Inflammatory prognostic index score as a new parameter predicting overall survival in renal cell carcinoma

Ahmet Dirican 1, Ferhat Ekinci 2, Atike Pınar Erdoğan 2, Gamze Gökşel Öztürk 2

1Department of Medical Oncology, Izmir University of Economics, Medicalpark Hospital, Izmir, Turkey
2Celal Bayar University, Department of Medical Oncology, Manisa, Turkey

Abstract

Background/Aim: The importance of prognostic markers in the treatment and follow-up of metastatic renal cell carcinoma is gradually increasing. Currently used markers do not meet the exact needs in this regard. In this study, we evaluated the predictive and prognostic values of inflammatory prognostic index (IPI) scoring in metastatic Renal cell carcinoma (RCC) patients. In IPI scoring, we used four biochemical parameters related to inflammation, including albumin, CRP, neutrophils, and lymphocytes.

Methods: Medical records of fifty-seven patients with RCC treated in Celal Bayar University Medical Faculty Hospital Medical Oncology Clinic between February 2012 and April 2019 were retrospectively reviewed. The IPI was calculated as C-reactive protein × NLR (neutrophil/lymphocyte ratio)/serum albumin. Univariate and multivariate analyses were performed to assess the prognostic value of relevant factors.

Results: The cut-off value for IPI in predicting mortality was 1.03 according to ROC curve analysis. Median OS of the patients with IPI ≥1.03 was 8 months (95 %CI 3-10.9). The relationship between overall survival and IPI score was remarkable. According to this analysis, comorbidity, metastasis to the lung, liver, lymph nodes, bone, the number of metastatic sites (one metastatic area), high NLR, high IPI were also significantly associated with OS (P<0.05 for each). In multivariate analyses, IPI was an independent prognostic factor in RCC. Patients with high IPI (>1.03) had an increased mortality risk compared to those with low IPI (<1.03) (HR: 8.5; 95 %CI, 2.303-31.42; P<0.001). Comorbidity, lung metastasis, lymph nodes and bone metastasis, high NLR, IMDC risk also independently predicted worse OS in RCC.

Conclusion: The relationship between many inflammatory markers, such as NLR and RCC, and overall survival was proven earlier, while the relationship with IPI is discussed for the first time. We would like to discuss the findings we obtained in our study in the light of other analyses in the literature investigating the relationship between other inflammation markers and RCC, IPI may be an easily accessible and independent prognostic index for RCC patients, and useful for clinical practice.

Keywords: Renal cell carcinoma, IPI scoring, Overall survival, Neutrophil/lymphocyte ratio, Inflammation mediators, C-reactive protein, Albumin
Introduction

Renal cell carcinoma (RCC) is the most common renal malignancy, and most originate from the renal parenchyma. Due to the lack of routine screening tests and late manifestation, it is often diagnosed at advanced stages. Most patients remain asymptomatic until later stages of the disease [1-3]. Therefore, as with most cancers, RCC misses the chance of surgery, which is the main curative treatment. In stage I RCC patients, the five-year disease-specific survival is about 80-95%, while in stage IV patients this rate is less than 10%, and the average overall survival is 10-15 months [3, 4].

The disease recurrence or metastasis in cancer depends on the complex relationship between the tumor and the inflammatory response established with the host [5]. In fact, the existence of this relationship was shown by Virchow for the first time in the 19th century. He observed leukocytes in the tumoral tissue and that cancer was more frequent in chronic inflammation sites [6]. However, the central role of inflammation in tumor formation was revealed more prominently with the research conducted in the last 15 years [7, 8]. Inflammation mediators are important components of the tumor microenvironment, especially in some cancers, and m inflammatory changes may occur before or after oncogenic changes. Inflammatory microenvironment in the tumor engages in angiogenesis or metastasis [8]. Some oncogenes are also mediated, and the tumor environment is rearranged [9, 10]. Hypoxia and lacking nutrients lead to necrotic cell death within the tumor nucleus. This leads to the release of proinflammatory cytokines from the tissue [10, 11]. DNA damage and genomic instability can be induced indirectly because of the mediators produced in case of inflammation [6, 12, 13]. DNA mismatch can also cause inactivation and suppression of repair genes, causing mutagenic effects. That and similar other mechanisms explain the relationship of inflammation and oncogenic mutations [6, 14]. T and NK cells activated because of tumorigenicity have anti tumoral properties with cytotoxic effect. In the tumor tissue developed due to inflammation, the pro-tumorigenic structure is induced by the triggering of the inflammatory cells, while the anti-tumorigenic effect continues with the cellular immune elements. Despite this dual mechanism, the net effect is often tumor growth and progression [15].

