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ORIGINAL RESEARCH ARTICLE

Predictive Impact of Peripheral Blood Markers and C-Reactive Protein in Nivolumab Therapy for Metastatic Renal Cell Carcinoma

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Abstract

Background Predictive factors that can be routinely used in clinical practice are critically needed for immune checkpoint inhibitor therapy in metastatic renal cell carcinoma (mRCC).

Objective To comprehensively analyze the predictive impact of peripheral blood markers and C-reactive protein (CRP) in nivolumab therapy for mRCC.

Methods Fifty-eight patients were retrospectively evaluated. We evaluated neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), absolute eosinophil count (AEC), and absolute monocyte count (AMC) as peripheral blood markers as well as serum CRP levels. The primary endpoints were progression-free survival (PFS) and overall survival (OS) after nivolumab initiation.

Results Median PFS was significantly shorter in patients with high NLR (≥ 3) versus low NLR ($p = 0.0356$), high MLR (≥ 0.3) versus low MLR ($p = 0.0013$), or high PLR (≥ 160) versus low PLR ($p = 0.0073$), and median OS was significantly shorter in patients with high NLR versus low NLR ($p = 0.0025$), high MLR versus low MLR ($p = 0.0025$), high PLR versus low PLR ($p = 0.0256$), or high CRP (≥ 1.0 mg/dl) versus low CRP ($p = 0.0006$). Multivariate analyses showed that MLR (HR 2.65, $p = 0.0068$) was an independent factor for PFS and that NLR (HR 3.34, $p = 0.0218$), MLR (HR 3.42, $p = 0.0381$), and CRP (HR 4.98, $p = 0.0108$) were independent factors for OS.

Conclusions The systemic inflammatory factors NLR, MLR, and CRP were predictive factors in nivolumab therapy for mRCC. These easily monitored factors can contribute to effective treatment and follow-up.

1 Introduction

Nivolumab, an anti-PD-1 monoclonal antibody, is standard systemic therapy for metastatic renal cell carcinoma (mRCC) [1]. A pivotal phase III trial, "CheckMate025", demonstrated that nivolumab conferred prolonged overall survival (OS) and a more favorable safety profile than everolimus in second- or third-line therapy after the failure of previous antiangiogenic regimens for advanced clear-cell RCC. In addition, other immune checkpoint inhibitors (ICIs) targeting PD-1 or other molecules, such as PD-L1 or CTLA-4, have been developed and tested in clinical trials as monotherapy or combination therapy [2]. Thus, there is an ongoing paradigm shift in the systemic therapy of mRCC.

However, the rate of patients who cannot obtain any therapeutic benefit from ICIs (i.e., patients with progressive disease as their best overall response) ranged from 20–35%, according to previous trials [3, 4]. Moreover, in the real world, similar or higher rates of such cases (33–47%) were recently reported [5–7]. Furthermore, a subset of patients can develop immediate progressive disease, such as hyperprogression, and these patients generally have poor prognosis [8–10]. In addition, the cost of ICI therapy has been debated [11]. Therefore, it is important to identify predictive or prognostic factors to provide effective therapy for patients with mRCC.

In mRCC, inflammatory factors such as neutrophil, platelet counts, and serum C-reactive protein (CRP) level and combinational markers consisting of these factors (e.g.,

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Key Points

The predictive impact of peripheral blood markers and C-reactive protein (CRP) in patients receiving nivolumab for metastatic renal cell carcinoma remains unclear.

Monocyte-to-lymphocyte ratio (MLR) was an independent factor for progression-free survival, and MLR, neutrophil-to-lymphocyte ratio (NLR), and CRP were independent factors for overall survival.

MLR was associated with objective response rates and clinical benefit, and NLR was associated with clinical benefit.

neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), modified Glasgow Prognostic Score), are intensively studied predictive or prognostic factors in molecular-targeted therapy [12–20]. Moreover, recent studies reported that these factors are associated with survival following ICI therapy in patients with melanoma [21, 22] or non-small-cell lung cancer (NSCLC) [23, 24]. In addition, several studies indicated that other peripheral blood markers, including eosinophil [25–27] and monocyte counts [25, 28], are associated with prognosis in ICI therapy. Thus, these factors can be effective in predicting the outcomes of ICI therapy in patients with mRCC. However, there is a limited number of clinical investigations that comprehensively analyze the predictive impact of these factors. Thus, in this retrospective study, we investigated the association between these peripheral blood markers and CRP and prognoses in nivolumab therapy for patients with mRCC.

