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C-reactive protein and neutrophil-lymphocyte ratio are prognostic in metastatic clear-cell renal cell carcinoma patients treated with nivolumab

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Abstract

Objective: To evaluate the impact of markers of systemic inflammation such as C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR) on outcomes of metastatic clear-cell renal cell carcinoma (m-ccRCC) patients treated with nivolumab.

Patients and methods: We retrospectively evaluated m-ccRCC patients treated with nivolumab and collected known prognostic factors and survival data. We used Kaplan-Meier survival analysis and cox proportional hazards regression analysis to study prognostic factors for overall survival (OS) and progression-free survival (PFS) since start of nivolumab. Harrell's C-index was used to evaluate the models.

Results: We included 113 patients. Median OS and PFS after initiation of nivolumab was 15 (interquartile range 7−28) and 4 months (interquartile range 3−11), respectively.

Elevated baseline CRP was associated with worse OS (HR per 25 mg/l 1.35, 95% CI 1.16−1.52, $P < 0.001$) and PFS (HR per 25 mg/l 1.19, 95% CI 1.08−1.35, $P = 0.001$), independent from the international metastatic renal cell carcinoma database consortium (IMDC) prognostic criteria, increasing the model's C-index from 0.72 to 0.77 for OS and 0.59 to 0.62 for PFS.

Elevated NLR was associated with worse OS (HR 1.10, 95% CI 1.04−1.17, $P = 0.002$) and PFS (HR 1.06, 95% CI 1.01−1.11, $P = 0.03$) independent from the other IMDC prognostic criteria. The model's C-index decreased from 0.72 to 0.70 for OS and increased from 0.59 to 0.60 for PFS.

Conclusions: Elevated baseline CRP and NLR predict worse OS and PFS on nivolumab in m-ccRCC patients. Including baseline CRP in the IMDC prognostic model improves its discriminatory power to predict OS and PFS since start of nivolumab. © 2020 Elsevier Inc. All rights reserved.

Keywords: Metastatic clear-cell renal cell carcinoma; Nivolumab; Immune checkpoint inhibitor; C-reactive protein; Neutrophil-lymphocyte ratio

1. Introduction

Renal cell carcinoma (RCC) accounts for about 3% of all malignancies worldwide. Up to 17% of newly diagnosed cases harbor metastases at presentation and up to one third of cases treated with curative intent will eventually relapse or develop metastases [1,2].

Recently, the advent of immunotherapy in RCC has yielded ex8cellent results and currently forms the backbone of systemic treatment of metastatic clear-cell RCC (m-ccRCC) [3]. The programmed cell death protein 1 inhibitor nivolumab is currently recommended in second or further line therapy after previous vascular endothelial growth

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factor receptor tyrosine kinase inhibitor (VEGFR-TKI) therapy, based on the results of a large randomized controlled phase III trial comparing nivolumab to everolimus. This trial showed improved objective response rates (ORR) and overall survival (OS) compared to everolimus in patients who had failed 1 or multiple lines of VEGFR-targeted therapy [4].

Currently, clinical prognostic tools such as the International Metastatic RCC Database Consortium (IMDC) risk criteria are used to predict patient outcomes. Based on 6 factors (anemia, hypercalcemia, low Karnofsky performance status, time from diagnosis to systemic treatment <12 months, neutrophilia and thrombocytosis), patients can be stratified into good, intermediate or poor prognostic categories [5]. Although initially developed in the targeted therapy era, the IMDC risk groups retain their prognostic value in patients treated with the currently available immunotherapy regimens [6].

Inflammation is a known hallmark of aggressive cancer and clinical outcomes are not only determined by the inherent tumor biology but also largely by the host's immune response to this malignant process [7]. Biomarkers reflecting this immune response may therefore predict clinical outcomes. Anemia, thrombocytosis and neutrophilia are inflammatory biomarkers, included in the IMDC risk score [8,9]. However, additional inflammatory biomarkers, such as C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR), not included in the IMDC risk score, have previously shown to be correlated to outcome in m-ccRCC pts treated with interferon-α and VEGFR-TKIs [10−13].

