The relationship between systemic immune inflammation index and survival in patients with metastatic renal cell carcinomatreated with tyrosine kinase inhibitors

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This study aims to investigate the prognostic value of the systemic immune-inflammation index (SII) and its impact on survival in patients with metastatic renal cell carcinoma (mRCC). A total of 706 patients with mRCC treated with tyrosine kinase inhibitors (TKIs) between January 2007 and June 2020 (i.e., sunitinib, pazopanib) were included in this study. SII was calculated in 621 patients with the following formula: [neutrophil (cells x 10^9/L) x platelet (cells x 10^9/L)] / lymphocyte (cells x 10^9/L).

All patients were classified into SII-high and SII-low groups based on the cut-off value of SII at 756, which was the median SII level of our study group. The minimal follow-up duration was 10 months in all cohorts. The median age of patients was 60 (interquartile range (IQR): 53–67) years. Three out of four patients were male. The majority of patients (85.7%) had clear cell histology, and sarcomatoid differentiation was observed in 16.9% of all patients. There were 311 and 310 patients in the SII-low and SII-high groups, respectively. In general, baseline characteristics were similar in each group. However, the rate of patients treated with sunitinib (63.3% vs. 49.0%, \( p < 0.001 \)) and those who underwent nephrectomy (83.6% vs. 64.2%, \( p < 0.001 \)) was higher in the SII-low group than in the SII-high group. On the other hand, patients with the IMDC poor risk (31.6% vs. 8.0%, \( p < 0.001 \)), those with bone (51.8% vs. 32.2%, \( p < 0.001 \)) or central nervous system (12.9% vs. 5.8%, \( p = 0.026 \)) metastasis, and those with Eastern Cooperative Oncology Group (ECOG) 2–4 performance score (28.1% vs. 17.7%, \( p = 0.045 \)) had higher SII levels.

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Renal cell carcinoma (RCC) accounts for 90–95% of all kidney cancers. In 2020, about 3% of all adult malignancies with an estimated 431,288 new RCC cases were observed across the world. More than 30% of patients diagnosed with RCC need systemic therapy for metastatic disease. In the last decade, huge improvements have been observed in the RCC treatment. Thus, immune checkpoint inhibitor (ICI) or ICI plus tyrosine kinase inhibitor (TKI) combinations improved survival in patients with metastatic RCC (mRCC).

In parallel to the improvements in the treatment of mRCC, prognostic risk tools became essential during the decision-making process in the treatment of mRCC patients. Thus, the International Metastatic RCC Database (IMDC) risk model is the standard for prognostic stratification of patients with mRCC treated with targeted therapies or ICIs. The IMDC risk score is calculated by the following six parameters: Karnofsky performance status, time from diagnosis to the first systemic treatment, hemoglobin concentration, neutrophils, platelets, and corrected calcium levels. Although the IMDC is a commonly used prognostic scoring system, efforts to find a novel scoring system with fewer parameters are still continuing. Inflammatory-related peripheral cells (e.g., neutrophils, lymphocytes, platelets) derived from the peripheral blood were associated with tumor progression in various tumors. The prognostic significance of inflammatory cell parameters, such as neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), C-reactive protein/albumin ratio, and systemic immune inflammation index (SII), were examined in many cancer types over the last ten years. SII is a combination based on the peripheral lymphocyte, neutrophil, and platelet counts. After Hu et al. showed its prognostic value in 2014, many studies established that SII could be a good prognostic marker in many cancer types.

In this retrospective analysis, we aimed to evaluate the prognostic significance of SII in patients with mRCC treated with TKIs.

**Methods**

The local ethical committee (Ankara University Faculty of Medicine Human Research Ethics Committee, approval number: 01-79-19) approved this retrospective cohort study. Informed consent was waived by “Ankara University Faculty of Medicine Human Research Ethics Committee” due to the retrospective nature of the study. This study was conducted in compliance with the “Declaration of Helsinki”.

**Patient population and data extraction.** The Turkish Oncology Group Kidney Cancer Consortium (TKCC) database consists of approximately 1,000 patients aged 18 years and older with mRCC from 13 cancer centers in Turkey. Patients with mRCC treated with sunitinib or pazopanib in the first-line setting were extracted from the TKCC database. Patients treated with TKIs between January 2007 and June 2020 were included in the study. The minimum follow-up duration in all patients was 10 months.

