Original Research Article

Prognostic significance of inflammatory markers in patients with rare kidney cancers

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ABSTRACT

Background: Although clear cell renal cell carcinoma (ccRCC) is the most common histological variety of malignant renal tumor, histological variants are often encountered in clinical practice which behaves differently. Paucity of such tumors makes them a subject of interest worldwide. As per European Association of Urology, since ccRCC is a non-designation, they included all non-clear cell RCC under one nomenclature as rare kidney cancer (RKC). The objective of our study is to determine influence of inflammatory markers on the prognosis of RKC.
Methods: Data from cancer registry was retrieved and all rare kidney cancer patient's data were analysed particularly the markers of inflammation like neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic inflammatory immune index (SIII) and C reactive protein (CRP) to albumin ratio and their probable influence on cancer free survival (CFS), progression free survival (PFS) and overall survival (OS).
Results: Data of 33 cases of rare kidney cancers were included in this study. The follow up duration ranges from 6.8 months to 38.6 months. In the univariate analysis, NLR had a significant influence on CFS, PFS and OS (cutoff value-3.2, 95% confidence interval [CI], CFS: $p<0.05$; PFS: $p=0.05$; OS: $p<0.05$), PLR in respect to CFS (cutoff value-67.5, 95% CI, $p<0.05$) and SIII had a significant impact on CFS and OS (cutoff value-8.67, 95% CI, 11.10-19.57, CFS: $p<0.05$; OS: $p<0.05$).
Conclusions: Inflammation markers such as NLR, PLR, SII Index and CRP or albumin ratio could be independent predictors of clinical outcome and prognostics factors in rare kidney cancers. However, this needs to be validated by multicentre randomised studies.

Keywords: Systemic inflammation, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Systemic imflammatory immune index, C reactive protein, Prognostic factors

INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common solid neoplasm of urinary tract accounting for about 3% of all malignancies in adult. Although clear cell renal cell carcinoma (ccRCC) is the most common histological variety of malignant renal tumor, rare histological variants are often encountered in clinical practice which behaves differently.[1] As per European Association of Urology, since ccRCC is a non-designation, they included all non-clear cell RCC under one nomenclature as rare kidney cancer (RKC).[1] RKCs compromise a broad spectrum of over dozen histopathological entities. Papillary RCCs (type 1 and type 2) and chromophobe RCC are more common than other RKCs.[1] Paucity of such tumors makes them a subject of interest worldwide. These variants have markedly different clinical behaviour and prognosis compared to the more common neoplasm.[2] While it may not be possible to make a definitive diagnosis based on the imaging features, knowledge of

these entities and their imaging characteristics can sometimes allow the prediction of probable histology.[2,3] A tumor is formed from cancer cells and a specific microenvironment that consists of microvessels, fibroblasts, endothelial cells, an extracellular matrix, and a complex of both innate and adaptive immune cells.[4] An important feature of the tumor is also hypoxia. Immune components and hypoxia play a crucial role in tumor development and clinical outcome; however, the functions of the different subsets of the microenvironment have not been precisely explained.[5,6] The most common kidney cancer subtype (60% to 70%) is clear-cell renal cell carcinoma. Inactivation of the von Hippel-Lindau (VHL) (tumor suppressor gene) leads to accumulation of hypoxia inducible factor (HIF-1a), which influences the transcription of genes important to the survival and hypoxic response of tumors, including vascular endothelial growth factor (VEGF).[7] There is evidence that hypoxia inducible factor may also be involved in the tumor microenvironment creation because it stimulate the production and secretion of chemokines and chemokine receptors that accelerate myeloid cell (monocytes or macrophages, neutrophils, and platelets).[8] Likewise, hypoxia may contribute to creating tumor derived inflammation by reinforcing the production of pro inflammatory cytokines in VHL-deficient renal cell cancer (RCC) cells. In RCC, high concentration of interleukin 6 (Il-6) and interleukin 8 (Il-8) is found in the plasma and these are chemotactic factors which may induce systemic inflammation that causes changes in circulating white blood cells and platelet count as well as in level of C-reactive protein (CRP).[9-11] The objective of our retrospective study is to determine influence of inflammatory markers on the prognosis of rare kidney cancers. Current consensus in such rare kidney cancers display variation in response to current therapy and need to be put on clinical trial to achieve optimum survival. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic imflammatory immune index (SII Index) and CRP or albumin ratio may be predictors of clinical outcome in patients with RKCs. These markers are inexpensive to test and routinely performed in the clinical setting. However, their prognostic values are yet to be explored in RKCs.

