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The Impact of Sodium on Prognosis in RCC and NSCLC Patients Receiving Second-line Nivolumab Treatment

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ABSTRACT

Objective: This study aimed to explore whether serum sodium concentrations could serve as a prognostic marker in patients with metastatic renal cell carcinoma (mRCC) and metastatic non-small cell lung cancer (mNSCLC) who were treated with nivolumab in the second-line setting.

Material and Methods: In this retrospective analysis, demographic, clinical, and pathological information on patients with mRCC or mNSCLC who were treated with second-line nivolumab was reviewed. Serum sodium levels were measured at baseline and at week 4 after treatment initiation, and survival outcomes were analyzed. The diagnostic impact of the sodium level was assessed with regression analyses.

Results: A total of 99 patients were included in the study: 18 with mRCC and 81 with mNSCLC. In mNSCLC, the median overall survival (mOS) for cohort members with pre-immune checkpoint inhibitors (ICI) sodium (Na) <140 (serum sodium measured within approximately 5 days of ICI initiation) was 6.5 months, compared with 12.2 months for those with pre-ICI Na ≥140 (p=0.049). Among patients with mNSCLC, the mOS of patients with post-ICI Na <140 (week-4 serum sodium values after ICI initiation) was 6.8 months, whereas that of patients with post-ICI Na ≥140 was 16.8 months (p=0.313). In mRCC, the median OS among patients with a pre-ICI Na <140 was 25.7 months, compared with 20.8 months for those with a pre-ICI Na ≥140 (p=0.514). In mRCC, the mOS of patients with post-ICI Na <140 was 12.7 months, whereas in those with post-ICI Na ≥140, the median was not reached (p=0.457). In multivariate Cox regression analysis, baseline serum sodium emerged as an independent predictor of OS in the mNSCLC cohort, underscoring its potential as a clinically relevant prognostic biomarker.

Conclusion: Baseline sodium levels appear to predict prognosis in mNSCLC, whereas this association was not evident in mRCC. In particular, pretreatment serum sodium demonstrated an independent relationship with OS in the mNSCLC cohort, suggesting its potential utility as a practical and inexpensive prognostic biomarker. More clinical studies are needed to understand the prognostic effects of sodium in patients receiving immunotherapy.

Keywords: Immunotherapy; nivolumab; non-small cell lung cancer; renal cell carcinoma; sodium; prognosis

INTRODUCTION

Immune checkpoint inhibitors (ICIs) restore antitumor immune activity by blocking inhibitory pathways such as the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4).[1] Although ICIs have revolutionized therapy across several cancers, patient responses remain highly variable.[2] Predictive markers, including PD-L1 expression and tumor mutation burden, have been evaluated, but they only partially explain this variability.[3] Nonetheless, these factors can account for only part of the heterogeneity among patients. The complex interplay of inherent and acquired factors collectively shapes the efficacy of immunotherapy (IO) for each patient.[4] However, most proposed biomarkers are not practical in routine clinical practice because of cost, tissue requirements, and their inability to reflect dynamic tumor-host interactions.[5] Thus, the identification of new prognostic biomarkers remains crucial for distinguishing those patients most likely to benefit from ICIs.

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Serum sodium has long been associated with outcomes in several conditions, including cancer.[6] Low serum sodium has repeatedly been associated with poorer survival, particularly in lung and renal cancers.[7,8] Significant evidence shows that the presence of hyponatremia adversely affects outcomes regardless of treatment modality or underlying disease; the prognostic effect of hyponatremia has been well established in patients treated with radiotherapy, chemotherapy, and targeted therapy.[9] However, little data exist from patients treated with ICIs regarding the impact of sodium on prognosis in patients receiving second-line nivolumab, a PD-1 inhibitor, for metastatic renal cell carcinoma (mRCC) and metastatic non-small cell lung cancer (mNSCLC).

In major studies of patients with mNSCLC (CheckMate 017 and 057), nivolumab has been shown to provide an overall survival (OS) benefit regardless of tumor histology.[10] Results from the CheckMate 025 study in mRCC have established nivolumab monotherapy as the standard treatment for patients progressing on antiangiogenic therapy since 2015. Moreover, compared with everolimus, nivolumab demonstrated higher response rates, prolonged survival, and better patient-reported quality of life.[11]

The effect of sodium state on cancer progression has been demonstrated in preclinical studies by impacting immune responses and it has been shown to have a potential role as a biomarker of IO response.[12,13] Emerging evidence suggests that patients with high sodium levels exhibit superior OS when treated with ICIs within a basket cohort.[14]

The current analysis examined the prognostic relevance of sodium concentrations in patients diagnosed with mRCC or mNSCLC who had been treated with nivolumab following systemic therapy.

MATERIAL AND METHODS

The research protocol was reviewed and approved by the institutional ethics review board, and all activities were carried out in conformity with the ethical principles delineated by the responsible committee and with the most recent Declaration of Helsinki. Since this was a retrospective study, informed consent from the patients was not required, as determined by the Ankara Bilkent City Hospital Institutional Clinical Research Ethics Committee (decision number: TABED 1-25-1176, date: 26.03.2025).

