Systemic Immune-Inflammation Index in Patients Treated With First-Line Immune Combinations for Metastatic Renal Cell Carcinoma: Insights From the ARON-1 Study

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Abstract

The treatment of metastatic renal cell carcinoma has evolved on last years. Nowadays immune-combinations are the standard treatment in first-line setting. There is no prognostic biomarker for metastatic renal cell carcinoma in the systemic immunotherapy treatment era. Systemic Immune-Inflammation Index is a cheap and readily available prognostic tool to be used in daily clinical practice.

Background: Systemic treatment with immune combinations is the gold standard for metastatic renal cell carcinoma (mRCC) worldwide. The systemic immune-inflammation index (SII) is a prognostic marker for several types of malignant neoplasms, including mRCC, in the era of tyrosine kinase inhibitor (TKI) treatment. Data regarding the prognostic value of the SII in patients with mRCC treated with immunotherapy are scarce and controversial. **Methods:** We retrospectively collected the data of patients with mRCC from 56 centers in 18 countries. SII (Platelet × Neutrophil/Lymphocyte count) was calculated prior to the first systemic treatment and cut-off was defined by a survival receiver operating characteristic (ROC) analysis. The primary objective of our retrospective study was to assess the outcomes of patients treated with first-line immunotherapy**. Results:** Data from 1034 mRCC patients was collected and included in this analysis. The SII cut-off value was 1265. After a follow-up of 26.7 months, and the overall survival (OS) and progression-free survival

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(PFS) were 39.8 and 15.7 months, respectively. According to SII (low vs. high), patients with low-SII had longer OS (55.7 vs. 22.2 months, $P < .001$), better PFS (20.8 vs. 8.5 months, $P < .001$), and higher overall response rate (52 vs. 37%, $P = .033$). **Conclusion:** A high SII is associated with poor oncological outcomes in patients with mRCC. SII could be an easily accessible prognostic indicator for use in clinical practice.

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Introduction

Globally, the incidence and mortality of Renal Cell Carcinoma (RCC) corresponds to about 430,000 new cases and around 179,000 deaths.[1] For patients presenting with metastatic disease, systemic treatment as an initial approach is preferred.[2,3] Currently, the combination of immune checkpoint inhibitor (ICI) plus ICI or ICI plus anti-Vascular Endothelial Growth Factor Receptor (VEGFR)-tyrosine kinase inhibitors (TKIs) is the gold standard first-line systemic treatment for metastatic RCC (mRCC).[3]

RCC is an immunogenic tumor, so the host inflammatory response and tumor microenvironment have an essential role in tumor development and progression.[4] Increasing evidence suggest that neutrophils are essential components of RCC microenvironment, and their migration to the tumor growth site controls tumor invasion by manipulating the collagen matrix and forming the metastatic niches.[5] It is also well known that evading T cell response is one of the hallmarks of RCC.[6] This tumor is also characterized by increased levels of Interleukine (IL)-6, which regulate the maturation stages of megakaryocytosis to stimulate platelet production.[7]

The combination of immune and inflammatory peripheral cells such as lymphocyte (L), neutrophil (N) and platelet (P) counts into a formula provides the systemic immune-inflammation index (SII).[8] SII has been associated with survival in several solid tumors, including urological cancers.[9] In the context of mRCC, there are data suggesting that SII could have a prognostic and predictive role in patients treated by different therapeutic approaches.[10,11]

The ARON-1 study (NCT05287464) was designed to globally collect real-world data on the use of immune combinations as first-line therapy for mRCC patients. In this analysis, we sought to investigate the relationship between SII and the oncological outcomes of mRCC patients treated with immune combinations.

Patients and Methods

Study Population

We included patients aged ≥18 years with a histologically confirmed diagnosis of RCC and histologically or radiologically confirmed metastatic disease and treated with first-line immune combinations between January 1st 2017 to February 1st 2023 from 56 centers from 18 countries.

The SII is based on P, N and L counts and was defined as follows: SII = P × N/L. SII was calculated using data from the most recent laboratory tests performed up to 30 days prior to initiation of systemic treatment. We retrospectively extracted from patients' paper and electronic charts data about age, gender, body mass index (BMI), tumor histology, nephrectomy, sites of metastases, type of immune-combination and response to therapy. Patients with insufficient data on tumor assessment or response to therapy were excluded.

First-line therapy was continued till the evidence of clinical and/or radiological tumor progression, unacceptable toxicities, or death. Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed following standard local procedures every 8 to 12 weeks.

This study was conducted in accordance with the "Declaration of Helsinki" and approved by local and central ethics committees (committee of Marche Region; approval number: 2021-492). Due to the retrospective nature of the study, informed consent was not required.

Study Endpoints

The primary objective was to assess the oncological outcomes according to SII of mRCC patients treated with first-line immune-combinations. Tumor radiological assessment was led according to the RECIST 1.1 criteria[12] and data of Overall Response Rate (ORR), ie, the proportion of patients who achieve a complete (CR) or partial responses (PR), as well as stable (SD) or progressive disease (PD) were collected and analyzed. Overall Survival (OS) was calculated from the start of treatment to death for any cause. Progression-Free Survival (PFS) was defined as the time from the start of first-line therapy to progression or death from any cause. Patients without a tumor progression to following line of treatment or death or lost at follow-up at the time of analysis were censored at their last follow-up date.

Statistical Analysis

OS, PFS and were estimated using the Kaplan-Meier method with Rothman's 95% confidence intervals (CI), and comparisons between survival distributions were led by using the log-rank test. Univariate and multivariate analyses were carried out by using Cox proportional hazard models, Hazard Ratio (HR) and their 95 % confidence intervals (95% CI). Factors that went into univariate analysis included: gender, age, BMI, nephrectomy status, tumor histology, sarcomatoid differentiation, IMDC group, most frequent sites of metastasis, type of first-line therapy and SII.

