Inflammatory Prognostic Index in Metastatic Renal Carcinoma Treated with Nivolumab

Ferhat Ekinci[1], Atike Pinar Erdogan[1], Serkan Yildirim[2], Gulcan Bulut[3], Cengiz Yilmaz[4] and Sabri Barutca[5]

[1]*Department of Medical Oncology, Manisa Celal Bayar University, Manisa, Turkey*
[2]*Department of Medical Oncology, Baskent University, Konya Application and Research Centre, Konya, Turkey*
[3]*Department of Medical Oncology, International Medicana Hospital, Izmir, Turkey*
[4]*Department of Medical Oncology, Bozyaka Training and Research Hospital, Izmir, Turkey*
[5]*Department of Medical Oncology, Aydın Adnan Menderes University, Aydın, Turkey*

ABSTRACT

Objective: To evaluate the utility of inflammatory prognostic index (IPI), albumin, c-reactive protein (CRP), and lactate dehydrogenase (LDH) as predictive biomarkers of oncologic outcome in metastatic renal cell cancer (mRCC) patients treated with nivolumab.

Study Design: Descriptive study.

Place and Duration of Study: Manisa Celal Bayar University, Aydın Adnan Menderes University, Bitlis Tatvan State Hospital and Private Hatay Defne Hospital Medical Oncology Clinics, Turkey, from January 2017 to June 2020.

Methodology: Seventy-five mRCC patients treated with nivolumab between January 2017 and June 2020 were enrolled. Several factors were retrospectively investigated, including IPI, CRP, LDH, and albumin level, for their association with progression-free survival (PFS) and overall survival (OS). The IPI was calculated as CRP × NLR/albumin. Univariate and multivariate analyses were performed to assess the prognostic value of relevant factors.

Results: When analysed according to the calculated IPI score, it is seen that the group with <2.153 has an OS duration of 96.3 months, while the group with ≥2.153 has a shorter time of 42.9 months (p=0.02). In the analysis performed according to albumin level, it was reported that those with low levels (22.8 months) had worse median OS than those with high levels (92.8 months) (p=0.004). According to the cox regression analysis results, it was determined that those with a high IPI score significantly increased the risk of death compared to those with a low score (HR:2.4, p=0.023). However, this significance could not be confirmed in the multivariate analysis. It was analysed that those with low albumin levels significantly increased the risk of death compared to both univariate analysis (HR:3.3, p=0.007) and multivariate analysis (HR:4.4, p=0.003).

Conclusion: Those with high IPI scores and low albumin levels were associated with worse median OS. However, only the multivariate analysis analysed albumin level as an independent prognostic variable. Prospective and more extensive research is needed to consolidate the potential prognostic power of these markers.

Key Words: *Albumin, Immune checkpoint inhibitor, IPI score, Metastatic renal cell carcinoma, Nivolumab, overall survival, Progression-free survival.*

How to cite this article: Ekinci F, Erdogan AP, Yildirim S, Bulut G, Yilmaz C, Barutca S. Inflammatory Prognostic Index in Metastatic Renal Carcinoma Treated with Nivolumab. *J Coll Physicians Surg Pak* 2022; **32(10)**:1288-1294.

INTRODUCTION

Renal cell carcinoma (RCC) is the most common kidney cancer and constitutes 3% of all malignancies.[1] In comparison, 30% of them present with *de-novo* metastasis at the time of diagnosis and metastasis may develop in up to 40% of those who are diagnosed at an early stage and undergo curative surgery.[1,2] Unfortunately, in the metastatic stage, the chance of cure cannot be provided with treatment options.

Correspondence to: Dr. Ferhat Ekinci, Department of Medical Oncology, Manisa Celal Bayar University, Manisa, Turkey
E-mail: drferhatekinci@hotmail.com
Received: May 13, 2022; Revised: August 13, 2022; Accepted: August 24, 2022
DOI: https://doi.org/10.29271/jcpsp.2022.10.1288

The fate of patients with metastatic RCC (mRCC), where conventional therapies such as chemotherapy and radiotherapy are ineffective, has begun to change significantly with the discovery of multikinase inhibitors. However, with immune checkpoint inhibitors (ICIs), more excellent response rates have been achieved.[3,4] Nivolumab is a first-use programmed cell death protein-1 (PD-1) antibody for mRCC that blocks PD-1 and strengthens the anticancer.

T-cell-mediated immune response, after these successful results, nivolumab was placed at the centre of mRCC treatment combined with monotherapy and other tyrosine kinase inhibitors (TKIs) and ICIs agents.[5-8] However, the main problem here is that not every patient responds to this treatment similarly and well. This leads to the need for markers that predict treatment response and survival. While the search for biomarkers that can predict response to treatment continues, no biomarker has yet entered daily clinical practice.[9]

Table I: Comparison of patient characteristics according to IPI cut-off value.