CRP is a nonspecific inflammatory acute-phase protein and thus a marker of a systemic inflammatory response. Elevated NLR has also been shown to reflect the patient's inflammatory response and portends a worse prognosis across a wide range of cancer types, including RCC [14,15]. In general, a state of neutrophilia with a relative lymphocytopenia reflects the complex interplay between the tumor and the host's immune system, shifted towards tumor progression [16].

In this study, we aimed to investigate the prognostic value of markers of systemic inflammation in m-ccRCC patients treated with nivolumab in any line in an attempt to refine existing prognostic risk categories.

2. Patients and methods

We performed a retrospective study on m-ccRCC patients from 2 institutional cohorts, treated with nivolumab. All consecutive m-ccRCC patients who started on nivolumab between November 2012 and February 2020 were included, regardless of treatment line. Patients who received prior interferon-α, VEGFR-TKIs or mammalian target of rapamycin inhibitors were included but patients who received prior immune checkpoint inhibitors (ICI) were excluded. Nivolumab was administered either 240 mg every 2 weeks or 480 mg every 4 weeks. Response evaluation was done with thoracic and abdominal computed tomography scan every 12 weeks by the investigator using the immune related response evaluation criteria in solid tumors.

We collected data on the 6 IMDC prognostic criteria, steroid use, immune related adverse events (irAE), baseline serum CRP levels and NLR. The standard cut-off of 5 mg/l was used for CRP and 3.0 for NLR. The primary objective was OS, which was calculated from start of nivolumab therapy. Secondary objectives were ORR and progression free survival (PFS). Of note, ORR and PFS are less reliable endpoints compared to OS since these might be influenced by pseudoprogression. Moreover, median PFS might not be influenced by nivolumab as ORRs are <25% and early progressive disease rates are high, approaching 50%. We performed 2 sensitivity analyses to assess what potential bias would be introduced to our results by the inclusion of certain cases. In a first sensitivity analysis we excluded patients who used steroids at baseline and in a second sensitivity analysis we excluded patients treated in third or later lines.

In descriptive analyses, continuous variables are presented as median and interquartile range (IQR) and compared using the Mann-Whitney *U* test. For categorical variables, frequencies and proportions are reported and compared using Fisher's exact *t* test. Kaplan-Meier survival analysis was used to estimate the survival distribution. Univariable and multivariable Cox proportional hazards regression models were used to study prognostic factors for OS and PFS. To avoid loss of information, CRP and NLR were not dichotomized, but were used as continuous variables [17]. The proportional hazards assumption was tested using the scaled Schoenfeld residuals. We compared a reference model with the IMDC criteria to extended models including either CRP or NLR to investigate their added value. Harell's C-index was used to calculate the models' discriminatory power. Notably, the extended model incorporating NLR did not take into account the IMDC criterium neutrophilia since this would overlap with the NLR parameter. The impact of baseline CRP and NLR on the occurrence of irAEs was assessed using a logistic regression model. Finally, we performed a Spearman correlation analysis between CRP, NLR and other variables in the IMDC prognostic model linked to inflammation. All tests were 2-sided and a *P* value of <0.05 was considered statistically significant. Data analysis was carried out in R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

We included 113 patients of which 2 (1.8%) were treated with nivolumab in first line, 76 (67.3%) in second line, 26 (23.0%) in third line, 7 (6.2%) in fourth line and 2 (1.8%) in fifth line. The baseline characteristics for our cohort are shown in Table 1. Of 102 patients who underwent prior nephrectomy, 37 harbored synchronous metastases and

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Table 1
Baseline characteristics for the total cohort and compared by baseline CRP and NLR.