The most common indicators of inflammatory response in cancer patients are a number of biochemical or hematological markers [16]. The most used are C-reactive protein, white cell, neutrophil and platelet count, and low albumin [17, 18]. These values have many uses, such as calculating neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (TLR), Glasgow Prognostic Score (using C-reactive protein and albumin) for prediction of disease recurrence, prognosis, and response to treatment [19]. In a study published by Dirican et al. [20], non-small cell lung cancer (NSCLC) patients’ survival was predicted by inflammatory prognostic index (IPI) using the level of C-reactive protein, NLR and Serum Albumin. In the light of this data, we think that there is a need for simple and accessible markers that can both predict postoperative recurrence in RCC and consequently establish a relationship with survival. For this reason, the main purpose of our study is to analyze the predictive
and prognostic value of IPI in metastatic RCC patients in addition to other markers currently used.

Materials and methods

Medical records of patients with RCC treated in Celal Bayar University Medical Faculty Hospital Medical Oncology Clinic between February 2012 and April 2019 were retrospectively reviewed. Of these patients, those in the metastatic stage and those with sufficient follow-up data were included in the study as a retrospective cohort. Clinicopathologic variables such as age, gender, performance status (PS), treatments, histopathology type, localization of metastasis, Comorbidity, International Metastatic RCC Database Consortium (IMDC) risk classification were recorded by an electronic medical record system. Patients’ performance statuses were noted based on the Karnofsky performance status scores. A total of 57 RCC patients were reviewed. Patients histologically diagnosed as RCC and staged according to the TNM criteria were included. Only metastatic patients were analyzed. The initial treatment modalities included operation, chemotherapy, targeted therapy, immunotherapy, and best supportive care. Other factors that could shorten survival were not excluded from the study to prevent bias (co-morbidity etc.). Patients who were under metastatic RCC treatment for a brief time and had to quit due to side effects or progression were included in the study. This study was approved by Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee with the decision number 20.478.486 dated 27/11/2019.

Laboratory data collection

Neutrophil, lymphocyte, hemoglobin level and biochemical parameters such as serum albumin, calcium level and CRP were recorded. IPI was calculated with the following formula: CRP × NLR / serum albumin.

Statistical analysis

A Kaplan-Meier analysis with log-rank test was performed to determine cumulative survival curves. Univariate and multivariate analyses for survival difference were performed using the Cox proportional hazards model and were expressed as hazard ratios (HRs) and 95% CIs. Overall survival (OS) was calculated from the metastasis diagnosis of the patient to either the date of death from any cause or the date of the last follow-up. Progression free survival (PFS) was calculated as the interval between the diagnosis and the progression of the disease, recurrence, or death from any cause. Categorical variables were presented as the number of patients and percentages and compared using Chi-square or Fisher’s exact test with odds ratio (OR), within a 95% confidence interval (CI). Receiver Operating Characteristics (ROC) curve analysis was used to determine the cut-off value for NLR and IPI. Tumor response was assessed according to response evaluation criteria in solid tumors (RECIST). Statistical analyses were performed using SPSS 18.0 software (SPSS Inc. Chicago, IL). All statistical assessments were two-sided and a P-value of 0.05 was considered statistically significant.
**Results**