2 Patients and Methods

2.1 Study Design

This study was approved by the Internal Ethics Review Board of the Tokyo Women's Medical University (ID: 5103) and performed in accordance with the principals outlined in the Declaration of Helsinki. Owing to the retrospective observational nature of this study, formal consent was not required.

The inclusion and exclusion criteria for this study are shown in Fig. 1. In our department and its affiliated institution, 76 patients received nivolumab therapy after at least one targeted therapy for mRCC between June 2013 and June 2019. Patients who lacked laboratory data of peripheral blood markers or CRP ($n = 11$) or lacked other detailed clinical data ($n = 3$) were excluded. Furthermore, patients whose duration of follow-up was less than 1 month were excluded ($n = 4$). Finally, the remaining 58 patients were included in this retrospective study. All clinical and laboratory data were obtained from an electronic database and patient medical records.

This study aimed to identify the predictive factors for oncological outcomes in nivolumab therapy. Thus, the primary endpoint was progression-free survival (PFS) and overall survival (OS) after nivolumab initiation. Furthermore, we evaluated objective response rates (ORRs) and clinical benefit (CB) during nivolumab therapy as the secondary endpoint. ORRs were the sum of complete response and partial response rates, and CB was the sum of complete response, partial response, and stable disease rates. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 [29].

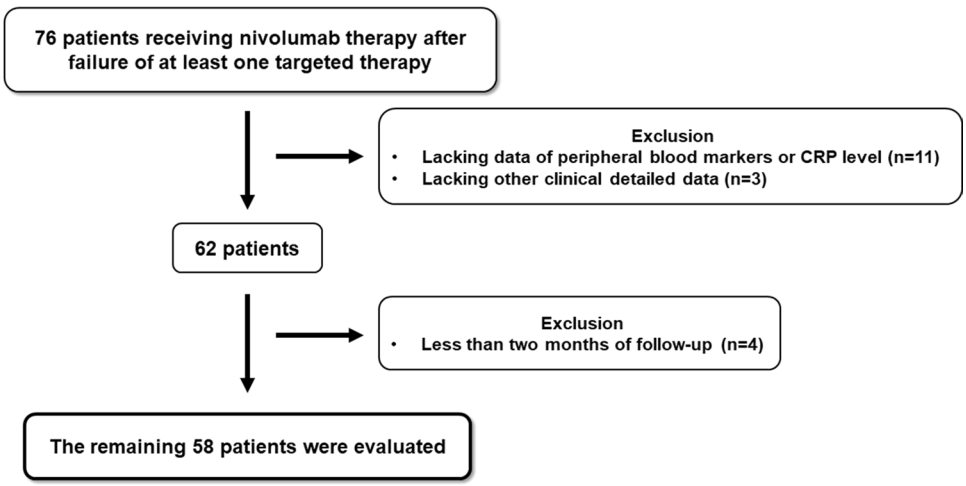

Fig. 1 Flow-chart of patient selection. *CRP* C-reactive protein

2.2 Protocol of Nivolumab Therapy

Nivolumab (3 mg/kg) was intravenously administered every 2 weeks following a protocol used in the CheckMate025 study [3]. Dose modifications were not allowed in any case. Instead, the interval between administrations could be modified according to the patient's condition or in cases of nivolumab-induced adverse events. In this study, all patients received nivolumab after failure of prior targeted therapy. The sequential targeted therapy regimen adopted in our departments was described in our previous studies [30, 31]. Post-treatment follow-up scans were obtained using computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis regularly at 4- to 12-week intervals, depending on the condition of the patient. Nivolumab was administered until radiographic or clinical disease progression or development of intolerable adverse events was observed.

2.3 Cut-off Values of Peripheral Blood Markers and C-Reactive Protein (CRP)

In this study, we evaluated NLR, monocyte-to-lymphocyte ratio (MLR), PLR, absolute eosinophil count (AEC), and absolute monocyte count (AMC) as the peripheral blood markers. Furthermore, as one of the most intensively studied inflammatory factors, serum CRP levels were evaluated. We set cut-off values of these factors based on those in previous studies. For NLR, the cut-off value was set at 3 based on review or meta-analysis in the setting of systemic therapy including targeted therapy for mRCC [17, 32]; for MLR, the cut-off value was set at 0.3 based on studies in the setting of non-metastatic clear-cell RCC [33, 34]; for PLR, the cut-off value was set at 160 based on one meta-analysis and one study in the setting of nivolumab for NSCLC [35, 36]; for AEC, the cut-off value was set at 100/μl based on one study in the setting of nivolumab for mRCC [6]; for AMC, the cut-off value was set at 650/μl based on one study in the setting of ipilimumab for melanoma [25]; for CRP, the cut-off value was set at 1.0 mg/dl based on studies in the setting of mRCC [37, 38]. We evaluated the data for these factors in all patients within 2 weeks before initiation of nivolumab therapy.

