Impact of the systemic immune-inflammation index for the prediction of prognosis and modification of the risk model in patients with metastatic renal cell carcinoma treated with first-line tyrosine kinase inhibitors

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Abstract

Introduction: International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria are the most representative risk model for patients with metastatic renal cell carcinoma (mRCC). However, the intermediate-risk group of IMDC criteria is thought to include patients with different prognoses because many of the patients are classified into the intermediate-risk group. In this study, we investigated the impact of systemic immune-inflammation index (SII), which is calculated based on neutrophil count, platelet count, and lymphocyte count, on predicting the prognosis in patients with mRCC, and its usefulness for re-classification of patients with a more sophisticated risk model.

Methods: From January 2008 to January 2018, 179 mRCC patients with a pretreatment and SII were retrospectively investigated. All patients were classified into either a high-SII group or a low-SII group based on the cutoff value of a SII at 730, as reported in previous studies; the overall survival (OS) rates in each group were compared.

Results: The median age was 65 years old. Males and females comprised 145 and 34 cases, respectively. The categories of favorable-, intermediate-, and poor-risk groups in the IMDC model were assessed in 39, 102, and 38 cases, respectively. The median observation period was 24 months. The low-SII and high-SII groups consisted of 73 and 106 cases, respectively. The 50% OS in the high-SII group was 21.4 months, which was significantly worse than that in the low-SII group (49.7 months; p<0.0001). Multivariate analysis showed that a high SII was an independent predictive factor for a worse OS. Next, we constructed a modified IMDC risk model that included the SII instead of a neutrophil count and a platelet count. By using this modified IMDC model, all cases were re-classified into four groups of 33, 52, 81, and 13 cases with 50% OS of 88.8, 45.9, 29.4, and 4.8 months, respectively.

Conclusions: The SII is useful for establishing a more sophisticated prognostic model that can stratify mRCC patients into four groups with different prognoses.

Introduction

While increased screening has led to greater detection rates of clinically localized renal cell carcinoma (RCC), more than 30% of patients with RCC have metastases at initial presentation.[1] The introduction of targeted agents, especially tyrosine kinase inhibitors (TKIs), has led to improved prognosis of metastatic RCC (mRCC) in the past decade.[2] In addition, some randomized control trials showed the effectiveness of immune checkpoint inhibitors (ICIs) for mRCC patients.[3,4] Several guidelines recommend the choice of a first-line agent based on risk model.[5,6]

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk model[7] is one of the most widely used for mRCC; however, several patients with relatively different prognoses are thought to be classified into the intermediate-risk group. It is important to establish a more sophisticated prognostic model.

Several molecules or indexes related to the inflammation response derived from blood samples have been demonstrated as candidates of biomarkers predicting the effect of the treatment or prognosis of mRCC regardless of therapeu-

tic option.[8] Two of six parameters of the IMDC prognostic model, neutrophil and platelet count, are also involved in the inflammatory response. The systemic immune inflammation index (SII) was defined as follows: platelet count × neutrophil count / lymphocyte count.[9] SII has been reported as a prognostic marker for several malignant diseases, and it can represent the balance of inflammation and immune response of hosts.[10] We investigated the prognostic impact of SII in patients with mRCC treated with first-line TKI and assessed a modified IMDC risk model using SII.

Methods

Patients

From January 2008 to January 2018, 179 patients with pathologically diagnosed mRCC treated with TKI as first-line agents at our institute and affiliated hospitals in Hiroshima Prefecture in Japan were retrospectively investigated after approval by the Ethical Committee of Hiroshima University (allowance notification number E-45). Upon starting the prescription of first-line targeted agents, SII was calculated based on the data. The cutoff value of SII was determined to be 730, as reported in previous studies.[10] Cases with pretreatment SII were 730 or higher, and the others were classified into a high-SII or low-SII group.