**Patient characteristics**
A total of fifty-seven mRCC patients were evaluated retrospectively. Among all, 71.9% (41) were male, and 28.1% (16) were female. The median age was 57 (range 21-78) years. Patients with at least one metastatic lesion were included in the study. Three patients (13%) had metastasis at diagnosis. Other clinical and pathological features are shown in Table 1. Patients were grouped according to IMDC risk classification. The favorable, intermediate, and poor risk groups had 7 (12.3%), 35 (61.4%) and 15 (26.3%) patients, respectively.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Median age (range)</th>
<th>Male</th>
<th>Female</th>
<th>Histological type</th>
<th>Clear cell</th>
<th>Non-clear cell</th>
<th>Localization of metastasis</th>
<th>Lung</th>
<th>Liver</th>
<th>Brain</th>
<th>Bone</th>
<th>Lymph nodes</th>
<th>Other</th>
<th>Number site of metastasis</th>
<th>IMDC</th>
<th>Sex</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>57</td>
<td>37 (21-78)</td>
<td>41 (71.9)</td>
<td>16 (28.1)</td>
<td>38 (66.7)</td>
<td>18 (31.6)</td>
<td>39 (68.4)</td>
<td>22 (38.6)</td>
<td>5 (8.8)</td>
<td>18 (31.6)</td>
<td>43 (75.4)</td>
<td>21 (36.8)</td>
<td>13 (22.8)</td>
<td>20 (35.1)</td>
<td>24 (42.1)</td>
<td>7 (12.3)</td>
<td>35 (61.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>57</td>
<td>37</td>
<td>41</td>
<td>16</td>
<td>38</td>
<td>18</td>
<td>39</td>
<td>22</td>
<td>5</td>
<td>18</td>
<td>43</td>
<td>21</td>
<td>13</td>
<td>20</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>

**Treatment**

Of the patients, 82.5% (47) received first-line treatment, 42.1% (24) received second-line treatment, and 26.3% (15) received third-line treatment. The treatments received by the patients were interferon (n=12), sunitinib (n=33), pazopanib (n=9), axitinib (n=12), everolimus (n=9), and nivolumab (n=7). These are all the standard treatments our patients receive.

**Survival analysis**

The NLR cut off value was 2.77. The median OS of 36 (63.2%) patients was 52 months (95% CI 15.3-88.6) with NLR <2.77 and median OS of 21 (36.8%) patients was 8 months (95% CI 3.4-12.5) with NLR ≥2.77 (Figure 1). The cut off value for IPI was 1.03. The median OS of 19 (33.3%) patients was NR (not reached) with IPI <1.03 and median OS of 38 (66.7%) patients was 8 months (95% CI 3.4-12.5) with IPI ≥1.03 (Figure 2). The median OS of 7 (12.3%) patients in the favorable risk group, 35 patients (61.4%) in the intermediate risk group and 15 patients (26.3%) in the poor risk group were 49 months, 41 months, and 2 months, respectively (P=0.022). Comorbidity, lung metastasis, liver metastasis, lymph node metastasis, bone metastasis, number of metastatic sites (one metastatic area), high NLR, high IPI were also significantly associated with OS. However, OS did not differ in terms of age (P=0.797), gender (P=0.671), brain metastasis (P=0.575) and the number of metastatic sites (P=0.066 for two metastatic sites and P=0.136 for ≥3 metastatic sites). In multivariate analyses, IPI was an independent prognostic factor in RCC. Patients with high IPI (≥1.03) had increased mortality risk compared with those with low IPI (<1.03) (HR; 8.5; 95% CI; 2.303-31.42; P<0.001).

Comorbidity, lung, lymph node and bone metastasis, high NLR, IMDC risk also independently predicted worse OS in RCC. All multivariate survival analyses are presented in Table 2.

Table 2: Results of univariate and multivariate Cox’s proportional hazard models in terms of OS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.018 (0.981-1.051)</td>
<td>0.797</td>
</tr>
<tr>
<td>Sex</td>
<td>1.23 (0.469-3.241)</td>
<td>0.671</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>4.63 (1.720-12.495)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lung metastasis</td>
<td>3.42 (1.087-10.809)</td>
<td>0.035</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>3.98 (1.306-12.155)</td>
<td>0.155</td>
</tr>
<tr>
<td>Lymph nodes metastasis</td>
<td>0.16 (0.041-0.673)</td>
<td>0.012</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td>0.19 (0.082-0.623)</td>
<td>0.006</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>0.600 (0.106-3.404)</td>
<td>0.575</td>
</tr>
<tr>
<td>Other metastasis</td>
<td>1.78 (0.648-4.893)</td>
<td>0.263</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td>0.027</td>
<td>0.055</td>
</tr>
<tr>
<td>(one metastatic site, two metastatic sites and ≥3 metastatic sites)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(high risk, intermediate risk and poor risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLR</td>
<td>0.23 (0.025-1.100)</td>
<td>0.066</td>
</tr>
<tr>
<td>IMDC risk</td>
<td>3.08 (0.702-13.581)</td>
<td>0.136</td>
</tr>
<tr>
<td>NLR</td>
<td>3.601 (1.263-10.287)</td>
<td>0.017</td>
</tr>
<tr>
<td>High NLR</td>
<td>10.0 (2.596-38.523)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Discussion

