International Journal of Clinical Oncology (2019) 24:526–532
https://doi.org/10.1007/s10147-018-01390-x

ORIGINAL ARTICLE

External validation of the systemic immune-inflammation index as a prognostic factor in metastatic renal cell carcinoma and its implementation within the international metastatic renal cell carcinoma database consortium model

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Received: 15 October 2018 / Accepted: 26 December 2018 / Published online: 2 January 2019

Abstract

Background We conducted a study to validate the influence of the systemic immune-inflammation index (SII) on overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC) and to verify whether the implementation of the SII in place of neutrophil and platelet counts within the International Metastatic Renal Cell Carcinoma Consortium (IMDC) model might increase its prognostic accuracy.

Patients and methods We retrospectively analyzed consecutive patients with mRCC, who were treated with first-line tyrosine kinase inhibitors from 2008 to 2016 in two major oncology centres in Poland. We stratified patients into low SII (<730) and high SII (≥730) groups according to a recent literature report. We used multivariable Cox proportional hazards regressions (CPHRs) to assess the impact of the SII on OS and concordance, global 'goodness-of-fit', calibration and reclassification measures to quantify a potential prognostic benefit from the modification of the IMDC model.

Results Overall, 502 patients (294 with low and 208 with high SII) were included. Median OS was 36.7 months [95% confidence interval (CI) 30.4–41.5 months] and 17.0 months (95% CI 12.5–19.6 months) in the low and high SII groups, respectively. The SII status was significant in CPHRs with the hazard ratio ranging from 1.38 to 1.68. All prognostic accuracy measures favored the SII-modified-IMDC model over the original IMDC model.

Conclusions Using an external dataset, we showed that high SII was an independent factor for poor OS. The addition of the SII to the IMDC model in place of neutrophil and platelet counts increased the model's prognostic performance.

Keywords International metastatic renal cell carcinoma database consortium model · Overall survival · Prognostic factor · Systemic immune-inflammation index · Tyrosine kinase inhibitors

Introduction

Systemic treatment of patients with metastatic renal cell carcinoma (mRCC) has been dramatically improved over the past 12 years by introducing molecular targeted therapies (MTTs) into clinical practice. The median overall survival (OS) in the first-line setting increased from 13 months for interferone-alfa (IFN-α) used in the pre-MTT era to 22 months for vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (TKI) and over 30 months with recently reported nivolumab [a programmed death 1 (PD-1) receptor antibody] and ipilimumab [an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody] combination [1–3]. However, this progress in survival prolongation was not accompanied by an identification of

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10147-018-01390-x) contains supplementary material, which is available to authorized users.

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predictive markers of antitumor response, neither for TKIs nor for immune-oncology agents. Therefore, a routine patient evaluation as well as stratification in clinical trials still relies on survival prognosis which is made using baseline clinical characteristics. The most widely used prognostic model developed in the MTT era is the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model. It consists of six factors associated with decreased probability of survival: Karnofsky performance status (KPS) less than 80%, diagnosis-to-treatment interval (DTI) less than 12 months, hemoglobin concentration less than the lower limit of normal (LLN) and serum corrected calcium, neutrophil and platelet counts greater than the upper limit of normal (ULN) [4–6]. However, since the introduction of the IMDC model in 2009, additional factors were reported to have an independent influence on OS. They include systemic inflammation indices, for example, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio which were also found to increase the prognostic accuracy of the IMDC model when incorporated in place of neutrophil and platelet counts [7, 8]. The advantage of these markers is that they may possess more prognostic information than their either component alone with still being easy and low-cost to obtain. Recently, the systemic immune-inflammation index (SII) which is based on whole blood counts of neutrophils, lymphocytes, and platelets, was reported by Lolli et al. to have a powerful impact on clinical outcomes in 335 mRCC patients treated with sunitinib [9]. Herein, we aimed to validate the prognostic significance of the SII status using an external dataset of patients from two major oncology centres in Poland. We also tried to verify, whether the replacement of neutrophil and platelet counts by the SII within the IMDC model might improve its prognostic performance.

Patients and methods

Patients

The present study retrospectively evaluated consecutive patients with mRCC who were treated from 2008 to 2016 in Department of Oncology, Military Institute of Medicine and Department of Genitourinary Cancers, Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, Poland. The inclusion criteria comprised a diagnosis of mRCC of any histopathological subtype, the use of TKI as first-line systemic therapy for metastatic disease and the absence of other malignancies. Patients who had been treated with interferone-based immunotherapy prior to the initiation of a TKI were not allowed. Additionally, patients who had received neoadjuvant, adjuvant or any investigational therapy were excluded from analysis. The information about patients was gathered from individual medical records.

