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Platelet to lymphocyte Ratio (PLR) as an indicator of survival in rare histopathological subtypes of Renal Cell Carcinoma

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ABSTRACT

Objective: Inflammatory markers have prognostic significance for renal cell carcinomas (RCC) as in many types of cancer. The prognostic effect of inflammatory markers in the rare histological subtypes of RCC has not been adequately evaluated. In our study, we aimed to evaluate the relationship between basal inflammatory indices (neutrophil to lymphocyte ratio [NLR], platelet to lymphocyte ratio [PLR], lymphocyte to monocyte ratio [LMR], and systemic immune-inflammation [SII]) and survival (progression-free survival [PFS] and overall survival [OS]).

Material and Methods: Patients with metastatic non-clear cell RCC (nccRCC) or RCC with sarcomatoid differentiation (sRCC) were included in the study. The relationship between inflammatory indices, which was calculated before any systemic treatment and survival, were retrospectively assessed.

Results: Thirty patients, predominantly males (n = 20, 66.7%), with a median age of 59.1 (IQR, 52.5-70.3) years, were included in the study. Median PFS achieved with first-line tyrosine kinase inhibitors for patients with a PLR level less or greater than the median value (238) was 12.6 (95% CI 1.4-23.9) months and 4.8 (95% CI, 2.3-7.3) months, respectively (p = 0.021). Median OS for patients with a PLR level less or greater than the median (238) was 16.7 (95% CI, 3.7-29.7) months and 8.6 (95% CI, 4.9-12.3) months (p = 0.008), respectively. In the Cox-regression model (including gender, age, presence of metastasis at diagnosis, NLR, PLR, LMR, SII) only PLR was the independent predictive factor for both PSF (HR = 0.131; 95% Cl 0.028-0.620, p = 0.010) and OS (HR = 0.199; 95% Cl 0.048-0.819, p = 0.025).

Conclusion: In rare RCC subtypes such as nccRCC and sRCC, lower PLR may be associated with better PFS and OS.

INTRODUCTION

Kidney and renal pelvis malignancies constitute 4.1% of newly diagnosed cancers (1). Approximately 85% of kidney tumors are renal cell carcinomas (RCC), mostly with clear cell histopathology (2, 3). Other subtypes are papillary, chromophobe, translocation, Bellini duct (collecting duct) and medullary renal cell carcinomas, the most common of which are papillary carcinomas (2, 3). Besides, sarcomatoid differentiation is also a rare entity accompanying RCC. Sarcomatoid differentiation is defined as exhibiting pronounced cytological atypia and containing malignant spindle cells resembling sarcoma (4). Sarcomatoid differentiation in all RCCs is around 5-8% (5, 6). Since both non-clear cell RCC (nccRCC) and RCC with sarcomatoid differentiation (sRCC) are rare conditions, the prognostic factors have not been clearly defined due to the low representation rate in clinical trials.

Besides being a promoting factor for cancer, inflammation also affects tumour progression and cancer patients' survival (7, 8). It has been reported that inflammatory markers (such as neutrophil to lymphocyte ratio [NLR]) may have prognostic significance for RCC, as in many cancer types (9, 10). The systemic immune-inflammation (SII) index is calculated by using neutrophil, lymphocyte and platelet counts, which is thought to reflect inflammation better (11).

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SII is associated with poor outcomes in patients with hepatocellular carcinoma (HCC) (**11**). Although the prognostic significance of inflammatory markers has been evaluated in many types of cancer, it has not been adequately examined for rare histological subtypes of kidney tumours such as nccRCC or sRCC (8, 12, 13).

A retrospective analysis has shown that platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) were determinants of shorter survival for both progression-free survival (PFS) and overall survival (OS) in metastatic nccRCC (**14**). Similarly, a high preoperative NLR was associated with poor clinical and pathological parameters in papillary RCC (**15**).

In our study, we aimed to evaluate the relationship between basal inflammatory indices (NLR, PLR, LMR and SII), PFS achieved with first-line tyrosine kinase inhibitors (TKIs) and OS in metastatic nccRCC and sRCC.

MATERIAL and METHODS

Patients with metastatic rare histological subtype RCC followed up in the medical oncology clinic of a tertiary referral center between November 2011 and March 2021 were included in the study. Rare histological subtypes were identified as nccRCC and sRCC. Patients' medical records were reviewed retrospectively. Exclusion criteria were as follows: clear cell histological subtype, non-metastatic disease, presence of rheumatologic, immunological and infectious (i.e. acute infections, active tuberculosis, or active chronic viral infections) disease that can affect inflammatory markers, secondary malignancy, use of drugs that can affect inflammatory markers and insufficient medical records.