The main purpose of our study was to analyze the predictive and prognostic value of IPI in metastatic RCC patients. In IPI scoring, we used four biochemical parameters related to inflammation, including albumin, CRP, neutrophils, and lymphocytes. The relationship of overall survival in RCC and NLR has been previously proven, while its relationship with...
IPI is discussed for the first time. We would like to discuss the findings we obtained considering the relationship between other inflammation markers and RCC.

The most recent meta-analysis was performed by Shen et al. in 2019 to investigate the prognostic value of neutrophil count in pretreatment metastatic renal cell carcinoma. In a total of thirteen studies, 3021 patients were included. An elevated pretreatment neutrophil count resulted in worse OS (HR: 2.17, 95% CI 1.68–2.79, \( P<0.001 \)) and PFS (HR: 1.78, 95% CI 0.91–3.49, \( P<0.001 \)). In view of the heterogeneity of the studies in this publication, it seems reasonable to consider the neutrophil count a common marker of inflammation [21]. The high neutrophil count was the basis of the proportional formula in our study. However, it was confirmed with other inflammation parameters [22,23]. We found that high NLR (≥2.77) and high IPI (≥1.03) were associated with decreased median OS. There are data proving that some of the neutrophil-related factors may induce genetic mutations in tumors or may secrete factors that promote tumor cell proliferation. Although the mechanism is not fully explained, neutrophils play a significant role in physiological angiogenesis, which may explain its key role in tumorigenesis [5,6,22]. There are studies showing that neutrophils have a prominent role in tumorigenesis, tumor cell proliferation and metastasis [6]. This makes it a key marker in the investigation of the relationship between inflammation and prognosis.

In a recent meta-analysis, which included twenty-four studies by Nunno et al., the relationship between NLR and both metastatic and localized RCC was investigated. A total of 10034 patients were included. A higher NLR was significantly associated with poor OS with a pooled HR of 1.57 (95% CI: 1.27–1.94) and 2.05 (95% CI: 1.74–2.41) in localized (n=1933) and metastatic (n=2318) patients, respectively. The same significance applies to PFS. Higher NLR resulted in worse PFS with a pooled HR of 1.69 (95% CI: 1.42–2.01) with a high level of heterogeneity. Higher NLR resulted in worse PFS with a pooled HR of 1.69 (95% CI: 1.42–2.01) in both localized (n=2656) and metastatic disease (n=1847). There are comparable results in our study in which high NLR is associated with poor survival rates. However, other parameters of inflammation were not included in this analysis. Although patient heterogeneity has been a problem in designing a meta-analysis, the substantial number of patients is an important advantage in this study [11]. In our study, the NLR cut-off value was 2.77. The short survival time in cases with high NLR and longer OS in those with low NLR were similar the study results in the literature [4,24].

CRP is a good indicator of inflammation because it is sensitive and responds more rapidly to changes in clinical status. Albumin is a negative acute phase reactant and a negative prognostic factor in cancer patients [4]. Using these two markers alone can predict prognosis in renal cell carcinoma. However, this index was an independent prognostic factor in many tumors, including kidney cancer [25]. In the study published in 2019 by T. Tsujino et al., C-reactive protein-albumin ratio (CAR) was studied as a prognostic factor in renal cell carcinoma. In that study, data obtained from studies involving 699 patients were analyzed. Five-year OS rates for patients in low and high CAR groups were 92.1% and 61.4%, respectively, illustrating a significant prognostic difference in terms of CAR among RCC patients (OS: \( P<0.001 \), in log-rank test). However, non-metastatic patients who underwent nephrectomy were included in this study. Similar results were observed in 72 patients who were subsequently metastatic. Two important aspects of this study are that it was conducted with two important parameters of inflammation that we use in IPI scoring and an elevated CAR was associated with shorter survival, and an independent predictor for OS [25].