We compared the clinical and pathological data, including age, sex, histological finding, metastasis status, choice of drug, prior nephrectomy, Karnofsky performance status (KPS), anemia, serum calcium, neutrophil count, platelet count collected for all patients, and the distribution of these parameters in each group. The overall survival (OS) of each group classified according to these parameters was analyzed.

The modified IMDC model was determined using five poor prognostic factors, including KPS <80%, time from diagnosis to treatment <1 year, anemia, hypercalcemia, and SII >730. Cases were classified into four groups based on the presence of the number of these factors, 0, 1, 2–3, or 4–5.

Statistical analysis

The differences in the distribution of variables among groups were evaluated using a Chi-squared test for categorical variables and a Mann-Whitney test for continuous variables. Pearson correlation coefficients were assessed between SII and other inflammatory parameters. Tumor responses were determined using an investigator assessment according to the response evaluation criteria in solid tumor (RECIST), version 1.1. The OS was determined using the Kaplan-Meier method, and the differences between groups were analyzed using log-rank testing. Multivariate analyses of parameters associated with OS were evaluated using the Cox proportional hazards regression model. All statistical analyses were conducted using the JMP 10.0.0 (SAS Institute Inc., NC, U.S.), and $p<0.05$ was considered to be statistically significant.

Results

One hundred seventy-nine patients with mRCC treated with first-line TKI were investigated in this study. SII was 94.6–4603.1 (median 609.7), and positive correlations were found between SII and other inflammatory parameters, including C-reactive protein (CRP), neutrophil count, platelet count, and neutrophil-to-lymphocyte ratio (NLR) (Fig. 1). The characteristics of patients in this study cohort are listed in Table 1. The low-SII and high-SII groups consisted of 106 and 73 cases, respectively. The rate of cases with anemia, neutrophilia, thrombocytosis, hypercalcemia, time from diagnosis to treatment <1 year, and with IMDC poor-risk classification were higher in the high-SII group than in the low-SII group (Table 1).

The median observation period was 24 months, and the 50% OS in the entire cohort was 43.3 months (Fig. 2A). Maximum effects of the first-line agents determined based on the RECIST criteria in each group are shown in Table 2. In the high-SII group, the rate of cases with complete response (CR) and partial response (PR) was significantly lower ($p=0.0394$), and that with progressive disease (PD) was significantly higher ($p=0.0038$) than in the low-SII group.

The 50% OS in the high-SII group was 21.4 months, which was significantly worse than that in the low-SII group (49.7 months, $p<0.0001$) (Fig. 2B). Multivariate analysis showed that a high SII, as well as non-clear histology, hypercalcemia, and time from diagnosis to treatment <1 year were independent predictive factors for worse OS (Table 3). Next, we

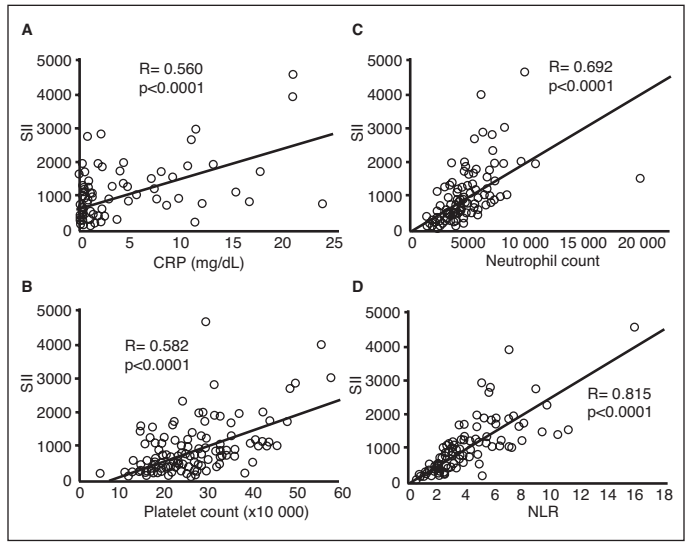

Fig. 1. Correlation between systemic immune inflammation index (SII) and other inflammatory parameters, including ***(A)*** C-reactive protein (CRP); ***(B)*** platelet count; ***(C)*** neutrophil count; and ***(D)*** neutrophil-to-lymphocyte ratio (NLR).