Patient Selection

We retrospectively identified adult patients (≥18 years) diagnosed with mRCC or mNSCLC who were treated with second-line nivolumab at the oncology outpatient clinics of two tertiary oncology centers in Türkiye between 1 January 2018 and 1 June 2024. Patients without available sodium measurements at either time point (before or after nivolumab initiation) were excluded. Demographic, clinical, and pathological data were retrospectively retrieved from patient charts and electronic medical records systems. Patients' records were used to obtain serum sodium levels (mEq/L) at the beginning of nivolumab treatment and 4 weeks after treatment.

Evaluation of the Sodium Levels

The analysis included pre-ICI sodium (Na) (serum sodium levels within about 5 days of ICI initiation) and post-ICI Na (week 4 values of serum sodium after ICI initiation). Baseline sodium values were obtained from routine laboratory results drawn within five days before the first nivolumab infusion, whereas post-treatment sodium values corresponded to the first control test performed during the fourth week (±3 days) after treatment initiation. All measurements were performed under fasting conditions using standardized institutional biochemical analyzers. Hyperglycemia can lead to dilutional hyponatremia due to movement of intracellular fluid into the extracellular space. The evaluation of serum glucose levels with serum sodium levels simultaneously in our patients was helpful in ruling out pseudohyponatremia. A value <140 mEq/L was considered the cut-off for low serum sodium, and patients were stratified into two cohorts according to their sodium level (≥140 mEq/L and <140 mEq/L). This threshold was adopted from prior IO cohorts in which 140 mEq/L consistently delineated the prognostically favorable range of normonatremia, reflecting both clinical convention and previously validated cut-offs in nivolumab-treated populations.[2,15-17]

Outcome

Our main endpoint was OS, defined as the time interval between nivolumab initiation and either death or the last follow-up visit.

Statistical Analysis

All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive results for categorical variables were presented as frequencies and percentages. Continuous variables were summarized either as mean ± standard deviation or as median values with ranges, and their distribution was checked using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparisons of categorical variables, such as sex, pathological subtype, PD-L1 status, metastatic sites, The Eastern Cooperative Oncology Group Performance Status (ECOG PS), comorbidities, and hyponatremic drug use, were performed using the chi-square test or Fisher's exact test, as appropriate. Continuous

variables, including age, were compared between groups using the independent samples t-test. Survival distributions were estimated using Kaplan-Meier curves, and intergroup comparisons were made with the log-rank test. Statistical significance was set at a two-sided p-value <0.05.

RESULTS

Altogether, 81 patients with mNSCLC and 18 with mRCC who had received nivolumab in the second-line setting fulfilled the eligibility requirements and were included in the analysis. The median follow-up duration was 31.4 months [95% confidence interval (CI): 21.6-41.2] for mNSCLC and 21.4 months (95% CI: 3.3-39.6) for mRCC.

Table 1 provides an overview of the baseline features of the mNSCLC patient cohort. The mean age at diagnosis was 65 (±8) years, with a sex distribution of 11 (13.6%) females and 70 (86.4%) males. Comorbidities were present in 54 (66.7%) patients. The most frequent conditions were pulmonary disorders, cardiovascular diseases (and hypertension), and metabolic conditions (diabetes mellitus). Within the study cohort, ECOG PS 1 was the predominant performance category.

TABLE 1: Characteristics of the patients with metastatic non-small cell lung cancer.

		Mean (± SD)	n (%) 81 (100)
Age at diagnosis		65 (±8)	
Sex	Female		11 (13.6)
	Male		70 (86.4)
Comorbidities	No		27 (33.3)
	Yes		54 (66.7)
COPD	No		70 (86.4)
	Yes		11 (13.6)
CAD	No		59 (72.8)
	Yes		22 (27.2)
HT	No		49 (60.5)
	Yes		32 (39.5)
DM	No		59 (72.8)
	Yes		22 (27.2)
Hypothyroidism	No		79 (97.5)
	Yes		2 (2.5)
Other comorbidity	No		76 (93.8)
	Yes		5 (6.2)
ECOG PS	1		71 (87.7)
	2		10 (12.3)
Pathological subtype	NSCLC, NOS		8 (9.9)
	NSCLC, adenocarcinoma		51 (63)
	NSCLC, SCC		22 (27.2)
Hyponatremic drug	No		56 (69.1)
	Yes		25 (30.9)
Furosemide	No		80 (98.8)
	Yes		1 (1.2)
Thiazide	No		64 (79)
	Yes		17 (21)
Spironolactone	No		77 (95.1)
	Yes		4 (4.9)
Levetiracetam	No		80 (98.8)
	Yes		1 (1.2)
SSRI	No		76 (93.8)
	Yes		5 (6.2)
Mirtazapine	No		80 (98.8)
	Yes		1 (1.2)
Olanzapine	No		79 (97.5)
	Yes		2 (2.5)
PD-L1 status	negative		30 (37)
	1-49		30 (37)
	>50		9 (11.1)
	Unknown		12 (14.8)
Driver mutation status	Driver mutation not present		58 (71.6)
	Unknown		7 (8.6)
	K-ras exon 2		1 (1.2)
	Kit exon 9		1 (1.2)
	K-ras, codon 12		5 (6.2)
	K-ras G13D		1 (1.2)
	Stk11 mutant		1 (1.2)
	CDKN2A+2B loss and a K-ras G12D mutant		1 (1.2)
	K-ras G13C mutant		1 (1.2)
	Exon 20 mutant		2 (2.5)
	K-ras codon 61, Q61X mutant		1 (1.2)
	PIK3CA mutant		1 (1.2)
	BRAF R671Q mutant (of uncertain significance)		1 (1.2)
Opposite lung metastasis	No		51 (63)
	Yes		30 (37)
Bone metastasis	No		46 (56.8)
	Yes		35 (43.2)
Brain metastasis	No		65 (80.2)
	Yes		16 (19.8)
Liver metastases	No		67 (82.7)
	Yes		14 (17.3)
Adrenal metastases	No		70 (86.4)
	Yes		11 (13.6)
Metastatic elsewhere	No		44 (54.3)
	Yes		37 (45.7)

