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Research Article

Can platelet distribution width and lymphocyte ratio be a novel biomarker for predicting survival in metastatic renal cell cancer?

Trombosit dağılım genişliği lenfosit oranı, metastatik böbrek hücreli kanserde sağkalımı öngörmede yeni bir biyobelirteç olabilir mi?

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Abstract

Aim: The prognostic value of platelet distribution width to lymphocyte ratio (PDWLR) in patients with metastatic renal cell cancer using tyrosine kinase inhibitors is not clearly known. Our aim in this study is to evaluate the prognostic importance of PDWLR in patients with metastatic renal cancer.

Meterial and Methods: This retrospective study included 66 patients with metastatic renal cell cancer who were currently receiving Tyrosine kinase inhibitor treatment between January 2010 and December 2020. The cut off value was determined by ROC curve analysis. The best cut-off value for RDWLR was determined as 9.33. Sensitivity and specificity for RDWLR were 55.3% and 57.9%, respectively. Chi-square and Fisher exact tests were used to evaluate the relationship between PDWLR and clinicopathological variables. Cox proportional hazards model was used for multivariate analysis.

Conclusion: It has been determined that PDWLR measured during treatment in metastatic RCC patients using TKIs has no significant effect on Pfs, which is an important prognostic factor in predicting OS. In patients with metastatic renal cell cancer, PDWLR level can be used as a prognostic marker, but studies with a larger number of patients are needed.

Keywords: metastatic renal cell cancer, PDWLR, OS

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Öz

Amaç: Tirozin kinaz inhibitörü kullanan metastatik böbrek hücreli kanserli hastalarda trombosit dağılım genişliğinin lenfosit oranı (PDWLR)'nın prognostik değeri net olarak bilinmemektedir. Bu çalışmada amacımız PDWLR 'nin metastatik renal kanserli hastalarda prognostik önemini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ocak 2010-Aralık 2020 tarihleri arasında halen Tirozin kinaz inhibitörü tedavisi alan 66 metastatik renal hücreli kanserli hasta dahil edildi .Cut off değeri ROC curve analizi ile tesbit edildi. RDWLR için en iyi cut off değeri 9.33 olarak tesbit edildi.RDWLR için sensivite ve spesivite sırasıyla %55.3, %57.9 idi. PDWLR ve klinikopatolojik değişkenler arasındaki ilişkiyi değerlendirmek için ki kare ve Fisher exact testleri kullanıldı. Multivariate analiz için Cox oransal hazards modeli kullanıldı.

Sonuç: TKİ kullanan metastaik rcc hastalarında tedavi esnasında bakılan PDWLR 'nin OS tahmin etmede önemli prognostik faktör olduğu Pfs üzerine anlamlı etkisinin olmadığı tespit edilmiştir.Metastatik renal hücreli kanserli hastalarda , PDWLR düzeyi prognostik bir marker olarak kullanılabilir, ancak daha fazla hasta sayısı ile yapılacak çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: metastatik renal hücreli kanser, PDWLR, OS

Introduction

Renal cell carcinoma (RCC) constitutes 3% of all malignant tumors in the adult patient population (1). As in other cancer processes, inflammation affects each step of tumor formation, including initiation of tumorigenesis, tumor promotion, and metastatic progression in RCC (2,3). It is widely accepted that C-reactive protein, fibrinogen, neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio, and platelet-lymphocyte ratio (PLR) are markers of inflammation in bothin flammatorydi seases and malign ant diseaseprocesses (2,3). Furthermore, a relatively high NLR wasreportedto be associated with an unfavorableprognosisandreducedoverallsurvival in urological cancers (4,5). Platelets can secreteactivemetabolitesandproteinsandtake a significant role in variousprocessessuch as inflammation, sepsis, andtissueregeneration (5). In addition, it is knownthatthey can releasegrowthfactors, including platelet-derivedgrowthfactor (PDGF), transforminggrowthfactor-beta, andvascularendothelialgrowthfactor (VEGA), whichmayallinducetumorangiogenesisandgrowth (6). Inlinewiththesefindings, Touring et al. reportedthatplateletcountcould be an independent prognostic marker of overallsurvivalandrecurrence-freesurvivalforpatients withlocalizedRCC(7).Additionally,Wangetal.statedthatahighPLR value indicated an unfavorable prognosis in allurologicalcancers (8). Althoughseveralstudiesinvestigatedthesignificance of hematologicalindicessuch as NLR and PLR in localizedormetastatic RCC (MCC), none focused on theplateletdistributionwidth-lymphocyte ratio (PDWLR) (7,9,10). Therefore, thisstudyaimedtoanalyzetheprognosticsignificance of theseplateletparameters in patientswithmRCC