Patient characteristics		Total	CRP normal (≤5 mg/l)	CRP elevated (>5 mg/l)	*P* value	NLR normal (≤3)	NLR elevated (>3)	*P* value
Number of patients		113	37	76	/	48	55	/
Age at start of Nivolumab (yr.)		66 (59-73)	68 (64-76)	65 (59-71)	**0.04**	65 (58-74)	66 (60-71)	0.77
Male, no. (%)		83/113 (73.5)	22/37 (59.5)	61/76 (80.3)	**0.02**	27/48 (56.3)	49/55 (89.1)	**<0.001**
Fuhrman grade 4, no. (%)		46/108 (42.6)	14/37 (37.8)	32/71 (45.1)	0.54	19/47 (40.4)	26/51 (51.0)	0.32
No nephrectomy, no. (%)		11/113 (9.7)	1/37 (2.7)	10/76 (13.2)	0.10	1/48 (2.1)	9/55 (16.4)	**0.02**
Karnofsky<80, no. (%)		51/113 (45.1)	13/37 (35.1)	38/76 (50.0)	0.16	15/48 (31.3)	29/55 (52.7)	**0.03**
Neutrophils >7.700/mm^3, no. (%)		10/112 (8.9)	2/37 (5.4)	8/75 (10.7)	0.49	0/48 (0.0)	9/55 (16.4)	**0.003**
Platelets >400.000/mm^3, no. (%)		10/113 (8.9)	1/37 (2.7)	9/76 (11.8)	0.16	2/48 (4.2)	6/55 (10.9)	0.28
Hemoglobin <11.5 g/dl (women) or <13 g/dl (men), no. (%)		73/113 (64.6)	17/37 (46.0)	56/76 (73.7)	**0.01**	25/48 (52.1)	43/55 (78.2)	**0.007**
LDH >1.5x ULN, no. (%)		6/111 (5.4)	4/37 (10.8)	2/74 (2.7)	0.09	3/48 (6.3)	2/54 (3.7)	0.66
Corrected calcium >10 mg/dl, no. (%)		8/105 (7.6)	1/37 (2.7)	7/68 (10.3)	0.26	4/46 (8.7)	4/54 (7.4)	>0.99
Time nephrectomy to start of systemic treatment <12 months, no. (%)		59/113 (52.2)	14/37 (37.8)	45/76 (59.2)	**0.045**	19/48 (39.6)	33/55 (60.0)	**0.049**
Site of metastasis, no. (%)	Lung	74/113 (65.5)	20/37 (54.1)	54/76 (71.1)	0.09	29/48 (60.4)	37/55 (67.3)	0.54
	Lymph nodes	62/113 (54.9)	13/37 (35.1)	49/76 (64.5)	**0.01**	23/48 (47.9)	32/55 (58.2)	0.33
	Liver	32/113 (28.3)	15/37 (40.5)	17/76 (22.4)	0.07	17/48 (35.4)	12/55 (21.8)	0.19
	Brain	13/113 (11.5)	5/37 (13.5)	8/76 (10.5)	0.76	5/48 (10.4)	7/55 (12.7)	0.77
	Bone	54/113 (47.8)	14/37 (37.8)	40/76 (52.6)	0.16	18/48 (37.5)	32/55 (58.2)	**0.048**
	Pancreas	15/113 (13.3)	6/37 (16.2)	9/76 (11.8)	0.56	11/48 (22.9)	4/55 (7.3)	**0.047**
	Number of metastatic sites	3 (2-4)	3 (2-4)	3 (2-4)	0.44	3 (2-4)	3 (2-4)	0.60
IMDC category, no. (%)	Favourable	11/112 (9.8)	7/37 (18.9)	4/75 (5.3)	**0.04**	10/48 (20.8)	1/55 (1.8)	**0.003**
	Intermediate	69/112 (61.6)	26/37 (70.3)	43/75 (57.3)	0.22	31/48 (64.6)	34/55 (61.8)	0.84
	Poor	32/112 (28.6)	4/37 (10.8)	28/75 (37.3)	**0.004**	7/48 (14.6)	20/55 (36.4)	**0.01**

CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio.
Significant *P* values are in bold.