Statistical analysis

The study outcome was OS, which was defined as the time from the start of first-line TKI therapy to death from any cause or last follow-up. The SII was calculated as follows: neutrophil count multiplied by platelet count and divided by lymphocyte count. It was further dichotomized using a cut point of 730 ($\times 10^9$ per 1 L) proposed by Lolli et al. to stratify patients into low (<730) and high (≥ 730) SII groups. The Kaplan–Meier method was used to plot OS curves and the log-rank test was used to compare two survival distributions. The median follow-up time was estimated using the Schemper and Smith method [10]. The influence of SII on OS was assessed using multivariable Cox proportional hazards regressions (CPHRs) with adjustment for (1) all other collected variables (2) all six IMDC criteria and (3) four IMDC criteria: KPS, DTI, hemoglobin and serum corrected calcium concentrations. The last five-factor formula, named the SII-modified IMDC model (SII-IMDC), was then compared to the original IMDC model to assess whether the replacement of neutrophil count and platelet count the SII status within the IMDC model might improve its prognostic ability. The SII-IMDC model used the same rule as the original IMDC model to segregate patients into favorable-, intermediate- and poor-risk groups (0 versus 1–2 versus ≥ 3 adverse factors, respectively). To provide more robust confidence intervals (CI) of the parameter estimates, internal validation was performed using bootstrap procedure based on 1000 samples generated randomly with replacement from the original dataset [11].

The prognostic accuracy of the models was assessed separately for individual risk factors and the three risk groups using (1) concordance index, (2) Bayesian Information Criterion (BIC), (3) generalized R^2, (4) calibration plot, (5) Integrated Discrimination Improvement (IDI) and (6) continuous Net Reclassification Index (cNRI). Concordance index is a measure of discrimination which is the ability of the model to separate patients with different outcomes. Its value ranges from 0.5 (no ability to separate) to 1 (perfect predictive discrimination). BIC and generalized R^2 refer to the global 'goodness-of-fit' concept and rely on distances between observed and predicted outcomes. Lower BIC value and greater generalized R^2 (within the rage from 0 to 1) indicate better overall fit. The calibration plot presents predicted survival probabilities (the x-axis) versus corresponding Kaplan–Meier survival estimates (the y-axis) at 24 months since first-line TKI initiation. A line positioned closer to a 45° line indicates better calibration. IDI and cNRI quantify the degree of correct reclassification after switching patients from the standard model to the new model. IDI may is a difference between

increase in average sensitivity and increase in average 'one minus specificity' whereas cNRI focuses on the direction of changes in the predicted probabilities of the individuals. Both IDI and cNRI are calculated separately for patients who were dead or alive, herein at 24 months since first-line TKI initiation. The larger positive value of IDI and cNRI, the better net reclassification of patients with the SII-IMDC model compared to the IMDC model [12–14].

P values less than 0.05 (two-sided) indicated statistical significance for all tests. Computations were performed using Stata, version 14.2 (StataCorp, USA) and R, version 3.2.5 (The R Foundation for Statistical Computing, Austria).

Table 1 Patient characteristics at the start of first-line treatment (total $N = 502$)

Variable	*N* (%)
Median age, years (range)	62 (22–88)
Male gender	339 (67.5)
Histology	
Clear cell	486 (96.8)
Other	16 (3.2)
Nephrectomy or NSS	502 (100)
Centre	
Military Institute of Medicine	285 (56.8)
Maria Sklodowska-Curie Memorial Cancer Centre	217 (43.2)
First-line TKI treatment	
Sunitinib	456 (90.8)
Pazopanib	46 (9.2)
Karnofsky performance status	
100	215 (42.8)
90–80	279 (55.6)
≤ 70	8 (1.6)
Diagnosis-to-treatment interval < 12 months	239 (47.6)
Hemoglobin < LLN	81 (16.1)
Corrected calcium > ULN	48 (9.6)
Neutrophil count > ULN	37 (7.4)
Platelet count > ULN	57 (11.4)
Lymphocyte count < LLN	29 (5.8)
Risk groups by the IMDC model	
Favorable	203 (40.4)
Intermediate	256 (51.0)
Poor	43 (8.6)

IMDC International Metastatic Renal Cell Carcinoma Database Consortium, *LLN* lower limit of normal, *NSS* nephron sparing surgery, *TKI* tyrosine kinase inhibitor, *ULN* upper limit of normal

