low [13.8 months 95% CI; (0.0-33.1)] and high [11.7 months 95% CI; (4.5-18.9)] sodium subgroups (log-rank, p=0.507). (Figure 1A) However, patients with higher post-ICI sodium had significantly longer PFS [30.9 months

95% CI; (2.0-59.9)] than those with lower post-ICI sodium levels [3.4 months 95% CI; (0.0-7.1)], (log-rank, p<0.001). (Figure 1B). Moreover, ECOG PS and histological grade were the other significant factors that influenced PFS in univariate analysis. (Table 2)

Table 1. Clinicopathological Characteristics According to the Baseline and 8th Week Sodium Values

	All Patients	Pre-ICI Med. Sodium Based Dichotom		Post-ICI Med. Sodium Based Dichotom	
	(n=55) n, (%)	Na≤13 (n=29) n, (%)	Na>138 (n=26) n, (%)	Na≤137 (n=28) n, (%)	Na>137 (n=27) n, (%)
Age					
<65 years	33 (60.0)	13 (44.8)	20 (76.9)	13 (46.4)	20 (74.1)
≥65 years	22 (40.0)	16 (55.2)	6 (23.1)	15 (53.6)	7 (25.9)
Sex					
Female	11 (20.0)	5 (17.2)	6 (23.1)	7 (25.0)	4 (14.8)
Male	44 (80.0)	24 (82.8)	20 (76.9)	21 (75.0)	23 (85.2)
ECOG PS					
0-1	41 (75.5)	19 (65.5)	22 (84.6)	17 (60.7)	24 (88.9)
2	14 (24.5)	10 (34.5)	4 (15.4)	11 (39.3)	3 (11.1)
Smoking History					
Non-smoker	22 (40.0)	10 (34.5)	12 (46.2)	10 (35.7)	12 (44.4)
Smoker	33 (60.0)	19 (65.5)	14 (53.8)	18 (64.3)	15 (55.6)
History of Nephrectomy					
No	14 (24.5)	7 (24.1)	7 (26.9)	9 (32.1)	5 (18.5)
Yes	41 (75.5)	22 (75.9)	19 (73.1)	19 (67.9)	22 (81.5)
Histological Type					
Clear Cell RCC	45 (81.8)	23 (79.3)	22 (84.6)	23 (82.1)	22 (81.5)
Non-Clear Cell RCC	10 (18.2)	6 (22.7)	4 (15.4)	5 (17.9)	5 (18.5)
Histological Grade					
1-2	14 (24.5)	9 (31.0)	5 (19.2)	11 (39.3)	3 (11.1)
3-4	41 (75.5)	20 (69.0)	21 (80.8)	17 (60.7)	24 (88.9)
Sarcomatoid Differantiation					
No	8 (14.5)	24 (82.8)	23 (88.5)	24 (85.7)	23 (85.2)
Yes	47 (85.5)	5 (17.2)	3 (11.5)	4 (14.3)	4 (14.8)
First-Line Treatment					
Sunitinib	37 (67.3)	17 (58.6)	20 (76.9)	19 (67.9)	18 (66.7)
Pazopanib	14 (25.5)	11 (37.9)	3 (11.5)	9 (32.1)	5 (18.5)
Other	4 (7.3)	1 (3.4)	3 (11.5)	0 (0.0)	4 (14.8)
Nivolumab Treatment Line					
Second Line	49 (89.0)	26 (89.7)	23 (88.5)	26 (92.9)	23 (85.2)
Subsequent Line	6 (11.0)	3 (10.3)	3 (11.5)	2 (7.1)	4 (14.8)
IMDC Risk					
Good Risk	14 (25.5)	5 (17.2)	9 (34.6)	4 (14.3)	10 (37.0)
Intermediate Risk	33 (40)	20 (69.0)	13 (50.0)	18 (64.3)	15 (55.6)
Poor Risk	8 (14.5)	4 (13.8)	4 (15.4)	6 (21.4)	2 (7.4)
Body Mass Index					
<30 kg/m2	46 (83.6)	25 (86.2)	21 (80.8)	25 (89.3)	21 (77.8)
≥30 kg/m2	9 (16.4)	4 (13.8)	5 (19.2)	3 (10.7)	6 (22.2)
Glomerular Filtration Rate					
<60 ml/min/1.73m2	22 (40.0)	13 (44.8)	9 (34.6)	14 (50.0)	8 (29.6)
≥60 ml/min/1.73m2	33 (60.0)	16 (55.2)	17 (65.4)	14 (50.0)	19 (70.4)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, IMDC: International Metastatic RCC Database Consortium, Na: Sodium, Med.: Median RCC: Renal Cell Carcinoma

Table 2. Univariate and Multivariate Analysis For Progression Free Survival for Nivolumab