Demographic data (e.g., date of birth, gender, comorbidities, medications), date of diagnosis with RCC, the initial date of systemic treatment in the metastatic setting, Eastern Cooperative Oncology Group (ECOG) performance score, laboratory findings (e.g., neutrophil, platelet, lymphocyte counts, hemoglobin concentration, corrected calcium level), start and end dates of TKIs, and dates of progression and death were extracted from the TKCC database.

SII was calculated by using the following formula: [neutrophil (cells x 10⁹/L) x platelet (cells x 10⁹/L)] / lymphocyte (cells x 10⁹/L). All values were obtained from a complete blood count (CBC) up to 30 days before the first dose of TKIs. If there were more than one CBC result, the closest one to the initiation of TKI was used. The best cut-off value for SII was determined by using the median value of 756. In this regard, patients were divided into two groups: SII-high (≥756) and SII-low (<756). The primary outcome was overall survival (OS), and the secondary outcome was progression-free survival (PFS).

**Statistical analyses.** To summarize data, median with interquartile range (IQR) or mean with standard deviation and percentages were used for continuous and categorical variables, respectively. The independent sample *t*-test or Mann–Whitney U and chi-square tests were performed to compare continuous and categorical variables, respectively. Survival curves were estimated using the Kaplan–Meier method, and the differences between groups were analyzed by using log-rank test. Cox proportional hazards regression model was used for multivariable analyses of parameters associated with OS and PFS. OS was calculated from the initial date of TKIs to death. PFS was calculated from the initial date of TKI to disease progression or death. Hazard ratio (HR) and 95% confidence interval (CI) were used to describe the risk factors. Harrell’s concordance index (C-index) was calculated to compare the predictive value of SII and the IMDC risk scores for OS and PFS. Differences were considered significant if the p-value was less than 0.05. All statistical analyses were performed using the SPSS 27.0 for Mac (IBM Corp., Armonk, NY).

$\rho = 0.002$ were more common in the SII-high group than in the SII-low group. The median overall survival (OS) was longer in the SII-low group than in the SII-high group (34.6 months vs. 14.5 months, $\rho < 0.001$). Similarly, the median progression-free survival (PFS) was longer in the SII-low group than in the SII-high group (18.0 months vs. 7.7 months, $\rho < 0.001$). In multivariable analysis, SII was an independent prognostic factor for OS (hazard ratio (HR): 1.39, 95% confidence interval (CI): 1.05–1.85, $\rho = 0.001$) and PFS (HR: 1.60, 95% CI: 1.24–2.05, $\rho < 0.001$). Pre-treatment level of high SII might be considered a predictor of poor prognosis in patients with mRCC treated with TKIs.
Results

Baseline characteristics. A total of 706 patients with mRCC were included in this study and SII was calculated in 621 patients. The median age of patients was 60 (IQR: 53–67) years. Three out of four patients were male. Most patients (85.7%) had clear cell histology, and 16.9% of all patients had sarcomatoid differentiation. The ECOG PS was 0 or 1 in most patients (83.5%). Approximately one out of four patients were in the IMDC poor-risk group, 404 (57.2%) and 302 (42.8%) patients were treated with sunitinib and pazopanib, respectively. Approximately half of the patients received interferon before TKI treatment. About three out of four patients underwent nephrectomy before starting systemic treatment. The lung was the most common metastatic site (51.4%).

There were 311 and 310 patients in the SII-low and SII-high groups, respectively. The rate of patients who underwent nephrectomy was higher in the SII-low group than in the SII-high group (83.9% vs. 64.4%, \( p < 0.001 \)). Similarly, the rate of patients treated with sunitinib was higher in the SII-low group than in the SII-high group (63.3% vs. 49.0%, \( p < 0.001 \)). The IMDC poor-risk patients’ rate was higher in the SII-high group than in the SII-low group (34.6% vs. 8.8%, \( p < 0.001 \)).

Survival outcomes.

At the median follow-up of 48.6 months, the median OS and PFS were 26.1 months (95% CI: 22.5–29.7) and 11.9 months (95% CI: 10.5–13.3), respectively. The median OS was longer in the SII-low group than in the SII-high group (34.6 months vs. 14.5 months, \( p < 0.001 \)). Similarly, the median PFS was longer in the SII-low group than in the SII-high group (18.0 months vs. 7.7 months, \( p < 0.001 \)). Kaplan–Meier estimates of OS and PFS are shown in Figs. 1, 2.