2.4 Statistical Analysis

Categorical variables were analyzed using Fisher's exact test. PFS was calculated from initiation of nivolumab therapy until disease progression or death, whichever came first. Patients who were alive without disease progression were censored at the time of last follow-up. OS was calculated from initiation of nivolumab therapy until death due to any cause. Patients lost to follow-up were censored at the time of last contact. Survival was calculated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazards regression models were used to identify risk factors for PFS and OS. Multivariate analyses were conducted using factors whose statistical significance was identified by univariate analyses. Risk was expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted using JMP software (version 14; SAS Institute Inc., Cary, NC, USA), with $p < 0.05$ indicating statistical significance.

3 Results

3.1 Patient Characteristics

Patient characteristics are shown in Table 1. Briefly, 45 patients (77.6%) were male and 34 patients (58.6%) were more than 65 years old. Forty-five patients (77.6%) were diagnosed with a clear-cell histotype. Based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk at nivolumab initiation [39], four (6.90%), 32 (55.2%), and 22 (37.9%) patients were categorized as favorable, intermediate, and poor risk, respectively. Nivolumab was administered in the third- or later-line in 24 patients (41.4%), and most of the previous targeted therapies were tyrosine kinase inhibitors, both in the first- (57/58, 98.3%) and second-line therapies (20/22, 90.9%). High NLR (≥ 3), high MLR (≥ 0.3), high PLR (≥ 160), low AEC (< 100/μl), high AMC (≥ 650/μl), and high CRP (≥ 1 mg/dl) were observed in 34 (58.6%), 37 (63.8%), 38 (65.5%), 23 (39.7%), nine (15.5%), and 34 (58.6%) patients, respectively.

3.2 Survival According to Peripheral Blood Markers and CRP

During the follow-up period, 44 (75.9%) and 21 (36.2%) patients experienced disease progression and died due to any cause, respectively (Table 1). Median PFS was significantly shorter in patients with high NLR, MLR, or PLR than in those with low NLR, MLR, or PLR (NLR 4.24 (95% CI 2.33–5.92)] vs. 8.38 (4.04–13.4) months, $p = 0.0356$; MLR 3.62 (2.27–5.19) vs. 10.1 (5.95–58.9) months, $p = 0.0013$; PLR: 3.76 (2.66–5.49) vs. 10.5 (5.92 not reached (NR)) months, $p = 0.0073$) (Fig. 2). The other factors were not significantly associated with median PFS (AEC 6.30 (3.58–10.1) vs. 4.34 (2.70–7.89) months, $p = 0.731$; AMC 6.97 (0.46–13.1) vs. 5.19 (3.62–8.05) months, $p = 0.735$; CRP 5.19 (2.33–8.38) vs. 5.95 (3.91–13.4) months, $p = 0.184$). Median OS was significantly shorter in patients with high NLR, MLR, PLR, or CRP than in those with low NLR, MLR, PLR, or CRP (NLR 22.0 (7.36–26.0) vs. NR