METHODS

This is a retrospective study in the Department of Urology and Renal Transplant, Gauhati medical college and Hospital, Guwahati for a period of 7 years from February 2012 to January 2019. Ethical approval obtained from ethical committee. A retrospective analysis of data from cancer registry of our department was retrieved and detect all rare kidney cancer patients were analysed. In this retrospective cohort, the clinical and pathological records of 212 consecutive patients who underwent partial or radical nephrectomy for renal tumors were reviewed. Clinical data were assessed for age, gender, symptomatic presentation, differential white blood cell count, platelets count, CRP, lactate

dehydrogenase, contrast-enhanced computed tomography whole abdomen findings such as size, laterality and location of tumour, whether exophytic or endophytic or presence of necrosis and calcification, underwent surgical procedure, histopathological findings and further post-operative follow up. Inflammatory markers were measured 1 to 2 days before surgery. We included in the analysis only the rare kidney cancer with variant histology and we excluded the most common histological variable clear cell renal cell carcinoma from this study. Survival was calculated from the date of surgery. The survival endpoint was cancer-related death or the date of last follow-up. Data for patients who died from other than metastatic disease were censored at the time of death. Attempt were made to analyse the influence of inflammatory markers such as NLR, PLR, SII Index and CRP or albumin ratio on prognosis in the form of cancer free survival (CFS), progression free survival (PFS) and/or overall survival (OS) in patients with rare kidney cancers with variant histology.

Statistical analysis

Continuous normally distributed variables are given as mean value±SD, continuous non-normally distributed variables as median values and interquartile ranges. Differences were considered statistically significant when p<0.05. PFS was calculated from the start of first-line treatment until disease progression or last follow-up. OS was calculated from the start of first-line treatment until death or last follow-up. Survival curves were estimated according to the Kaplan– Meier method and differences in survival were evaluated by the log-rank test. Survival rates at 5 years including 95% asymptotic confidence interval are given if appropriate. To identify a potential threshold for different inflammatory markers such as NLR, PLR, SII Index and CRP or albumin ratio hazard ratios (HRs) for a range of possible cutoff points were estimated and tested in a univariable cox proportional hazard regression model. If heterogeneity was significant, analyses were conducted to investigate factors significantly influencing HR. Statistical analyses were performed using SPSS 26 software.

RESULTS

Literature search

In this retrospective cohort, we assessed 212 consecutive patients who underwent partial or radical nephrectomy for renal tumor at our institution between February 2012 to January 2019. After assessment of histopathological findings, we excluded 179 patients of clear cell renal cell carcinoma. we are analysing the influence of inflammatory markers (such as NLR, PLR, SII Index and CRP or albumin ratio) in patient with rare kidney cancers with variant histology. The clinicopathological features of the different subtypes are summarized in Table 1. The series comprised 33 extensively rare kidney cancers with variant histology. Out of 33 patients the following

morphotypes were encountered, type II papillary RCC-7, type I papillary RCC-2, chromophobe RCC-6, ccRCC with sarcomatoid changes-4, papillary RCC with sarcomatoid changes-3, unclassified RCC-2, Adult wilms tumour-2, Ewing sarcoma-1, clear cell sarcoma-1, papillary RCC with rhabdoid differentiation-1, transitional cell carcinoma-1, renal squamous cell carcinoma-1, primitive neuroendocrine tumour-2. The mean age of the 33 patients was 57.3 (range 31.2 to 65.8) years and 75.7% (25 patients) were male. Out of these 33 patients tumor presented on imaging as exophytic in 29

