Precision Medicine and Imaging

Clinical Cancer Research

Association of Systemic Inflammation Index and Body Mass Index with Survival in Patients with Renal Cell Cancer Treated with Nivolumab

Ugo De Giorgi[1], Giuseppe Procopio[2], Diana Giannarelli[3], Roberto Sabbatini[4], Alessandra Bearz[5], Sebastiano Buti[6], Umberto Basso[7], Manfred Mitterer[8], Cinzia Ortega[9], Paolo Bidoli[10], Francesco Ferraù[11], Lucio Crinò[12], Antonio Frassoldati[13], Paolo Marchetti[14], Enrico Mini[15], Alessandro Scoppola[16], Claudio Verusio[17], Giuseppe Fornarini[18], Giacomo Cartenì[19], Claudia Caserta[20], and Cora N. Sternberg[21]

Abstract

Purpose: Inflammation indexes and body mass index (BMI) are easily evaluated, predict survival, and are potentially modifiable. We evaluated the potential association of inflammatory indexes and BMI with the clinical outcome of patients with renal cell carcinoma (RCC) undergoing immune checkpoint inhibitor therapy.

Experimental Design: A prospective cohort of patients with metastatic RCC treated with nivolumab enrolled in the Italian Expanded Access Program from July 2015 through April 2016 was examined. Reference measures of inflammation were identified for neutrophil-to-lymphocyte ratio (NLR) </≥ 3, systemic immune inflammation index (SII) </≥ 1,375, and platelet-to-lymphocyte ratio (PLR) </≥ 232. Patients were classified as high BMI (≥25 kg/m^2) versus normal BMI (<25 kg/m^2).

Results: Among 313 evaluable patients, 235 (75.1%) were male, and median age was 65 years (range, 40–84 years), with 105 (33.69%) ≥70 years. In univariate analysis, age, performance status, BMI, SII, NLR, and PLR were able to predict outcome. In multivariate analyses, SII ≥1,375, BMI <25 kg/m^2, and age ≥70 years independently predicted overall survival [OS; HR = 2.96, 95% confidence interval (CI), 2.05–4.27; HR = 1.59, 95% CI, 1.10–2.30; and HR = 1.65, 95% CI, 1.07–2.55, respectively). A patient with both SII ≥1,375 and BMI <25 kg/m^2 was estimated to have much worse OS (HR, 3.37; 95% CI, 2.29–4.95; P <0.0001) than a patient with neither or only one risk factor. SII changes at 3 months predicted OS (P <0.0001).

Conclusions: Normal BMI combined with inflammation tripled the risk of death, suggesting that these biomarkers are critical prognostic factors for OS in patients with RCC treated with nivolumab.

Introduction

Nivolumab is a mAb that targets programmed death-1 receptor (PD-1). It has been approved as monotherapy for the treatment of patients with advanced renal cell carcinoma (RCC) progressing after prior antiangiogenic therapy (1). Biomarkers predicting clinical outcome with nivolumab would allow early identification of nonresponders and timely use of other therapies.

Two novel prognostic indicators are receiving increasing attention across many cancer types and RCC in particular. These are body mass index (BMI) and an elevated neutrophil-to-lymphocyte ratio (NLR, a measure of systemic inflammation). Obesity is an established risk factor for RCC and is associated with a better prognosis in these patients (2). The potential correlation between high BMI and more favorable treatment outcome to VEGF-targeted therapy in metastatic RCC has also been shown (3, 4). The role of blood cell count indexes as possible biomarkers of response and efficacy has been recently

[1]Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy. [2]Department of Medical Oncology, Istituto Nazionale dei Tumori IRCCS, Milan, Italy. [3]Department of Statistics, Regina Elena National Cancer Institute IRCCS, Rome, Italy. [4]Department of Medical Oncology, AOU di Modena, Modena, Italy. [5]Department of Medical Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy. [6]Department of Medical Oncology, AOU di Parma, Parma, Italy. [7]Department of Medical Oncology, Istituto Oncologico Veneto (IOV) IRCCS, Padua, Italy. [8]Department of Medical Oncology, Ospedale "Franz Tappeiner," Merano, Italy. [9]Department of Medical Oncology, Ospedale S. Lazzaro ASL CN2 Alba-Bra, Cuneo, Italy. [10]Department of Medical Oncology, Ospedale San Gerardo, Monza, Italy. [11]Department of Medical Oncology, Ospedale "S. Vincenzo," Taormina, Italy. [12]Department of Medical Oncology, AO Perugia, Perugia, Italy. [13]Department of Medical Oncology, "Arcispedale S. Anna," Ferrara, Italy. [14]Department of Medical Oncology, Ospedale Sant'Andrea, Rome, Italy. [15]Department of Oncology, Careggi University Hospital, Florence, Italy. [16]Department of Medical Oncology, Istituto Dermopatico dell'Immacolata, Rome, Italy. [17]Department of Medical Oncology, P.O. di Saronno, Varese, Italy. [18]Department of Medical Oncology, Ospedale "S. Martino," Genova, Italy. [19]Department of Medical Oncology, AO "A. Cardarelli," Naples, Italy. [20]Department of Medical Oncology, AOU Santa Maria, Terni, Italy. [21]Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York.