A survival receiver operating characteristic (ROC) analysis from response rate was used to identify potential cut-offs to better stratify patients in risk groups. According to ROC result the optimal SII cut-off was 1265, therefore overall population was divided into 2 SII groups (high SII ≥1265 vs. low SII <1265). The chi-square test was employed to compare groups for categorical variables. Significance levels were set at a value of 0.05, and all P values were 2-sided. The statistical analysis was performed by MedCalc version

Table 1 Baseline Patients' Characteristics

Patients	Overall 1034 (%)	SII≥1265 715 (%)	SII<1265 319 (%)	*P*
Gender				.632
Male	762 (74)	533 (75)	229 (72)	
Female	272 (26)	182 (25)	90 (28)	
Median age, years (y)	64	64	63	-
Range	25-88	31-88	25-88	
BMI ≥ 25 kg/m²	603 (58)	456 (63)	147 (46)	**.016**
Previous nephrectomy	645 (62)	501 (70)	144 (45)	**<.001**
Clear cell histology	906 (88)	635 (89)	271 (85)	.402
Sarcomatoid differentiation	141 (14)	98 (14)	43 (13)	.837
IMDC				
Good risk	179 (17)	163 (23)	16 (5)	**<.001**
Intermediate risk	597 (58)	450 (63)	147 (46)	**.016**
Poor risk	258 (25)	102 (14)	156 (49)	**<.001**
Common sites of metastasis				
Lung	717 (69)	481 (67)	236 (74)	.279
Bone	346 (33)	222 (31)	124 (39)	.237
Liver	188 (18)	106 (15)	82 (26)	.055
Brain	78 (8)	46 (6)	32 (10)	.298
Type of immuno-combination				.249
IO + IO	399 (39)	258 (36)	141 (44)	
IO + TKIs	635 (61)	457 (64)	178 (56)	

19.6.4 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).

Results

Study Population

We included 1034 patients, with a median follow-up time of 26.7 months (95% CI: 21.0-33.8); 762 patients (74%) were male. The median age was 64y (range 25-88). Tumor histology was clear cell RCC in 906 patients (88%) and sarcomatoid differentiation was reported in 141 patients (14%). Most patients underwent a nephrectomy (64%), had lung metastases (69%), and were classified as intermediate IMDC risk score (58%). Regarding the first-line treatment, 635 (61.5%) and 399 patients were treated with ICI plus TKI and ICI plus ICI, respectively (Table 1).

Survival Analysis

Overall Population. The median OS (mOS) and PFS (mPFS) were 39.8 (95% CI: 32.7-55.7) and 15.7 months (95% CI: 13.9-17.9), respectively; 256 patients were dead at the time of analysis.

Considering the SII cut-off (≥1265) 319 patients (31%) were high-SII (≥1265) and 715 patients (69%) were low-SII (<1265).

The mOS (55.7 months, 95% CI: 40.6-55.7 vs. 22.2 months, 16.0-51.6, $P < .001$) and mPFS (20.8 months, 95% CI: 17.1-27.9 vs. 8.5 months, 6.7-11.1, $P < .001$) were higher in the low-SII patients (Figure 1).

SII and BMI. The survival benefit for low-SII group was observed in both patients with BMI≥25 kg/m² (mOS: 55.7 months, 95% CI: 55.7-55.7, vs. 25.0 months, 95% CI: 17.2-51.6, $P < .001$; mPFS: 20.5 months, 95% CI: 16.3-26.5, vs. 8.5 months, 95% CI: 6.5-12.0, $P < .001$) and <25 kg/m² (mOS: not reached (NR), 95%CI: NR-NR, vs. 18.0 months, 95% CI: 11.7-29.7, $P < .001$; mPFS: 23.1 months, 95%CI 15.5-32.3, vs. 8.5 months, 95% CI: 5.9-13.0, $P < .001$) (Supplemental Figure 1).

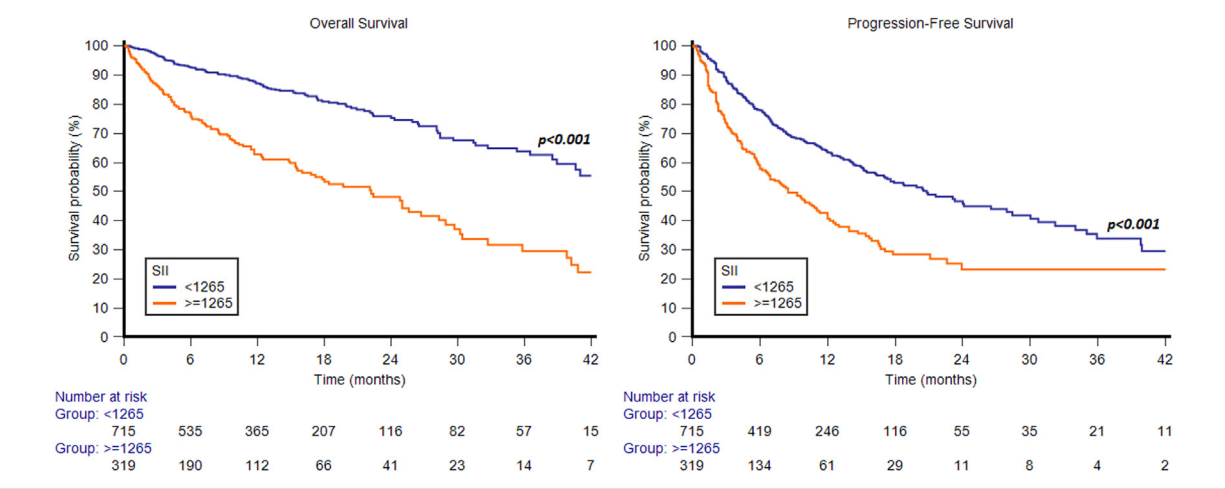
SII and Nephrectomy

The survival benefit for low-SII group was also observed in patients who underwent (mOS: NR, 95% CI: NR-NR, vs. 26.7 months, 95% CI: 17.2-51.6, $P < .001$; mPFS: 28.4 months, 95% CI: 20.9-35.9, vs. 12.2 months, 95% CI: 8.3-16.5, $P < .001$) or not previous nephrectomy (mOS: 28.4 months, 95% CI: 22.4-35.3, vs. 17.8 months, 95% CI: 11.4-40.8, $P < .001$; mPFS: 14.5 months, 95% CI: 9.7-17.6, vs. 6.9 months, 95% CI: 5.1-9.6, $P < .001$) (Supplemental Figure 2).