Table 1 Patient characteristics

	All ($n=58$)
Sex	
Male	45 (77.6%)
Age, (years)	
≥ 65	34 (58.6%)
Histopathology	
Clear-cell carcinoma	45 (77.6%)
IMDC risk at nivolumab initiation	
Favorable	4 (6.90%)
Intermediate	32 (55.2%)
Poor	22 (37.9%)
KPS, (%)	
≥ 80	47 (81.0%)
Number of previous targeted therapies	
≥ 2	24 (41.4%)
Previous targeted therapies	
First-line	58 (100%)
TKIs	57 (98.3%)
Sunitinib	27 (46.6%)
Pazopanib	11 (19.0%)
Sorafenib	17 (29.3%)
Axitinib	2 (3.45%)
mTORis	1 (1.72%)
Everolimus	0
Temsirolimus	1 (1.72%)
Second-line	22 (37.9%)
TKIs	20 (34.5%)
Sunitinib	3 (5.17%)
Pazopanib	1 (1.72%)
Sorafenib	1 (1.72%)
Axitinib	15 (25.9%)
mTORis	2 (3.45%)
Everolimus	2 (3.45%)
Temsirolimus	0
Number of metastatic organs	
Multiple	35 (60.3%)
Liver metastasis status	
Present	13 (22.4%)
Bone metastasis status	
Present	14 (24.1%)
Brain metastasis status	
Present	2 (3.45%)
NLR	
≥ 3	34 (58.6%)
MLR	
≥ 0.3	37 (63.8%)
PLR	
≥ 160	38 (65.5%)
AEC, (/μl)	
< 100	23 (39.7%)
AMC, (/μl)	
≥ 650	9 (15.5%)
CRP level, (mg/dl)	
≥ 1	34 (58.6%)
Number of patients with disease progression	44 (75.9%)
Number of patients dying	21 (36.2%)
[a]Duration from nivolumab initiation to initial radiographic evaluation, months	1.84 (1.38–2.34)
[a]Follow-up duration, months	13.1 (6.39–22.1)

IMDC International Metastatic Renal Cell Carcinoma Database Consortium, *KPS* Karnofsky Performance Status, *TKI* tyrosine kinase inhibitor, *mTORi* mammalian target of rapamycin inhibitor, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *AEC* absolute eosinophil count, *AMC* absolute monocyte count, *CRP* C-reactive protein

[a]Shown as median (interquartile range)

(21.4–NR) months, $p=0.0025$; MLR 15.4 (7.36–NR) vs. NR (21.4–NR) months, $p=0.0025$; PLR 22.0 (9.30–NR) vs. NR (21.4–NR) months, $p=0.0256$; CRP 21.4 (8.02–NR) vs. NR (NR–NR) months, $p=0.0006$) (Fig. 3). The other factors were not significantly associated with median OS (AEC 23.3 (21.4–NR) vs. NR (8.02–NR) months, $p=0.685$; AMC 22.0 (0.72–NR) vs. NR (21.4–NR) months, $p=0.0538$).

3.3 Factors for Survival

Univariate analysis showed that histopathology, IMDC risk, NLR, MLR, and PLR were significant factors for PFS (all, $p<0.05$) (Table 2). Univariate analysis also showed that IMDC risk, Karnofsky Performance Status score, liver metastasis status, NLR, MLR, PLR, and CRP were significant factors for OS (all, $p<0.05$). Multivariate analysis for PFS showed that MLR (HR 2.65 (95% CI 1.30–5.86), $p=0.0068$) was a sole independent factor (Table 3). Multivariate analysis for OS showed that NLR (HR 3.34 (1.18–11.9), $p=0.0218$), MLR (HR 3.42 (1.06–15.3), $p=0.0381$), and CRP (HR 4.98 (1.39–31.9), $p=0.0108$) were independent factors.

3.4 Objective Response Rates and Clinical Benefit According to Peripheral Blood Markers and CRP

We also evaluated an association between ORRs and CB and peripheral blood markers and CRP. As shown in Table 4, MLR was significantly associated with ORRs (18.9% vs. 52.4%, $p=0.0166$) and CB (48.6% vs. 85.7%, $p=0.0057$), and NLR was significantly associated with CB (47.1% vs. 83.4%, $p=0.0064$).