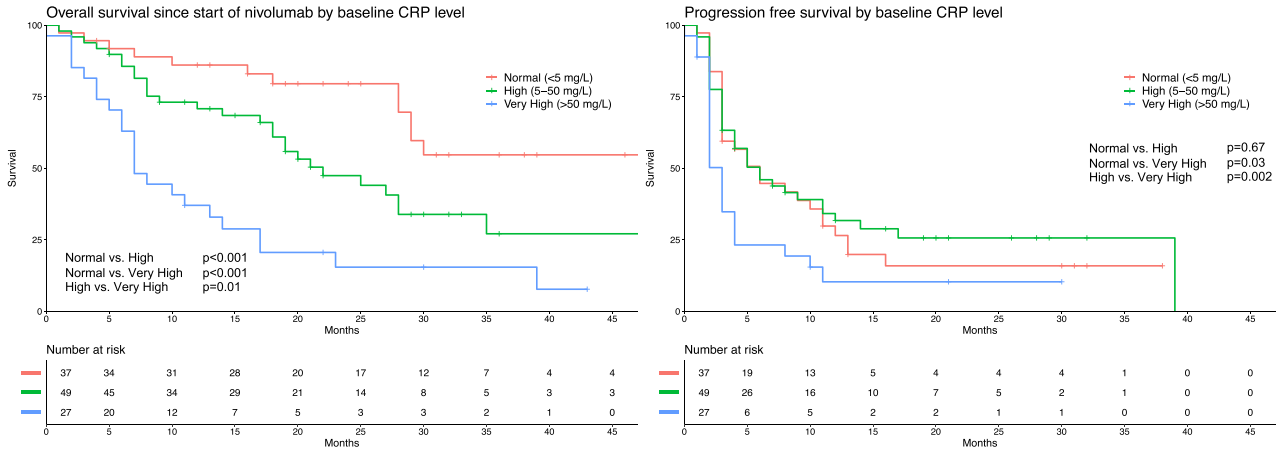


Fig. 1. Kaplan-Meier curves for OS and PFS stratified by baseline CRP level.

underwent cytoreductive surgery. Significantly more patients were in the IMDC poor prognostic risk category in the group with elevated baseline CRP and the group with elevated baseline NLR. Median OS and PFS after initiation of nivolumab was 15 (IQR 7−28) and 4 months (IQR 3 −11), respectively.

In a continuous analysis, higher baseline CRP was associated with worse OS (HR per 25 mg/l: 1.35, 95% CI 1.16 −1.52, $P < 0.001$) and PFS (HR per 25 mg/l: 1.19, 95% CI 1.08−1.35, $P < 0.001$). Fig. 1 shows the Kaplan-Meier curve for OS and PFS for our cohort stratified by normal (<5 mg/l), high (5−50 mg/l) and very high CRP levels (>50 mg/l). Response rates were not significantly different for patients with normal, compared to elevated CRP levels (25.9% vs. 36.5%, $P = 0.63$). When adding baseline CRP to the 6 individual IMDC criteria in a multivariable Cox proportional hazards regression model, CRP was independently associated with worse OS (HR per 25 mg/l 1.35, 95% CI 1.16−1.52, $P < 0.001$) and PFS (HR per 25 mg/l 1.19, 95% CI 1.08−1.35, $P = 0.001$). The model's C-index increased from 0.72 to 0.77 for OS and 0.59 to 0.62 for PFS by adding baseline CRP (Table 2).

When included in a model with the 3 IMDC risk categories, CRP was an independent predictor for both OS and PFS and C-index improved from 0.65 to 0.70 and 0.58 to 0.60, respectively (Supplementary Table 1).

In a continuous analysis, higher NLR was associated with worse OS (HR 1.12, 95% CI 1.06−1.18, $P < 0.001$) and PFS (HR 1.06, 95% CI 1.01−1.12, $P = 0.01$). Fig. 2 shows the Kaplan-Meier curve for OS and PFS for our

Table 2
Multivariable cox proportional hazards model without (reference model) and with (extended model) baseline CRP.