After adjusting for confounding factors (age, sarcomatoid feature, nephrectomy, systemic treatment with sunitinib or pazopanib, anemia, hypercalcaemia, LDH elevation, ECOG PS, time from diagnosis to systemic treatment, the total number of systemic treatment (except for IFN), and presence of bone or central nervous system (CNS) metastasis for OS; sarcomatoid feature, nephrectomy, anemia, hypercalcaemia, LDH elevation, ECOG PS, time from diagnosis to systemic treatment, and presence of bone or CNS metastasis for PFS), SII was an independent prognostic factor for OS (HR: 1.41, 95% CI: 1.06–1.87, \( p = 0.018 \)) and PFS (HR: 1.64, 95% CI: 1.28–2.10, \( p < 0.001 \)). Uni- and multivariable analyses of OS and PFS are shown in Tables 2, 3.

In the subgroup analysis of patients who were not treated with IFN, the median OS was longer in the SII-low group than in the SII-high group (36.4 months vs. 16.6 months, \( p = 0.001 \) in patients previously untreated with interferon). Similarly, the median PFS was also longer in the SII-low group than in the SII-high group (19.7 months vs. 8.1 months, \( p < 0.001 \)).

Harrell’s C-index with SII, IMDC, and MSKCC risk scores was 0.60, 0.63, 0.63 for OS, and 0.59, 0.60, 0.61 for PFS, respectively.

Discussion

In this multicenter study, we investigated the prognostic value of SII in patients with mRCC treated with TKIs. To the best of our knowledge, our study has the largest number of patients among studies examining the relationship between SII and survival outcomes in patients with mRCC. The results showed that low (\(< 756\)) and high (\(\geq 756\)) SII levels had a statistically significant difference in terms of OS and PFS. Thus, SII might have a prognostic value in patients with mRCC treated with TKIs.

Many previous studies have widely investigated the relationship between inflammation and cancer. Inflammatory cells (e.g., neutrophils, macrophages, lymphocytes) and cytokines are effective in transformation, proliferation, and metastasis in all tumor stages. Neutrophils can secrete cytokines related to the stimulation of the tumor microenvironment and have a tumor-promoting activity, including cancer cell survival and proliferation, angiogenesis, and metastasis. Conversely, lymphocytes inhibit tumor cell proliferation by secreting cytokines. On the other hand, platelets regulate cancer invasion, migration, and angiogenesis by secretion of numerous chemokines and growth factors. In 2014, Hu et al. developed SII to predict the prognosis of patients who underwent curative resection for hepatocellular carcinoma and established that a high SII score (>330 \(\times 10^9\) cells/L) went curative resection for hepatocellular carcinoma and established that a high SII score (>330 \(\times 10^9\) cells/L) increased the accuracy of the IMDC risk model.

It should be noticed that they also used a cut-off value of 730 \(\times 10^9\) cells/L, which is almost the same as our study. In 2014, Hu et al. developed SII to predict the prognosis of patients who underwent curative resection for hepatocellular carcinoma and established that a high SII score (>330 \(\times 10^9\) cells/L) increased the accuracy of the IMDC risk model. It should be noticed that they also used a cut-off value of 730 \(\times 10^9\) cells/L for SII, which is almost the same as our study.

The studies concluded that SII was an accurate prognostic marker irrespective of disease stage in RCC patients. The studies concluded that SII was an accurate prognostic marker irrespective of disease stage in RCC patients. The studies concluded that SII was an accurate prognostic marker irrespective of disease stage in RCC patients. The studies concluded that SII was an accurate prognostic marker irrespective of disease stage in RCC patients.
Furthermore, as a result of efforts to find a novel prognostic marker in patients with mRCC, Başal et al. showed that SII could predict survival in each IMDC risk group. Our survival results were also compatible with the pivotal study of sunitinib, including previously untreated patients with mRCC. They reported that the median OS was 26.4 months and PFS was 11 months in patients with mRCC receiving sunitinib, which was also numerically close to our study's survival results.