COPD: Chronic obstructive pulmonary disease; CAD: Coronary arterial disease; HT: Hypertension; DM: Diabetes mellitus; ECOG PS: The eastern cooperative oncology group performance score; NSCLC: Non-small cell lung cancer; NOS: Not otherwise specified; SCC: Squamous cell carcinoma; SSRI: Selective serotonin reuptake inhibitors; SD: Standard deviation; PD-L1: Programmed death-ligand 1.

The pathological subtypes were NSCLC not otherwise specified (NOS) in 8 patients (9.9%), adenocarcinoma in 51 patients (63%), and squamous cell carcinoma (SCC) in 22 patients (27.2%). Twenty-five patients (30.9%) were taking medications associated with hyponatremia, including furosemide, thiazide diuretics, spironolactone, levetiracetam, selective serotonin reuptake inhibitors, mirtazapine, and olanzapine. The PD-L1 status was negative in 30 patients (37%), 1-49% positive in 30 patients (37%), greater than 50% positive in 9 patients (11.1%), and unknown in 12 patients (14.8%). The majority of the patients (71.6%) exhibited no detectable driver mutations. Metastatic spread was prevalent, with involvement of the contralateral lung, bone, brain, liver, adrenal glands, and other sites. Furthermore, brain metastases were identified in 16 patients (19.8%).

Table 2 presents the baseline characteristics of the mRCC cohort. Patients were diagnosed at a mean age of 59 (±8) years; the group consisted of 8 women (44.4%) and 10 men (55.6%). The majority of the patients (61.1%) had at least one comorbidity, with hypertension being the most prevalent (50%). ECOG PS 1 was observed in 72.2% of patients, and all patients exhibited clear-cell histology. The patients were stratified into three risk categories according to the IMDC risk score: intermediate-risk patients constituted the majority (14 patients, 77.8%), followed by poor-risk patients (3 patients, 16.7%) and favorable-risk patients (1 patient, 5.6%). Nephrectomy was performed in 8 (44.4%) patients. The table also provides details on the use of hyponatremic drugs, thiazide diuretics, and levetiracetam, and on the presence of metastases in various sites.

Table 3 presents the clinical and treatment data for the patients with mNSCLC and mRCC. In the mNSCLC group, median pre-ICI Na was 139 (128-145) mEq/L, and median post-ICI Na was 139 (125-146) mEq/L. Common first-line treatments included carboplatin plus paclitaxel and cisplatin plus pemetrexed. Most patients experienced progression in the lungs and bones, while fewer patients experienced progression in the brain, liver, kidneys, or other sites. After receiving nivolumab as second-line therapy, 50 patients (61.7%) progressed, 26 (32.1%) received one additional line of treatment, and 4 developed hypothyroidisms. For the mRCC group, median pre-ICI Na was 140.5 mEq/L (range 133–145) and median post-ICI Na was 140 mEq/L (range 133-144). Sunitinib and pazopanib were common first-line therapies. The majority of patients had progression in the lungs and bones, while fewer experienced progression at other sites. Following second-line therapy, 11 patients (61.1%) experienced disease progression, and 4 patients (22.2%) received an additional line of therapy.

When patients were grouped according to sodium levels, no significant differences were observed in demographic or

TABLE 2: Characteristics of the patients with metastatic renal cell cancer.

		Mean (± SD)	n (%) 18 (100)
Age at diagnosis		59 (±8)	
Sex	Female		8 (44.4)
	Male		10 (55.6)
Comorbidities	No		7 (38.9)
	Yes		11 (61.1)
COPD	No		17 (94.4)
	Yes		1 (5.6)
CAD	No		16 (88.9)
	Yes		2 (11.1)
HT	No		9 (50)
	Yes		9 (50)
DM	No		15 (83.3)
	Yes		3 (16.7)
Hypothyroidism	No		16 (88.9)
	Yes		2 (11.1)
ECOG PS	1		13 (72.2)
	2		5 (27.8)
Pathological subtype	clear cell		18 (100)
IMDC score	Favorable-risk group		1 (5.6)
	Intermediate-risk group		14 (77.8)
	Poor-risk group		3 (16.7)
Nephrectomy	Yes		10 (55.6)
	No		8 (44.4)
Hyponatremic drug	No		11 (61.1)
	Yes		7 (38.9)
Thiazide	No		14 (77.8)
	Yes		4 (22.2)
Levetiracetam	No		14 (77.8)
	Yes		4 (22.2)
Lung metastasis	No		3 (16.7)
	Yes		15 (83.3)
Bone metastasis	No		11 (61.1)
	Yes		7 (38.9)
Brain metastasis	No		15 (83.3)
	Yes		3 (16.7)
Liver metastases	No		16 (88.9)
	Yes		2 (11.1)
Adrenal metastases	No		17 (94.4)
	Yes		1 (5.6)
Metastatic elsewhere	No		13 (72.2)
	Yes		5 (27.8)

COPD: Chronic obstructive pulmonary disease; CAD: Coronary arterial disease; HT: Hypertension; DM: Diabetes mellitus; ECOG PS: The Eastern cooperative oncology group performance score; IMDC score: International metastatic RCC database consortium score; SD: Standard deviation.