	OS				PFS			
	Reference model (c = 0.72)		Extended model (c = 0.77)		Reference model (c = 0.59)		Extended model (c = 0.62)	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Neutrophils >7.700/mm^3	3.85 (1.87−7.89)	**<0.001**	9.79 (4.04−23.76)	**<0.001**	1.90 (0.95−3.81)	0.07	3.97 (1.76−8.95)	**<0.001**
Karnofsky performance status (<80)	2.17 (1.28−3.69)	**0.004**	1.50 (0.83−2.70)	0.18	1.29 (0.84−2.01)	0.25	0.74 (0.44−1.27)	0.28
Hemoglobin <11.5 g/dl (women) or <13 g/dl (men)	1.22 (0.68−2.19)	0.52	0.76 (0.39−1.45)	0.40	1.07 (0.66−1.73)	0.79	0.83 (0.49−1.38)	0.46
Corrected calcium >10 mg/dl	2.44 (1.03−5.79)	**0.04**	1.71 (0.63−4.62)	0.29	1.66 (0.72−3.83)	0.23	1.20 (0.49−2.98)	0.69
Blood platelets count >400.000/mm^3	0.61 (0.21−1.77)	0.36	0.36 (0.11−1.16)	0.09	1.01 (0.43−2.39)	0.98	0.74 (0.30−1.83)	0.51
Time from diagnosis to systemic treatment <12 months	1.59 (0.93−2.70)	0.09	2.24 (1.27−3.95)	**0.006**	1.18 (0.76−1.84)	0.45	1.32 (0.83−2.08)	0.24
Baseline CRP (per 25 mg/l)	/	/	1.35 (1.16−1.52)	**<0.001**	/	/	1.28 (1.08−1.35)	**0.001**

C = concordance index; CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; NLR = neutrophil-lymphocyte ratio; OS = overall survival; PFS = progression-free survival.

Significant *P* values are in bold.

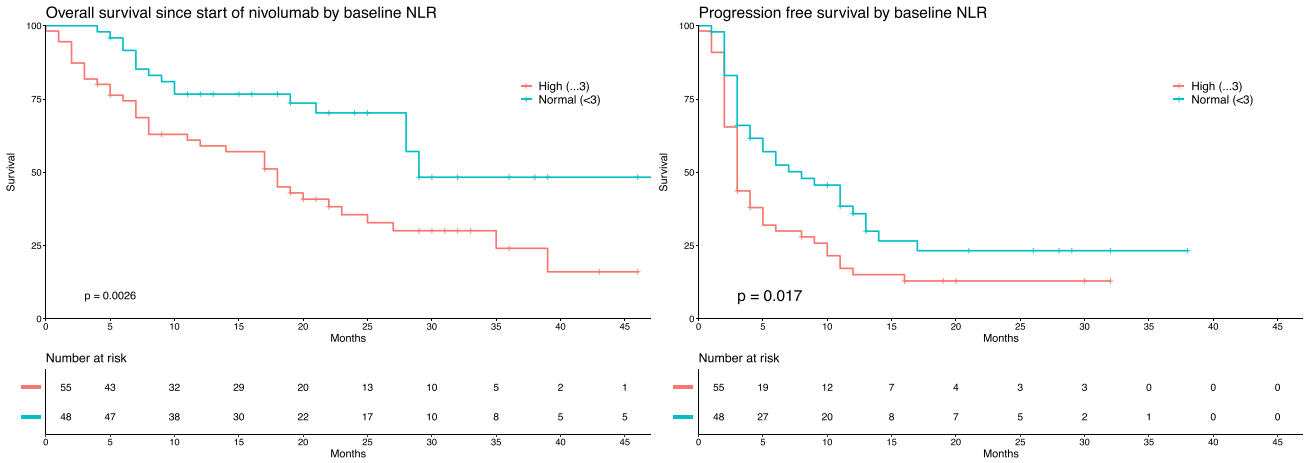


Fig. 2. Kaplan-Meier curves for OS and PFS stratified by baseline NLR.

cohort stratified by normal (<3.0) or elevated (≥3.0) NLR. Response rates were not significantly different for patients with normal compared to elevated NLR (42.4% vs. 25.6%, $P = 0.35$). When assessing the IMDC risk criteria but considering NLR instead of neutrophilia in a multivariable Cox proportional hazards regression model, NLR was independently associated with worse OS (HR 1.10, 95% CI 1.04−1.17, $P = 0.002$) and PFS (HR 1.06, 95% CI 1.01−1.11, $P = 0.03$). However, the model's C-index decreased from 0.72 to 0.70 for OS and only marginally increased from 0.59 to 0.60 for PFS (Table 3).