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Corresponding Author: Ugo De Giorgi, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) - IRCCS, Via Maroncelli 40, Meldola, FC, 47014, Italy. Phone: 3934-9222-1235; Fax 3905-4373-9151; E-mail: ugo.degiorgi@irst.emr.it

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Translational Relevance

Inflammation indexes associated with body mass index (BMI) are risk factors associated with survival of patients with metastatic renal cell carcinoma (RCC) treated with VEGF-targeted therapies. We investigated whether lower BMI and higher inflammatory indexes combining neutrophils (N), platelets (P), and lymphocytes (L), as NLR (N/L), PLR (P/L), and SII (N × P/L) are associated with overall survival (OS) in metastatic RCC treated with nivolumab. In a cohort of 313 patients with metastatic RCC, age younger than 70 years, elevated SII, and normal BMI were independently associated with poor OS. Because BMI and SII are commonly collected and potentially modifiable, they have a high potential for clinical use in determining prognosis and may help guide interventions to optimize survival with nivolumab in metastatic RCC.

investigated. NLR is the most tested prognostic index and has been associated with prognosis in several tumors including RCC treated with antiangiogenic agents (5–10). Thrombocytosis and lymphopenia have also been associated with prognosis in metastatic RCC treated with first-line VEGF-targeted treatment (11, 12). Systemic immune inflammation index (SII) combines these three parameters: neutrophils, platelets, and lymphocytes, and has been previously significantly associated with prognosis in several tumor types including metastatic RCC (13–15).

Both inflammation and BMI may be able to identify patients with poor prognosis to VEGF-targeted therapies, but the relationship between these factors and their independent associations with survival are not well studied. Recent trials underscore the importance of systemic inflammation as a driver of muscle degradation in patients with far advanced disease, but other studies have suggested that similar processes may occur in patients with localized disease. Elevated inflammatory indexes as NLR were present in nearly half of patients and were associated with decreased BMI as predictive of poorer survival even in patients with nonmetastatic colorectal cancer (16, 17). In RCC, the "obesity paradox" of longer survival in patients with high BMI has been explained by altered fatty acid pathways in obese relative to normal weight patients with marked downregulation of fatty acid synthase, which could have an impact in immune inflammatory function with potential impact on cancer survival (4, 18, 19).

To our knowledge, no prior study has examined the combined associations of the host systemic inflammatory response and BMI with RCC survival. Moreover, no prior study has evaluated the potential association of BMI and inflammatory indexes with clinical outcome of patients undergoing immune checkpoint inhibitor therapy. Accordingly, we conducted an analysis to determine whether pretreatment inflammatory indexes and BMI could predict clinical outcome to nivolumab using data from patients with metastatic RCC enrolled in the Italian Expanded Access Program (EAP). Subsequently, we assessed the independent and combined associations of these two prognostic indicators with survival.

Materials and Methods

Study cohort

The purpose of the EAP was to provide nivolumab to patients with RCC who had progressed on VEGF-targeted treatment while the drug was evaluated by the European Medicines Agency. Key inclusion criteria were histologically confirmed metastatic RCC, Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, at least one prior VEGF-targeted therapy in the advanced setting, and presence of asymptomatic brain metastases. Patients with active or suspected autoimmune disease were excluded. Treatment consisted of nivolumab 3 mg/kg every 2 weeks until unacceptable toxicity, disease progression, or patient choice. The study protocol was reviewed and approved by local Ethics Committees and in accordance with the precepts established by the Declaration of Helsinki. Written informed consent was obtained from all study participants. All data were prospectively collected on electronic patient files.

From July 2015 to April 2016, 389 patients were treated with at least one dose of nivolumab in the EAP in Italy. Of these, 313 (80.5%) had baseline complete blood counts necessary for the inflammatory indexes and all clinical data available and were considered fully evaluable for this post hoc analysis.