The baseline demographic characteristics (i.e. age, gender) of the patients, disease characteristics (i.e. tumor histological subtype, presence of metastasis at the time of diagnosis, metastatic sites) were recorded. Before any treatment (interferon or TKIs), the patients' neutrophil, lymphocyte, monocyte, and thrombocyte counts were recorded in the database. Neutrophil to lymphocyte ratio (NLR), PLR, LMR, and SII (platelet count × neutrophil count/lymphocyte count) were calculated. First-line treatment agents, PFS obtained with first-line therapy, and OS were also recorded. Progression-free survival was defined as the time of the start of TKI therapy which was used as the first line (with or without previous interferon) treatment to progression. Overall survival was defined as the time from diagnosis of metastatic disease to death or last follow-up.

The patients were subgrouped according to the calculated inflammatory index (NLR, PLR, LMR, and SII) scores (less or greater than median value), gender, age (less or greater than median value), and presence of metastasis at diagnosis. All subgroups were compared about PFS and OS. Statistical analysis was performed using SPSS software (SPSS for Windows, version 24.0., SPSS Inc., Chicago, USA). The distribution of data was evaluated by using the Kolmogorov–Smirnov test. Non-parametric data were presented as median (interquartile range-IQR), and categorical data were presented as frequency (percentage).

A ROC analysis was performed to determine cut-off values of systemic indexes. However, appropriate cut-off values with high sensitivity and specificity for systemic indexes could not found. Therefore median values of systemic inflammatory parameters were used as cut-off points. Survival rates were estimated by Kaplan–Meier method, and the groups were compared by log-rank test for survival differences. The Cox regression model was carried out using multivariate analyses. All statistical analyses were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Study Population

Thirty patients, predominantly males (n = 20, 66.7%), with a median age of 59.1 (IQR, 52.5-70.3) years, were included in the study. Median follow-up was 7.3 (IQR, 2.4-13.8) months. The most common tumour histological subtype was papillary carcinoma (n = 10, 33.3%). Thirteen (43.3%) patients had metastatic disease at diagnosis. Seventeen (56.7%) patients had an early-stage disease at diagnosis, and metastatic disease developed later. Twenty-one (70%) patients had lung metastasis.

According to the International Metastatic RCC Database Consortium risk classification, the highest number of patients was in the intermediate-risk group (n = 17, 56.7%). Main patient characteristics are shown in table 1. Inflammatory indices (NLR, PLR, LMR, and SII) at diagnosis of metastatic disease are given in table 2. Twenty-three patients (76.7%) had TKIs as first-line therapy. Of the patients who received TKIs, 16 (69.6%) received pazopanib and 7 (30.4%) sunitinib. Partial remission, stable disease and progressive disease on TKIs were observed in 5 (21.7%), 8 (34.8%) and 10 (43.5%) patients, respectively.

Table 1. Main patient characteristics

Characteristics		n (%)
Age, median (IQR)		59.1 (52.5-70.3)
Gender		
	Male	20 (66.7%)
	Female	10 (33.3%)
Histological subtype		
	Papillary	10 (33.3%)
	Sarcomatoid	9 (30.0%)
	Chromophobe	3 (10.0%)
	Bellini duct	1 (3.3%)
	Oncocytic	1 (3.3%)
	Undifferentiated	6 (20.0%)
Metastasis at diagnosis		
	Yes	13 (43.3%)
	No	17 (56.7%)
Metastasis Site		
	Lung	21 (70.0%)
	Bone	17 (56.7%)
	Lymph node	12 (40.0%)
	Liver	5 (16.7%)
	Brain	4 (13.3%)
IMDC risk group		
	Favorable	1 (3.3%)
	Intermediate	17 (56.7%)
	Poor	11 (36.7%)
	Unknown	1 (3.3%)

IMDC, International Metastatic RCC Database Consortium

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Table 2. Baseline inflammatory indices

Index	Median (IQR)
NLR	3.7 (2.9-5.4)
PLR	238 (161-323)
LMR	2.7 (1.7-4.5)
SII	1197 (692-1918)

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SII, systemic immune-inflammation index

Survival

Median PFS was 6.7 (95% CI, 3.8-9.7) months for all patients (n = 23) who received a TKI as first-line therapy. Results of PFS analysis according to subgroups are shown in table 3. In this subgroup analysis, only PLR had a significant effect on PSF obtained by using first-line TKI. Median PFS for patients with a PLR level less (n = 12) or greater (n = 11) than median was 12.6 (95% CI 1.4-23.9) months and 4.8 (95% CI, 2.3-7.3) months, respectively (p = 0.021).