On Spearman correlation, there was a significant positive correlation between both NLR and CRP as well as an association of both with hemoglobin, neutrophils and platelets. (Table 4) An irAE occurred in 22 (19.5%) patients. Neither baseline CRP (OR per 25 mg/l 0.98, 95% CI 0.78−1.17, $P = 0.87$), nor baseline NLR (OR 0.94, 95% CI 0.77−1.07, $P = 0.44$) were significantly correlated to the occurrence of irAEs.

In our cohort, 16 (14.2%) patients already used steroids at the initiation of nivolumab of whom 9 (8.0%) for brain metastases, 6 (5.3%) for pre-existing autoimmune conditions such as rheumatoid arthritis and polymyalgia rheumatica and 1 (1.8%) for chronic obstructive pulmonary disease. In a first sensitivity analysis, we excluded these cases since they could potentially bias our results. In this sensitivity analysis, both CRP and NLR were still significantly associated with decreased OS (HR per 25 mg/l: 1.35,

Table 3
Multivariable Cox proportional hazards model without (reference model) and with (extended model) baseline NLR.

	OS				PFS			
	Reference model (c = 0.72)		Extended model (c = 0.70)		Reference model (c = 0.59)		Extended model (c = 0.60)	
Predictor	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Baseline NLR	/	/	1.10 (1.04−1.17)	**0.002**	/	/	1.06 (1.01−1.11)	**0.03**
Neutrophils >7.700/mm^3	3.85 (1.87−7.89)	**<0.001**	/	/	1.90 (0.95−3.81)	0.07	/	/
Karnofsky performance status (<80)	2.17 (1.28−3.69)	**0.004**	1.73 (0.95−3.16)	0.07	1.29 (0.84−2.01)	0.25	1.11 (0.68−1.82)	0.68
Hemoglobin <11.5 g/dl (women) or <13 g/dl (men)	1.22 (0.68−2.19)	0.52	1.30 (0.69−2.45)	0.43	1.07 (0.66−1.73)	0.79	1.11 (0.67−1.84)	0.70
Corrected calcium >10 mg/dl	2.44 (1.03−5.79)	**0.04**	2.04 (0.75−5.55)	0.16	1.66 (0.72−3.83)	0.23	1.35 (0.54−3.40)	0.52
Blood platelets count >400.000/mm^3	0.61 (0.21−1.77)	0.36	0.52 (0.16−1.69)	0.27	1.01 (0.43−2.39)	0.98	1.37 (0.47−2.75)	0.78
Time from diagnosis to systemic treatment <12 months	1.59 (0.93−2.70)	0.09	1.77 (0.98−3.21)	0.06	1.18 (0.76−1.84)	0.45	1.13 (0.71−1.80)	0.61

C = concordance index; CI = confidence interval; HR = hazard ratio; NLR = neutrophil-lymphocyte ratio; OS = overall survival; PFS = progression-free survival.

Significant *P* values are in bold.

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Table 4
Spearman correlations for variables linked to inflammation.

	Baseline CRP levels	Baseline NLR	Baseline hemoglobin	Baseline neutrophils	Baseline platelets
Baseline CRP levels	1				
Baseline NLR	**0.36**	1			
Baseline hemoglobin	**-0.37**	**-0.16**	1		
Baseline neutrophils	**0.25**	**0.67**	-0.01	1	
Baseline platelets	**0.39**	**0.27**	**-0.19**	**0.49**	1

CRP = C-reactive protein; NLR = neutrophil-lymphocyte ratio.

Significant associations are in bold. Positive values indicate a positive association between the variables: high levels for one variable indicate on average high levels for the other variable. The higher the value the stronger this association, with a maximum value of 1. Negative values indicate a negative association.

95% CI 1.22−1.52, $P < 0.001$ for CRP and HR 1.10, 95% CI 1.03−1.21, $P = 0.004$ for NLR) and PFS (HR per 25 mg/l: 1.19, 95% CI 1.08−1.28, $P = 0.001$ for CRP and HR 1.08, 95% CI 1.01−1.21, $P = 0.04$ for NLR).