TABLE 3: Clinical and treatment data for patients with metastatic non-small cell lung cancer (mNSCLC) and metastatic renal cell carcinoma (mRCC).

		mNSCLC		mRCC	
		n (%) 81 (100)	Median (minimum-maximum)	n (%) 18 (100)	Median (minimum-maximum)
Pre-ICI Na			139 (128-145)		140.5 (133-145)
Post-ICI Na			139 (125-146)		140 (133-144)
GFR			90 (46-130)		72 (31-111)
First-line treatment	Carboplatin and paclitaxel	36 (44.4)			
	Cisplatin and pemetrexed	35 (43.3)			
	Pemetrexed	1 (1.2)			
	Cisplatin and gemcitabine	8 (9.8)			
	Vinorelbine	1 (1.2)			
	Sunitinib			8 (44.4)	
	Pazopanib			9 (50)	
	Cabozantinib			1 (5.6)	
Lung progression	No	29 (35.8)		6 (33.3)	
	Yes	52 (64.2)		12 (66.7)	
Bone progression	No	56 (69.1)		14 (77.8)	
	Yes	25 (30.9)		4 (22.2)	
Brain progression	No	72 (88.9)		16 (88.9)	
	Yes	9 (11.1)		2 (11.1)	
Liver progression	No	64 (79)		16 (88.9)	
	Yes	17 (21)		2 (11.1)	
Kidney progression	No	80 (98.8)		12 (66.7)	
	Yes	1 (1.2)		6 (33.3)	
Other progression	No	58 (71.6)		12 (66.7)	
	Yes	23 (28.4)		6 (33.3)	
Second-line treatment	Nivolumab	81 (100)		18 (100)	
Second-line progression	No	31 (38.3)		7 (38.9)	
	Yes	50 (61.7)		11 (61.1)	
Treatment lines after nivolumab	0	47 (58)		11 (61.1)	
	1	26 (32.1)		4 (22.2)	
	2	5 (6.2)		2 (11.1)	
	3	3 (3.7)		1 (5.6)	
Side effects after immunotherapy	No	77 (95.1)		18 (100)	
	Hypothyroidism	4 (4.9)		0	

mNSCLC: Metastatic non-small cell lung cancer; mRCC: Metastatic renal cell carcinoma; pre-ICI Na: Serum sodium levels within about 5 days of immune checkpoint inhibitor initiation; post-ICI Na: Week 4 values of serum sodium after ICI initiation; GFR: Glomerular filtration rate; ICI: Immune checkpoint inhibitor.

pathological characteristics, including age, sex, histological subtype, PD-L1 status, or comorbidities (p>0.05). Before IO (pre-ICI), patients with sodium levels <140 mmol/L had significantly fewer opposite-lung metastases than those with sodium levels ≥140 mmol/L (p=0.047). After treatment (post-ICI), brain metastases were significantly more common among patients with sodium levels <140 mmol/L (p=0.013). Neither other metastatic sites (bone, liver, adrenal gland, and other locations) nor ECOG performance status differed significantly between sodium groups (Table 4).

TABLE 4: Baseline clinical and pathological features of patients with metastatic non-small cell lung cancer stratified by serum sodium level (<140 vs ≥140 mEq/L).