	Univariate Analysis		Multivariate Analysis	
Variables	P Value	HR	95% CI	P Value
Age				
<65 years	0.442	1.00 (Ref.)		0.732
≥65 years		0.873	(0.401-1.900)	
Sex				
Female	0.494	1.00 (Ref.)		0.142
Male		1.880	(0.810-4.366)	
ECOG PS				
0-1	0.009	1.00 (Ref.)		0.496
2		1.292	0.618-2.705	
Smoking History				
Non-smoker	0.721			
Smoker				
History of Nephrectomy				
No	0.591			
Yes				
Histological Type				
Clear Cell RCC	0.707			
Non-Clear Cell RCC				
Histological Grade				
1-2	0.099	1.00 (Ref.)		0.684
3-4		1.191	(0.513-2.768)	
Sarcomatoid Differantiation				
No	0.720			
Yes				
Body Mass Index				
<30 kg/m2	0.259	1.00 (Ref.)		0.722
≥30 kg/m2		0.840	(0.321-2.200)	
IMDC Risk				
Good Risk	0.229	1.00 (Ref.)		0.272
Intermediate Risk		0.533	(0.225-1.264)	
Poor Risk		0.800	(0.260-2.459)	
Glomerular Filtration Rate				
<60 ml/min/1.73m2	0.215	1.00 (Ref.)		0.743
≥60 ml/min/1.73m2		0.888	(0.436-1.807)	
Pre-ICI Na				
≤138 mEq/L	0.507	1.00 (Ref.)		0.128
>138 mEq/L		1.781	(0.847-3.745)	
Post-ICI Na				
≤137 mEq/L	<0.001	1.00 (Ref.)		<0.001
>137 mEq/L		0.288	(0.149-0.559)	

CI: Confidence Interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HR: Hazard Ratio IMDC: International Metastatic RCC Database Consortium

According to the multivariate analysis of PFS, the sole factor reaching statistical significance was post-ICI sodium levels, favoring the group with high sodium levels (>137 mEq/L) [HR: 0.288; 95% CI 0.149-0.559, (p<0.001)]. Pre-ICI sodium levels, age, sex, ECOG PS, histological grade, IMDC risk score, and GFR were not statistically significant. (Table 2)

Overall Survival Analyses

Univariate OS analyses showed that the median OS was similar between the low [24.0 months 95% CI; (15.9-32.1)] and high [36.8 months 95% CI; (NA-NA)] pre-ICI sodium value (log-rank, p=0.292). (Figure 2A) However, patients with higher post-ICI sodium levels had significantly longer OS than those with lower sodium levels [9.1 months 95% CI; (0.0-22.6)], (log-rank, p<0.001). (Figure 2B) The median OS in the high post-ICI group was not reached. Age and ECOG PS also reached statistical significance in univariate analyses for OS. (Table 3)

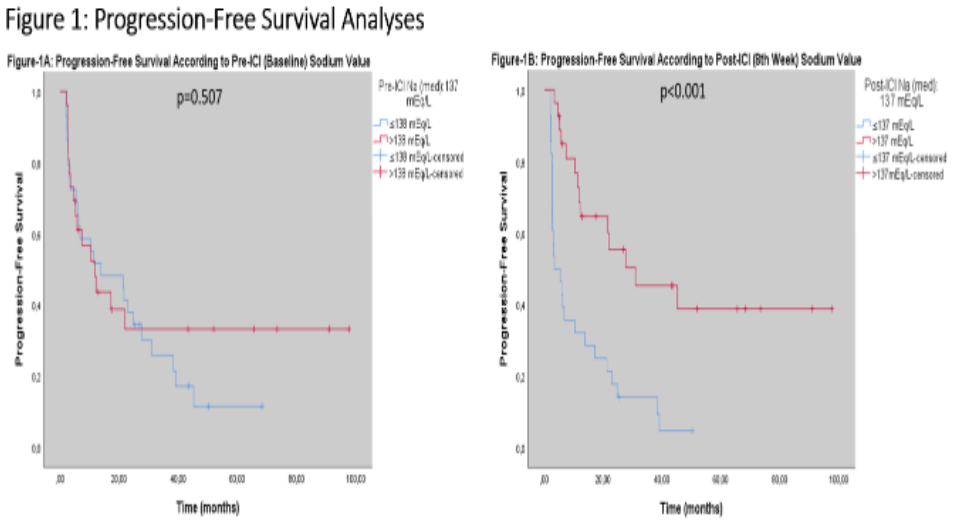

Figure 1- A: The PFS was similar for pre-ICI low [13.8 months 95% CI; (0.0-33.1)] and high [11.7 months 95% CI; (4.5-18.9)] sodium subgroups (log-rank, p=0.507). B: The PFS was longer for post-ICI sodium group [30.9 months 95% CI; (2.0-59.9)] than those with lower post-ICI sodium levels [3.4 months 95% CI; (0.0-7.1)], (log-rank, p<0.001).