Table 3. Progression-free survival analysis by subgroups

Parameter	Median (Range) (95% CI)	*p*-value
Gender		0.885
Male (n = 15)	6.7 (3.9-9.6)	
Female (n = 8)	3.9 (0.0-10.7)	
Age		0.472
< 59.1 (n = 13)	6.0 (1.4-10.6)	
> 59.1 (n = 110)	2.1 (2.7-10.8)	
Metastasis at diagnosis		0.584
Yes (n = 11)	5.5 (3.3-7.8)	
No (n = 12)	7.4 (0.0-19.8)	
NLR		0.746
< 3.7 (n = 14)	6.7 (3.3-10.2)	
> 3.7 (n = 9)	6.0 (0.0-12.1)	
PLR		**0.021**
< 238 (n = 12)	12.6 (1.4-23.9)	
> 238 (n = 11)	4.8 (2.3-7.3)	
LMR		0.456
< 2.7 (n = 11)	6.7 (3.5-10.0)	
> 2.7 (n = 12)	5.5 (0.0-11.5)	
SII		0.404
< 1197 (n = 13)	7.4 (0.0-15.7)	
> 1197 (n = 10)	4.8 (1.5-8.1)	

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SII, systemic immune-inflammation index

Median OS was 11.5 (95% CI, 9.2-13.8) months for all patients (N = 30). Results of OS analysis according to subgroups are shown in Table 4. In this subgroup analysis, only PLR had a significant effect on OS.

Median OS for patients with a PLR level less (n = 15) or greater (n = 15) than median was 16.7 (95% CI, 3.7-29.7) months and 8.6 (95% CI, 4.9-12.3) months (p = 0.008), respectively.

Kaplan-Meier curves of the OS analysis by grouping the patients based on inflammatory indices (NLR, PLR, LMR, and SII), such as greater or less than the median value, are shown in Figure 1.

In the Cox-regression model (including gender, age, presence of metastasis at diagnosis, NLR, PLR, LMR, SII) PLR was the only independent predictive factor for both PSF (HR = 0.131; 95% Cl 0.028-0.620, p = 0.010) and OS (HR = 0.199; 95% Cl 0.048-0.819, p = 0.025).

Table 4. Overall survival analysis by subgroups.

Parameter	Median (Range) (95% CI)	*p*-value
Gender		0.302
Male (n = 20)	10.6 (8.9-12.4)	
Female (n = 10)	11.6 (2.8-20.4)	
Age		0.503
< 59.1 (n = 15)	8.6 (3.0-14.1)	
> 59.1 (n = 15)	12.3 (10.9-13.7)	
Metastasis at diagnosis		0.744
Yes (n = 13)	10.6 (7.2-14.0)	
No (n = 17)	12.3 (6.4-18.2)	
NLR		0.258
< 3.7 (n = 15)	14.9 (6.8-23.1)	
> 3.7 (n = 15)	11.5 (6.3-16.7)	
PLR		**0.008**
< 238 (n = 15)	16.7 (3.7-29.7)	
> 238 (n = 15)	8.6 (4.9-12.3)	
LMR		0.135
< 2.7 (n = 15)	11.5 (6.4-16.6)	
> 2.7 (n = 15)	11.6 (9.0-14.2)	
SII		0.105
< 1197 (n = 15)	14.9 (7.1-22.7)	
> 1197 (n = 15)	10.6 (3.6-17.7)	

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SII, systemic immune-inflammation index