		Pre-ICI Na					Post-ICI Na				
		<140		≥140			<140		≥140		
		Mean (± SD)	n (%)	Mean (± SD)	n (%)	p-value	Mean (± SD)	n (%)	Mean (± SD)	n (%)	p-value
Age at diagnosis		64 (±9)		67 (±7)		0.132	64 (±8)		68 (±7)		0.060
Sex	Female		5 (11.4)		6 (16.2)	0.537		6 (11.5)		5 (17.2)	0.473
	Male		39 (88.6)		31 (83.8)			46 (88.5)		24 (82.8)	
Pathological subtype	NSCLC, NOS		6(13.6)		2 (5.4)	0.447		3 (5.8)		5 (17.2)	0.125
	NSCLC, adenocarcinoma		26 (59.1)		25 (67.6)			32 (61.5)		19 (65.5)	
	NSCLC, SCC		12 (27.3)		10 (27)			17 (32.7)		5 (17.2)	
PD-L1 status	Negative		17 (38.6)		13 (35.1)	0.421		18 (34.6)		12 (41.4)	0.486
	1-49		17 (38.6)		13 (35.1)			19 (36.5)		11 (37.9)	
	>50		6 (13.6)		3 (8.1)			5 (9.6)		4 (13.8)	
	Unknown		4 (9.1)		8 (21.6)			10 (19.2)		2 (6.9)	
Opposite lung metastasis	No		32 (72.7)		19 (51.4)	0.047*		32 (61.5)		19 (65.5)	0.722
	Yes		12 (27.3)		18 (48.6)			20 (38.5)		10 (34.5)	
Bone metastasis	No		23 (52.3)		23 (62.2)	0.371		29 (55.8)		17 (58.6)	0.804
	Yes		21 (47.7)		14 (37.8)			23 (44.2)		12 (41.4)	
Brain metastasis	No		36 (81.8)		29 (78.4)	0.699		46 (88.5)		19 (65.5)	0.013*
	Yes		8 (18.2)		8 (21.6)			6 (11.5)		10 (34.5)	
Liver metastases	No		34 (77.3)		33 (89.2)	0.239		46 (88.5)		21 (72.4)	0.067
	Yes		10 (22.7)		4 (10.8)			6 (11.5)		8 (27.6)	
Surrenal metastases	No		36 (81.8)		34 (91.9)	0.214		45 (86.5)		25 (86.2)	0.967
	Yes		8 (18.2)		3 (8.1)			7 (13.5)		4 (13.8)	
Metastatic elsewhere	No		21 (47.7)		23 (62.2)	0.326		26 (50)		18 (62.1)	0.296
	Yes		23 (52.3)		14 (37.8)			26 (50)		11 (37.9)	
ECOG PS	1		38 (86.4)		33 (89.2)	0.748		46 (88.5)		25 (86.2)	0.740
	2		6 (13.6)		4 (10.8)			6 (11.5)		4 (13.8)	
Comorbidities	No		17 (38.6)		10 (27)	0.656		18 (34.6)		9 (31)	0.840
	Yes		27 (61.4)		27 (73)			34 (65.4)		20 (69)	
Hyponatremic drug	No		27 (61.4)		29 (78.4)	0.099		38 (73.1)		18 (62.1)	0.304
	Yes		17 (38.6)		8 (21.6)			14 (26.9)		11 (37.9)	

ICI: Immune checkpoint inhibitor; Na: Sodium; NSCLC: Non-small cell lung cancer; mNSCLC: Metastatic non-small cell lung cancer; mRCC: Metastatic renal cell carcinoma; PD-L1: Programmed death-ligand 1; SCC: Squamous cell carcinoma; ECOG PS: Eastern cooperative oncology group performance status; OS: Overall survival; CI: Confidence interval; SD: Standard deviation; NOS: Not otherwise specified.

In the univariate analysis, ECOG performance status (p=0.042) and pre-ICI sodium levels (p=0.049) were found to be significantly associated with OS. Patients with ECOG PS ≥1 had worse survival than those with ECOG PS 0. Similarly, patients with pre-ICI sodium levels ≥140 mmol/L showed better survival outcomes than those with lower sodium levels. In the multivariate analysis, pre-ICI sodium remained a significant independent predictor of OS (p=0.047), while ECOG PS lost statistical significance. Other clinical parameters, including age, sex, pathological subtype, metastatic sites, comorbidities, and PD-L1 status, were not significantly correlated with survival (Table 5).

The median OS (mOS) for the patients diagnosed with mNSCLC was as follows: the NOS subtype, 7.6 (95% CI: 5.3-9.9) months; the adenocarcinoma subtype, 6.8 (95% CI: 2.2-11.4) months; and the SCC subtype, 12.2 (95% CI: 6-12.4)

TABLE 5: Univariate and multivariate Cox regression analyses for OS in patients with metastatic non–small cell lung cancer (mNSCLC).

	Variables	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age at diagnosis		0.98 (0.95-1.01)	0.434		
Female	**Female**	1	0.426		
	Male	0.75 (0.38-1.49)			
Pathological subtype	**NSCLC, NOS**	1	0.447		
	NSCLC, adenocarcinoma	0.85 (0.36-2.03)			
	NSCLC, SCC	0.61 (0.23-1.58)			
PD-L1 status	**Negative**	1	0.491		
	1-49	1.01 (0.56-1.79)			
	>50	0.48 (0.18-1.28)			
	Unknown	0.87 (0.41-1.85)			
Opposite lung metastasis	**No**	1	0.869		
	Yes	1.04 (0.62-1.75)			
Bone metastasis	**No**	1	0.060		
	Yes	1.61 (0.98-2.67)			
Brain metastasis	**No**	1	0.437		
	Yes	1.27 (0.68-2.36)			
Liver metastases	**No**	1	0.969		
	Yes	0.98 (0.51-1.89)			
Surrenal metastases	**No**	1	0.697		
	Yes	1.15 (0.56-2.34)			
Metastatic elsewhere	**No**	1	0.921		
	Yes	1.02 (0.62-1.68)			
ECOG PS	**N0**	1	**0.042***		
	N1	2.09 (1.02-4.21)			
Comorbidities	**No**	1	0.143		
	Yes	0.67 (0.40-1.14)			
Hyponatremic drug	**No**	1	0.193		
	Yes	0.67 (0.37-1.21)			
Pre-ICI Na	**<140**	1	**0.049***	1	**0.047***
	≥140	0.60 (0.36-1.00)		0.87 (0.96-2.54)	
Post-ICI Na	**<140**	1	0.315		
	≥140	0.76 (0.45-1.29)			

OS: Overall survival; OR: Odds ratio; CI: Confidence interval; PD-L1: Programmed death-ligand 1; ECOG PS: Eastern cooperative oncology group performance status; ICI: Immune checkpoint inhibitor; NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma; Na: Sodium; NOS: Not otherwise specified.

months (p=0.442) (Figure 1). Among patients with mNSCLC, the mOS was considerably lower among those with pre-ICI serum Na <140 (6.5 months, 95% CI: 5.3-7.6) than among those with pre-ICI Na ≥140 (12.2 months, 95% CI: 5.5-18.9). This difference was statistically significant (p=0.049; Figure 2A). Among patients with mNSCLC, those with post-ICI Na <140 had a mOS of 6.8 months, whereas those with post-ICI Na ≥140 had a mOS of 16.8 months. Although the difference was not statistically significant (p=0.313), it was numerically meaningful (Figure 2B).