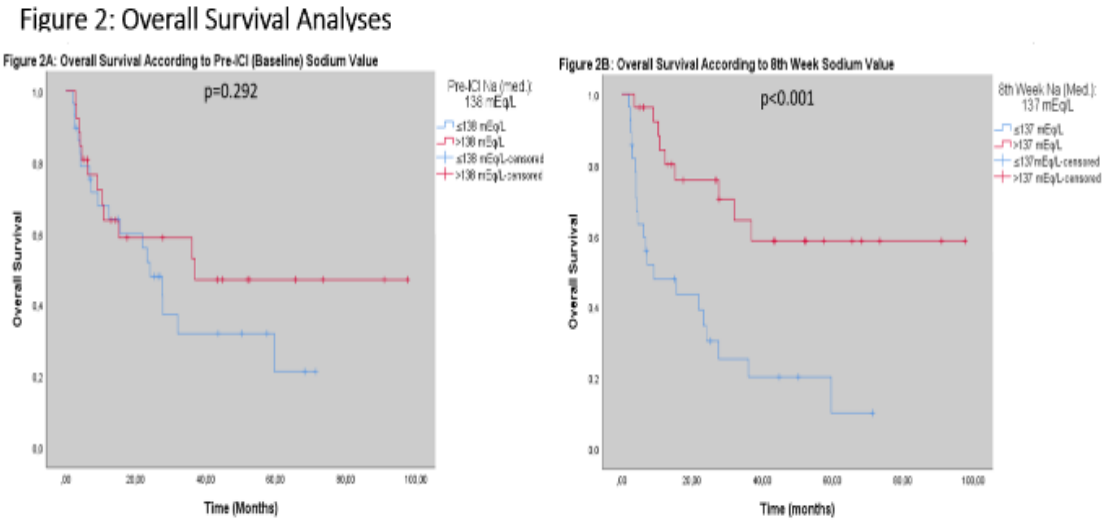

Figure 2-A: The median OS was similar between the low [24.0 months 95% CI; (15.9-32.1)] and high [36.8 months 95% CI; (NA-NA)] pre-ICI sodium value (log-rank, p=0.292). B: The patients with higher post-ICI sodium levels (the median OS was not reached) had significantly longer OS than those with lower sodium levels [9.1 months 95% CI; (0.0-22.6)], (log-rank, p<0.001).

Table 3. Univariate and Multivariate Analysis For Overall Survival for Nivolumab

	Univariate Analysis		Multivariate Analysis	
Variables	P Value	HR	95% CI	P Value
Age				
<65 years	0.034	1.00 (Ref.)		0.218
≥65 years		1.704	(0.730-3.977)	
Sex				
Female	0.981	1.00 (Ref.)		0.293
Male		1.704	(0.730-3.977)	
ECOG PS				
0-1	0.006	1.00 (Ref.)		0.452
2		1.419	(0.570-3.534)	
Smoking History				
Non-smoker	0.622			
Smoker				
History of Nephrectomy				
No	0.472			
Yes				
Histological Type				
Clear Cell RCC	0.209	1.00 (Ref.)		0.076
Non-Clear Cell RCC		2.129	0.924-4.904	
Histological Grade				
1-2	0.850	1.00 (Ref.)		
3-4		1.191	(0.513-2.768)	
Sarcomatoid Differantiation				
No	0.785			
Yes				
Body Mass Index				
<30 kg/m2	0.311	1.00 (Ref.)		
≥30 kg/m2		0.840	(0.321-2.200)	
IMDC Risk				
Good Risk	0.103	1.00 (Ref.)		0.337
Intermediate Risk		0.721	(0.248-2.093)	
Poor Risk		1.485	(0.366-6.013)	
Glomerular Filtration Rate				
<60 ml/min/1.73m2	0.665			
≥60 ml/min/1.73m2				
Pre-ICI Na				
≤138 mEq/L	0.292	1.00 (Ref.)		0.398
>138 mEq/L		1.426	(0.626-3.247)	
Post-ICI Na				
≤137 mEq/L	<0.001	1.00 (Ref.)		<0.001
>137 mEq/L		0.239	(0.107-0.533)	

CI: Confidence Interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HR: Hazard Ratio IMDC: International Metastatic RCC Database Consortium

In multivariate analyses for OS, it was observed that the post-ICI sodium value significantly affected OS [HR: 0.239; 95% CI, 0.107-0.533, (p<0.001)]. The pre-ICI sodium level, age, sex, ECOG PS, histological subtype, and IMDC risk score did not reach statistical significance. (Table 3)

Discussion

We demonstrated that a higher sodium value measured at the 8th week of subsequent

nivolumab treatment was a positive independent prognostic factor for PFS and OS in patients with metastatic RCC. Sodium levels above 137 mEq/L were associated with a better prognosis than those with lower post-ICI eighth-week sodium levels. In addition, the DCR was significantly higher in the high post-ICI high sodium group. However, the baseline pre-ICI sodium levels measured before the beginning of nivolumab treatment, with a cut-off median value of 138 mEq/L did not significantly affect the response rates, PFS, or OS.