SII and Histology

The survival benefit for low-SII group was showed for both patients with clear cell mRCC (mOS: NR, 95% CI: NR-NR, vs. 22.4 months, 95% CI: 16.8-51.6, $P < .001$; mPFS: 20.8 months, 95% CI: 17.6-28.4, vs. 9.3 months, 95% CI: 6.6-11.3, $P < .001$) and non-clear cell mRCC (mOS: 36.5 months, 95% CI: 20.4.7-40.1, vs. 10.7 months, 95% CI: 7.3-26.7, $P < .001$; mPFS: 17.1 months, 95% CI: 16.3-26.5, vs. 6.9 months, 95% CI: 4.4-16.4, $P < .001$), as well as tumors with sarcomatoid differentiation (mOS: NR, 95% CI: NR-NR, vs. 22.2 months, 95% CI: 6.0-25.0, $P <$

Figure 1 Median overall survival and progression-free survival in mRCC patients treated with immune combinations stratified by SII.



.001; mPFS: 12.3 months, 95% CI: 6.0-18.7, vs. 6.7 months, 95% CI: 2.2-14.7, $P < .001$) (Figure 2).

SII and IMDC Risk Classification

The mOS and mPFS were also significantly longer in low-SII patients compared high-SII patients in good (mOS: NR, 95% CI: NR-NR, vs. 25.6 months, 95% CI: 3.2-25.6, $P < .001$; mPFS: 30.7 months, 95% CI: 28.4-35.0, vs. 17.8 months, 95% CI: 2.3-17.8, $P = .049$), intermediate (mOS: 55.7, 95% CI: 38.9-55.7, vs. 25.0 months, 95% CI: 19.7-51.6, $P < .001$; mPFS: 17.3 months, 95% CI: 14.5-21.6, vs. 9.7 months, 95% CI: 6.9-13.9, $P < .001$) and poor risk patients (mOS: 24.0, 95% CI: 16.2-32.7, vs. 15.5 months, 95% CI: 10.7-25.0, $P = .023$; mPFS: 11.4 months, 95% CI: 6.7-24.1, vs. 6.5 months, 95% CI: 4.4-10.8, $P = .027$) (Figure 3).

SII and Site of Metastasis

The survival benefit for the low-SII group was reported independently from the presence of lung (mOS: NR, 95% CI: NR-NR, vs. 25.0 months, 95% CI: 17.1-51.6, $P < .001$; mPFS: 19.9 months, 95% CI: 15.4-23.3, vs. 8.5 months, 95% CI: 95% CI: 6.0-11.1, $P < .001$), bone (mOS: 35.3, 95% CI: 26.4-55.7, vs. 12.3 months, 95% CI: 9.5-22.2, $P < .001$; mPFS: 14.2 months, 95% CI: 11.4-17.6, vs. 6.7 months, 95% CI: 4.3-8.5, $P < .001$), liver (mOS: 55.7, 95% CI: 25.9-55.7, vs. 15.5 months, 95% CI: 9.5-32.7, $P < .001$; mPFS: 11.5 months, 95% CI: 7.5-53.3, vs. 6.9 months, 95% CI: 3.4-11.3, $P = .042$) or brain metastases (mOS: 28.2, 95% CI: 18.4-28.2, vs. 16.8 months, 95% CI: 5.9-26.7, $P = .006$; mPFS: 16.2 months, 95% CI: 7.8-35.9, vs. 5.7 months, 95% CI: 1.4-10.4, $P = .024$) (Supplemental Figure 3).

SII and First-Line Systemic Treatment

The survival benefit for low-SII group was also observed for the use of first-line IO+IO (mOS: NR, 95% CI: NR-NR, vs. 18.4 months, 95% CI: 11.4-51.6, $P < .001$; mPFS: 11.5 months, 95% CI: 8.1-15.2, vs. 5.8 months, 95% CI: 4.4-8.5, $P = .002$) or IO+TKIs (mOS: NR, 95% CI: NR-NR, vs. 22.1 months, 95% CI: 15.5-32.7, $P < .001$; mPFS: 30.7 months, 95% CI: 23.1-53.3, vs. 12.0 months, 95% CI: 8.1-15.4, $P < .001$) in first-line therapy (Figure 4).

Univariate and Multivariate Analyses

At univariate analysis, age, BMI, previous nephrectomy, tumor histology, sarcomatoid differentiation, IMDC group, the presence of bone or liver or brain metastases, type of first-line therapy and SII were significant predictors of OS, and their prognostic role was confirmed at multivariate analysis, except for BMI, liver metastases and type of immune combination systemic treatment (Table 2).

As for PFS, previous nephrectomy, sarcomatoid differentiation, IMDC group, the presence of bone or liver metastases, type of first-line therapy and SII were significantly correlated with PFS at univariate analysis, while IMDC and brain metastases did not prove to be associated with PFS at multivariate analysis (Table 2).

Response to Treatment

The ORR In the overall study population was 48%. In the high-SII and low-SII group the ORR was 37 and 52%, respectively. The difference between high- and low-SII was statistically significant in terms of ORR ($P = .033$) and rate of primary refractory to first-line therapy (31% vs. 15%, $P = .007$) (Table 3).

Discussion

Chronic inflammation plays a key role in the development of cancer. In this chronic inflammatory immune environment, neutrophils (N) can impair the host immune response against cancer cells and thereby trigger cell proliferation, platelets (P) are associated with potentiation of endothelial proliferation and metastasis and high levels of platelets have been associated with angiogenesis and impaired cytolysis.[5–7] On the other hand, lymphocytes (L)

Figure 2 Median overall survival and progression-free survival in mRCC patients treated with immune combinations stratified by histology and SII.