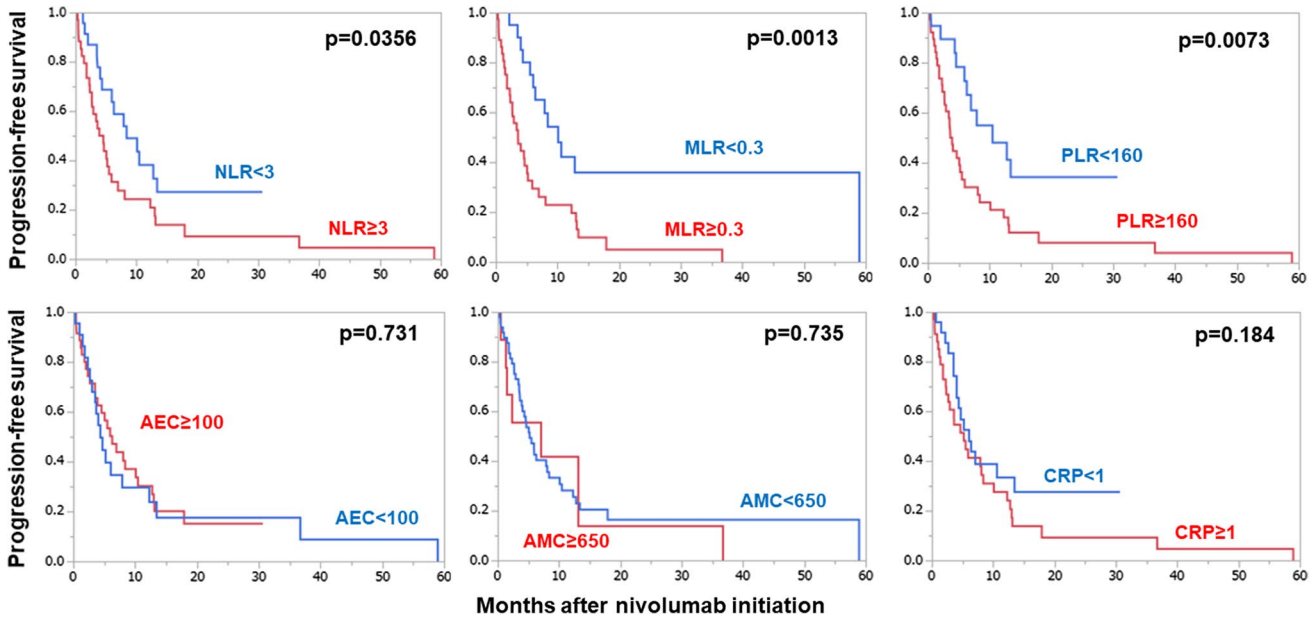

Fig. 2 Progression-free survival according to peripheral blood markers and CRP. Higher NLR (≥3), higher MLR (≥0.3), and higher PLR (≥160) were significantly associated with shorter median PFS (NLR 4.24 vs. 8.38 months, $p=0.0356$; MLR: 3.62 vs. 10.1 months, $p=0.0013$; PLR 3.76 vs. 10.5 months, $p=0.0073$). Other factors, namely AEC, AMC, or CRP, were not associated with PFS (AEC: 6.30 vs. 4.34, $p=0.731$; AMC: 6.97 vs. 5.19, $p=0.735$; CRP 5.19 vs. 5.95, $p=0.184$). *CRP* C-reactive protein, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *PFS* progression-free survival, *AEC* absolute eosinophil count, *AMC* absolute monocyte count