Post hoc analysis variable definitions

For this *post hoc* analysis, three inflammatory indexes were determined on the basis of baseline values of neutrophils (N), lymphocytes (L), and/or platelets (P) in patients with metastatic RCC included in the EAP: SII defined as P × N/L, NLR defined as N/L, platelet–lymphocyte ratio (PLR) defined as P/L. X-tile 3.6.1 software was used to determine the most appropriate discriminatory cut-off values for SII, NLR, and PLR for the analysis (13). The cutoffs were selected as the values that maximize differences between overall survival (OS) in the two groups identified (below and above the cutoff). We selected the height and weight obtained closest to beginning of nivolumab treatment to calculate the BMI defined as the ratio of weight divided by the height squared. Patients were classified into BMI groups defined by the World Health Organization: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–<25 kg/m^2), overweight (BMI 25–<30 kg/m^2), and obese (BMI $\geq$ 30 kg/m^2) and condensed to high BMI ($\geq$25 kg/m^2) versus normal BMI (<25 kg/m^2).

Statistical analysis

Data were presented by absolute frequency and percentage for categorical variables and by median and range for continuous variables (e.g., age). Association between categorical variables was assessed using the χ^2 test. Differences were considered statistically significant when $P < 0.05$. The primary clinical outcome was OS. OS was defined as the time period between nivolumab initiation and the date of death, or it was censored on the day of the last follow-up visit. Objective response rate (ORR) was defined as the proportion of patients who achieved a complete or partial response in all evaluated patients. Disease control rate (DCR) was defined as the proportion of patients who achieved a complete or partial response or stable disease in all evaluated patients. The Kaplan–Meier method was used to estimate OS and the log-rank test was used to assess differences between survival. Cox proportional hazards regression model was used to estimate HRs and their 95% confidence intervals (CI). A multivariate analysis was carried out considering only factors significant at the univariate analysis and based on a stepwise forward procedure with enter and remove limits of 0.05 and 0.10, respectively.

The impact of change on survival outcomes was evaluated by the landmark analysis at 3 months. For this analysis, patients with

early disease progression/death or patients lost to follow-up before the landmark time were excluded. All statistical analyses were conducted by an experienced biostatistician with SPSS Statistical software, version 21.0.

Results

Patient characteristics

A total of 313 cases were considered for this analysis, with a median age before starting nivolumab of 65 years (range 40–84), 235 (75.1%) male. The histotype was clear cell RCC in 280 (89.5%) cases. Only 69 (22.1%) patients received nivolumab as second-line therapy after a VEGF-targeted treatment, most cases received nivolumab as third-line ($n = 107$, 34.3%) or further line of therapy ($n = 136$, 43.6%). Baseline clinical characteristics are shown in Table 1. An optimal cut-off point for the SII of $1{,}375 \times 10^9$ stratified these patients into high ($\geq$1,375, $n = 96$, 30.7%) and low SII (<1,375, $n = 217$, 69.3%) groups, cutoff for NLR was 3 and categorized as high ($\geq$3, $n = 195$, 62.3%) and low NLR (<3, $n = 118$, 37.7%), for PLR was 232 with high ($\geq$232, $n = 108$, 34.5%) and low PLR (<232, $n = 205$, 65.5%). Normal BMI < 25 kg/m^2 was reported in 50.2% of patients, high BMI $\geq$ 25 kg/m^2 in 49.8%. The percentage of cases with BMI < or $\geq$25 kg/m^2 was independent from the line of therapy.

Table 1. Patient characteristics at baseline ($N = 313$)

Characteristics	*N* (%)
Age in years, median (range)	65 (40–84)
$\geq$70 years, *n* (%)	105 (33.6%)
Gender, male/female	235/78
ECOG Performance status	
0	143 (47.2%)
1	146 (48.2%)
2	14 (4.6%)
NA	10
IMDC Prognostic group	
Favorable (0 risk factors)	53 (19.0%)
Intermediate (1–2 risk factors)	194 (69.8%)
Poor ($\geq$3 risk factors)	31 (11.2%)
NA	35
Nephrectomy	295 (94.3%)
Histology	
Clear cell	280 (89.5%)
Nonclear cell	28 (8.9%)
Undifferentiated/unknown	5 (1.6%)
Metastasis site	
Lung	230 (73.5%)
Lymph node	193 (61.7%)
Bone	154 (49.2%)
Liver	106 (33.9%)
Brain	30 (9.6%)
Number of prior therapy lines	
1	69 (22.1%)
2	107 (34.3%)
$\geq$3	136 (43.6%)
NA	1
Hemoglobin level (mg/dL)	
$\geq$12	139 (44.4%)
<12	174 (55.6%)
BMI	
<18.5	7 (2.4%)
Normal, 18.5–<25	140 (47.8%)
Overweight, 25–<30	111 (37.9%)
Obese, $\geq$30	35 (11.9%)
NA	20

Abbreviation: NA, not available.

Systemic inflammation, BMI, and response

In the overall population of 313 cases, an ORR was reported in 70 of 286 (24.5%) assessable patients, including complete response in 1 (0.4%) case, partial response in 69 (24.1%), stable disease was reported in 106 cases (37.1%) and progressive disease in 110 (38.4%), whereas in the remaining 27 cases (8.6%) the tumor response was not assessed, in the majority of cases because of clinical deterioration before the first CT scan evaluation. Lower ORRs were associated with higher values of inflammatory indexes at baseline, and these results were consistent across all markers of systemic inflammation.