		<2.153 (n-%) (n=47)	>=2.153 (n-%) (n=28)	Total (n-%) (n=75)	p-value
Age category	<65 years old	23 (48.90)	20 (71.40)	43 (57.30)	0.096
	≥65 years old	24 (51.10)	8 (28.60)	32 (42.70)	
Gender	Male	25 (53.20)	15 (53.60)	40 (53.30)	>0.99
	Female	22 (46.80)	13 (46.40)	35 (46.70)	
Presentation of metastasis	Recurrence	22 (46.80)	8 (28.60)	30 (40.00)	0.188
	De novo	25 (53.20)	20 (71.40)	45 (60.00)	
Lung metastasis	No	14 (29.80)	5 (17.90)	19 (25.30)	0.382
	Yes	33 (70.20)	23 (82.10)	56 (74.70)	
Liver metastasis	No	35 (74.50)	20 (71.40)	55 (73.30)	0.986
	Yes	12 (25.50)	8 (28.60)	20 (26.70)	
Brain metastasis	No	42 (89.40)	26 (92.90)	68 (90.70)	0.706
	Yes	5 (10.60)	2 (7.10)	7 (9.30)	
Bone metastasis	No	27 (57.40)	21 (75.00)	48 (64.00)	0.199
	Yes	20 (42.60)	7 (25.00)	27 (36.00)	
LN metastasis	No	18 (38.30)	8 (28.60)	26 (34.70)	0.545
	Yes	29 (61.70)	20 (71.40)	49 (65.30)	
Other metastasis	No	32 (68.10)	11 (39.30)	43 (57.30)	0.028*
	Yes	15 (31.90)	17 (60.70)	32 (42.70)	
Number of metastasis sites	<3	27 (57.40)	12 (42.90)	39 (52.00)	0.325
	≥3	20 (42.60)	16 (57.10)	36 (48.00)	
IMDC risk	Favourable	24 (51.10)	8 (28.60)	32 (42.70)	0.065
	Intermediate	19 (40.40)	13 (46.40)	32 (42.70)	
	Poor	4 (8.50)	7 (25.00)	11 (14.70)	
Initial therapy before nivolumab	IFN	7 (14.90)	3 (10.70)	10 (13.30)	0.64
	Sunitinib	20 (42.60)	15 (53.60)	35 (46.70)	
	pazopanib	20 (42.60)	10 (35.70)	30 (40.00)	
LDH level	Low	26 (55.30)	20 (71.40)	46 (61.30)	0.254
	High	21 (44.70)	8 (28.60)	29 (38.70)	
Albumin level	Low	4 (8.50)	7 (25.00)	11 (14.70)	0.088
	High	43 (91.50)	21 (75.00)	64 (85.30)	
Progression status under nivolumab	No	22 (46.80)	10 (35.70)	32 (42.70)	0.485
	Yes	25 (53.20)	18 (64.30)	43 (57.30)	
Best response to nivolumab	PR	20 (42.60)	10 (35.70)	30 (40.00)	0.507
	CR	7 (14.90)	3 (10.70)	10 (13.30)	
	SD	12 (25.50)	6 (21.40)	18 (24.00)	
	PD	8 (17.00)	9 (32.10)	17 (22.70)	
Number of lines taken for treatment	1	1 (2.10)	1 (3.60)	2 (2.70)	0.904
	2	19 (40.40)	9 (32.10)	28 (37.30)	
	3	19 (40.40)	11 (39.30)	30 (40.00)	
	4	7 (14.90)	6 (21.40)	13 (17.30)	
	5	1 (2.10)	1 (3.60)	2 (2.70)	
CRP level	Low	14 (29.80)	2 (7.10)	16 (21.30)	0.043*
	High	33 (70.20)	26 (92.90)	59 (78.70)	
irAEs due to nivolumab	No	32 (68.10)	23 (82.10)	55 (73.30)	0.288
	Yes	15 (31.90)	5 (17.90)	20 (26.70)	
Exitus status	No	32 (68.10)	15 (53.60)	47 (62.70)	0.312
	Yes	15 (31.90)	13 (46.40)	28 (37.30)	

The relationship between clinicopathological results and IPI score was evaluated with the chi-square test. IPI: Inflammatory prognostic index, LN: Lymph node, IMDC: International mRCC database consortium, IFN: Interferon, LDH: Lactate dehydrogenase, PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease, irAEs: Immune-related adverse events, CRP: C-reactive protein.