The mOS among patients with clear-cell mRCC was 20.8 months (Figure 3). In mRCC, the mOS for patients with pre-ICI Na <140 was 25.7 months (95% CI: 0.6-51.9), compared with 20.8 months (95% CI: 0.6-41) for patients with pre-ICI Na ≥140 (p=0.514; Figure 4A). In mRCC (Figure 4B), The mOS of patients with post-ICI Na <140 was 12.7 months, while the median for those with post-ICI Na ≥140 was not reached (p=0.457).

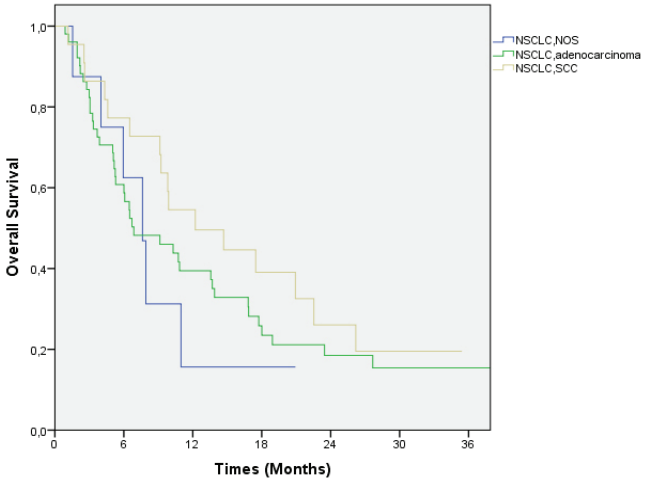

FIGURE 1: Kaplan-Meier overall survival curve for all patients with metastatic non–small cell lung cancer (mNSCLC) receiving second-line nivolumab. The median OS was 9.7 months (95% CI 5.8-13.6), (p=0.442).

OS: Overall survival; mNSCLC: Metastatic non-small cell lung cancer; CI: Confidence interval; SCC: Squamous cell carcinoma; NOS: Not otherwise specified.

DISCUSSION

Across various solid tumors, including NSCLC and RCC, hyponatremia has consistently been associated with poorer outcomes.[9,18] A correlation has been observed between hyponatremia and a poorer prognosis in patients with mRCC and mNSCLC who are receiving tyrosine kinase inhibitors and cytotoxic chemotherapy.[19,20] The aim of our study was to assess the prognostic value of sodium in patients with mRCC and mNSCLC receiving nivolumab as second-line treatment.

In summary, patients with mNSCLC who presented with higher pretreatment sodium levels experienced markedly longer OS, whereas this association was not statistically significant in the smaller mRCC cohort, likely because of limited statistical power. According to the multivariate Cox regression model, pretreatment serum sodium emerged as an independent determinant of OS among patients with mNSCLC receiving nivolumab, even after controlling for ECOG PS, PD-L1 expression, comorbidities, and metastatic distribution. Posttreatment sodium elevation was associated with a favorable, though not statistically significant, trend toward improved survival among mNSCLC cases.

Based on these results, lower pretreatment sodium levels were associated with shorter OS in patients with mNSCLC. The data suggest a trend toward improved OS among mNSCLC patients with higher post-treatment sodium levels following IO; however, this finding requires further validation to establish statistical significance and to clarify the underlying mechanisms. In contrast, pre-treatment and post-treatment