Table 1. Characteristics of 179 patients with metastatic renal cell carcinoma who underwent targeted therapy

	High SII (≥730)	Low SII (<730)	p	
No. of patients	(n=73)	(n=106)		(n=179)
Age (median)	64 (40–85)	67 (40–85)	0.1624	65 (40–85)
Sex (%)				
Male	61 (83.6)	84 (79.2)	0.4694	145 (81.0)
Female	12 (16.4)	22 (20.8)		34 (19.0)
Histological type (%)				
Clear	61 (83.6)	96 (90.6)	0.1607	157 (87.7)
Non-clear	12 (16.4)	10 (9.4)		22 (12.3)
KPS (%)				
≥80%	65 (89.0)	101 (95.3)	0.1138	166 (92.7)
<80%	8 (11.0)	5 (4.7)		13 (7.3)
Anemia (%)				
(-)	45 (61.6)	36 (34.0)	0.0003	81 (45.3)
(+)	28 (38.4)	70 (66.0)		98 (54.7)
Neutrophilia (%)				
(-)	50 (68.5)	100 (94.3)	<0.0001	150 (83.8)
(+)	23 (31.5)	6 (5.7)		29 (16.2)
Thrombocytosis (%)				
(-)	51 (69.9)	104 (98.1)	<0.0001	155 (86.6)
(+)	22 (30.1)	2 (1.9)		24 (13.4)
Hypercalcemia (%)				
(-)	66 (90.4)	106 (100)	0.0011	172 (96.1)
(+)	7 (9.6)	0 (0)		7 (3.9)
Metastatic organs (%)				
1	6 (42.9)	8 (30.8)	0.4446	14 (35.0)
≥2	8 (57.1)	18 (69.2)		26 (65.0)
Time from diagnosis to treatment (%)				
≥1 year	20 (27.4)	45 (42.5)	0.0396	65 (36.3)
<1 year	53 (72.6)	61 (57.5)		114 (63.7)
IMDC risk				
Favorable	8 (11.0)	31 (29.3)	0.0036	39 (21.8)
Intermediate	31 (42.5)	71 (67.0)		102 (57.0)
Poor	34 (46.6)	4 (3.8)	<0.0001	38 (21.2)
Metastatic site				
Lung	48 (65.8)	80 (75.4)		128 (71.5)
Lymph node	25 (34.3)	30 (28.3)		55 (30.7)
Liver	9 (12.3)	13 (12.3)		22 (12.3)
Bone	20 (27.4)	26 (24,5)		46 (25.7)
Pancreas	2 (2.7)	7 (6.6)		9 (5.0)
Adrenal gland	7 (9.6)	7 (6.6)		14 (7.8)
Contralateral kidney	5 (6.8)	10 (9.4)		15 (8.4)
Brain	3 (4.1)	4 (3.7)		7 (3.9)
Soft tissue	4 (5.5)	4 (3.7)		8 (4.5)
Prior nephrectomy, n (%)				
Radical	28 (38.4)	65 (61.3)	0.0025	93 (52.0)
Cytoreductive	33 (45.2)	34 (32.1)		67 (37.4)
None	12 (16.4)	7 (6.6)	0.0358	19 (10.6)
First-line agents, n (%)				
Sunitinib	55 (75.3)	59 (55.7)		114 (63.7)
Pazopanib	5 (6.8)	7 (6.6)		12 (6.7)
Sorafenib	13 (17.8)	38 (35.9)		51 (28.5)
Axitinib	0 (0)	2 (1.9)		2 (1.1)

KPS: Karnofsky performance status, IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; SII: systemic immune inflammation index.

constructed a modified IMDC risk model that included SII instead of neutrophil and platelet count. Using this modified IMDC model, all cases were re-classified into four groups of 33, 52, 81, and 13 cases with 50% OS of 88.8, 45.9, 29.4, and 4.8 months, respectively (p<0.0001); 102 cases (57% of total), were classified into the intermediate-risk group based on the conventional IMDC model (Fig. 3).