Cancer-related inflammation is associated with poorer treatment response and poorer survival in many cancers, including RCC.[8-10] Many parameters such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic inflammation index (SII), albumin-alkaline phosphatase ratio (AAPR) and Glasgow Prognostic Score (GPS) (c-reactive protein and albumin), which reflect the inflammatory status and can be easily obtained, have also been investigated in many cancers including RCC.[11] After obtaining statistically significant results with c-reactive protein (CRP), NLR and albumin-based inflammatory prognostic index (IPI), which were first investigated by Dirican *et al*. in non-small cell lung cancer, it was also studied in many different cancers.[12-14] However, its efficacy in mRCC patients treated with nivolumab has not yet been studied. Therefore, the primary purpose of this study was to analyse the predictive and prognostic value of IPI in mRCC patients.

METHODOLOGY

The data of patients diagnosed with mRCC, who were treated at Manisa Celal Bayar University, Aydın Adnan Menderes University, Bitlis Tatvan State Hospital and Private Hatay Defne Hospital Medical Oncology Clinics, Turkey, between January 2017 and June 2020 were retrospectively analyzed. Those with a history of secondary malignancy or any ICI treatment prior to nivolumab or with insufficient laboratory data were excluded from the study. Also, those who had used the given nivolumab therapy for at least three months were included.

Table II: Comparison of the patient characteristics with OS and PFS results.

		Median OS (95% CI Min-Max)	p-value	Median PFS (95% CI Min- Max)	p-value
Age category	<65 years old	92.8 (61.6-124.0)	0.565	8.0 (3.5-12.4)	0.742
	≥65 years old	82.9 (78.4-87.5)		13.7 (7.9-19.6)	
Gender	Male	82.4 (79.4-85.5)	0.931	8.0 (4.4-11.5)	0.696
	Female	92.8 (55.5-130.0)		13.5 (7.7-19.3)	
Presentation of metastasis	Recurrence	112.0	0.001	9.9 (0.6-19.2)	0.739
	De novo	47.5 (21.4-73.5)		10.7 (5.4-16.0)	
Lung metastasis	No	92.8 (81.7-103.8)	0.067	13.5 (0.9-26.1)	0.788
	Yes	82.4 (28.9-136.0)		9.4 (5.9-13.0)	
Liver metastasis	No	82.9 (69.5-96.4)	0.688	8.9 (5.1-12.7)	0.707
	Yes	96.3 (30.7-161.9)		11.7 (6.0-17.3)	
Brain metastasis	No	82.4 (60.7-104.2)	0.591	10.7 (5.2-16.3)	0.434
	Yes	96.3 (68.9-123.7)		4.7 (2.2-7.2)	
Bone metastasis	No	112.0	0.022	13.5 (7.1-19.8)	0.008
	Yes	81.1 (28.1-134.0)		5.4 (3.7-7.2)	
LN metastasis	No	82.9 (63.6-102.3)	0.6	7.3 (5.2-9.4)	0.142
	Yes	82.4 (55.2-109.7)		13.9 (7.2-20.7)	
Other metastasis	No	96.3 (74.1-118.5)	0.916	8.0 (5.2-10.7)	0.495
	Yes	82.4 (29.0-135.9)		11.7 (6.9-16.5)	
Number of metastasis sites	<3	92.8 (75.2-110.3)	0.24	8.9 (5.8-12.0)	0.743
	≥3	82.4 (33.1-131.8)		10.7 (4.5-16.9)	
IMDC risk	Favourable	81.1 (10.6-151.5)	0.097	14.5 (6.9-22.1)	0.842
	Intermediate	96.3 (80.1-112.5)		9.9 (5.4-14.5)	
	Poor	47.5 (10.8-84.1)		6.6 (2.7-10.4)	
Initial therapy before nivolumab	IFN	71.7 (20.5-112.9)	0.641	14.8 (12.0-17.7)	0.503
	Sunitinib	82.9 (80.1-85.8)		9.9 (2.1-17.7)	
	pazopanib	92.8 (17.2-168.3)		9.4 (3.5-15.4)	
Progression status under nivolumab	No		<0.001		
	Yes	47.5 (6.3-88.6)			
Reason for discontinuation of nivolumab	Progression	71.5 (21.9-121.5)	<0.001		
	Hyperprogression	10.4 (5.0-15.7)			
	irAEs				
irAEs due to nivolumab	No	82.4 (41.0-123.9)	0.152	9.9 (5.8-14.0)	0.421
	Yes			14.5 (0-30.7)	
Retreatment after irAEs	No			4.0 (1.7-6.3)	0.012
	Yes			14.8 (2.2-27.4)	
IPI score	<2.153	96.3 (69.9-122.8)	0.02	11.7(5.9-17.4)	0.286
	≥2.153	42.9 (42.6-43.1)		7.6(2.6-12.6)	
CRP level	Low	92.8 (0-194.9)	0.323	8.0 (3.9-12.1)	0.277
	High	82.9 (56.0-109.9)		11.7 (5.9-17.4)	
LDH level	Low	82.4 (65.8-99.1)	0.948	9.9 (3.5-16.3)	0.946
	High	92.8 (67.3-118.2)		9.4 (0-19.1)	
Albumin level	Low	22.8 (2.5-43.1)	0.004	13.9 (0-35.5)	0.511
	High	92.8 (76.4-109.1)		9.9 (5.7-14.1)	
Total		82.9 (68.5-97.4)		9.9 (4.4-15.4)	