Sodium is an easy, fast, and affordable test that is feasible for almost all patients. Therefore, many studies have investigated sodium levels. The effect of serum sodium on immunity is not well-defined. However there are hypothetic theories. The direct pathway is the activation of T cells and macrophages by elevated sodium concentration. The indirect pathway is the immunmodulation through endocrine system [15]. The clinical implication of this effect is still being investigated.

In Checkmate 025, the pivotal study of second-line nivolumab, there is no effective biomarker for ICI response in later-line treatment [14]. Therefore, the search for a convenient marker continued. In 2021, the Meet-Uro Score was highlighted as outperforming the IMDC risk score as a prognostic factor in patients who received second- or later-line nivolumab by the Meet-Uro 15 study [16]. In the bone-metastatic subset analysis of the Meet-Uro 15 study, pre- and post-ICI (4th-week) sodium levels were tested as prognostic markers in 120 patients, and the cut-off sodium value was set as 140 for both sets. Multivariate analysis showed that post-ICI high sodium levels significantly reduced the risk of progression and death. However, the pre-ICI sodium levels showed modest significance only for OS (p=0.04) [17]. Consistent with our results, they reported that previous nephrectomy history did not significantly affect PFS and OS. In addition, post-ICI sodium levels were prognostic factors in our study, despite the different cut-off values and measurement times. Another study by Catalano et al., which is a multicenter, retrospective analysis composed of 355 patients receiving second or later-line nivolumab reported that post-ICI (4th-week) sodium median levels significantly altered the OS outcomes favoring the high sodium groups but not PFS. Nevertheless, pre-ICI sodium levels were significant for OS but not for PFS in multivariate analyses. Unlike our study, they found that previous nephrectomy, better Karnofsky Performance Score (≥80%), and being in the good-risk group at the IMDC risk categorisation were significantly associated with improved PFS and OS [10]. Although the 4th-week sodium levels significantly affected the prognosis in these two studies, we demonstrated that the 8th-week sodium level was the sole strong prognostic factor. Our results are consistent with the literature since higher post-ICI sodium levels were associated with a better prognosis in our study.

A recent post-hoc analysis of serum electrolytes of IMvigor 221 and IMmotion 151 which included metastatic RCC patients receiving first-line atezolizumab plus bevacizumab, reported that elevated baseline serum sodium reported that elevated baseline sodium levels directly associated with an increased benefit from immunotherapy. These results suggestthat a high sodium level might serve as a predictive biomarker for immunotherapy response [18]. Beyond the predictive value for immunotherapy, there are many studies in metastatic RCC patients treated with the tyrosine kinase inhibitors, everolimus reporting that hyponatremia is associated with a worse prognosis regardless of the IMDC risk score and the treatment agent [9,11,19,20].

Age, ECOG PS, and IMDC risk score have proven to be independent prognostic factors for metastatic RCC [5]. Nevertheless, the small size of our study cohort might have prevented the identification of these variables from reaching prognostic significance.

Limitations

The major limitations of our study were its retrospective design and the limited number of study patients. Moreover, the single-center data could have led to unintentional patient selection bias. In contrast, the strong prognostic effect of the post-ICI 8th-week sodium level is a unique result despite its limitations.

Conclusions

In conclusion, our study revealed that high levels

of post-ICI 8th-week sodium (>137 mEq/L) were associated with longer PFS and OS than lower levels (≤137) in metastatic RCC patients treated with second or later-line nivolumab. However, baseline sodium levels were not associated with either PFS or OS. These results suggest that the patients with lower 8th-week sodium levels may be followed closer for progression and the therapeutic stragies should be managed knowing the poor prognosis these patients might have. The accumulating data in the literature are promising for both the predictive and prognostic value of higher sodium levels in metastatic RCC patients treated with ICI. However, comprehensive, randomized studies are needed to determine the consequences of this evolving subject, as it is feasible and affordable.

Conflict of Interest: The authors declare no conflict of interest related to this article.

Funding sources: The authors declare that this study has received no financial support.

Ethics Committee Approval: Antalya Eğitim ve Araştırma Hastanesi Etik Kurul Komitesi (Onay No: Approval No: 10/37, 11.07.2024) / Antalya Training and Research Hospital Ethical Committee (Approval No: 10/37, 11.07.2024).

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Peer-review: Externally peer reviewed.

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