Discussion

In this study, we assessed the impact of SII for predicting the prognosis of cases with mRCC treated with TKI, and we showed the usefulness of SII to modify the IMDC risk model. To the best of our knowledge, this study is the first report on the impact of SII for establishing a modified prognostic model.

Several prognostic classifications are available for mRCC.[11] Of these, the Memorial Sloan Kettering Cancer Center (MSKCC) and the IMDC risk models are two of the most widely used ones. The former was based on data from patients who were enrolled in clinical trials of cytokine therapy, and the latter was derived from patients treated with targeted agents. In both models, patients are stratified into three categories: favorable-, intermediate-, and poor-risk groups. However, because many patients with different prognoses are thought to be included in the same intermediate-risk group, improvement in risk stratification, especially in the intermediate-risk group, is required for both models.

Some investigators focused on the relationship between the number of positive risk factors. Tamada et al[12] and Sella et al[13] reported that mRCC patients treated with targeted agents in the intermediate-risk group of the MSKCC model could be divided into two groups with different prognoses. Others were re-stratified into intermediate-risk group patients based on the CRP level,[14,15] which has been demonstrated as a predictive factor for prognosis and therapeutic efficacy in many reports.[16,17] In addition to CRP, various reports have demonstrated the association of enhanced inflammatory response with the progression of RCC, including peripheral

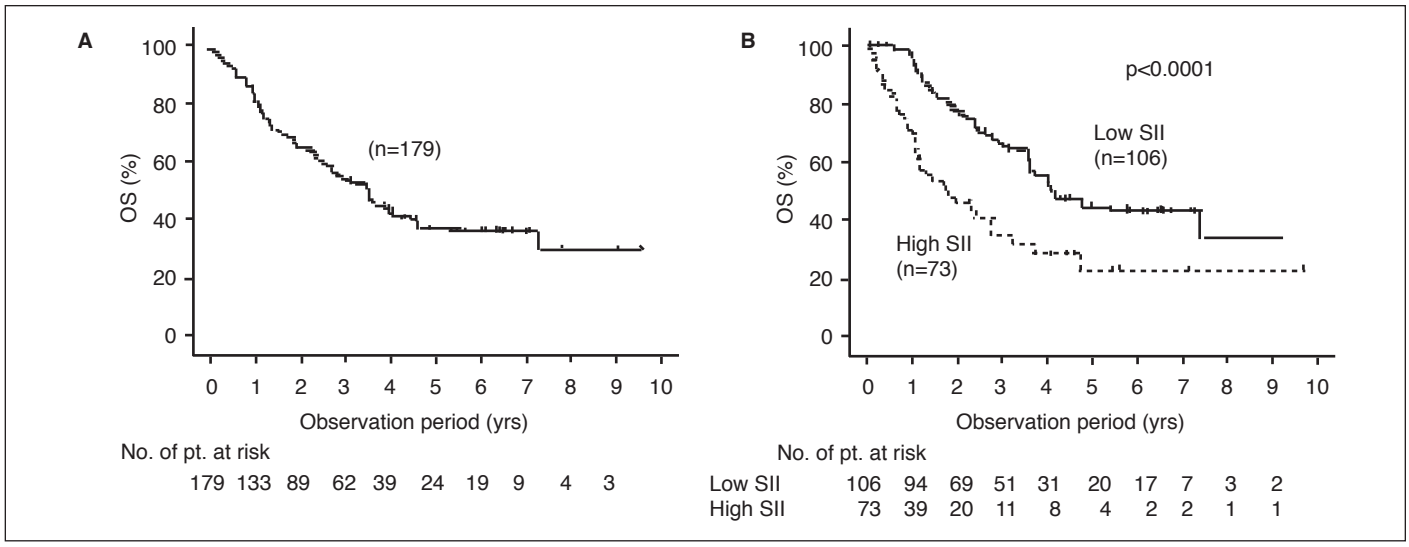

Fig. 2. Overall survival (OS) ***(A)*** for all cases and ***(B)*** OS stratified based on pretreated systemic immune inflammation index (SII).