The relationship between IPI score and OS-PFS was analysed using the Kaplan-Meier method with log-rank statistics. OS: Overall survival, PFS: Progression-free survival, Min: Minimum, Max: Maximum, IPI: Inflammatory prognostic index, LN: Lymph node, IMDC: International mRCC database consortium, IFN: Interferon, LDH: Lactate dehydrogenase, PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease, irAEs: Immune-related adverse events CRP: C-reactive protein.

The study was designed as a multicenter retrospective cohort. Age, gender, presentation of metastasis (recurrence or *de novo*), metastasis sites (lung, liver, bone, brain, lymph node and other sites), number of metastasis sites, international metastatic RCC Database Consortium (IMDC) risk situations, initial therapy before nivolumab, the reason for discontinuation of nivolumab, progression status under nivolumab, the best response to nivolumab, immune-related adverse events (irAEs) due to nivolumab, and retreatment status after irAEs were recorded. Albumin, CRP, lactate dehydrogenase (LDH), lymphocyte and neutrophil values measured at the time of metastasis were noted.

The statistical analysis of the data obtained in this study was performed with the SPSS (Statistical Package for the Social Sciences) 16.0 package program. The IPI was calculated by the formula CRP×NLR/albumin. The Youden Index method was used to find the cut-off value for the IPI variable according to the ROC curve, and this value was obtained as 2.153. The threshold value for each biological baseline parameter was defined as albumin= 3.5 g/dL, CRP=0.5 mg/dL, and lactate dehydrogenase level=248 U/L. They were analysed to see whether they were higher or lower than these threshold values. The endpoints of this study included Progression-free survival (PFS) and overall survival (OS). PFS was obtained by calculating the difference, in months, between the start of nivolumab therapy and the time to progression. OS was obtained by calculating the time (in months) between the date of diagnosis and the date of exitus (data cut-off for non-exitus patients). Tumour response was analyzed according to the Immune Response Evaluation Criteria in Solid Tumours (irRECIST).

Table III: Univariate and multivariate COX regression analysis results of OS and PFS.