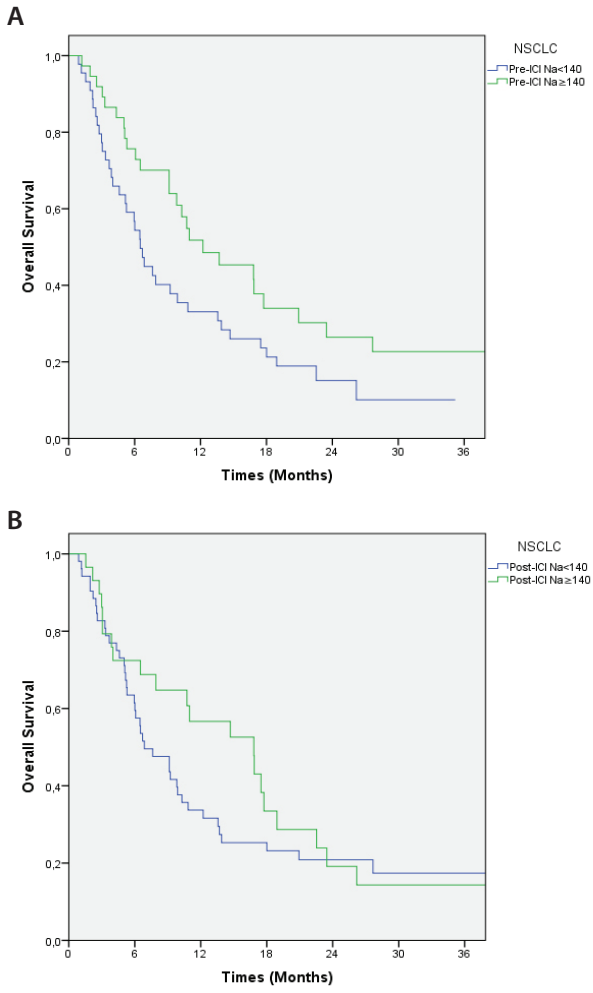

FIGURE 2: Kaplan-Meier survival analysis according to serum sodium level before (A) and after (B) initiation of immune checkpoint inhibitor (ICI) therapy in patients with mNSCLC. (A) Pre-ICI Na <140 mEq/L: median OS 6.5 months (95% CI: 5.3-7.6); Pre-ICI Na ≥140 mEq/L: 12.2 months (95% CI: 5.5-18.9); p=0.049. (B) Post-ICI Na <140 mEq/L: 6.8 months; Post-ICI Na ≥140 mEq/L: 16.8 months; p=0.313.

mNSCLC: Metastatic non-small cell lung cancer; CI: Confidence interval

sodium levels were not significantly associated with survival in mRCC. These findings should not be interpreted as evidence of a causal relationship. Rather, low serum sodium likely reflects an underlying constellation of disease burden, systemic inflammation, and impaired nutritional status, all of which may contribute to inferior outcomes independent of response to IO.[6,21,22]

Our findings are broadly consistent with those of Catalano et al.[8] and Fucà et al.[17], who independently reported that maintaining normal serum sodium (≥140 mEq/L) predicts improved survival in patients receiving ICIs. In the multicenter study by Catalano et al.[8], sodium normalization at baseline and at week four correlated with longer OS, whereas in our

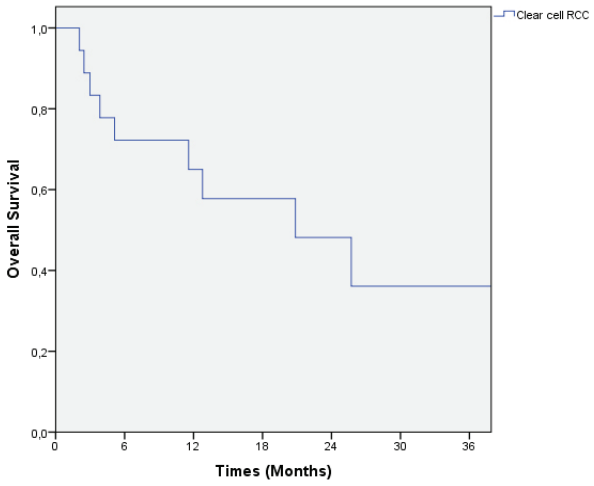

FIGURE 3: Kaplan-Meier overall survival (OS) curve for patients with metastatic RCC treated with second-line nivolumab. The median OS for the overall cohort was 20.8 months (95% CI: 0.6-41.0).

RCC: Renal cell carcinoma; CI: Confidence interval.

smaller mRCC subgroup, statistical significance was not achieved, likely owing to limited sample size. These consistent observations support the growing view that sodium levels may reflect host condition and immune competence rather than serve as a direct determinant of treatment efficacy.

Biologically, serum sodium may act as a proxy for the host's metabolic and immune balance. Experimental work suggests that sodium supports antitumor immunity by enhancing T-cell activation and promoting M1 macrophage polarization, whereas hyponatremia favors an immunosuppressive environment. These observations align with previous mechanistic studies highlighting sodium's role as an indirect marker of immune competence rather than a direct effector of ICI response.[23-25]

Fucà et al. found that hyponatremia was associated with a lower survival benefit in mNSCLC patients receiving IO therapy.[17] In a study including 88 patients with mNSCLC who received first-line pembrolizumab or atezolizumab treatment, they found that baseline serum sodium values above 140 mEq/L were correlated with longer OS compared with values below 140 mEq/L.[15] In mRCC patients receiving nivolumab as part of an IO regimen as second- or later-line therapy, those exhibiting a sodium value below 140 both prior to treatment and 4 weeks after treatment had a poorer OS.[8] In the present study, it was established that pretreatment sodium levels can be a significant prognostic factor for OS in patients with mNSCLC. While post-treatment sodium levels did not prove to be a significant independent prognostic factor in mNSCLC patients, they showed a numerical association. In contrast to the findings of previous studies, pretreatment