blood markers and indexes constructed from these components. Neutrophils can secrete various growth factors and cytokines, and they are associated with the stimulation of the tumor microenvironment.[18] Lymphocytes can show an anti-tumoral role through the induction of cytotoxic cell death,[19,20] and perioperative lymphopenia was reported to be associated with inferior prognosis in patients with mRCC.[21] NLR is one of the most representative indexes that has been reported in terms of its prognostic impact on mRCC.[18,22,23] Tanaka et al[24] established a modified IMDC model using NLR. Platelets have been reported to be capable of inducing epithelial-to mesenchymal transition, promoting migration and metastasis, and protecting the autoimmune system from cancer cells.[25] SII can represent these three peripheral blood parameters involving different molecular mechanisms of cancer cells. Also, previous studies have reported the prognostic impact of SII for mRCC treated with targeted agents and ICIs.[26] As shown in Table 1, the rates of cases with parameters for poor prognosis were significantly higher than those in the high-SII group. Moreover, according to multivariate analysis, high SII was an independent predictive factor for OS (Table 3). These were consistent with the data from previous studies that have reported the association of elevated SII with poor prognosis of patients with malignant diseases, including mRCC.[9,10]

The simplicity of any risk model is important for use in the real world of clinical practice. Because SII is calculated using neutrophils and platelets, which are parameters in the IMDC

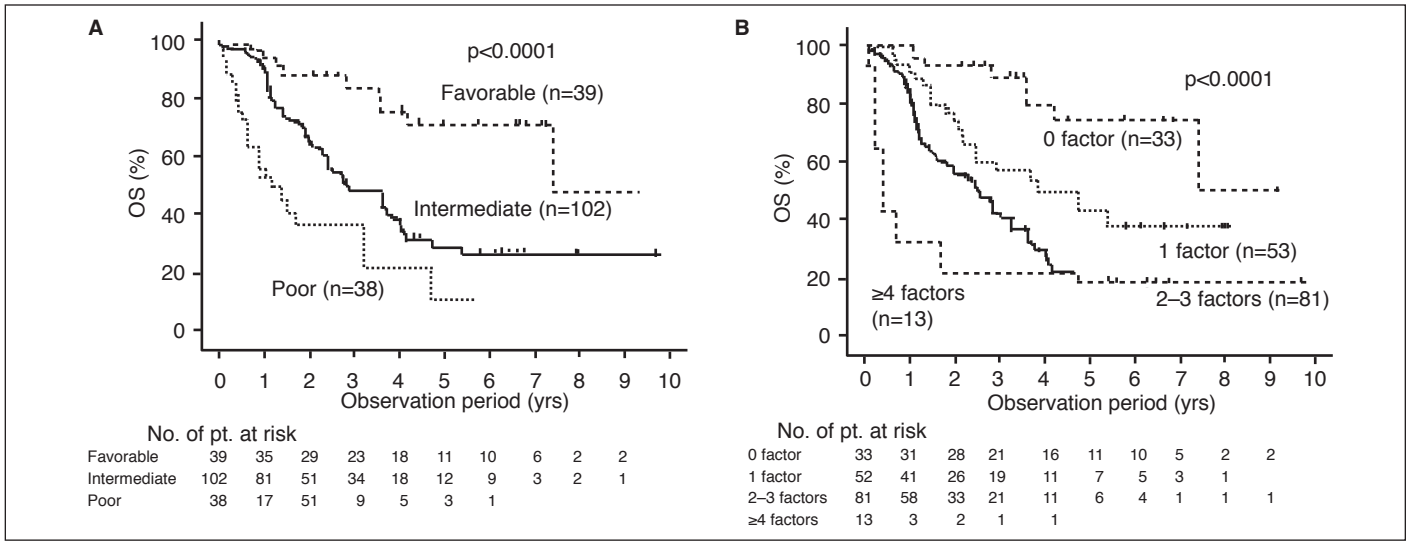

Fig. 3. Overall survival (OS) stratified based on ***(A)*** International Metastatic Renal Cell Carcinoma Database consortium (IMDC) risk model and ***(B)*** modified version of IMDC risk model consisting of five factors including systemic immune inflammation index (SII).