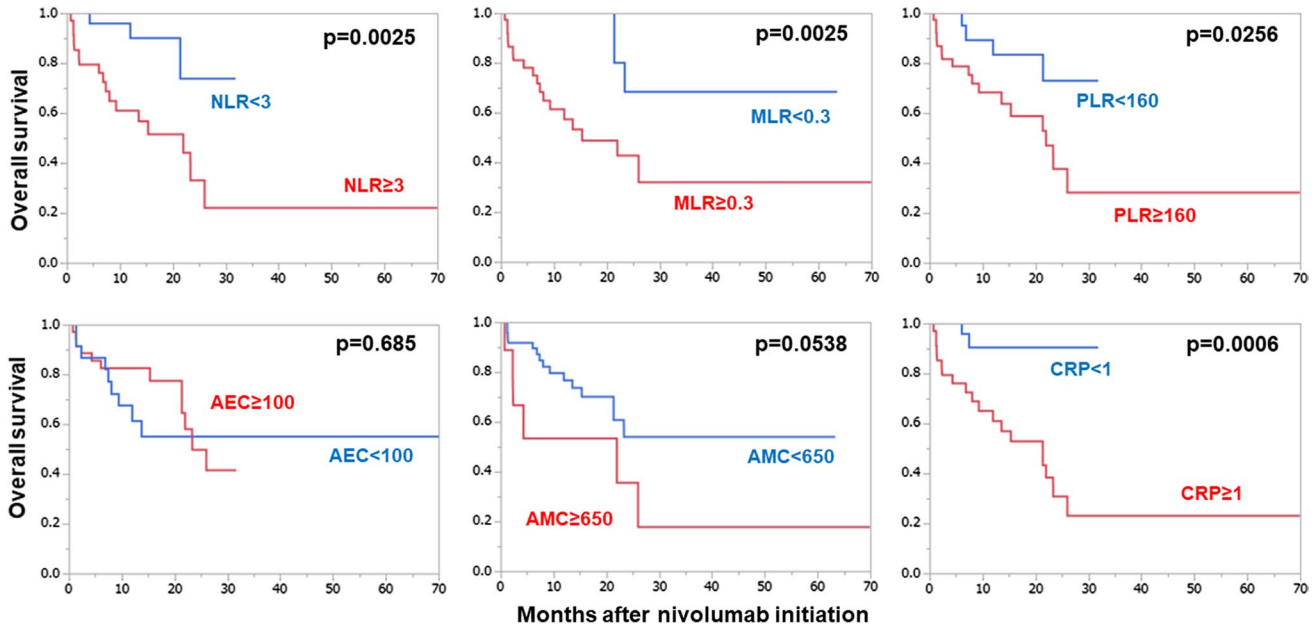

Fig. 3 Overall survival according to peripheral blood markers and CRP. Higher NLR (≥3), higher MLR (≥0.3), higher PLR (≥160), and higher CRP (≥1 mg/dl) were significantly associated with shorter median OS (NLR: 22.0 months vs. NR, $p=0.0025$; MLR: 15.4 vs. NR, $p=0.0025$; PLR: 22.0 months, vs. NR, $p=0.0256$; CRP: 21.4 months vs. NR, $p=0.0006$). Other factors, namely AEC or AMC, were not associated with OS (AEC: 23.3 vs. NR, $p=0.685$; AMC: 22.0 vs. NR, $p=0.0538$). *CRP* C-reactive protein, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *OS* overall survival, *AEC* absolute eosinophil count, *AMC* absolute monocyte count

Table 2 Univariate analyses for progression-free and overall survival

Variable	PFS HR (95% CI)	*p*	OS HR (95% CI)	*p*
Sex		0.282		0.436
Male (ref. female)	0.66 (0.33–1.44)		0.66 (0.26–2.03)	
Age, years		0.0752		0.509
≥ 65 (ref. < 65)	0.58 (0.32–1.06)		0.75 (0.31–1.80)	
Histopathology		0.0309		0.255
Clear-cell carcinoma (ref. non-clear cell carcinoma)	0.44 (0.22–0.92)		0.56 (0.22–1.58)	
IMDC risk		0.0095		0.0052
Favorable	0.60 (0.096–2.03)	0.456	2.37e−9 (0–1.94)	0.149
Intermediate	ref.	–	ref.	–
Poor	2.57 (1.33–4.95)	0.0052	3.32 (1.37–8.32)	0.0080
KPS score, (%)		0.155		< 0.0001
≥ 80 (ref. < 80)	0.57 (0.28–1.26)		0.14 (0.058–0.35)	
Number of previous targeted therapies		0.699		0.851
≥ 2 (ref. < 2)	0.89 (0.48–1.61)		1.09 (0.45–2.67)	
First-line therapy		0.775		0.723
Sunitinib (ref. others)	1.09 (0.60–1.98)		1.17 (0.49–2.81)	
Number of metastatic organs		0.797		0.479
Multiple (ref. solitary)	1.08 (0.60–2.02)		1.38 (0.57–3.64)	
Liver metastasis status		0.580		0.0186
Present (ref. absent)	1.23 (0.57–2.40)		3.41 (1.25–8.70)	
Bone metastasis status		0.270		0.418
Present (ref. absent)	1.47 (0.72–2.80)		1.50 (0.53–3.72)	
NLR		0.0340		0.0018
≥ 3 (ref. < 3)	1.94 (1.05–3.72)		4.68 (1.71–16.4)	
MLR		0.0011		0.0014
≥ 0.3 (ref. < 0.3)	2.85 (1.50–5.78)		5.44 (1.83–23.4)	
PLR		0.0058		0.0196
≥ 160 (ref. < 160)	2.49 (1.29–5.18)		3.24 (1.19–11.3)	
AEC, (/μl)		0.732		0.688
≥ 100 (ref. < 100)	0.90 (0.49–1.68)		0.84 (0.35–2.05)	
AMC, (/μl)		0.739		0.0838
≥ 650 (ref. < 650)	1.14 (0.49–2.35)		2.47 (0.88–6.11)	
CRP level, (mg/dl)		0.180		0.0002
≥ 1 (ref. < 1)	1.51 (0.83–2.86)		8.43 (2.44–53.0)	

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *ref* reference, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *KPS* Karnofsky Performance Status, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *AEC* absolute eosinophil count, *AMC* absolute monocyte count, *CRP* C-reactive protein

4 Discussion

This retrospective study showed that NLR, MLR, and PLR were associated with PFS and that NLR, MLR, PLR, and CRP were associated with OS. Multivariate analyses further showed that MLR was the sole independent factor for PFS and that NLR, MLR, and CRP were independent factors for OS. In addition, MLR was associated with ORRs and CB, and NLR was associated with CB during nivolumab therapy. To the best of our knowledge, this study is the first comprehensive investigation of the predictive impact of peripheral blood markers and CRP in nivolumab therapy for patients with mRCC.