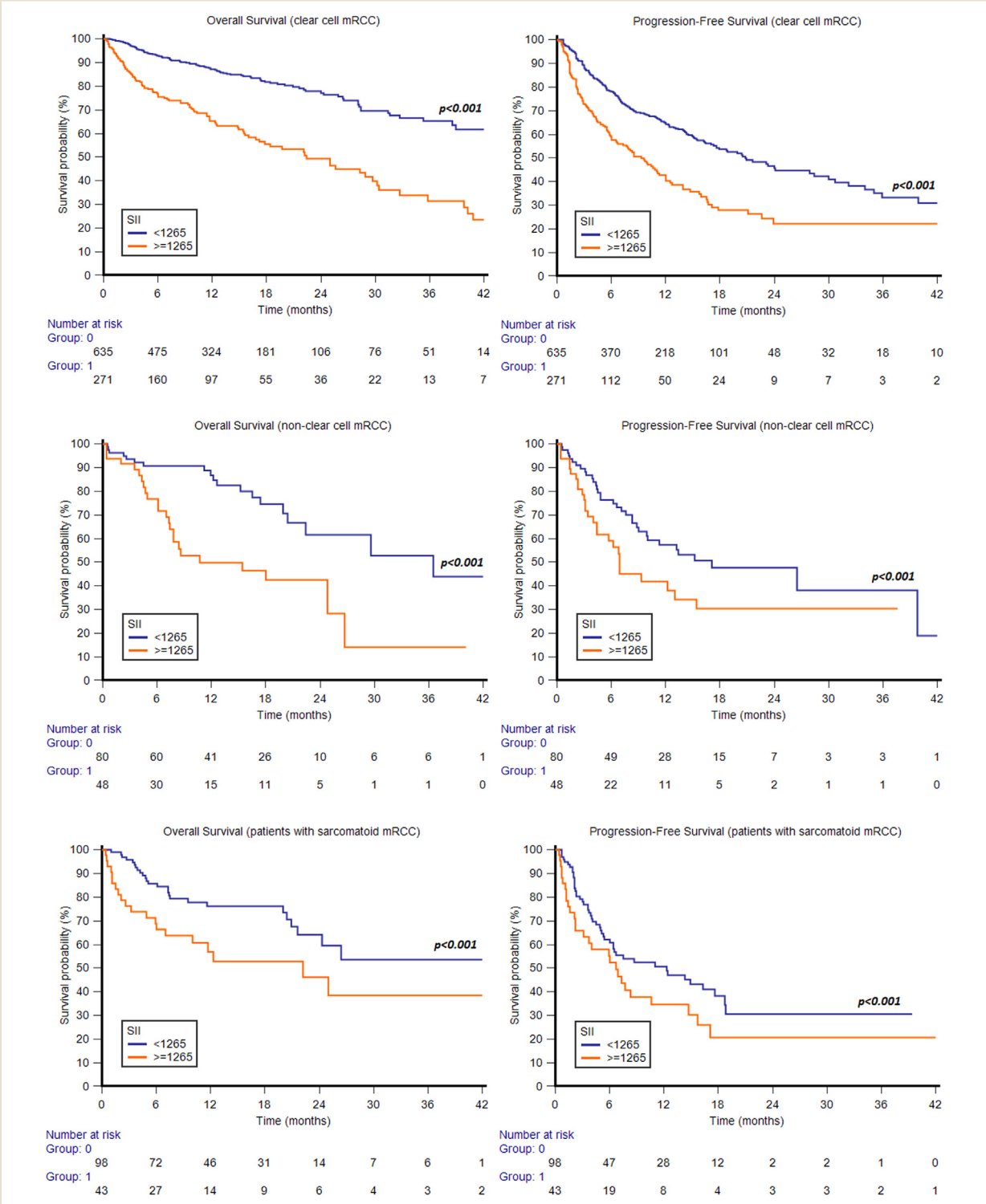


Figure 3 Median overall survival and progression-free survival in mRCC patients treated with immune combinations stratified by IMDC group and SII.