### Table 1. Baseline characteristics.

|                      | All patients | SII-low patients | SII-high patients | p  |
|----------------------|--------------|------------------|-------------------|----|
| Age-years, median (IQR) | 60 (53–67)  | 60 (53–69)       | 60 (53–70)        | 0.710 |
| Sex                  |              |                  |                   | 0.317 |
| Male                 | 531          | 229              | 73.6              | 239  |
| Female               | 175          | 82               | 26.4              | 71   |
| Histological Type    |              |                  |                   | 0.196 |
| Clear Cell           | 563          | 241              | 77.5              | 257  |
| Non-clear Cell       | 94           | 46               | 14.8              | 36   |
| Missing              | 49           | 24               | 7.7               | 17   |
| Sarcomatoid Feature  |              |                  |                   | 0.830 |
| Yes                  | 83           | 35               | 11.3              | 39   |
| No                   | 407          | 182              | 58.5              | 192  |
| Missing              | 216          | 94               | 30.2              | 79   |
| Fuhrman Grade        |              |                  |                   | 0.076 |
| 1–2                  | 124          | 63               | 20.3              | 43   |
| 3–4                  | 297          | 129              | 41.4              | 133  |
| Missing              | 285          | 119              | 38.3              | 134  |
| Previous Nephrectomy |              |                  |                   | <0.001 |
| Yes                  | 525          | 260              | 83.6              | 199  |
| No                   | 177          | 50               | 16.1              | 110  |
| Missing              | 4            | 1                | 0.6               | 1    |
| Systemic Treatment   |              |                  |                   | <0.001 |
| Sunitinib            | 404          | 197              | 63.3              | 152  |
| Pazopanib            | 302          | 114              | 36.7              | 158  |
| IMDC Risk            |              |                  |                   | <0.001 |
| Favorable            | 116          | 83               | 26.7              | 33   |
| Intermediate         | 332          | 175              | 56.3              | 152  |
| Poor                 | 128          | 25               | 8.0               | 98   |
| Missing              | 130          | 28               | 9.0               | 27   |
| MSKCC Risk           |              |                  |                   | <0.001 |
| Favorable            | 91           | 64               | 20.6              | 27   |
| Intermediate         | 279          | 148              | 47.6              | 128  |
| High                 | 87           | 27               | 8.7               | 59   |
| Missing              | 249          | 72               | 23.2              | 96   |
| Previous Cytokine Use|              |                  |                   | 0.032 |
| Yes                  | 334          | 152              | 48.9              | 125  |
| No                   | 372          | 159              | 51.1              | 185  |
| Metastatic Sites     |              |                  |                   | <0.001 |
| Lung                 | 319          | 161              | 51.8              | 158  |
| Bone                 | 259          | 100              | 32.2              | 159  |
| Liver                | 92           | 42               | 13.5              | 50   |
| CNS                  | 58           | 18               | 5.8               | 40   |
| Performance Status   |              |                  |                   | 0.026 |
| ECOG 0–1             | 515          | 243              | 78.1              | 207  |
| ECOG 2–3–4           | 149          | 55               | 17.7              | 87   |
| Missing              | 42           | 13               | 4.2               | 16   |

ECOG eastern cooperative oncology group, IMDC international metastatic renal cell carcinoma database consortium, IQR interquartile range, MSKCC memorial sloan kettering cancer center. Significant values are in bold.
Our study has several limitations due to its retrospective nature. First, we had a lack of data to calculate SII in some patients. Because of this reason, we had to exclude those patients from our study. Second, the time interval between obtaining laboratory values to calculate SII and the initial date of TKIs might be different in each included center. Third, mRCC patients treated with interferon before TKI treatment were included in our study. ICI plus TKI or ICI plus ICI combinations are accepted as the standard of care in the first-line treatment of patients with mRCC. Although combinations are considered standard treatment, there is still a subgroup of patients who benefit from TKI alone. ICI plus TKI studies concluded that no clear difference between the sunitinib and combination arms in survival outcomes in the IMDC favorable risk group. All these findings suggest that we cannot completely abandon TKIs in the treatment of patients with mRCC.

**Figure 1.** Kaplan-Meier estimates of overall survival (OS). SII systemic immune inflammation index.

**Figure 2.** Kaplan-Meier estimates of progression-free survival (PFS). SII systemic immune inflammation index.
In conclusion, our study showed the prognostic value of SII in mRCC patients treated with TKIs. In this context, SII, an easily accessible marker, might lead to establishing novel therapeutic strategies or risk models in patients with mRCC treated with TKIs. Although studies evaluated prognostic effect of SII on patients treated with ICI, the relationship of ICIs plus TKIs combinations with SII has not been investigated yet. SII may be a potential prognostic marker for RCC patients treated with ICI and TKIs combination from a future perspective.