Among these factors, NLR is one of the most intensively studied inflammatory factors and has recently been reported to be associated with survival in mRCC patients treated with nivolumab [6, 40] and in patients with melanoma [21, 22] and NSCLC [23] treated with ICIs. Elevated NLR reflects

Table 3 Multivariate analyses for progression-free and overall survival

Variable	PFS HR (95% CI)	*p*
NLR		0.188
≥ 3 (ref. < 3)	1.55 (0.81–3.13)	
MLR		0.0068
≥ 0.3 (ref. < 0.3)	2.65 (1.30–5.86)	
PLR		0.152
≥ 160 (ref. < 160)	1.78 (0.81–4.18)	
Variable	OS HR (95% CI)	*p*
NLR		0.0218
≥ 3 (ref. < 3)	3.34 (1.18–11.9)	
MLR		0.0381
≥ 0.3 (ref. < 0.3)	3.42 (1.06–15.3)	
PLR		0.211
≥ 160 (ref. < 160)	2.06 (0.68–7.68)	
CRP level, (mg/dl)		0.0108
≥ 1 (ref. < 1)	4.98 (1.39–31.9)	

The multivariate model for progression-free survival was built by adjusting for histopathology and the IMDC risk, which were identified by univariate analysis

The multivariate model for overall survival was built by adjusting for IMDC risk and liver metastasis status, which were identified by univariate analysis

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *ref* reference, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *CRP* C-reactive protein, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium

high activity of the immune system. Chronic inflammation favors tumor development by preventing or suppressing the antitumor activity of the immune system, resulting in tumor growth [41, 42].

PLR has been also indicated as a predictive factor in several cancers including RCC. Platelets also play an active role in inflammation by releasing VEGF, which mediates the migration and extravasation of leukocytes, and PDGF, a chemokine that recruits neutrophils and monocytes [43]. The association between PLR and prognoses has already been reported during ICI therapy in NSCLC [36, 44]. Furthermore, in markers consisting of monocytes including AMC and MLR, AMC was reported to be associated with prognoses in ICI therapy for melanoma [25] and NSCLC [28]. Monocytes are progenitors of monocyte-derived macrophages. Recent studies revealed the mechanistically specific properties of monocytes—inflammatory monocytes are required for the efficacy of transferred activated cytotoxic T-cells but can exert potent tissue-damaging effects. On the other hand, other monocytes can provoke resistance to chemotherapy and aid tumor growth [45]. Interestingly, from our data, oncological outcomes were associated with MLR rather than AMC. Possibly, this superior predictive performance of MLR may be caused by inclusion of lymphocyte counts in MLR, which also have the potential to predict prognoses.

A recent study showed that these systemic inflammatory factors including NLR, MLR, and PLR had potential for outcome prediction during ICI therapy for advanced cancers whose major components of histology were melanoma and gastrointestinal and lung/head and neck cancers [46]. However, another study investigated the predictive performance of PLR in nivolumab therapy for mRCC and concluded that PLR was not an independent factor for OS based on multivariate analysis [47].

Decreased eosinophil count is also reported to be associated with poor prognosis in ICI therapy for patients with melanoma [25–27]. Eosinophils have a tumor surveillance function, and they have been reported to be effector cells for tumor rejection [48, 49]. Recently, Zahoor et al. indicated a significant association between low AEC and poor prognosis in nivolumab therapy for mRCC [6], which is inconsistent with our findings. One explanation for this discrepancy may be the differences in patient cohorts.