Results

Patient characteristics and outcomes

Overall, 502 patients were eligible for the analysis. The detailed characteristics of patients at the start of the first-line TKI are presented in Table 1. The majority of patients had clear cell histology (96.8%), presented good or very good performance status (98.4%) and received sunitinib as initial systemic therapy (90.8%). At the end of survival data collection, 317 (63.1%) patients had died. The median follow-up time was 52.5 months (95% CI 46.7–62.0 months). The median OS was 25.9 months (95% CI 23.3–28.9 months). According to the IMDC classification, 203 (40.4%) patients were in favorable-risk group with the median OS of 40.9 months (95% CI 31.9–49.9 months), 256 (51.0%) patients were in intermediate-risk group with the median OS of 22.0 months (95% CI 18.2–26.1 months) and 43 (8.6%) patients were in poor-risk group with the median OS of 7.1 months (95% CI 4.4–11.3 months, Fig. 1a). Two hundred and twenty-one (44.0%) patients were treated with second-line targeted therapy, which included everolimus, axitinib, cabozantinib and sorafenib in 166 (33.0%), 48 (9.6%), 5 (1.0%)

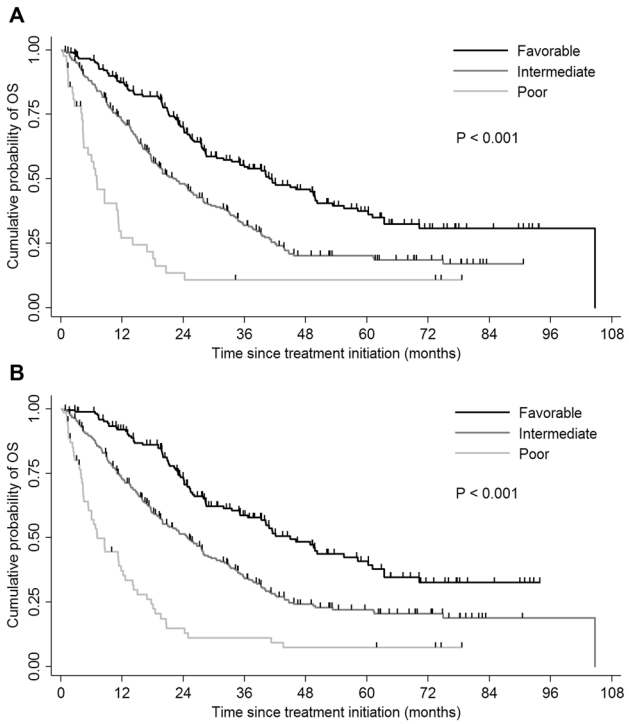

Fig. 1 Kaplan–Meier Curve for overall survival (OS) stratified by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (**a**) and Systemic Immune-inflammation Index-modified International Metastatic Renal Cell Carcinoma Database Consortium (SII-IMDC) (**b**) risk groups

and 2 (0.4%) patients, respectively. At the data collection end, no patients were identified to have received immune-checkpoint inhibitors as subsequent therapy.

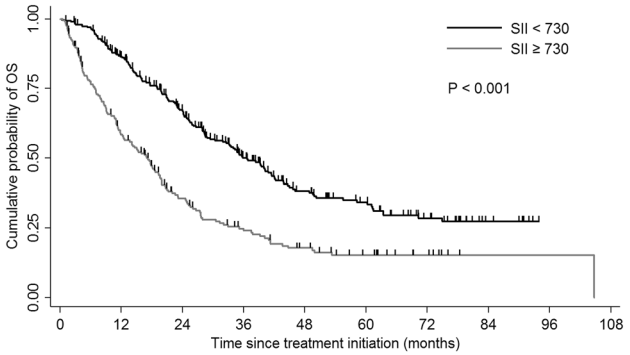

Fig. 2 Kaplan–Meier curves for overall survival (OS) stratified by the Systemic Immune-inflammation Index (SII) status

The impact of the SII on OS

The median (range) SII in the whole cohort was 636 (58–9359) and was lower than a threshold of 730 adopted from Lolli et al. study to separate patients into low and high SII. Overall, 294 (58.6%) patients were in the low SII group and 208 (41.4%) patients were in the high SII group. Survival distributions differed between the two groups (the log-rank $P < 0.001$) with a median OS of 36.7 months (95% CI 30.4–41.5 months) and 17.0 months (95% CI 12.5–19.6 months) in low and high SII patients (Fig. 2). In all three CPHRs high SII independently contributed to worse survival with hazard ratio ranging from 1.38 to 1.68. The statistical significance of the SII status was retained even after bootstrap procedures were applied for each regression (Table 2, Table S1).