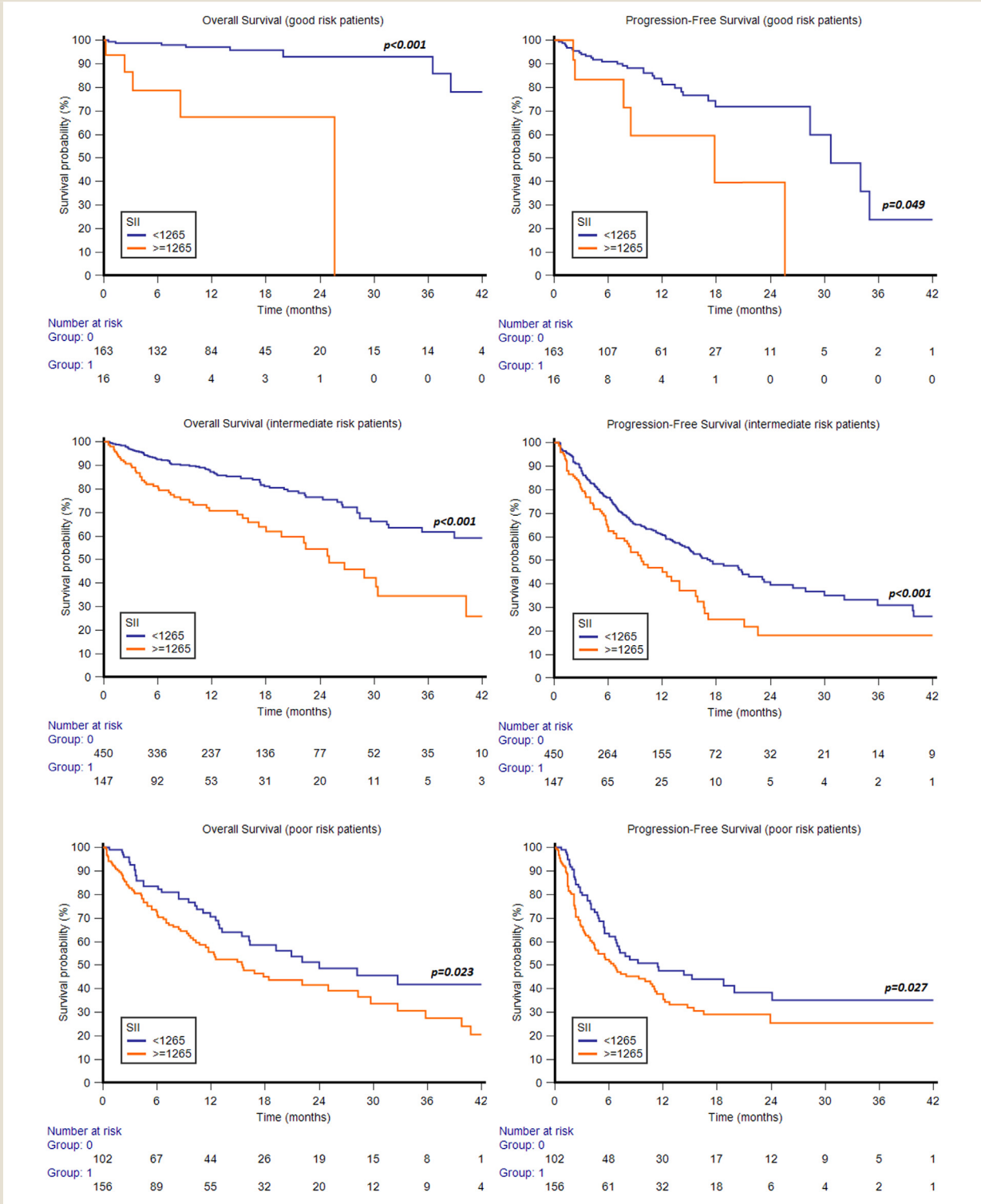


Table 2 Univariate and Multivariate Analyses of Predictors of Overall Survival and Progression-Free Survival in mRCC Patients

OS	Univariate Cox Regression		Multivariate Cox regression	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Gender (females vs. males)	1.04 (0.79-1.38)	.756		
Age (≥65 y vs. <65 y)	1.33 (1.04-1.70)	.024	1.42 (1.11-1.82)	.006
BMI (≥25 kg/m^2 vs. <25 kg/m^2)	0.72 (0.56-0.92)	.008	0.98 (0.75-1.26)	.852
Nephrectomy (yes vs. no)	0.38 (0.29-0.48)	<.001	0.55 (0.42-0.71)	<.001
Histology (ccRCC vs. nccRCC)	0.45 (0.67-0.90)	.010	0.68 (0.49-0.96)	.027
Sarcomatoid features (yes vs. no)	1.44 (1.04-1.98)	.027	1.43 (1.03-1.99)	.032
IMDC group	2.43 (1.98-2.98)	<.001	1.48 (1.16-1.88)	.002
Lung metastases (yes vs. no)	1.25 (0.94-1.65)	.124		
Bone metastases (yes vs. no)	1.87 (1.46-2.39)	<.001	1.67 (1.29-2.15)	<.001
Liver metastases (yes vs. no)	1.76 (1.34-2.32)	<.001	1.23 (0.92-1.65)	.160
Brain metastases (yes vs. no)	1.80 (1.23-2.63)	.003	1.55 (1.04-2.30)	.030
IO+IO vs. IO+TKI	1.53 (1.19-1.97)	<.001	1.26 (0.97-1.64)	.083
SII (≥1265 vs. <1265)	3.04 (2.38-3.89)	<.001	1.99 (1.50-2.64)	<.001
PFS	Univariate Cox Regression		Multivariate Cox Regression	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Gender (females vs. males)	1.08 (0.87-1.33)	.483		
Age (≥65 y vs. <65 y)	1.00 (0.82-1.20)	.972		
BMI (≥25 kg/m^2 vs. <25 kg/m^2)	0.93 (0.77-1.13)	.485		
Nephrectomy (yes vs. no)	0.56 (0.46-0.68)	<.001	0.68 (0.55-0.84)	.001
Histology (ccRCC vs. nccRCC)	0.87 (0.66-1.14)	.313		
Sarcomatoid features (yes vs. no)	1.59 (1.24-2.03)	<.001	1.49 (1.15-1.92)	.002
IMDC group	1.70 (1.46-1.97)	<.001	1.08 (0.90-1.30)	.402
Lung metastases (yes vs. no)	1.21 (0.98-1.50)	.076		
Bone metastases (yes vs. no)	1.63 (1.34-1.97)	<.001	1.54 (1.26-1.89)	<.001
Liver metastases (yes vs. no)	1.49 (1.19-1.86)	<.001	1.28 (1.01-1.61)	.042
Brain metastases (yes vs. no)	1.50 (1.10-2.04)	.011	1.32 (0.95-1.82)	.099
IO+IO vs. IO+TKI	1.98 (1.64-2.40)	<.001	1.84 (1.50-2.25)	<.001
SII (≥1265 vs. <1265)	1.93 (1.59-2.35)	<.001	1.57 (1.26-1.94)	<.001