(87.8%) patients, necrosis in 27 (81.8%) and calcification present in 21 (63.6%) patients. Patients were classified as pT1 (24.4%), pT2 (48.4%), pT3 (24.2%) and pT4 (3%). Lymph node involvement (pN1) was present in 18 patients (54.5%) and 12 patients (36.3%) had evidence of distant metastatic disease (cM1). Most of these tumors presented with higher stage so underwent radical nephrectomy in 31 (93.9%) patients and partial nephrectomy were done in only 2 (6.1%) patients subsequently came to type I and type II papillary RCC.
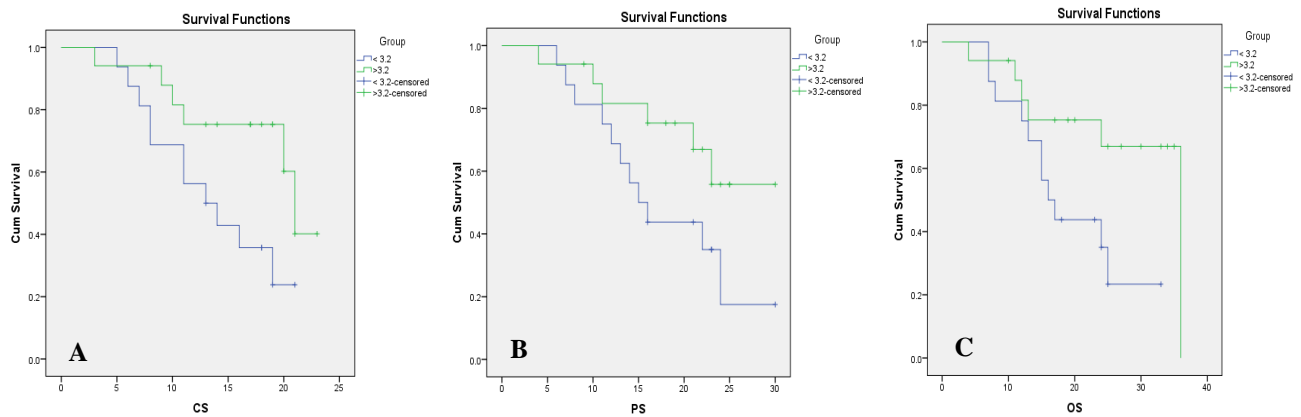
Figure 1 (A-C): Survival correlation with NLR.
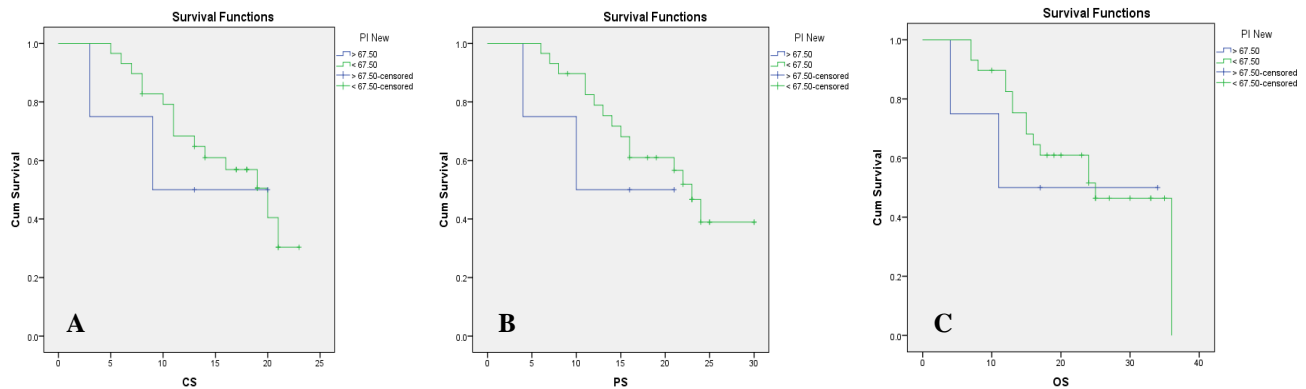
Figure 2 (A-C): Survival correlation with PLR.
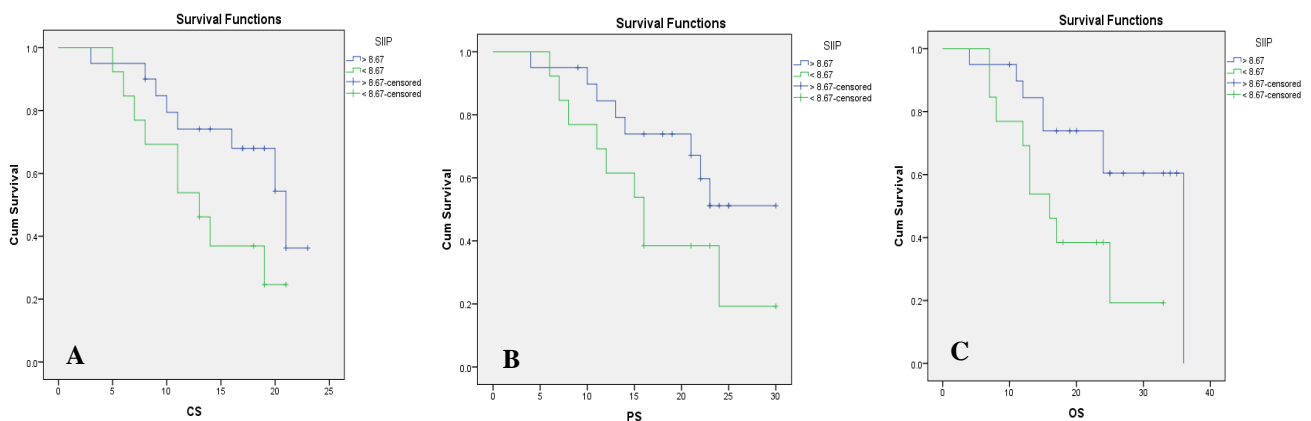
Figure 3 (A-C): Survival correlation with SII index.