Table 2 Multivariable Cox proportional hazard regressions

A: The IMDC model (individual criteria)					
Variable	HR	95% CI	*P* value	95% CI[a]	*P* value[a]
Karnofsky performance status ≤ 70	4.59	2.12–9.95	< 0.001	2.01–10.50	< 0.001
Diagnosis-to-treatment interval < 12 months	1.49	1.19–1.87	0.001	1.19–1.87	0.001
Hemoglobin < LLN	2.46	1.84–3.28	< 0.001	1.70–3.56	< 0.001
Corrected calcium > ULN	1.56	1.09–2.23	0.014	0.98–2.50	0.059
Neutrophil count > ULN	1.43	0.93–2.21	0.106	0.80–2.55	0.227
Platelet count > ULN	1.65	1.17–2.32	0.004	1.05–2.59	0.031
B: The IMDC model (the three risk groups)					
Risk group	HR	95% CI	*P* value	95% CI[a]	*P* value[a]
Favorable	1				
Intermediate	1.82	1.43–2.32	< 0.001	1.43–2.32	< 0.001
Poor	4.54	3.07–6.71	< 0.001	2.50–8.24	< 0.001
C: The SII-IMDC model (individual criteria)					
Variable	HR	95% CI	*P* value	95% CI[a]	*P* value[a]
Karnofsky performance status ≤ 70	4.74	2.19–10.25	< 0.001	0.07–338.9	0.475
Diagnosis-to-treatment interval < 12 months	1.44	1.15–1.80	0.002	1.15–1.81	0.002
Hemoglobin < LLN	2.28	1.71–3.04	< 0.001	1.56–3.33	< 0.001
Corrected calcium > ULN	1.49	1.04–2.13	0.029	0.93–2.39	0.099
SII ≥ 730	1.68	1.32–2.13	< 0.001	1.30–2.17	< 0.001
D: The SII-IMDC model (the three risk groups)					
Risk group	HR	95% CI	*P* value	95% CI[a]	*P* value[a]
Favorable	1				
Intermediate	1.88	1.44–2.44	< 0.001	1.46–2.41	< 0.001
Poor	4.85	3.41–6.90	< 0.001	3.05–7.71	< 0.001

CI confidence interval, *HR* hazard ratio, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *LLN* lower limit of normal, *SII* systemic immune-inflammation index, *ULN* upper limit of normal

[a]Values after bootstrap procedure

Comparison of the prognostic accuracy of the IMDC and SII-IMDC models

In the present cohort, all IMDC criteria except neutrophil count were significantly associated with survival. Addition of the SII status to those six factors not only retained non-significant result of neutrophil count, but also eliminated platelet count from the list of significant covariates (Table S1). On the other hand, the SII-IMDC model that incorporated the SII criterion in place of neutrophil and platelet counts was found to have all five variables significantly influencing survival (Table 2). Within the SII-IMDC model, 166 (33.1%) patients with no adverse factors were in the favorable-risk group in which a median OS was 45.0 months (95% CI 35.2–60.3 months). 274 (54.6%) patients with 1–2 adverse factors were in the intermediate-risk group in which a median OS was 24.8 months (95% CI 19.9–28.0 months). Finally, 62 (12.4%) patients with 3–5 adverse factors were in the poor-risk group in which a median OS was 7.2 months (95% CI 5.4–11.8 months, Fig. 1b).

All prognostic accuracy measures favored the SII-IMDC model over the IMDC model. For individual risk factors, concordance index was 0.679 (95% CI 0.646–0.712) versus 0.661 (95% CI 0.628–0.694), BIC was 3437 versus 3451, and generalized R^2 was 0.181 versus 0.169, respectively. For the three risk groups, concordance index was 0.644 (95% CI 0.613–0.675) versus 0.626 (95% CI 0.595–0.657), BIC was 3450 versus 3464, and R^2 was 0.129 versus 0.104, respectively. The SII-IMDC model was slightly better calibrated than the IMDC model (Figs. S1 and S2). In total, the risk group did not change in 435 (86.5%) patients after switching from the IMDC model to the SII-IMDC model, while it was decreased by 1 category in 62 (12.3%) patients and increased by 1 category in 6 (1.2%) patients (Fig. S3). IDI was 0.008 ($P=0.729$) and 0.019 ($P=0.224$) for individual risk factors and the three risk groups, respectively; cNRI was 0.144 ($P=0.048$) and 0.051 ($P=0.112$) for individual risk factors and the three risk groups, respectively (Table S2).