Table 2. Best objective response of first-line agents in each group

	High SII	Low SII	Total
No. of patients	(n=64)	(n=88)	(n=152)
CR/PR	8 (12.5)	23 (26.1)	31 (20.4)
SD	40 (62.5)	58 (65.9)	98 (64.5)
PD	16 (25.0)	7 (8.0)	23 (15.1)

CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease; SII: systemic immune inflammation index.

model, and lymphocytes, which are measured alongside neutrophils, the modified risk model including SII can be used without any additional examination. Recent randomized controlled trials have demonstrated the effectiveness of combination regimens that consists of one TKI and one ICI (with the exception of one trial that included two ICIs[4]).[27,28] While options for first-line therapy for mRCC have increased, it is still unclear how to decide on the best one. The IMDC model was established based on the data of patients who underwent target therapy, therefore, patients with higher risk in the IMDC model are thought to represent resistance to targeted agents. As such, re-stratification to more subgroups of this model can help guide therapeutic decisions.

Investigators have previously focused on many molecules as candidates for serum biomarkers, including growth factors[29,30], microRNA,[31] and cell-free DNA.[32] However, clinically applying these molecules as biomarkers for mRCC is difficult. Alternatively, components of SII are routinely measured in real clinical practice during the management of patients with mRCC undergoing systemic therapy. Our data indicate the possibility of SII as a biomarker to enable us to improve the prognostic model for mRCC in the near future.

The limitation of the present report is that it is a relatively small, retrospective study. Because the data were derived from real-world clinical practice, some selection bias of patients or therapeutic options is inevitable. In addition, inflammatory factors do not represent the sensitivity of targeted agents but the status of progressiveness of mRCC; therefore, they can be affected by other therapeutic options.[26,33,34] Further prospective study with higher patient volume is required to confirm the impact of the SII for predicting the prognosis of patients with mRCC.

Conclusions

We demonstrated the impact of SII for the prediction of the prognosis and modification of risk model in patients with mRCC treated with first-line TKI. SII is promising as a prognostic factor for mRCC patients, and this finding might lead to the establishment of novel therapeutic strategies and multiple options for mRCC.

Competing interests: The authors report no competing personal or financial interests related to this work.

Table 3. Multivariate analyses of association between various parameters and overall survival

		Univariate		Multivariate		
		HR	p	HR	95% CI	p
Age	>65	Reference	0.0641			
	≤65	1.539				
Sex	Male	Reference	0.4369			
	Female	1.257				
Pathology	Non-clear	Reference	0.0035	Reference		0.0110
	Clear	0.432		0.477	0.269–0.844	
KPS	≥80%	Reference	0.2527			
	<80%	1.573				
Anemia	(-)	Reference	0.0004	Reference		0.0658
	(+)	2.201		1.557	0.971–2.495	
Hypercalcemia	(-)	Reference	<0.0001	Reference		0.0005
	(+)	10.315		5.233	2.074–13.203	
Time from diagnosis to treatment	<1 year	Reference	0.0002	Reference		0.0072
	≥1 year	0.407		0.479	0.280–0.819	
Liver metastasis	(+)	Reference	0.2816			
	(-)	0.705				
Bone metastasis	(+)	Reference	0.3267			
	(-)	0.793				
SII	≤730	Reference	<0.0001	Reference		0.0259
	>730	2.424		1.721	1.067–2.774	

CI: confidence interval; HR: hazard ratio; KPS: Karnofsky Performance Status; SII: systemic immune inflammation index.

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