Table 1: Clinicopathological features of the different subtypes.

Demographic and clinicopathological features		Type II papillary	Type I papillary	Chromophobe RCC	ccRCC+ sarcomatoid	Papillary+ sarcomatoid	Uncalssified	Papillary+ rhabdoid	Wilm' tumor	Ewing sarcoma	Clear cell sarcoma	TCC	Renal SCC	PNET
Number of cases		7	2	6	4	3	2	1	2	1	1	1	1	2
Age	Mean (range)=57.3 (31.2-65.8 years)	51.3 (31.2-61.3)	56 (49.6-62.4)	58.8 (54.4-64)	59.1 (57-63)	63.3 (61.7-65.8)	62.9 (62.8-63)	57	52.7 (51.2-54.3)	61.9	59.8	62	56.8	56.6 (54.5-58.7)
Sex	Male or female	6/1	2/0	4/2	3/1	1/2	2/0	1/0	1/1	1/0	1/0	0/1	1/0	2/0
Right or left		4/3	0/2	1/5	1/3	2/1	2/0	0/1	0/2	1/0	1/0	0/1	0/1	0/1
Symptoms	H/P/M/	6/1/1	1/1/0	6/6/1	2/0/1	2/0/1	2/0/0	1/0/1	1/0/1	0/0/1	0/0/1	1/0/0	1/0/1	1/0/1
Capsular invasion	Yes or no	6/1	2/0	2/4	2/2	2/1	1/1	1/0	2/0	1/0	1/0	0/1	1/0	2/0
Exo or endo		7/0	2/0	5/1	2/2	3/0	1/1	1/0	2/0	1/0	1/0	0/1	1/0	1/0
Necrosis	Yes or no	7/0	2/0	4/2	3/1	2/1	2/0	1/0	2/0	0/1	1/0	0/1	1/0	2/0
Calcification	Yes or no	7/0	0/2	3/3	3/1	2/1	1/1	1/0	1/1	0/1	1/0	0/1	1/0	1/1
T stage	T1a	1	1	0	0	0	0	0	0	0	0	0	0	0
	T1b	1	0	2	0	1	0	0	0	1	0	1	0	0
	T2a	1	0	0	2	1	1	0	1	0	0	0	0	0
	T2b	2	1	1	2	1	1	0	1	0	0	0	0	1
	T3a	1	0	3	0	0	0	1	0	0	0	0	1	1
	T3b	0	0	0	0	0	0	0	0	0	0	0	0	0
	T3c	1	0	0	0	0	0	0	0	0	0	0	0	0
	T4	0	0	0	0	0	0	0	0	0	1	0	0	0
Lymph node	N1	3	2	3	3	2	2	1	0	0	0	0	0	2
Metastasis	M1	1	1	2	2	2	1	1	1	0	0	0	0	1
Surgery	Radical or partial	6/1	1/1	6	4	3	2	1	2	1	1	1	1	2
Perilesional invasion		5	1	4	4	3	2	1	2	1	1	1	1	2

SCC: squamous cell carcinoma; TCC: transitional cell carcinoma; PNET: primitive neuroectodermal tumor.