Discussion

Numerous studies have revealed an immunogenic nature of renal cell carcinoma [15, 16]. This character may be described by antitumor efficacy of immune-related compounds used in mRCC treatment as well as by the impact of tumor infiltrating cells and their secretions on clinical outcomes. Interleukin-2 (IL-2) stimulates T cell proliferation and differentiation while IFNα promotes antigen presentation and dendritic cell maturation. Both cytokines were used in the pre-MTT era with no survival benefit proven; however, IL-2 had a potential of durable, but infrequent responses [17]. Recently, a comeback of immunotherapy based on checkpoint inhibitors is observed. PD-1 and CTLA-4 suppress the cytokine release and the cytotoxic activity of T cells and this blockade is reversed by nivolumab and ipilimumab [3, 18]. On the other hand, the presence of intratumoral neutrophils is associated with shorter survival in patients with localized and metastatic disease [19, 20]. The tumor infiltrating neutrophils promote renal cell carcinoma progression via VEGFa/hypoxia inducible factor 2α and estrogen receptor β signal pathways [21]. Patients whose tumor tissue expresses high levels of lymphocytic attractant chemokines have favorable outcomes while high level of intratumoral CD45RO+ memory T cells is independently associated with poor prognosis [22, 23]. Platelets are known to regulate the processes of cancer invasion, migration, angiogenesis, and immunomodulation through secretion of numerous molecules, including metalloproteinases, growth factors and chemokines [24, 25]. The assessment of such factors, however, requires advanced and expensive methods, thus it is not probable they will serve for a routine survival prediction [26].

There is no direct evidence that immune cells collected from peripheral blood samples are representative to those found in tumor microenvironment. Nevertheless, neutrophil, platelet, and lymphocyte counts as well as their combinations were found to influence survival of patients with mRCC [4, 7, 8, 26, 27]. Recently, Lolli et al. reported that the SII was strongly associated with clinical outcomes in 335 patients treated with first-line sunitinib. The median OS was 43.6 months in patients with low (< 730) SII and 13.5 months in those with high (≥ 730) SII [9]. Bir Yucel et al. found that the median OS in patients with low (< 844) pre-treatment SII was twice as long as in those with high (> 844) SII (22 versus 11 months, respectively) [28]. In a cohort of 346 patients treated with subsequent-line nivolumab, De Giorgi et al. showed that 1-year survival rate was 77% and 36% in low (< 1375) and high (≥ 1375) SII groups [29]. However, it might be difficult to translate those results into practice because all these studies used different cut points for the SII and did not include the SII status in a modeling process to seek for potential improvement in prognostic accuracy of the IMDC model, which is a principal tool for survival prediction in the MTT era.

To answer our research questions with preservation of fully external validation character, we did not calculate the best SII cut point from our dataset, but we took a value of 730 proposed by Lolli et al. because this author and our cohorts were quite similar: all patients received TKI as initial therapy, more than 90% of patients had clear cell histology and presented KPS score of 80–100%. The distribution of patients within the IMDC risk groups was also comparable: assignment to favorable-, intermediate- and poor-risk groups was observed in 40.4%, 51.0% and 8.6% our patients and in 35.0%, 52.5% and 12.5% patients in Lolli et al. study.

The proportion of patients with high (≥730) SII was around 40% in the two studies. Hazard ratio for the SII status ranged from 1.38 to 1.68 in our study and was a little bit lower than the hazard ratio of 1.84 reported by Lolli et al. What is important in our study is that the regression analysis not only confirmed significant impact of the SII status on OS, but also showed weaker influence of neutrophil and platelet counts on the outcome. Additionally, the proposed five-factor SII-IMDC model performed slightly better than the IMDC model in terms of all prognostic accuracy measures.

A noteworthy limitation of the present study is its retrospective design and the collection of the data from only two centres. However, the number of patients exceeding 500 and the similarity of patient characteristics and survival outcomes in our and Lolli et al. studies increase the reliability of the current research. Nevertheless, we are aware that our findings need to be confirmed in a multicentre study of patients treated with checkpoint inhibitors to be a practice-changing for survival prediction in the forthcoming era of immune-oncology agents in mRCC.

Conclusions

The SII with a threshold of 730 is now a validated prognostic factor in patients with mRCC treated with first-line TKIs. The implementation of the SII in place of neutrophil and platelet counts within the IMDC model results in more accurate prediction about patient survival than the prediction obtained with the original IMDC criteria. Validation of the SII-IMDC model in patients treated with modern immunotherapy is pending.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The local ethics committee approved the study (Agreement no. 1/WIM/2014).

Informed consent The individual informed consent was not required due to retrospective nature of the study.

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