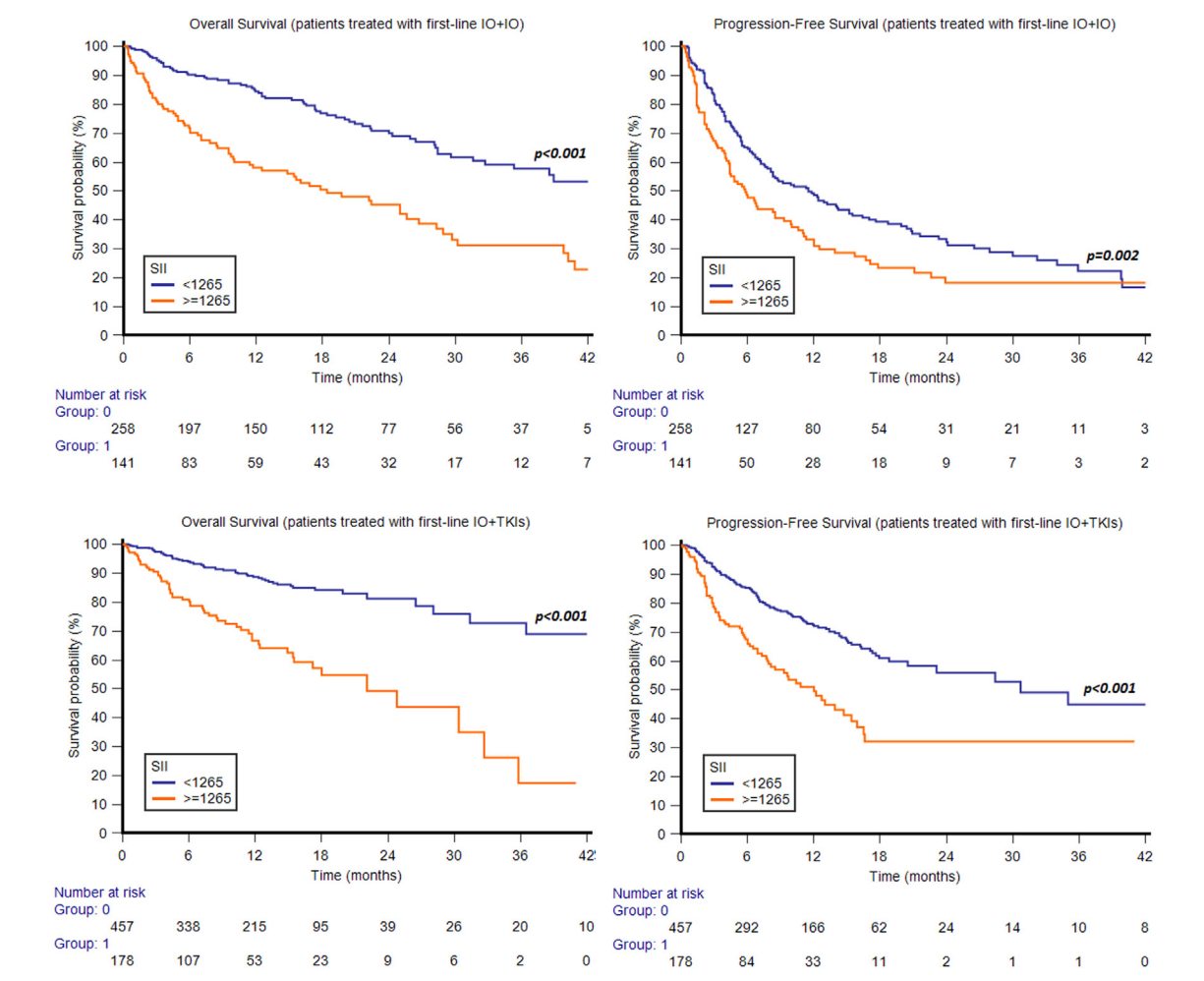
Abbreviations: ccRCC = clear cell Renal Cell Carcinoma; CI = confidence interval; HR = hazard ratio; nccRCC = non-clear cell Renal Cell Carcinoma; OS = overall survival; PFS = progression-free survival; SII = Systemic Immune-Inflammation Index.
Statistically significant values were reported in bold.

Table 3 Summary of Response Rate

Best Overall Response	Overall (%)	SII≥1265(%)	SII<1265(%)
Objective response rate (CR + PR)	48	37	52
		P = .033	
CR	7	4	8
PR	41	33	44
SD	33	31	33
PD	19	32	15
Objective response rate (CR + PR) in patients treated with IO+IO	40	37	52
		P = .033	
Objective response rate (CR + PR) in patients treated with IO+TKI	52	43	55
		P = .090	

Abbreviations: CR = complete response; PR = partial response; PD: progressive disease; SD = stable disease.

Figure 4 Median overall survival and progression-free survival in mRCC patients stratified by type of first-line immune combination and SII.



are associated with T cell antitumor mediated response playing an essential role in inhibiting tumorigenesis and tumor recurrence and high level of lymphocytes is associated with better prognostic in RCC.[6,13,14] In this context, SII that combines the N, P, and L cell counts into an equation (P x N/L) is a useful tool to demonstrate the systemic immune and inflammation environment. For mRCC there are data showing that SII is associated with oncological outcomes in patients treated with TKI's or IO + IO combination in first-line setting. A retrospective trial with 621 patients treated with TKIs (pazopanib or sunitinib) demonstrated that high SII (≥756) is associated with poor OS (HR 1.70, 95% CI: 1.40-2.08, $P < .001$) and PFS (HR 1.38, 95% CI: 1.38-2.00, $P < .001$).[10] A retrospective trial with 43 patients who received nivolumab + ipilimumab showed that SII ≤561.7 is associated with better 1-year PFS rate than SII >561.7 (90.0 vs. 54.8%, $P = .023$).[15] Another retrospective trial with 49 patients who were treated nivolumab + ipilimumab demonstrated that high SII (≥788) is an independent prognostic factor for poor PFS (HR 2.70, $P = .014$) and OS (HR 10.53, $P = .025$).[11]

Considering trials evaluating SII as a prognostic factor in mRCC patients, our international multicenter study has the largest number of patients and it is the first trial to include patients who were treated with the standard immune combinations (ie, IO + IO or IO + TKI) in first-line setting. The population characteristics of our study are consistent with those of pivotal trials of immunotherapy combinations in first-line treatment, most of them are male, with intermediate IMDC risk score, previously submitted to nephrectomy, with the lung as the site of metastatic disease and with clear cell histology.

The study result demonstrated that low-SII patients (< 1265) has better OS (55.7 vs. 22.2 months, $P < .001$) and PFS (20.8 vs. 8.5 months, $P < .001$) than high-SII patients (≥ 1265). This result is in line with the studies cited above, even if the SII cut-off of our study is higher, although this difference should be related to the greater

number of patients included in our analysis. We also demonstrated that low-SII patients have higher ORR (52 vs. 37%, $P = .03$). Similar results were found by Huang et al. in a meta-analysis with 3074 patients with urologic cancers showing that high-SII patients has worse OS (HR 2.58, $P = .001$) and PFS (HR 1.92, $P = .001$) and low-SII is associated with a higher ORR (HR 0.40, $P = .002$).[16] Another meta-analysis including 3180 patients with RCC Jin et al. showed that high-SII is associated with poor OS (HR 1.75, $P < .001$), however without effect on PFS (HR 1.22, $P = .293$).[17]

Another differential of our study, the inclusion of patients who were treated only with IO + IO or IO + TKI in the first-line setting, provided real world survival data. In this sense, the OS benefit in low-SII patients was demonstrated for both IO + IO (NR vs. 18.4 months, $P < .001$) and IO + TKI (NR vs. 22.1, $P < .001$). There was also PFS benefit for low-SII patients for both IO + IO (11.5 vs. 5.8 months, $P = .002$) and IO + TKI (30.7 vs. 12 months, $P < .001$). However, for PFS it was observed only for high-SII patients who was treated with IO + IO in first-line setting.