	Univariate OS HR (95% CI) (Min-max)	p-value	Multivariate OS HR (95% CI) (Min-max)	p-value	Univariate PFS HR (95% CI) (Min-max)	p-value
Age category <65 years old *vs.* ≥65 years old	1.2 (0.5-2.6)	0.565			0.9 (0.4-1.6)	0.742
Gender Male *vs.* Female	1.0 (0.4-2.2)	0.931			1.1 (0.6-2.0)	0.696
Presentation of metastasis De novo *vs.* Recurrence	4.4 (1.7-11.4)	0.002	3.0 (1.1-7.9)	0.025	1.1 (0.5-2.0)	0.739
Lung metastasis Yes *vs.* No	2.6 (0.9-7.5)	0.077			1.0 (0.5-2.1)	0.788
Liver metastasis Yes *vs.* No	1.1 (0.5-2.7)	0.688			0.8 (0.4-1.6)	0.708
Brain metastasis Yes *vs.* No	0.7 (0.2-2.1)	0.592			1.4 (0.5-3.7)	0.437
Bone metastasis Yes *vs.* No	2.3 (1.1-5.1)	0.026	2.4 (1.0-5.5)	0.033	2.2 (1.2-4.2)	0.01
LN metastasis Yes *vs.* No	1.2 (0.5-2.7)	0.6			0.6 (0.3-1.1)	0.145
Other metastasis Yes *vs.* No	1.0 (0.4-2.1)	0.916			0.8 (0.4-1.4)	0.496
Number of metastasis sites ≥3 *vs.* <3	1.5 (0.7-3.3)	0.244			0.9 (0.4-1.6)	0.743
IMDC risk Intermediate vs. Favorable Poor *vs.* Favorable	0.7 (0.3-1.6) 2.1 (0.8-5.7)	0.453 0.126			1.2 (0.6-2.3) 1.1 (0.4-2.9)	0.564 0.763
Initial therapy before nivolumab Sunitinib *vs.* IFN Pazopanib *vs.* IFN	1.3 (0.3-4.7) 1.7 (0.4-6.2)	0.647 0.394			1.8 (0.6-5.3) 1.7 (0.5-5.3)	0.254 0.299
Progression status under nivolumab Yes *vs.* No	9.5 (2.2-40.2)	0.002	7.2 (1.6-32.1)	0.009		
Reason for discontinuation of nivolumab Hyperprogression vs. Progression irAEs *vs.* Progression	1.0 (0.1-8.0) 11.8 (1.1-121.0)	0.953 0.036				
irAEs due to nivolumab Yes *vs.* No	0.4 (0.1-1.3)	0.162			0.7 (0.3-1.5)	0.423
Retreatment after irAEs No *vs.* Yes	0.6 (0.06-7.7)	0.763			5.7 (1.2-26.8)	0.025
Number of lines taken for treatment Increase per unit					1.6 (1.1-2.2)	0.003
IPI score ≥2.153 *vs.* <2.153	2.4 (1.1-5.3)	0.023	1.6 (0.6-4.0)	0.271	1.3 (0.7-2.5)	0.288
CRP level High *vs.* Low	0.6 (0.2-1.5)	0.3			0.6 (0.3-1.3)	0.28
LDH level High vs. Low	1.0 (0.4-2.1)	0.948			1.0 (0.5-1.8)	0.946
Albumin level Low *vs.* High	3.3 (1.3-7.9)	0.007	4.4 (1.6-12.0)	0.003	1.3 (0.5-2.9)	0.513

The relationship between IPI score and OS-PFS was analyzed using the Kaplan-Meier method with log-rank statistics. OS: Overall survival, PFS: Progression-free survival, Min: Minimum, Max: Maximum, IPI: Inflammatory prognostic index, LN: Lymph node, IMDC: International mRCC database consortium, IFN: Interferon, LDH: Lactate dehydrogenase, PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progressive disease, irAEs: Immune-related adverse events CRP: C-reactive protein. All variables were insignificant (p-value >0.05) in the cox regression multivariate analysis for PFS.

The cut-off value of the IPI score based on OS and PFS was determined by analysing the sensitivity and specificity values and calculating the area under the ROC curve. The IPI value was categorised by determining the cut-off value with the ROC curve, and then the chi-square test was applied. The relationship between IPI score and OS-PFS was evaluated using the Kaplan-Meier method with log-rank statistics.

Univariate and multivariate Cox Regression Analysis methods were used to calculate the respective hazard ratios (HRs) and 95% confidence intervals (CIs). These results were presented as median (minimum-maximum), mean and standard deviation and the categorical variables were expressed as counts and percentages. While examining the normality distribution of quantitative data according to categorical variables, the Shapiro-Wilk test was used in those with n <30 group numbers, while the Kolmogorov-Smirnov test was used in those with n >30. For all statistical results, a p-value of <0.05 was considered statistically significant.

RESULTS

A total of 75 mRCC patients treated with nivolumab were evaluated. When the patients are categorised according to age and gender, it is seen that <65 years old (57.3%, n=43) and male (53.3%, n=40) gender predominate. The most common site of metastasis was the lung (74.7%, n=56). When the IMDC risk groups are examined, it is seen that the favourable (42.7%, n=32) and intermediate (42.7%, n=32) groups are equally distributed, while the poor (14.7%, n=11) group is in the minority. When pre-nivolumab treatments are examined, it is seen that there is a balanced distribution between pazopanib (40.0%, n=30) and sunitinib (46.7%, n=35). IrAEs were observed in 26.7% (n=20) of the patients.

At the end of the data analysis, 37.3% (n=28) of the patients were *exitus* (Table I).