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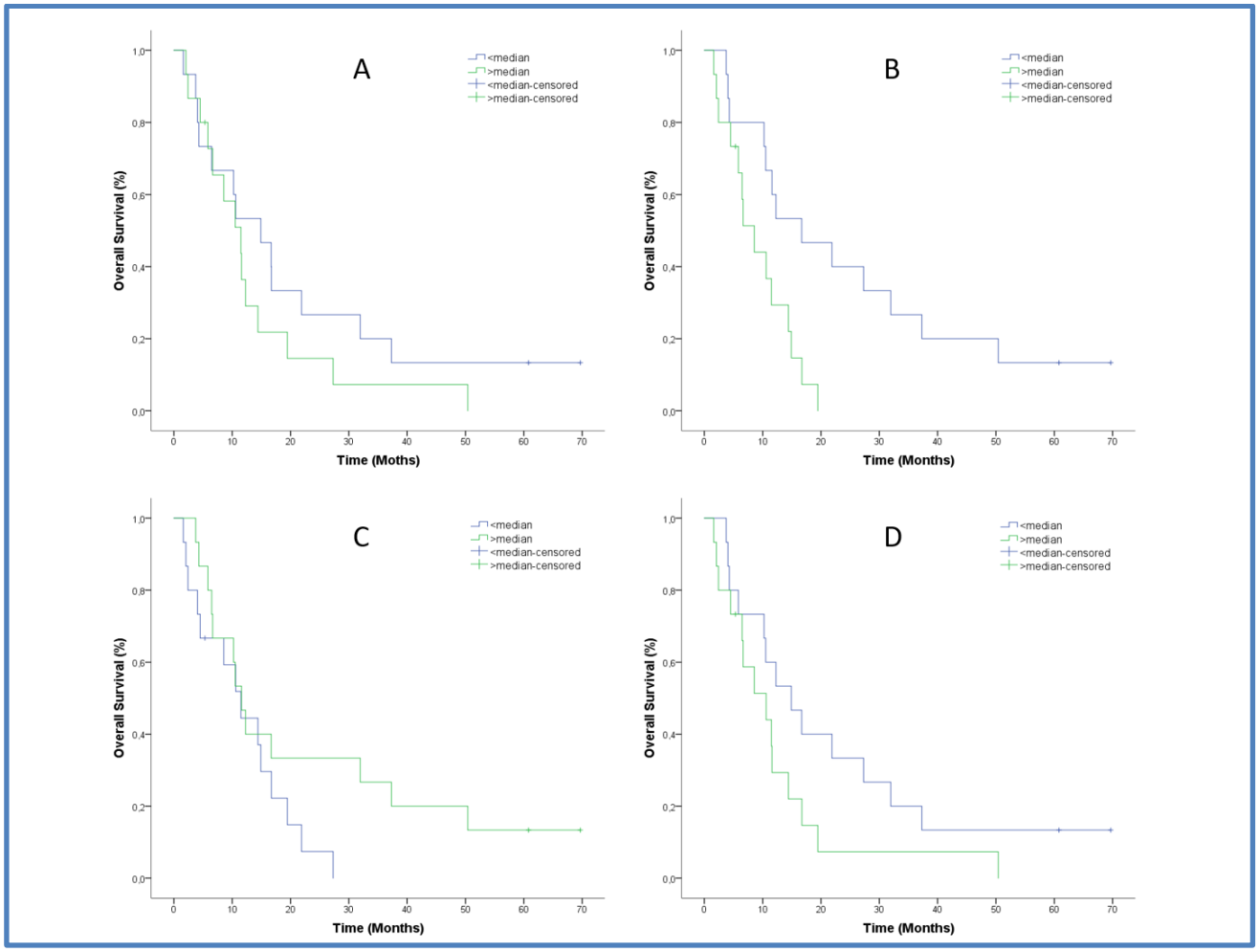

Figure 1. Kaplan-Meier curves of the overall survival analysis based on inflammatory indices; **A.** NLR, **B.** PLR, **C.** LMR, and **D.** SII.

DISCUSSION

In our study, both median PFS with first-line TKI and median OS were statistically better in the PLR lower group. Moreover, there were noticeable numerical differences for PSF of first-line TKI treatment in subgroup analysis performed according to the SII. Similarly, in the subgroup analysis performed according to NLR and SII, numerical differences for OS may have clinical significance. However, there was no statistically significant difference in PFS and OS analysis for either NLR or SII. Numerous prognostic factors and prognostic models have been evaluated for RCC, but none of them was shown to predict prognosis accurately (16). A novel prognostic nomogram for metastatic RCC is promising, but there has not been sufficient clinical experience with this nomogram (17). Although there have been studies evaluating prognostic factors in RCC, the literature data on prognosis for rare histological subtypes (such as nccRCC and sRCC) is quite insufficient.

The Cancer Genome Atlas (TCGA) Research Network showed that a CpG island methylator phenotype (CIMPA) in a distinct subgroup of type 2 papillary RCC (18). This subgroup was characterized by poor survival and mutation of the gene encoding fumarate hydratase (18). Similarly, according to the gene expression data, low tumour suppressor gene CKDN1A mRNA and protein mutation were associated with poor OS for chromophobe RCC (19).