Association in systemic inflammatory markers level and clinical outcome

Median duration of follow up was 20.7 months (interquartile range 6.8-38.6). Of these, 17 patients (51.5%) died during follow-up. The median CFS, PFS and OS were 18.4 months (95% confidence interval (CI) 7.5-26.51), 19.7 months (95% CI 6.8-31.32) and 22.5 months (95% CI 7.5-38.6). NLR have been recognized as potential markers of systemic inflammatory response that could be associated with clinical outcome in patients with rare kidney cancers. A low pre-treatment NLR was associated with shorter median CFS, PFS and OS compared with a high level of markers and the difference was clinically significant. Cut off value of NLR in our studies varied from <3.2 and >3.2 (cut off value-3.2, 95% CI, CFS: p<0.05; PFS: p=0.05; OS: p<0.05). There was evidence that patients with a lower pretreatment NLR

level have a less CFS, PFS and OS. Higher preoperative PLR had a significant impact in low overall survival (cut off value-67.5, 95% CI, p<0.05) but no significant relation with CFS and PFS. Whereas Lower preoperative SII Index have tendency toward poor prognosis in form of CFS and OS (cut off value-8.67, 95% CI, 11.10-19.57, CFS: p<0.05; OS: p<0.05) but no significant relation with PFS. We also evaluated the CRP or albumin ratio with cut off value of 1.2 but didn't find any significant influence on CFS, PFS and OS (Table 2). This performed analysis demonstrated that inflammatory markers such as NLR, PLR, and SII index may be used as important and independent factors on the prognosis of rare kidney cancers. Although the statistical significance in survival rates could not be calculated between different variants because of the limited number of cases, the Kaplan Meyer curves leave no doubt that these entities represent a quite different clinical behaviour.

Table 2: Univariate analysis for cancer-free survival, progression-free survival and overall survival.

No.			No. of patients	Event	Median CFS (months) (95% CI)	P value	Median PFS (months) (95% CI)	P value	Median OS (months) (95% CI)	P value
1	NLR	<3.2	16	11	13 (7.5-18.4)		15 (13.6-21.8)		16 (14.9-24.2)	
		>3.2	17	6	21 (19.09-20.9)	0.042	23.6 (19.3-27.8)	0.001	33.5 (22.5-36)	0.045
2	PLR	<67.5	29	15	20 (13.7-26.3)		23 (18.1-24.4)		25 (20.7-29.4)	
		>67.5	4	2	9 (14.1-25.4)	0.47	10 (6.8-21.1)	0.321	11 (7.5-33.9)	0.036
3	SIII	<8.67	13	9	13 (7.9-18.03)		17.3 (12.6-22.1)		16 (13.0-29.4)	
		>8.67	20	8	21 (15.4-26.5)	0.007	23.1 (19.2-26.9)	0.104	34 (22.7-38.6)	0.04
4	CRP or albumin ratio	<1.2	5	2	19 (13.9-24.04)		22 (12.8-31.3)		24 (13.2-35.1)	
		>1.2	28	15	20 (13.7-26.3)	0.95	23 (19.7-26.7)	0.977	24.4 (19.9-28.9)	0.97

CFS, cancer-free survival; CI, confidence interval; CRP, C reactive protein; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progression-free survival; PLR, platelet to lymphocyte ratio; SII, systemic inflammatory immune index.

DISCUSSION

Many studies evaluated the role of prognostic scores based on peripheral inflammation cells in several tumors, particular in RCC.[4] Tumor microenvironment and systemic Inflammation proinflammatory factors are considered as potential markers for the prognosis of patients with cancer because inflammation associated with the tumor has a great influence on the development of cancer, its progression and its response to the administered therapy.[5,6] Neutrophils that collaborate the tumor microenvironment take part in extracellular matrix degradation and stimulation of expression of adhesion molecules that enhance the attachment of circulating metastatic cells.[9] Lymphocytes promote antitumor response by cytotoxic and humoral mediated immune responses.[10] However, a high neutrophil level in patients with cancer was reported as an independent factor of poor prognosis. Neutrophil-lymphocyte ratio is probably the most commonly tested prognostic index and was associated with prognosis in several tumors such as breast, lung, pancreatic, colorectal, gastric, urothelial and also kidney cancers.[11,13,14] Lymphopenia in preoperative

blood count was also associated with poor prognosis in patients with RCC. Platelets were also associated with prognosis in RCC, considered mainly as regulators of hemostasis. Stimulated platelets release peptides that include growth factors and chemotactic factors. SII Index combines these three parameters and has been seen to significantly associated with prognosis in hepatocellular carcinoma and in colorectal cancer. CRP is a protein produced by the liver as a consequence of the changes in the concentrations of inflammatory associated cytokines in plasma.[14,15] A main function of CRP is recognition of foreign pathogens and damaged cells, facilitating activation of innate immune system.[16] Researchers have found that patients with mRCC with increased CRP levels had more metastatic sites and a poorer IMDC score.[17-19] Because these inflammatory markers also included in the IMDC model, we are analysing for the first time the prognostic power of inflammatory markers such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic inflammatory immune index (SIII) and CRP/albumin ratio in group of 33 cases of rare kidney cancers with variant histology.