At the data cut-off date (June 2020), the median follow-up was 52.8 (95% CI, 32.4-73.2) months. The median PFS of all patients was calculated as 9.9 (95% CI, 4.4-15.4) months and OS as 82.9 (95% CI, 68.5-97.4) months. When median OS is examined in terms of metastasis presentation, it is seen that those with recurrence were 112 months, and those who presented *de-novo* were 47.5 (95% CI, 21.4-73.5) months (p<0.001). However, this difference is not significant in PFS (p=0.739). When metastasis sites are examined, it is seen that those with bone metastases have statistically significantly shorter PFS (5.4 months, 95% CI, 3.7-7.2, p=0.008) and OS (81.1 months, 95% CI, 28.1-134.0, p=0.022). When the reasons for discontinuation of nivolumab treatment are examined, it is seen that OS is significantly lower in patients with hyper-progression (10.4 months, 95% CI, 5.0-15.7, p<0.001). Although, there are no significant survival results in terms of OS and PFS in those who develop irAEs, it is observed that those who retreatment after irAEs have longer PFS (14.8 months, 95% CI, 2.2-27.4, p=0.012). When analysed according to the calculated IPI score, it is seen that the group with <2.153 has an OS duration of 96.3 months (95% CI, 69.9-122.8), while the group with ≥2.153 has a shorter time of 42.9 (95% CI, 42.6-43.1) months (p=0.02). However, a similar difference in PFS could not reach statistical significance (p=0.286). In the analysis performed according to albumin level, it was reported that those with low levels (22.8 months, 95% CI, 2.5-43.1) had worse median OS than those with high levels (92.8 months, 95% CI, 76.4-109.1, p=0.004, Table II).

According to the cox regression analysis results, it was determined that those with a high IPI score significantly increased the risk of death compared to those with a low score (HR:2.4, 95% CI, 1.1-5.3, p=0.023). However, this significance could not be confirmed in the multivariate analysis. It was analysed that those with low albumin levels significantly increased the risk of death compared to both univariate analysis (HR:3.3, 95% CI,1.3-7.9 p=0.007) and multivariate analysis (HR:4.4, 95% CI,1.6-12.0, p=0.003). The power of these parameters to predict OS was not comparable in PFS (Table III).

DISCUSSION

Inflammation is a multifactorial process that prepares the ground for cancer development by taking part in all stages of tumour formation, and data are showing that it is clinically associated with disease recurrence, metastasis and poor prognosis.[3,15] Inflammation mediators are an essential component of the tumour microenvironment and are suggested to be the precursor of oncogenic change in some cancers and cause angiogenesis and metastasis development.[15] This situation causes genomic instability and DNA damage, leading to the settlement of the protumourigenic structure. The most common inflammatory response indicators are a set of biochemical or haematological markers in cancer patients. The most commonly used ones are the increase in CRP, leukocyte, neutrophil and thrombocyte counts, and low albumin and lymphocyte levels.[13,15] Here, it should be emphasised that albumin acts as both an indicator of nutritional status and a negative acute phase reactant, and its relationship with poor prognosis in many cancers, including RCC, has been proven[9,11,16] The IPI score, which incorporates CRP, neutrophil, lymphocyte, and albumin levels, was used for the first time in mRCC patients treated with nivolumab.

NLR is the most common parameter used to indicate treatment response and prognosis in mRCC patients treated with nivolumab. In a study conducted by Jeyakumar *et al*. involving 42 patients, it was observed that patients using other ICIs agents were included, although nivolumab was predominant.[17] Statistically, significantly shorter OS and PFS values were reported above the cut-off value determined for NLR (p=0.025, p=0.003). Another study of 142 patients conducted by Lalani *et al.* reported that NLR calculated at week 6 of nivolumab treatment predicted OS and PFS more strongly than baseline (p = 0.004, p<0.001). Similarly, high basal or post-treatment NLR levels have been associated with poor prognosis.[18] In a study conducted on the Japanese population in 2020, the prognostic role of NLR, TLR, lymphocyte/monocyte ratio (LMR) and LDH, which were examined before and six weeks after treatment, was investigated in 65 mRCC patients treated with nivolumab. In univariate analysis, LDH (p=0.026), TLR (p=0.001), and LMR affected disease-specific survival significantly. However, in multivariate analysis, LDH (p=0.0123, HR=3.92, 95% CI, 1.37-10.80) and TLR (p=0.0008, HR=7.95, 95% CI, 2.16-51.64) were reported to be analysed as independent prognostic markers. In this study, as a result of a separate analysis with the combination of LDH and PLR, it was concluded that this combination was the most important prognostic marker (p<0.0001).[19]

In a recent study of 45 patients by Fujiwara *et al*., the effect of modified GPS (mGPS) developed using serum albumin and CRP levels on prognosis in mRCC patients treated with nivolumab was investigated. In this scoring system, low albumin (≤3.5 g/dL) and high CRP (≤1.0 mg/dL) levels were arranged as score 2, none as score 0, and only low albumin or high CRP levels as score 1. In the multivariate analysis, it was reported that an increase in the score from 0 to 2 (p=0.004 (1 *vs.* 0), p=0.002 (2 *vs*. 0) has an independent prognostic value for survival.[20] In this scoring, CRP and albumin levels were used with a logic similar to the IPI score in this study. However, unlike the IPI score, NLR is also included. This study concluded that only albumin (p=0.003) was an independent prognostic variable in the regression analysis of CRP and albumin levels separately.