A transcriptomic analysis containing sRCC found that high PD-L1– and CD8-positive cell expression may account for their improved outcomes with immuno-therapies and showed that high MYC targets version 1 gene expression in these tumours was associated with poor outcome (20). The results of these precious trials on the prognostic factors in rare histological subtype RCCs enable us to look to the future with confidence. However, these prognostic parameters are not yet usable since they require high technology and are not easily accessible. Simple, cheap and accessible parameters are needed to predict prognosis in daily oncology practice.

Thrombocytosis was an independent poor prognostic factor in anti-vascular endothelial growth factor (VEGF) treatment-naive metastatic RCC (p = 0.01) (21). A large-scale meta-analysis, in which Gu et al included 25 studies of 11,458 patients with a diagnosis of RCC, have reported that an elevated platelet level was associated with poor OS (HR = 2.24, 95% CI 1.87-2.67, p <0.001) and cancer-specific survival (HR = 2.59, 95% CI 1.92-3.48, p <0.001) (22). Saroha et al in a study including 430 patients diagnosed with RCC, reported that lymphopenia was associated with worse OS regardless of other risk factors (pT and TNM stages, nuclear grade, age, tobacco smoking, and comorbidity index) (23). Evaluating the prognostic importance of PLR in RCC for the first time, Gündüz et al found that high PLR is an

independent negative predictive factor for PFS (p = 0.001) and OS (p = 0.013) (24). In a recent meta-analysis involving 1,528 RCC patients, an elevated PLR was an effective prognostic marker of both OS (HR = 2.10, 95% CI: 1.38-3.19, p = 0.001) and PFS (HR = 3.45, 95% CI: 1.61-7.40, p = 0.001) (25). However, in the metanalysis, including 1528 patients, only 91 patients were reported to have nccRCC histological subtype, but no information was given about the sRCC subtype (25). In our study, a PLR level below 238 was a positive factor for both PFS and OS. These findings are in accordance with the literature data and are important in terms of including nccRCC and sRCC cases, which are a group that has not been adequately evaluated.

In the study by Başal et al evaluating 187 patients with metastatic RCC, it was revealed that SII is an independent prognostic factor about survival for the favourable, intermediate, and poor IMDC groups (26). Similarly, Özbek et al observed an association between SII and increased TNM stage and poor prognosis in RCC patients undergoing radical nephrectomy (27). In our study, there was an absolute difference of 2.6 months in median PFS and 4.5 months in median OS in favour of the group with low SII. However, this difference did not reach a statistical significance.

In a recent meta-analysis, high NLR value was found to be a negative prognostic factor for OS (HR = 1.80; 95% CI 1.61-2.00) and PFS (HR = 1.69; 95% CI 1.42-2.01) in RCC in both metastatic and nonmetastatic patients (28). In three different trials involving patients with non-metastatic nccRCC, it was concluded that a high preoperative NLR was associated with poor DFS (15, 29, 30). In a retrospective analysis including 37 patients with metastatic nccRCC who received pazopanib as first-line therapy, lower basal NLR was associated with both better PFS (p = 0.009) and OS (p = 0.008) (31). In a similar retrospective study, it was stated that in 36 metastatic chromophobe RCC patients who received sunitinib treatment, pretreatment NLR<3 was associated with a better OS (HR = 0.55, p = 0.03) (32). Although we consider that NLR as a prognostic factor in our study, 3.4 months of OS advantage in patients with NLR <3.7 did not reach statistical significance.

Main limitations of our study are its retrospective nature and a small number of patients. It would be more appropriate to evaluate the prognostic significance of inflammatory parameters at homogeneous groups to be formed according to the histological subtypes of nccRCC and sRCC prospectively. However, it is difficult to perform this analysis due to the scarcity of patients. Another limitation is that the C-reactive protein/albumin ratio, whose prognostic importance in RCC is known (33), cannot be calculated since the C-reactive protein level is not routinely evaluated in the pre-treatment period. Nevertheless, we consider that our study has clinical value since it is conducted in a rare patient group that has not been adequately evaluated yet.

CONCLUSION

In rare RCC subtypes such as nccRCC and sRCC, PLR is associated with both PFS and OS. Systemic immune-inflammation index and NLR may also have prognostic significance for survival in this group.

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