In a second sensitivity analysis, we excluded patients treated in third or later lines. In this sensitivity analysis on 69 patients, both CRP and NLR were still significantly associated with decreased OS (HR per 25 mg/l: 1.28, 95% CI 1.16−1.45, $P < 0.001$ for CRP and HR 1.16, 95% CI 1.02 −1.33, $P = 0.01$ for NLR) and PFS (HR per 25 mg/l: 1.16, 95% CI 1.03−1.28, $P= 0.008$ for CRP and HR 1.09, 95% CI 1.01−1.18, $P = 0.03$ for NLR).

4. Discussion

The aim of the present study was to evaluate the prognostic value of baseline CRP and NLR, which are both markers of systemic inflammation, in m-ccRCC patients treated with the ICI nivolumab, which is currently recommended as second or further line systemic therapy. In our cohort, elevated baseline CRP and NLR were linked to worse OS and PFS on nivolumab. Using these findings, we were able to improve the prognostic accuracy of the IMDC risk criteria.

Our results on OS and PFS are in accordance with previously reported findings showing the poor prognostic impact of baseline elevated CRP on OS, PFS and ORR in patients treated with VEGFR-TKIs [10,11,19,20]. However, in the current study elevated baseline CRP was not significantly associated with ORR. Of note, the adverse effect of elevated CRP on OS and PFS was directly proportional with increasing increments of baseline CRP, with a HR of 1.32 and 1.16 per 25 mg/l increase in baseline CRP level for OS and PFS, respectively.

The prognostic impact of baseline CRP levels has also been shown in the postnephrectomy setting, in which elevated CRP levels predict metastatic relapse and poor OS [21−24]. Moreover, CRP is an important adverse prognostic marker for worse outcomes in metastatic RCC patients treated with the earliest forms of immunotherapy, namely interferon-α and interleukin-2 (IL-2) [11−13].

Ishihara et al. and Suzuki et al. studied metastatic RCC patients treated with nivolumab and found that elevated baseline CRP was correlated with poor OS and PFS in cohorts of 58 and 65 patients, respectively [25,26].

The prognostic effects of elevated NLR seem consistent across patient populations treated with different therapy regimens as well. Concerning VEGFR-TKIs, Keizman et al. studied 133 metastatic RCC patients treated with sunitinib and found that pretreatment NLR ≥3 was independently correlated with lower ORR and poorer PFS and OS [27]. Nader Marta et al. studied 276 metastatic RCC patients treated with sunitinib or pazopanib and found that baseline NLR >3.5 was associated with poor OS [28].

Elevated baseline NLR was also associated with poor OS and PFS of In the studies of Ishihara et al. and Suzuki et al. on metastatic RCC patients treated with nivolumab [25,26]. The present study shows the impact of NLR on patients treated with ICI monotherapy in multiple lines in a larger cohort. The results of a recent systematic review and meta-analysis by Shao et al. confirm the poor prognostic impact of elevated baseline NLR on OS and PFS in patients treated with ICIs [15].

Additionally, it was recently shown that elevated NLR was correlated to worse OS, PFS and ORR in patients treated with a first-line combination therapy of the programmed death ligand 1 inhibitor avelumab and the VEGFR-TKI axitinib [29].

This inflammatory status, marked by elevated baseline NLR and CRP, but also thrombocytosis, anemia and neutrophilia, is in part a consequence of an underlying more aggressive tumor biology and in part of a further evolved disease with a more important tumor burden and spread. This is reflected by the larger proportion of IMDC poor risk and smaller proportion of IMDC good risk patients in the group with elevated compared to normal baseline CRP or NLR.

The cause of the inflammatory state of these RCC patients is the abnormal production of a variety of cytokines and is a reflection of the inflammation in the tumor microenvironment [30]. Both elevated NLR and CRP are markers of this systemic inflammatory state. Besides IL-1 and tumor necrosis factor-α, IL-6 in particular is considered a major mediator of this acute phase response, resulting in elevated CRP levels and NLR [31,32]. Serum IL-6 concentrations are elevated in multiple different cancer types and are

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associated with both higher tumor stages and poor outcomes [33]. Although serum IL-6 levels are highly variable in RCC patients, high IL-6 concentrations have been correlated to poor survival in a recent systematic review and meta-analysis [34].