Semeniuk et al evaluated the effect of NLR, PLR, and CRP in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. In this meta-analysis, NLR (hazard ratio [HR], 2.01; 95% CI, 1.27-3.18; p=1⁄4.003) and PLR (HR, 6.96; 95% CI, 5.04-9.62; p<0.001) had a significant influence on PFS, whereas all considered proinflammatory markers had a significant impact on OS: NLR (HR, 2.14; 95% CI, 1.67-2.73; p<0.001), PLR (HR, 14.67; 95% CI, 11.10-19.57; p<0.001), and CRP (HR, 1.96; 95% CI, 1.26-3.05; p=1⁄4.003).[20]

Arda et al has observed that NLR values of tumors larger than 4 cm were significantly higher than tumors smaller than 4 cm (p=0.029). However, when the NLR and Fuhrman grade relation was examined, no difference was observed between the tumors smaller than 4 cm and the tumors larger than 4 cm (p=0.280). According to these results, the NLR can be used as a cheap parameter to predict the tumor size and also to anticipate about the prognosis of the patient.[21]

Viers et al showed that the NLR ≥4 was significantly associated with worse five-year cancer- specific (66% vs. 85%) and overall survival (66% vs. 85%) in patients with localized RCC (p<0.01). However, these studied has not categorised on clear call or non-clear cell RCC.[22]

Ohno et al. showed that 10-year recurrence-free survival rate for patients with a preoperative NLR ≥2.7 was significantly lower than that for those with a ratio of less than 2.7 with 64.4% to 83.7%, respectively (p=0.0004).[23]

In another study including localized non-clear cell RCC patients, the effect of the NLR on five- year disease-free survival was evaluated. It was shown that with each 1.0 ratio increase, a risk of recurrence was increased by 15% (p=0.0028). The authors concluded that the NLR is an independent prognostic factor for disease-free survival in localized non-clear cell renal cell carcinoma.[24]

In a study evaluating metastatic RCC patients treated with everolimus, patients were stratified into two groups as NLR >3 and NLR <3 cm. Progression-free survival and overall survival was significantly less in patients with NLR >3. It was demonstrated that the NLR has been shown as an independent prognostic factor also in metastatic patients.[25]

A PubMed database review that included 15 studies showed that an NLR <3 was predictive of a reduced risk of recurrence for localized RCC. Additionally, in metastatic or locally advanced RCC, an NLR <3 predicted better overall survival and progression-free survival.[26]

In our univariate analysis, we detected that low NLR had a significant impact on CFS, PFS and OS. Higher preoperative PLR had a significant impact in low overall survival. However, lower preoperative SII Index have

tendency toward poor prognosis in form of CFS and OS in RKCs. To the best of our knowledge, this is to analyse the host immune status as a prognostic factor in patients with rare kidney cancers with variant histology, that is engaged in the clinical course of the disease so that enable it meaning-full assessment of the patient's individual risk. We tried to explain the association between the immune system and cancer course but the knowledge about analysed dependences is relatively small, requiring further studies.

There are several limitations in our study. First, we used retrospective data with a relatively small sample size, which may have interfered with our survival analyses. Second, we found limited cases of different variant histology.

CONCLUSION

The vast majority of renal masses encountered are likely to represent renal cell carcinomas. However, we have presented a large number of rare kidney cancers with variant histology, many of which have vastly different prognoses and clinical outcomes. Inflammation markers such as NLR, PLR, SII Index and CRP or albumin ratio as representative markers of host immune status, are simple and easily available biomarkers which allow prediction of the clinical outcome in patients with rare kidney cancers. These Inflammation markers could be predictors of clinical outcome and prognostics factors in rare kidney cancers and these markers were associated with statistically different survival rates. Nevertheless, there are currently no recommendations on the use of these markers for rare kidney cancers follow-up. However, further prospective studies on large cohorts are warranted to validate the knowledge.

Clinical practice points

The clinical course of rare kidney cancers with variant histology varies and currently available prognostic scales do not allow specification of the response to therapy. Systemic inflammatory markers could be useful in the prediction of the clinical outcome in patients with rare kidney cancers with variant histology.

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