Table 2. Univariable and multivariable analysis of overall survival. CI confidence interval, CNS central nervous system, ECOG eastern cooperative oncology group, LDH lactate dehydrogenase, SII systemic immune-inflammation index. Significant values are in bold. *Except for interferon.
Table 3. Univariable and multivariable analysis of progression-free survival. CI confidence interval, CNS central nervous system, ECOG eastern cooperative oncology group, LDH lactate dehydrogenase, SII systemic immune-inflammation index. Significant values are in bold.

| Variable                        | Univariable hazard ratio | 95% CI     | p     | Multivariable hazard ratio | 95% CI     | p     |
|---------------------------------|--------------------------|------------|-------|-----------------------------|------------|-------|
| Age                             |                          | 0.116      |       |                             |            |       |
| < 65                            | 1                        |            |       |                             |            |       |
| ≥ 65                            | 1.15                     | 0.96–1.37  |       |                             |            |       |
| Sarcomatoid Feature             | 0.006                    | 0.013      |       |                             |            |       |
| No                              | 1                        |            |       |                             |            |       |
| Yes                             | 1.45                     | 1.11–1.89  | 0.49 | 1.08–2.04                   | 0.49       | 1.08–2.04 |
| Nephrectomy                     | < 0.001                  | 0.142      |       |                             |            |       |
| No                              | 1.77                     | 1.46–2.14  | 1.26 | 0.92–1.73                   | 1.26       | 0.92–1.73 |
| Yes                             | 1                        |            |       |                             |            |       |
| Systemic Treatment              | 0.289                    |            |       |                             |            |       |
| Sunitinib                       |                          |            |       |                             |            |       |
| Pazopanib                       | 0.91                     | 0.76–1.08  | 0.79 | 0.62–1.06                   | 0.79       | 0.62–1.06 |
| Anemia                          | < 0.001                  | 0.008      |       |                             |            |       |
| No                              | 1                        |            |       |                             |            |       |
| Yes                             | 1.65                     | 1.38–1.98  | 1.39 | 1.09–1.79                   | 1.39       | 1.09–1.79 |
| Hypercalcemia                   | 0.001                    | 0.565      |       |                             |            |       |
| No                              | 1                        |            |       |                             |            |       |
| Yes                             | 1.79                     | 1.25–2.57  | 1.15 | 0.70–1.91                   | 1.15       | 0.70–1.91 |
| LDH Elevation                   | 0.010                    | 0.848      |       |                             |            |       |
| No                              | 1                        |            |       |                             |            |       |
| Yes                             | 1.44                     | 1.09–1.91  | 1.04 | 0.64–1.70                   | 1.04       | 0.64–1.70 |
| ECOG Performance Score          | < 0.001                  |            |       |                             | < 0.001    |         |
| ECOG 0–1                        | 1                        |            |       |                             | 1          |       |
| ECOG 2–3–4                      | 2.24                     | 1.84–2.74  | 1.82 | 1.37–2.41                   | 1.82       | 1.37–2.41 |
| Time to Systemic Treatment      | < 0.001                  | 0.937      |       |                             |            |       |
| < 1 year                        | 1.51                     | 1.26–1.82  | 1.01 | 0.75–1.34                   | 1.01       | 0.75–1.34 |
| ≥ 1 year                        | 1                        |            |       |                             | 1          |       |
| Previous Cytokine Use           |                          | 0.567      |       |                             |            |       |
| No                              | 1                        |            |       |                             |            |       |
| Yes                             | 1.05                     | 0.88–1.24  | 0.89 | 0.69–1.14                   | 0.89       | 0.69–1.14 |
| Bone or CNS Metastasis          | < 0.001                  | 0.552      |       |                             |            |       |
| No                              | 1                        |            |       |                             | 1          |       |
| Yes                             | 1.48                     | 1.25–1.75  | 1.07 | 0.84–1.38                   | 1.07       | 0.84–1.38 |
| SII                             | < 0.001                  | < 0.001    |       |                             | 0.01       | 0.01  |
| Low                             | 1                        |            |       |                             | 1          |       |
| High                            | 1.66                     | 1.38–2.00  | 1.64 | 1.28–2.10                   | 1.64       | 1.28–2.10 |

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