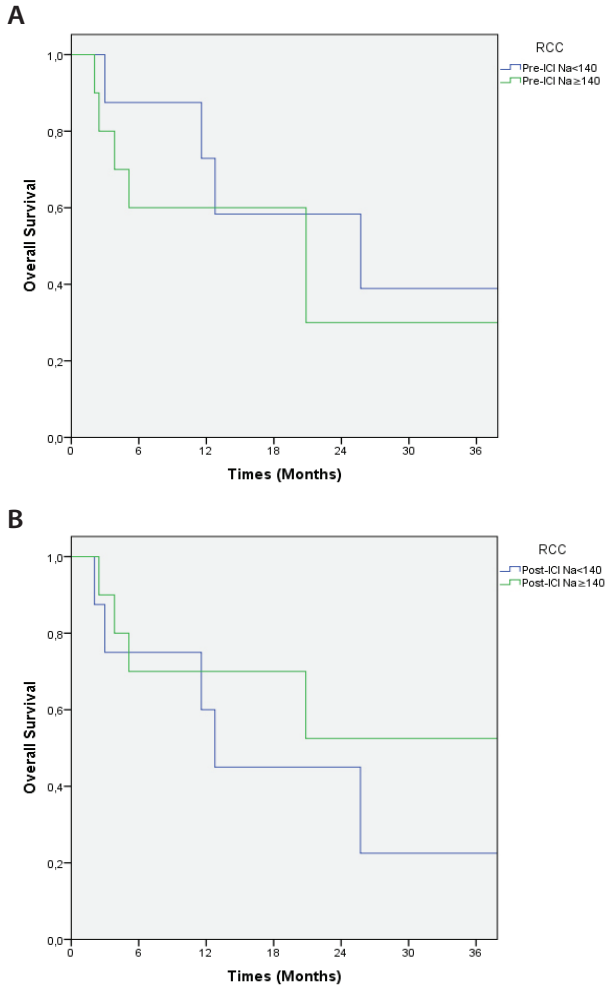

FIGURE 4: Kaplan-Meier survival analysis according to serum sodium level before (A) and after (B) initiation of ICI therapy in patients with mRCC. (A) Pre-ICI Na <140 mEq/L: median OS 25.7 months (95% CI: 0.6-51.9); Pre-ICI Na ≥140 mEq/L: 20.8 months (95% CI: 0.6-41.0); p=0.514. (B) Post-ICI Na <140 mEq/L: 12.7 months; post-ICI Na ≥140 mEq/L: median not reached; p=0.457.

ICI: Immune checkpoint inhibitor; CI: Confidence interval; OS: Overall survival; mRCC: Metastatic renal cell carcinoma; Na: Sodium.

and posttreatment sodium levels in mRCC patients did not demonstrate significant independent prognostic value. This may be attributable to the limited number of mRCC patients. Given the small number of patients, the mRCC subgroup analysis should be regarded as exploratory and hypothesis-generating rather than confirmatory. Because the number of mRCC participants was limited, the subgroup analysis lacked adequate statistical power, precluding definitive conclusions about the prognostic influence of serum sodium in this cohort.

Secondary analyses of the phase 3 trials IMmotion151 and IMvigor211 showed that patients with higher baseline serum

sodium levels had improved survival and responses to ICI therapy. Unlike other important serum electrolytes, such as calcium, magnesium, and potassium, sodium was the only one associated with a favorable prognosis in IO, implying a positive effect of elevated sodium levels. However, after adjustment for prognostic factors, high sodium values were not associated with better prognosis in comparison arms of studies, namely sunitinib and chemotherapy, respectively.[16] This suggests that the relationship between basal sodium and prediction may be limited to IO.

Study Limitations

The main limitations are its retrospective nature and small mRCC cohort. Additionally, the underlying mechanisms by which sodium levels may influence the efficacy of IO were not examined, and further research is needed to elucidate the specific pathways involved. Furthermore, there was no assessment of the impact of sodium supplementation or other interventions to maintain optimal sodium homeostasis on the outcomes of IO. Additionally, potential confounding effects from unmeasured factors-such as nutritional status, systemic inflammation, and disease burden-cannot be entirely excluded and may partially account for the observed association between serum sodium and survival. As the analysis relied on routine clinical data rather than prescheduled protocol assessments, a small degree of variation in the timing of sodium measurements may have occurred. Consequently, an element of measurement-related or immortal-time bias cannot be completely excluded, although all samples were taken within a narrow and clinically consistent window. Taken together, our findings strengthen the growing body of evidence that serum sodium serves as a simple and cost-effective prognostic marker in patients treated with ICIs. Further prospective research, particularly in the underpowered mRCC subgroup, is warranted to validate these associations and better define their clinical applicability.

CONCLUSION

Among patients with mNSCLC, our findings suggest that lower pretreatment sodium levels are associated with poorer OS. Conversely, in mRCC, pretreatment and posttreatment sodium levels did not significantly impact survival, potentially due to the small patient cohort size. Importantly, we examined mRCC and mNSCLC patients receiving second-line nivolumab, providing further evidence of the predictive value of pre-treatment sodium levels, particularly in the mNSCLC population. These results underline the prognostic significance of pretreatment sodium levels in mNSCLC patients receiving second-line nivolumab, supporting its potential as a valuable biomarker for clinical applications in this context.

Moreover, our findings demonstrated that pretreatment serum sodium concentration was an independent predictor of OS in the mNSCLC cohort, emphasizing its potential clinical utility as an accessible, low-cost prognostic biomarker in the context of IO.

Ethics

Ethics Committee Approval: The approved by the Ankara Bilkent City Hospital Institutional Clinical Research Ethics Committee (decision number: TABED 1-25-1176, date: 26.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.S., S.A.E., İ.K., Concept: İ.S., D.U., Design: İ.S., D.U., Data Collection or Processing: İ.S., S.A.E., İ.K., Analysis or Interpretation: İ.S., D.U., Literature Search: Ş.Y., Writing: İ.S., E.A., Ö.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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