In a recent study conducted by Yoshino *et al*. the prognostic power of albumin and alkaline phosphatase (ALP) ratio (AAPR) was evaluated in the same patient group.[11] The ALP level was included in the scoring in this study because it can regulate tumour development through its release from kidney cells and many other tissues and organs and suppression of inflammatory signals.[21] In this study, in which a total of 60 patients were evaluated, the median OS (p<0.0001) and PFS (p=0.0006) were found to be significantly shorter in the low AAPR group compared to the high group. In the multivariate analysis, although the AAPR score was reported as an independent prognostic variable for OS (p=0.015), this significant relationship could not be achieved for PFS (p=0.174).

The most extensive patient population study examining the relationship between mRCC-diagnosed inflammatory markers and survival treated with nivolumab included 303 cases. In the study conducted by De Giorgi *et al*., NLR, PLR, SII and body mass index (BMI) were used.[22] However, only a high SII (p <0.0001) score and low BMI (p=0.01) were reported as independent prognostic variables.

The significant limitations of this study are that it was designed retrospectively, and the IPI score does not have the ideal cut-off value that prevents routine use. The relatively small number of patients may also have prevented some factors from reaching statistical significance. In addition, this situation led to heterogeneity as the patients received nivolumab treatment at any stage after the first--line treatment.

CONCLUSION

In this study, involving mRCC patients treated with nivolumab, those with high IPI scores and low albumin levels were associated with worse median OS. However, only the multivariate analysis analysed the albumin level as an independent prognostic variable. Prospective and more extensive studies are required to corroborate the potential prognostic power of these markers.

ETHICAL APPROVAL:

The Health Sciences Ethics Committee approved this study of Manisa Celal Bayar University Faculty of Medicine with the decision dated 23.12.2020 and No. E-20478486.

PATIENTS' CONSENT:

Written consent was obtained from the participants.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

FE: Concept, design, and drafting.
APE, GB, SB: Materials.
FE, GB, SY, CY: Data collection and processing.
GB, FE: Analysis and interpretation.
FE, APE, SY: Literature search.
FE, APE, SB, GB: Critical review.
All the authors have approved the final version of the manuscript to be published.

REFERENCES

1. Massari F, Mollica V, Rizzo A, Cosmai L, Rizzo M, Porta C. Safety evaluation of immune-based combinations in patients with advanced renal cell carcinoma: A systematic review and meta-analysis. *Expert Opin Drug Saf* 2020; **19(10)**:1329-38. doi: 10.1080/14740338.2020.1811226.
2. Capitanio U, Montorsi F. Renal cancer. *The Lancet* 2016; **387(10021)**:894-906. doi: 10.1016/S0140-6736(15) 00046-X.
3. Peinemann F, Unverzagt S, Hadjinicolaou AV, Moldenhauer I. Immunotherapy for metastatic renal cell carcinoma: A systematic review. *J Evid Based Med* 2019; **12(4)**:253-62. doi: 10.1111/jebm.12362.
4. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, *et al*. Nivolumab *versus* everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015; **373(19)**:1803-13. doi: 10.1056/NEJMoa1510665.
5. Nishiyama N, Hirobe M, Kikushima T, Matsuki M, Takahashi A, Yanase M, *et al*. The neutrophil-lymphocyte ratio has a role in predicting the effectiveness of nivolumab in Japanese patients with metastatic renal cell carcinoma: A multi-institutional retrospective study. *BMC Urol* 2020; **20(1)**:110. doi: 10.1186/s12894-020-00679-2.
6. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, *et al*. Nivolumab plus Ipilimumab *versus* sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018; **378(14)**:1277-90. doi: 10.1056/NEJMoa17 12126.
7. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, *et al*. Nivolumab plus cabozantinib *versus* sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2021; **384(9)**:829-41. doi: 10.1056/NEJMoa2026982.
8. Monteiro FSM, Soares A, Debiasi M, Schutz FA, Maluf FC, Bastos DA, *et al*. First-line treatment of metastatic renal cell carcinoma in the immuno-oncology Era: Systematic review and network meta-analysis. *Clin. Genitourin Cancer* 2020; **18(4)**:244-51.e4. doi: 10.1016/j.clgc.2020.02.012.
9. Rebuzzi SE, Signori A, Banna GL, Maruzzo M, De Giorgi U, Pedrazzoli P, *et al*. Inflammatory indices and clinical factors in metastatic renal cell carcinoma patients treated with nivolumab: The development of a novel prognostic score (Meet-URO 15 study). *Ther Adv Med Oncol* 2021; **13**: 17588359211019642. doi: 10.1177/17588359211019642.
10. Bersanelli M, Cortellini A, Buti S. The interplay between cholesterol (and other metabolic conditions) and immune-checkpoint immunotherapy: Shifting the concept from the "inflamed tumour" to the "inflamed patient". *Hum Vaccin Immunother* 2021; **17(7)**:1930-4. doi: 10.1080/21645515. 2020.1852872.
11. Yoshino M, Ishihara H, Ishiyama Y, Tachibana H, Toki D, Yamashita K, *et al.* Albumin-to-alkaline phosphatase ratio as a novel prognostic marker of nivolumab monotherapy for previously treated metastatic renal cell carcinoma. *In Vivo*