The ORR for patients with SII < 1,375 was 29% (60/207 cases), whereas those with SII $\geq$ 1,375 was only 13% (10/79 cases; $P = 0.004$). The ORR for patients with NLR < 3 was 27% (31/114 cases), whereas those with NLR $\geq$ 3 was 23% (39/172 cases; $P = 0.38$). The ORR for patients with PLR < 232 was 29% (56/196 cases), whereas those with PLR $\geq$ 232 was 16% (14/90 cases; $P = 0.02$). The ORR in patients with normal BMI < 25 was 24% (32/132 evaluable cases), whereas those with high BMI $\geq$ 25 was 27% (37/136 evaluable cases; $P = 0.58$). The DCR for patients with SII < 1,375 was 68% (141/207 cases), whereas those with SII $\geq$ 1,375 was only 41% (32/79 cases; $P < 0.0001$). The DCR for patients with NLR < 3 was 64% (73/114 cases), whereas those with NLR $\geq$ 3 was 60% (103/172 cases; $P = 0.50$). The DCR for patients with PLR < 232 was 68% (133/196 cases), whereas those with PLR $\geq$ 232 was 35% (32/90 cases; $P < 0.0001$). The DCR in patients with normal BMI < 25 kg/m^2 was 58% (76/132 evaluable cases), whereas those with high BMI $\geq$ 25 kg/m^2 was 67% (91/136 evaluable cases; $P = 0.13$).

Baseline high inflammatory indexes were associated with International mRCC Database Consortium (IMDC) prognostic factors, but no with histotypes and metastatic sites (Table 2).

Survival analysis

Univariate and multivariate Cox proportional hazards regression analyses were performed to assess the associations between factors of interest and OS. In univariate analysis, the following clinical variables predicted OS: age, performance status and BMI; whereas among the blood cell count variables, neutrophil and platelets, but not lymphocytes predicted outcome; in addition, all three blood cell count indexes (SII, NLR, and PLR) were able to predict outcome (Table 2). As observed in the Kaplan–Meier curves, patients with normal BMI, those with SII $\geq$ 1,375, and <70-year-old patients had the worst survival (Fig. 1A–C). Moreover, we analyzed BMI as a continuous variable and correlated with OS (HR, 0.93; 95% CI, 0.88–0.99; $P = 0.02$), showing that an increase of the weight is directly correlated with better prognosis.

In multivariate analyses, SII $\geq$ 1,375, BMI < 25 kg/m^2, and age $\geq$ 70 years independently predicted OS (HR = 2.96, 95% CI, 2.05–4.27; HR = 1.59, 95% CI, 1.10–2.30; and HR = 1.65; 95% CI, 1.07–2.55, respectively; Table 3). Under the model of independent effects, a patient with both SII $\geq$ 1,375 and BMI < 25 kg/m^2 was estimated to have much worse OS (HR, 3.37; 95% CI, 2.29–4.95; $P < 0.0001$) than a patient with neither or only one risk factor.

When the SII groups (<1,375 or $\geq$1,375) were analyzed according to the BMI (<25 or $\geq$25), the four groups were as follows: (i) SII < 1,375 and BMI < 25 kg/m^2 in 94 (32.3%) cases, (ii) SII < 1,375 and BMI $\geq$ 25 kg/m^2 in 111 (38.1%), (iii) SII $\geq$ 1,375 and BMI $\geq$ 25 kg/m^2 in 35 (12.0%), and (iv) SII $\geq$ 1,375 and BMI < 25 kg/m^2 in 51 (17.5%). Figure 2 shows the OS according to these four groups.

Table 2. Association between baseline high inflammatory indexes and IMDC prognostic factors, histotypes, and metastatic sites