Moreover, elevated CRP has also been shown to correlate with higher levels of intratumoral infiltration by M2 macrophages and regulatory T-cells, which reflect an immunosuppressive tumor micro-environment [35]. Elevated NLR is the result of raised myeloid growth factors, tumor necrosis factor-α, IL-10 and transforming growth factor-β leading to neutrophilia with a relative lymphocytopenia [16]. Neutrophils promote cancer progression and metastasis by directly affecting tumor cells, suppressing T-cell mediated anti-tumor response and contributing to a stimulating tumor micro-environment [36,37]. Elevated CRP and NLR thus reflect an intricate and complex immunological interplay between the tumor and the immune system factors favoring tumor progression.

In the present study, there was a significant correlation among systemic markers of inflammation. Both CRP and NLR were significantly positively correlated among themselves but were also correlated with neutrophilia, anemia and thrombocytosis, which are equally measures of inflammation [8,9]. Overall, patients in a paraneoplastic inflammatory state have a generally poor prognosis, which is likely to be translated to a poorer IMDC prognostic score. However, markers of this systemic inflammation, such as CRP and NLR are easily measured, inexpensive and could therefore easily be implemented in clinical practice. Moreover, in this study, we have shown that the addition of baseline CRP could further improve the discriminatory power of the IMDC prognostic model for both OS and PFS, whereas the inclusion of NLR in the IMDC prognostic model only improved its discriminatory power for PFS. In this regard, the addition of a readily available biomarker to an established prognostic score can be of value to both patients and their treating clinicians to improve prognostication at the start of treatment. Although the IMDC prognostic model was validated for initial systemic treatment and might therefore not be the ideal risk stratification tool for further lines of therapy, the IMDC criteria seem to appropriately stratify patients in 3 risk groups in the second-line, third-line and fourth line settings for OS [6].

On the other hand, the fact that this inflammatory state, that has a prognostic value, remains correlated to outcome under treatment with ICIs, is somewhat counterintuitive. In fact, one could hypothesize that tumors eliciting an important immune reaction might be good candidates for ICI therapy [38].

The evolution of these markers of systemic inflammation during treatment could potentially predict outcome and evaluate the early effects of systemic treatment. Simonaggio et al. found that any increase in NLR at 6 weeks in metastatic RCC and non-small cell lung cancer patients was associated with worse PFS and OS [39]. Nishiyama et al. found no significant association of baseline NLR with outcomes in 52 metastatic RCC patients treated with nivolumab, but found that an elevated NLR ($\geq$3) at 4 weeks was predictive of worse OS and PFS [40]. Lalani et al. studied a cohort of 144 metastatic RCC patients treated with different types of ICIs and found that a higher 6-week NLR was associated with worse ORR, OS and PFS [41]. In the current study, insufficient data was available for CRP or NLR during treatment to reliably perform these analyses without selection bias.

The mRCC treatment landscape has been evolving at an unprecedented pace and ICI and/or VEGFR-TKI combination treatments have currently superseded single-agent VEGFR-TKIs as first-line treatment. However, it is still likely that a significant proportion of patients will receive ICI monotherapy in a certain line in the absence of disease progression after initial VEGFR-TKI monotherapy or due to restrictions in availability or reimbursement of other treatment agents. Moreover, biomarker driven approaches might lead to tailored treatment strategies in the future, since some patients might respond well to single-agent therapy, sparing them of potential treatment related toxicity of combination treatments. [18]

Although this study represents a nivolumab treated cohort in a real-world setting, it is limited by its retrospective design and the inherent associated biases. Despite being the largest study on the prognostic impact of these markers of systemic inflammation in nivolumab treated patients, its relatively small sample size might preclude some factors from reaching statistical significance. The fact that patients were treated with nivolumab in different lines might also influence our results. However, our findings were confirmed in a sensitivity analysis, excluding patients treated in third or later lines. Moreover, while the prognostic value of elevated markers of systemic inflammation is clear, the absence of a control group precludes any conclusions on their potential predictive value.

5. Conclusion

Higher baseline CRP and NLR predict worse OS and PFS since start of any-line nivolumab in m-ccRCC patients. Including baseline CRP, but not NLR, in the IMDC prognostic model improves its discriminatory power to predict OS and PFS since start of nivolumab.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2020.12.020.

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