2021; **35(5)**:2855-62. doi: 10.21873/invivo.12573.

12. Dirican N, Dirican A, Anar C, Atalay S, Ozturk O, Bircan A, *et al*. A new inflammatory prognostic index, based on c-reactive protein, the neutrophil to lymphocyte ratio and serum albumin is useful for predicting prognosis in non-small cell lung cancer case. *Asian Pac J Cancer Prev* 2016; **17(12)**:5101-6. doi: 10.22034/APJCP.2016.17.12.5101.
13. Dirican A, Ekinci F, Erdogan AP, Goksel G. Inflammatory prognostic index score as a new parameter predicting overall survival in renal cell carcinoma. *J Surg Medicine* 2021; **5(2)**:163-7. doi: 10.28982/josam.850739.
14. Erdoğan AP, Ekinci F, Karabaş A, Balcik OY, Barutça S, Dirican A. Could the inflammatory prognostic index predict the efficacy of regorafenib in patients with metastatic colorectal cancer. *J Gastrointest Cancer* 2022; **53(1)**:45-51. doi: 10.1007/s12029-021-00642-w.
15. Greten FR, Grivennikov SI. Inflammation and cancer: Triggers, mechanisms, and consequences. *Immunity* 2019; **51(1)**:27-41. doi: 10.1016/j.immuni.2019.06.025.
16. Ekinci F, Balcik OY, Oktay E, Erdogan AP. HALP score as a new prognostic index in metastatic renal cell cancer. *J Coll Physicians Surg Pak* 2022; **32(3)**:313-8. doi: 10.29271/jcpsp.2022.03.313.
17. Jeyakumar G, Kim S, Bumma N, Landry C, Silski C, Suisham S, *et al*. Neutrophil lymphocyte ratio and duration of prior anti-angiogenic therapy as biomarkers in metastatic RCC receiving immune checkpoint inhibitor therapy. *J Immunother Cancer* 2017; **5(1)**:82. doi: 10.1186/s40425-017-0287-5.
18. Lalani AA, Xie W, Martini DJ, Steinharter JA, Norton CK, Krajewski KM, *et al*. Change in neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. *J Immunotherapy Cancer* 2018; **6(1)**:**1-9**. doi: 10.1186/s40425-018-0315-0.
19. Yamamoto Y, Matsuyama H, Matsumoto H, Sakano S, Fuji N, Oba K, *et al*. Prognostic value of risk stratification using blood parameters for nivolumab in Japanese patients with metastatic renal-cell carcinoma. *Japanese Clin Oncol* 2020; **50(2)**:214-20. doi: 10.1093/jjco/hyz168.
20. Fujiwara R, Takemura K, Fujiwara M, Yuasa T, Yasuoka S, Komai Y, *et al*. Modified glasgow prognostic score as a predictor of prognosis in metastatic renal cell carcinoma treated with nivolumab. *Clin Genitourinary Cancer* 2021; **19(2)**:e78-e83. doi: 10.1016/j.clgc.2020.10.007.
21. Rao SR, Snaith AE, Marino D, Cheng X, Lwin ST, Orriss IR, *et al*. Tumour-derived alkaline phosphatase regulates tumour growth, epithelial plasticity and disease-free survival in metastatic prostate cancer. *Br J Cancer* 2017; **116(2)**:227-36. doi: 10.1038/bjc.2016.402.
22. De Giorgi U, Procopio G, Giannarelli D, Sabbatini R, Bearz A, Buti S, *et al*. Association of systemic inflammation index and body mass index with survival in patients with renal cell cancer treated with nivolumab. *Clin Cancer Res* 2019; **25(13)**:3839-46. doi: 10.1158/1078-0432.CCR-18-3661.