	Pts., *N*	SII > 1,375, *P*	NLR > 3, *P*	PLR > 232, *P*
IMDC Prognostic score				
Favorable (0 risk factors)	53	1 (2%)	21 (40%)	8 (15%)
Intermediate (1–2 risk factors)	194	58 (30%)	124 (64%)	68 (35%)
Poor (≥3 risk factors)	31	26 (84%)	27 (87%)	21 (68%)
		$P < 0.0001$	$P = 0.0005$	$P < 0.0001$
Bone metastases				
No	159	43 (27%)	96 (60%)	52 (33%)
Yes	154	52 (34%)	100 (65%)	55 (36%)
		$P = 0.18$	$P = 0.36$	$P = 0.58$
Brain metastases				
No	283	81 (29%)	179 (63%)	92 (32%)
Yes	30	14 (47%)	17 (57%)	15 (50%)
		$P = 0.04$	$P = 0.52$	$P = 0.05$
Lung metastases				
No	83	22 (26%)	53 (64%)	25 (30%)
Yes	230	73 (32%)	143 (62%)	82 (36%)
		$P = 0.31$	$P = 0.75$	$P = 0.32$
Liver metastases				
No	207	60 (29%)	131 (63%)	73 (35%)
Yes	106	35 (33%)	65 (61%)	34 (32%)
		$P = 0.47$	$P = 0.73$	$P = 0.60$
Lymph node metastases				
No	120	31 (26%)	75 (62%)	35 (29%)
Yes	193	64 (33%)	121 (63%)	72 (37%)
		$P = 0.19$	$P = 0.86$	$P = 0.15$
Clear cell histotype				
No	33	11 (33%)	18 (54%)	14 (42%)
Yes	280	84 (30%)	178 (64%)	93 (33%)
		$P = 0.72$	$P = 0.26$	$P = 0.30$

Abbreviation: pts, patients.

The change of the three inflammatory indexes over time was evaluable in 260 (83.1%) of 313 cases at one time point of the follow-up after 2–3 months. Patients with baseline SII < 1,375 with follow-up SII ≥ 1,375 were estimated to have a worse OS than those with follow-up SII < 1,375, $P < 0.0001$, as well as patients with baseline SII ≥ 1,375 with follow-up SII ≥ 1,375 were estimated to have a worse OS than those with follow-up SII < 1,375, $P = 0.05$. Patients with baseline NLR < 3 with follow-up NLR ≥ 3 were estimated to have a worse OS than those with follow-up NLR < 3, $P = 0.02$, as well as patients with baseline NLR ≥ 3 with follow-up NLR ≥ 3 were estimated to have a worse OS than those with follow-up NLR < 3, $P = 0.002$. Patients with baseline PLR < 232 with follow-up PLR ≥ 232 were estimated to have a worse OS than those with follow-up PLR < 232, $P = 0.001$, as well as patients with baseline PLR ≥ 232 with follow-up PLR ≥ 232 were estimated to have a worse OS than those with follow-up PLR <232, $P = 0.03$. Table 4 shows the progression-free survival (PFS) and OS according to SII changes.

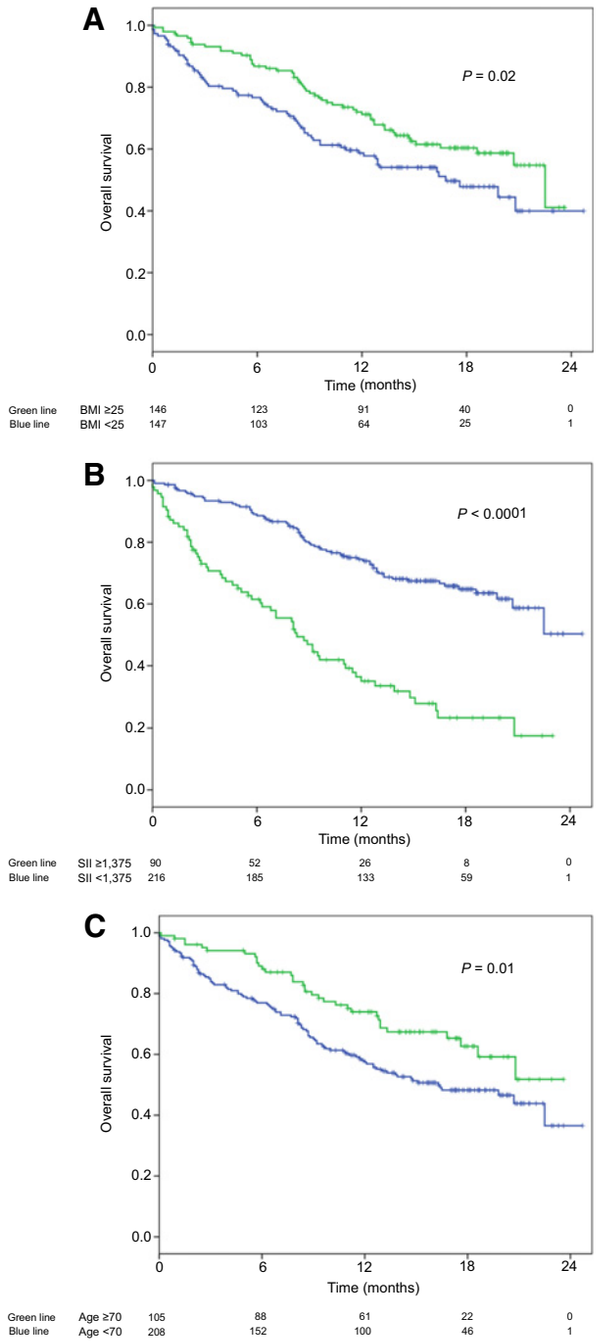


Figure 1.
Kaplan–Meier estimate of OS of patient according to BMI (**A**), SII (**B**), and age (**C**).