It is important to highlight that the SII was a prognostic factor for PFS in both univariate and multivariate analysis, however for OS it was demonstrated only in the univariate analysis. Regarding the IMDC risk score, Chrom et al. demonstrated in a retrospective trial that the addition of SII to the IMDC model in place of neutrophil and platelet counts improved the IMDC model's prognostic performance.[18] In this context, considering that in the IMDC model, the 2 clinical parameters may be critical because the assessment of Karnofsky performance status is subjective, and with the approval of pembrolizumab as an adjuvant treatment option, the time from diagnosis to start systemic treatment for less than 12 months may be invalidated. Furthermore, it was developed and validated based on patients who received TKIs (sorafenib or sunitinib) or interferon plus bevacizumab in the first-line setting. On this scenario, SII could play a role as prognostic factor in the era of combination therapies.[19]

Considering the retrospective design, our study has some limitations. The time between the laboratory tests with the data to calculate the SII and the start of systemic treatment was not predefined and may have been different in each participating center. The lack of a central radiological review can lead to a misinterpretation of tumor response. In addition, SII as prognostic tool for OS was not confirmed in a multivariate analysis. Finally, the absence of data regarding the treatment toxicity should be considered, since the dose reduction or even treatment discontinuation could have a negative effect on survival, especially in frail patients.

Conclusion

This international multicenter study with mRCC patients treated with systemic immune combinations in first-line setting demonstrated that high- SII is associated with poor OS, PFS, and ORR. Therefore, SII index could be used as a cheaper and accessible prognostic tool in daily practice.

Clinical Practice Points

- Systemic immune combinations are the standard first-line treatment option for patients with mRCC.
- Prognostic risk stratification for these patients was developed and validated in the TKI treatment era.
- There is no prognostic biomarker for metastatic renal cell carcinoma in the systemic immunotherapy treatment era.
- SII is associated with oncologic outcomes of patients with mRCC who were treated with ICI plus ICI or ICI plus TKI.
- SII could be a cheap and readily available prognostic tool to be used in daily clinical practice.

Disclosure

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CRediT authorship contribution statement

Fernando Sabino Marques Monteiro: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Supervision, Project administration. **Ondřej Fiala:** Formal analysis, Validation, Investigation, Data curation, Writing – review & editing. **Francesco Massari:** Investigation, Data curation, Writing – review & editing. **Zin W. Myint:** Data curation, Writing – review & editing. **Jindrich Kopecky:** Data curation, Writing – review & editing. **Jakub Kucharz:** Data curation, Writing – review & editing. **Thomas Büttner:** Data curation, Writing – review & editing. **Enrique Grande:** Data curation, Writing – review & editing. **Maria Teresa Bourlon:** Data curation, Writing – review & editing. **Javier Molina-Cerrillo:** Data curation, Writing – review & editing. **Renate Pichler:** Data curation, Writing – review & editing. **Tomas Buchler:** Data curation, Writing – review & editing. **Emmanuel Seront:** Data curation, Writing – review & editing. **Jawaher Ansari:** Data curation, Writing – review & editing. **Aristotelis Bamias:** Data curation, Writing – review & editing. **Dipen Bhuva:** Data curation, Writing – review & editing. **Nuno Vau:** Data curation, Writing – review & editing. **Camillo Porta:** Data curation, Writing – review & editing. **Andre Poisl Fay:** Data curation, Writing – review & editing. **Matteo Santoni:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Supervision, Project administration.

Data Availability

The data that support the results of this study are available on request from the corresponding author.