In 2017, a study by Ishihara et al. investigated the role of systemic inflammatory markers including CRP, NLR and platelet/lymphocyte ratio (PLR) in predicting survival among sixty-three patients with metastatic renal cell carcinoma receiving second-line molecular-targeted therapy (mTT). The cut-off values of CRP, NLR and PLR were 0.48, 2.53 and 183, respectively. In patients with high CRP, NLR and PLR values, PFS and OS were significantly lower than those with low values. The major contribution of this study to the literature is that it is the first study to show that pre-treatment NLR and PLR values are closely related and patients with high CRP, NLR, and PLR values have shorter PFS and OS with second-line mTT after first-line TKI failure in mRCC [26]. In a study published in 2017 by Sekar et al. a new preoperative inflammatory marker prognostic score was studied in patients with localized and metastatic RCC. They suggested that a combination of specific inflammatory markers, called the RCC Inflammatory Score (RISK), can be a rigorous prognostic indicator of OS in RCC. Markers included in the scoring were CRP, albumin, erythrocyte sedimentation rate (ESR), corrected calcium and aspartate transaminase to alanine transaminase (AST/ALT) ratio. A total of 391 localized or metastatic patients who underwent nephrectomy were examined. Each patient was given a total RISK score of 0 to 10 based on the sum of 0, 1 or 2 individual biomarker scores (baseline risk (RISK 0), low risk (RISK 1-3), intermediate risk (RISK 4-6), and high risk (RISK 7-10). Median survival among the high-risk group was 7.2 months (95% CI: 4.9-11.4), which was 14.5 months (95% CI: 10.1-21.5) among the intermediate risk group (\( P=0.008 \)). However, median survival was not reached among the low-risk and baseline groups. An importance of this study for us is that a template has been developed to include all three parameters used in IPI scoring. On the other hand, NLR was proven as a marker of inflammation at RCC [27]. Dirican et al. [20] published a study showing the prognostic value of the combination of NLR, CRP and albumin formulated as an IPI score in NSCLC patients. This study remains the only publication in the literature on IPI. They found that high IPI (≥215) was an indicator of poor OS, leading to 3.47-fold increase in the mortality risk (\( P<0.001 \)). This encouraged us to study the same parameter in RCC, where more diverse inflammation markers were needed. The significant relationship between IPI and survival results also led us to conduct this study. The median OS of 19 (33.3%) patients was NS (not significant) with IPI <1.03 and median OS of 38 (66.7%) patients was 8 months (95% CI: 3.10-9.1) with IPI ≥2.77. In multivariate analyses, IPI was an independent prognostic factor in RCC. Patients with high IPI (>1.03) had increased risk of death compared with those with low IPI (<1.03) (HR, 8.5; 95% CI, 2.303-31.4; \( P<0.001 \)). Comorbidity, lung, lymph nodes and bone metastasis, high NLR, IMDC risk also
independently predicted worse OS in RCC. We did not have the opportunity to compare these factors in RCC because there were no similar studies. However, in all the above-mentioned studies, the strong association of markers used in IPI scoring with survival was already proven [21, 24-27].

**Limitations**

The major limitations of our study are its retrospective design and that it cannot be performed with large patient series.

**Conclusion**

We think that IPI we developed will prove helpful because it is cheap and easy to use in routine clinical practice. Nowadays, prognosis has become especially important in the treatment decision of metastatic RCC and the search for new prognostic criteria increases the importance of our study. Studies evaluating this parameter in stage, locally advanced and metastatic stages may be needed. We believe that our study deserves attention as it is the first in the RCC literature.

**References**


This paper has been checked for language accuracy by JOSAM editors.

*The National Library of Medicine (NLM) citation style guide has been used in this paper.*