Discussion

The efficacy of immune checkpoint inhibitors in metastatic RCC varies greatly across individual patients and among different histotypes. Whereas PD-L1 expression on the primary tumor is now accepted as a potential biomarker indicating the use of these mAbs as a first-line approach, no substantial results have been reported with clinical and molecular biomarkers for nivolumab used as second or greater line of treatment in metastatic RCC (1). We previously conducted an analysis of the Italian RCC EAP, which showed that efficacy and safety of nivolumab for the treatment of metastatic RCC were comparable to phase III results; OS, PFS, and ORR in our cohort were similar to the observations in the CheckMate 025 studies (1, 20).

In this analysis, we showed that for patients with metastatic RCC treated with nivolumab, higher SII was independently

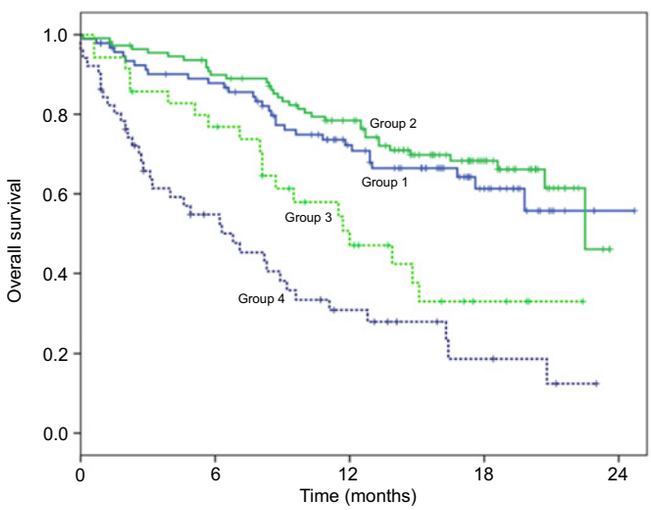
Table 3. Univariate and multivariate analyses of the association between baseline characteristics and OS

	Univariate analysis HR (95% CI), *P*	Multivariate analysis HR (95% CI), *P*
Age (<70 vs. ≥70)	1.66 (1.12–2.44), 0.01	1.62 (1.05–2.50), 0.03
Gender (male vs. female)	1.34 (0.88–2.03), 0.17	—
ECOG PS		
(1 vs. 0)	1.41 (0.99–2.02), 0.06	—
(2 vs. 0)	2.28 (1.03–5.03), 0.04	
IMDC Prognostic groups		
(1–2 vs. 0)	1.92 (1.06–3.47), 0.03	—
(≥3 vs. 0)	4.25 (2.11–8.56), <0.0001	
Clear cell (no vs. yes)	1.23 (0.62–2.43), 0.55	—
Bone metastases (yes vs. no)	1.06 (0.74–1.53), 0.73	—
Brain metastases (yes vs. no)	1.16 (0.64–2.11), 0.62	—
Lung metastases (yes vs. no)	1.14 (0.74–1.75), 0.55	—
Liver metastases (yes vs. no)	1.05 (0.72–1.53), 0.81	—
Lymph node metastases (yes vs. no)	1.01 (0.70–1.46), 0.96	—
Hb baseline (<12 vs. ≥12 mg/dL)	1.67 (1.05–2.67), 0.03	—
Neutrophils (≥8,000 vs. <8,000)	2.62 (1.73–3.99), <0.0001	-
Lymphocytes (≤1,000 vs. >1,000)	1.30 (0.87–1.94), 0.20	—
Platelets (≥400,000 vs. <400,000)	2.48 (1.67–3.70), <0.0001	—
SII (≥1,375 vs. <1,375)	3.35 (2.38–4.73), <0.0001	2.99 (2.07–4.31), <0.0001
NLR (≥3 vs. < 3)	2.23 (1.52–3.28), <0.0001	—
PLR (≥232 vs. <232)	2.37 (1.69–3.35), <0.0001	—
BMI (<25 vs. ≥25)	1.50 (1.05–2.15), 0.02	1.58 (1.09–2.28), 0.01

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Hb, hemoglobin.

associated with worse outcomes in terms of reduced ORR, DCR, and shorter OS, whereas a relative increase of BMI was associated with better OS, and the combination of these two factors (high SII with normal BMI) nearly tripled the risk of death, suggesting that these biomarkers are prognostic factors for OS in patients with metastatic RCC treated with nivolumab. We also showed that high levels of inflammatory parameters at 2- or 3-month follow-up were associated with OS, in particular SII changes showed a stronger impact on OS (Table 4). Further studies should investigate SII changes over time associated with changes on the radiological response and the clinical outcome of these patients.