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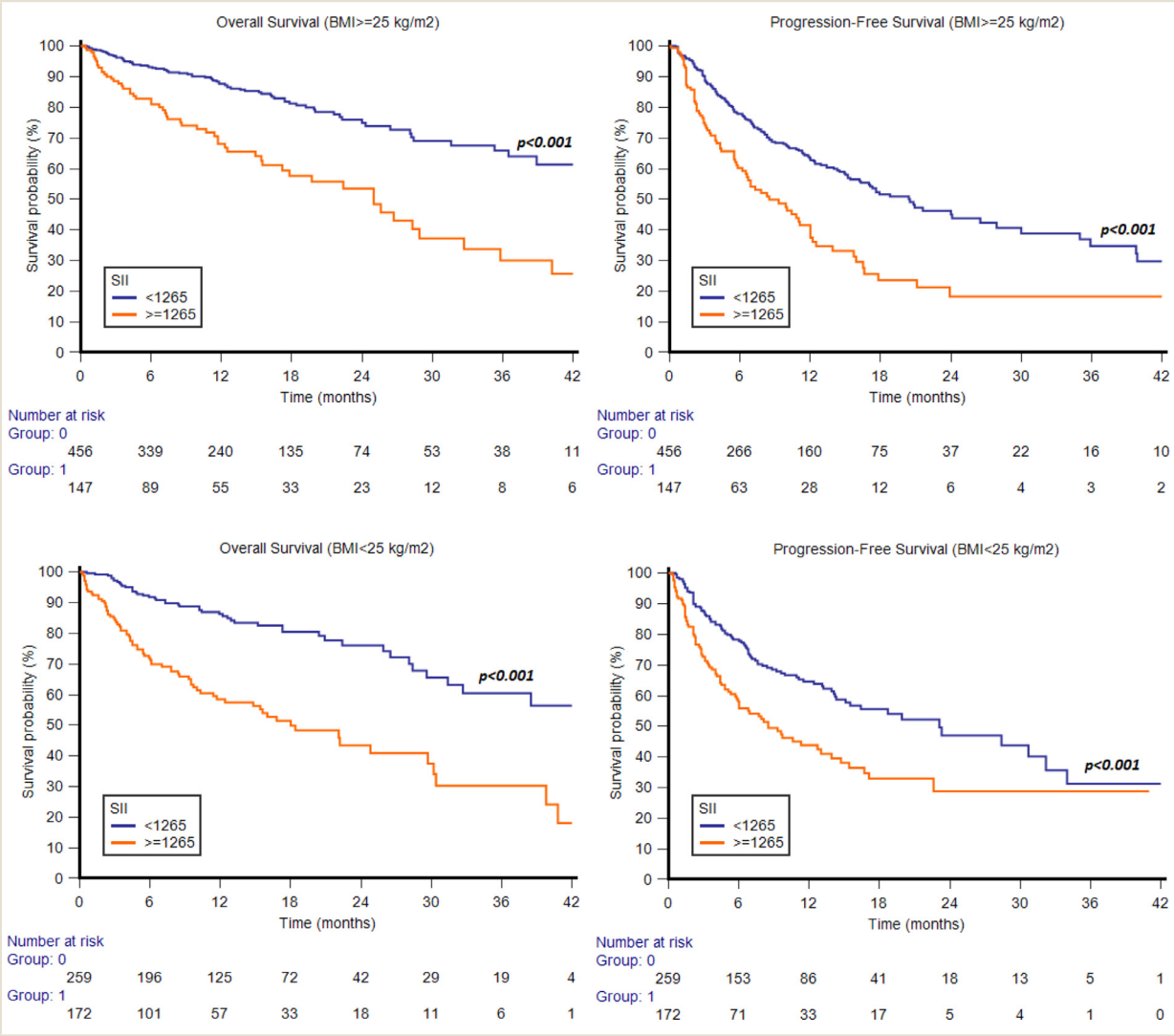
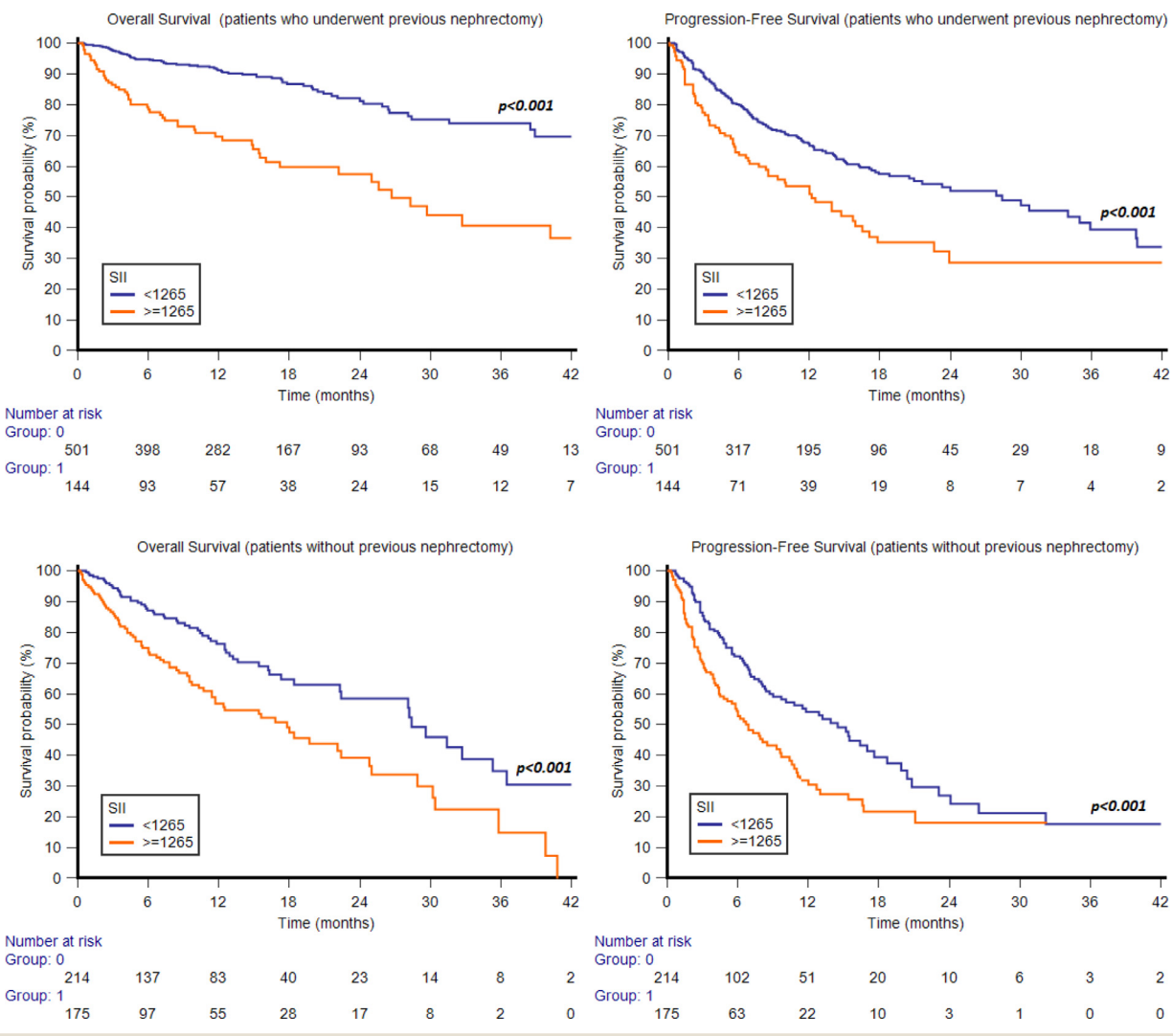
Supplementary materials

Supplemental Figure 1 Median overall survival and progression-free survival in mRCC patients stratified by BMI and SII.



Supplemental Figure 2 **Median overall survival and progression-free survival in mRCC patients stratified by nephrectomy and SII.**



Supplemental Figure 3 **Median overall survival and progression-free survival in mRCC patients stratified by site of metastases and SII.**