Finally, CRP is also a well-studied effective predictive factor representing inflammation in targeted therapy for

Table 4 Objective response rates and clinical benefit according to peripheral blood markers and CRP

Variable	CR	PR	SD	PD	ORRs	*p*	CB	*p*
NLR						0.162		0.0064
≥ 3	2 (5.88%)	6 (17.7%)	8 (23.5%)	18 (52.9%)	23.6%		47.1%	
< 3	1 (4.17%)	9 (37.5%)	10 (41.7%)	4 (16.7%)	41.7%		83.3%	
MLR						0.0166		0.0057
≥ 0.3	2 (5.41%)	5 (13.5%)	11 (29.7%)	19 (51.4%)	18.9%		48.6%	
< 0.3	1 (4.76%)	10 (47.6%)	7 (33.3%)	3 (14.3%)	52.4%		85.7%	
PLR						0.767		0.0506
≥ 160	2 (5.26%)	9 (23.7%)	9 (23.7%)	18 (47.4%)	29.0%		52.6%	
< 160	1 (5.00%)	6 (30.0%)	9 (45.0%)	4 (20.0%)	35.0%		80.0%	
AEC, (/μl)						0.257		1.000
≥ 100	3 (8.57%)	10 (28.6%)	9 (25.7%)	13 (37.1%)	37.2%		62.9%	
< 100	0	5 (21.7%)	9 (39.1%)	9 (39.1%)	21.7%		60.9%	
AMC, (/μl)						0.438		1.000
≥ 650	1 (11.1%)	3 (33.3%)	2 (22.2%)	3 (33.3%)	44.4%		66.7%	
< 650	2 (4.08%)	12 (24.5%)	16 (32.7%)	19 (38.8%)	28.6%		61.2%	
CRP level, (mg/dl)						1.000		0.593
≥ 1	2 (5.88%)	9 (26.5%)	9 (26.5%)	14 (41.2%)	32.4%		58.8%	
< 1	1 (4.17%)	6 (25.0%)	9 (37.5%)	8 (33.3%)	29.2%		66.7%	
All	3 (5.17%)	15 (25.9%)	18 (31.0%)	22 (37.9%)	18 (31.0%)		36 (62.1%)	

ORRs including CR + PR rates

CB including CR + PR + SD rates

CRP C-reactive protein, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORRs* objective response rates, *CB* clinical benefit, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *AEC* absolute eosinophil count, *AMC* absolute monocyte count, *CRP* C-reactive protein

mRCC [13, 14, 18], but its potential for prediction remains unknown in ICI therapy. Thus, to the best of our knowledge, this is the first report to indicate the significant association between CRP and prognoses in nivolumab therapy for mRCC. In other cancers, the predictive impact of CRP has been reported in ICI therapy [24, 27]. Moreover, in gastric cancer, a significant correlation between the development of ICI-induced hyperprogression and elevated CRP was reported [50]. Another study suggested that IL-6, which induces CRP production from the liver, and CRP were predictive factors in melanoma patients treated with ICIs [51]. Their in vitro data also suggested that CRP can affect T-cell signaling and activation. Thus, these data may support our findings in terms of the close association between high inflammatory status and poor prognosis and lower tumor response.

Taken together, our analyses indicate that among multiple factors, systemic inflammation has the potential to predict oncological outcomes. These identified factors can contribute to improve the predictive performance of existing prognostic models. For example, a previous study reported that addition of NLR to the IMDC risk model instead of neutrophil count significantly improved the predictive performance for OS in targeted therapy [12]. Thus, our identified factors may be considered for inclusion in future clinical research or trials to build effective predictive or prognostic models in ICIs for mRCC.

This study has several limitations. First, this study was conducted retrospectively using a small sample size. Thus, any findings could be affected by the unavoidable selection biases. Second, peripheral blood markers might be affected by previous targeted therapies (i.e., neutropenia or thrombocytopenia), which can affect the results of our analyses. Third, in this study, nivolumab was administered as a second- or later-line therapy after the failure of previous targeted therapies regardless of the IMDC risk classification in all patients, although this regimen has been not strongly recommended under the current guideline [1]. Fourth, the relatively short duration of follow-up and the small number of patients who died can affect the analyses, especially in OS.

5 Conclusions

This retrospective study showed that systemic inflammation factors including NLR, MLR, and CRP were significant predictive factors in nivolumab therapy for patients

with mRCC. Because these factors can be easily evaluated and monitored in routine clinical practice, usage of these factors can contribute to effective treatment and follow-up. However, further prospective large-scale studies are needed to confirm our findings.

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Compliance with Ethical Standards

Conflict of interest Tsunenori Kondo received honoraria from Ono Pharmaceutical. Hiroki Ishihara, Hidekazu Tachibana, Toshio Takagi, Hironori Fukuda, Kazuhiko Yoshida, Junpei Iizuka, Hirohito Kobayashi, Masayoshi Okumi, Hideki Ishida, and Kazunari Tanabe have no conflicts of interest to declare.

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