Interestingly, the results seen at univariate analysis confirmed the pretreatment impact on OS of neutrophils and platelets, but not lymphocytes, as already demonstrated in the IMDC prognostic classification (12, 21). As expected, high inflammatory indexes were associated with IMDC prognostic factors (Table 2); however, the IMDC prognostic score did not remain significant at multivariate analysis (Table 3). Among the three derived indexes NLR, PLR, and SII, only SII remained significant at multivariate analysis, as a consequence of using both neutrophil and platelet levels. Taken together these data confirm the prognostic role of platelets and neutrophils and suggest the combined index SII as the strongest inflammatory index for metastatic RCC. Our findings are consistent with and build upon previous reports evaluating NLR in patients with RCC treated with nivolumab (22–24), but suggest that SII appears superior to NLR as an inflammatory,



Group 1 - SII < 1,375 & BMI < 25	94	78	51	20	1 - Blue line
Group 2 - SII < 1,375 & BMI ≥ 25	111	97	77	36	0 - Green line
Group 3 - SII ≥ 1,375 & BMI ≥ 25	35	26	14	4	0 - Green dotted line
Group 4 - SII ≥ 1,375 & BMI < 25	51	23	11	4	0 - Blue dotted line

Figure 2.
Kaplan–Meier estimate of OS according to the four groups identified using SII and BMI at baseline.

Table 4. Change in immune inflammation index and clinical outcome

SII Groups[a]		Median PFS (95% CI)	HR (95% CI)	*P*	1-Year OS	HR (95% CI)	*P*
Low-Low	138	7.7 (6.2–9.2)			86%	1	
Low-High	49	5.7 (4.0–7.4)	1.32 (0.91–1.94)	0.14	48%	3.4 (2.1–5.8)	<0.0001
High-Low	28	4.6 (2.5–6.7)	1.43 (0.89–2.29)	0.14	53%	3.2 (1.7–5.9)	<0.0001
High-High	43	3.0 (2.6–3.4)	2.36 (1.61–3.44)	<0.0001	34%	6.1 (3.6–10.2)	<0.0001

NOTE: For this analysis, patients with early disease progression/death or patients lost to follow-up before the landmark time were excluded.
[a]Four groups of SII changes: (i) low-low (baseline SII < 1,375 and follow-up SII < 1,375); (ii) low-high (baseline SII < 1,375 and follow-up SII $\geq$ 1,375); (iii) high-low (baseline SII $\geq$ 1,375 and follow-up SII < 1,375); and (iv) high-high (baseline SII $\geq$ 1,375 and follow-up SII $\geq$ 1,375).

readily available, prognostic marker in patients with metastatic RCC treated with immune checkpoint inhibitors in metastatic RCC, and warrants further larger prospective validation.

BMI has been already shown to be a robust biomarker for outcomes in RCC both in the preoperatory localized disease and in the metastatic VEGF–targeted treated population (2–4). In our experience, BMI was associated with OS but not with either ORR ($P = 0.58$) or DCR ($P = 0.13$); as such it may be speculated that BMI represents a simple biomarker for "better RCC". However, improved OS in obese patients with cancer compared with those with normal BMI, has been recently observed also in patients with melanoma treated with immune checkpoint inhibitors (25). In addition, these clinical finding are corroborated by preclinical data indicating that obesity increases T-cell aging resulting in higher PD-1 expression and dysfunction, which is driven by leptin signaling, this effect leaves tumors notably more sensitive to checkpoint blockade (26).

Patient age and gender are arising as potential prognostic/predictive factors for immunotherapy response. In melanoma, older patients' $\geq$60 years responded more efficiently to anti-PD-1 agents, and the ORR to these drugs increased with age (27). In RCC, elderly patients' $\geq$70 years were associated with increased ORR of nearly 30% higher than the nearly 20% reported in younger patients (820). Results of a meta-analysis of 20 randomized clinical trials with immune checkpoint inhibitors in solid tumors suggest that males derive more benefit than females, even if only the CheckMate 025 trial included patients with RCC and the HR was unadjusted for other confounding factors (28). Moreover, a recent large retrospective analysis of the IMDC has shown that gender has no impact on the efficacy of nivolumab (29). Results of the multivariate analysis of this study, confirmed the positive prognostic impact of older age ($\geq$70 years) of patients with RCC, whereas it did not show any impact based on gender (Table 3), suggesting that the conclusions of the above-mentioned meta-analysis may not be generalizable to the setting of RCC. Median values of BMI in healthy people is approximately 24.5 kg/m^2 for men and 21.5 kg/m^2 for women (30), thus a possible explanation of the marginal advantage of male gender on the efficacy of nivolumab in the CheckMate 025 trial could be also due to the higher BMI in males than females (1, 28). However, in the recent retrospective study in patients with metastatic melanoma, obesity, compared with normal BMI, has been associated with improved PFS and OS in patients treated with immunotherapy (pembrolizumab or nivolumab or atezolizumab, total of 331 cases), and this association has been mainly observed in male patients (255). Future research should consider BMI exploring the effectiveness of immunotherapies in men and women.

An unmet need is the development of biomarkers of clinical outcome to immune checkpoint inhibitors to identify patients who are likely to respond and obtain clinical benefit from such treatments. This aspect is particularly relevant for tumors with low response rates, such as metastatic RCC treated with nivolumab which has response rates $\leq$25%–30%, but long-term survival of more than 4 years in 20%–25% of cases (31, 32).

To our knowledge, this is the first study to examine the relationship between biomarkers of systemic inflammation and BMI in RCC, and the only study to examine whether inflammatory indexes and BMI are independently associated with OS in metastatic RCC. As in any retrospective analyses, in our study several potential biases should be considered. In addition, other limitations are the use of BMI as the only morphometric parameter, because it does not provide information on muscle mass and fat repartition, and lacks metabolic biomarkers. Finally, lack of a validation cohort is a concern, however our data refer to a late use of nivolumab, mostly in third or fourth line (Table 1), whereas the current use in mainly in second-line and in the first-line with the combination of nivolumab plus ipilimumab (1, 33). Therefore, our findings should be considered only hypothesis generating and require additional validation in larger series with immune checkpoint inhibitors in earlier therapeutic settings.

In conclusion, SII, BMI, and older age of patients were independent prognostic factors in metastatic RCC treated with nivolumab. SII and BMI are routinely collected in clinical practice and thus deserve a potential role for use as prognostic indices, if these findings are confirmed by further studies. We also found that the cooccurrence of normal BMI and high inflammatory indexes identified patients with a more than 3-fold risk of mortality compared with patients with neither condition. A better understanding of biological mechanisms may help to guide interventions to optimize survival outcomes with nivolumab in metastatic RCC. Further studies are needed to clarify whether reducing systemic inflammation or possibly increasing low BMI with supportive care can enhance OS outcomes exploring the effectiveness of nivolumab in men and women. The mechanisms that are responsible for these findings will potentially be of great interest.

Disclosure of Potential Conflicts of Interest

U. De Giorgi is a consultant/advisory board member for Bristol-Myers Squibb, Ipsen, Pfizer, Novartis, Merck, Astellas, Janssen, Sanofi, and Bayer. R. Sabbatini is a consultant/advisory board member for Bristol-Myers Squibb, Ipsen, Pfizer, Novartis, Astellas, Janssen, and Sanofi. U. Basso is a consultant/advisory board member for Janssen, Incyte, and MSD. P. Bidoli is a consultant/advisory board member for Eli Lilly, Bristol-Myers Squibb, and Boheringer. P. Marchetti reports receiving speakers bureau honoraria from Bristol-Myers Squibb and MSD, and is a consultant/advisory board member for Bristol-Myers Squibb, MSD, and Roche. C. Verusio reports receiving speakers bureau honoraria from Edra Edition. C. Sternberg reports receiving speakers bureau honoraria from Bristol-Myers Squibb, Novartis, Pfizer, and Ipsen, and is a consultant/advisory board member for Eisai, Pfizer, Ipsen, Bristol-Myers Squibb, Roche, Bayer, and MSD. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The financial sponsor of the trial had no role in the design or conduct of the trial, data collection or analysis, and preparation of the article.

Authors' Contributions

Conception and design: U. De Giorgi, G. Procopio, P. Bidoli, P. Marchetti, G. Cartenì, C.N. Sternberg
Development of methodology: U. De Giorgi, D. Giannarelli, L. Crinò, G. Fornarini, G. Cartenì, C.N. Sternberg
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): U. De Giorgi, R. Sabbatini, A. Bearz, S. Buti, U. Basso, M. Mitterer, C. Ortega, P. Bidoli, F. Ferraù, L. Crinò, A. Frassoldati, P. Marchetti, E. Mini, C. Verusio, G. Cartenì, C. Caserta, C.N. Sternberg
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): U. De Giorgi, D. Giannarelli, P. Bidoli, L. Crinò, A. Frassoldati
Writing, review, and/or revision of the manuscript: U. De Giorgi, D. Giannarelli, R. Sabbatini, S. Buti, U. Basso, M. Mitterer, P. Bidoli, A. Frassoldati, P. Marchetti, E. Mini, A. Scoppola, C. Caserta, C.N. Sternberg
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): U. De Giorgi, D. Giannarelli
Study supervision: U. De Giorgi, G. Procopio, G. Cartenì, C.N. Sternberg

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