Material and Methods

Adult (i.e., age≥18) patients diagnosed with mRCC and prescribed tyrosine-kinase inhibitors in Ankara Diskapi Yildirim Beyazit Training and Research Hospital Department of Internal Medicine, Division of Medical Oncology between January 2010 and December 2020 constituted the target population of this study. Patient data were retrospectively reviewed and retrieved from electronic patient folders after approval from the Ethical Review Committee of the same institution. Patients with incomplete data or those who did not consent to the use of their medical data for study purposes were excluded.

The collected data included demographic parameters such as age and gender and clinical data including date of diagnosis of mRCC, the side of the renal tumor (right/left), history of radical nephrectomy, history of metastasectomy, presence or absence of lymphovascular invasion (LVI), and renal vein thrombosis, first-line treatment (sunitinib/pazopanib), Eastern Cooperative Oncology Group (ECOG) performance score (0 or ≥1), the number of metastatic sites and mortality status. In addition, the calculated hematological indices were PLR, PDWLR, and red cell distribution width (RDW). The PLR was calculated as the PLT count divided by the lymphocyte count, while PDWLR was calculated as the platelet distribution width divided by the lymphocyte count.

All patients were followed at the medical oncology outpatient clinic at 8-week intervals and evaluated as per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) using thoraco-abdominopelvic computerized tomography or upper and lower abdominal magnetic resonance imaging (11). Disease progression was defined as a ≥20% increase in the longest diameter according to RECIST or the development of any novel metastatic lesions.

Statistical analysis

All statistical analyses were performed via STATISTICA 13 software. The qualitative data were presented as percentages and analyzed by Fisher's exact and chi-square tests. Univariate and multivariate analyses were conducted by the Cox proportional hazards regression model. Finally, the receiver operator characteristics (ROC) curves were plotted to calculate the ideal cut-off values of PLR and PDWLR in predicting survival. A difference was considered statistically significant if the p value was lower than 0,05.

Results

Overall, 66 patients were included. Among those, 49 (74.2%) were male, and 17 (25.8%) were female (Table 1).

Table 1. Demographic data, clinical and histopathological features of the patients

Age <65 >65	Number (Percentage) 42 (63.6) 24 (36.4)
Gender Male Female	 49 (74.2) 17 (25.8)
Tumor localization Right Left	 30 (45.5) 36 (54.5)
History of radical nephrectomy Present Absent	 52 (78.8) 14 (21.2)
History of metastasectomy Present Absent	 3 (4.5) 63 (95.5)
Lymphovascular invasion Present Absent	 14 (21.2) 52 (78.8)
Renal vein thrombosis Absent Present	 56 (84.8) 10 (15.2)
First-line treatment Sunitinib Pazopanib	 43 (65.2) 23 (34.8)
ECOG performance score <0 ≥1	 21 (31.8) 45 (68.2)
Number of metastatic sites 1 vs 2 3	 30 (66.7) 17 (33.3)

The median patient age was 58 [37-86] years, while the median overall survival (OS) was 19 months. The OS rates calculated at the 24th, 36th, and 60th months were 78.7%, 54%, and 20,2%, respectively. The median progression-free survival was calculated as 9 months. The median follow-up duration was 32.7 months.

The review regarding first-line treatment regimens revealed that 43 (65.2%) patients were prescribed sunitinib while the remaining 23 (34.8%) were on pazopanib treatment. Twenty-one (31.8%) patients had an ECOG performance score of 0, while 45 (68.2%) scored 1 or higher. While 30 (66.7%) patients had 1 or 2 metastatic sites, 17 (33.3%) had at least 3 (Table 1).

According to the ROC analysis, the optimal cut-off value for PDWLR was 9.33 (sensitivity 59.6%, specificity 59.6%). Among all patients, 32 had an PDWLR lower than 9.33, while 34 had an RDWLR higher than 9.33. Comparison between these patients regarding OS revealed that median OS was significantly higher in the former group than the latter (26 vs. 9 months, p=0.04) (Figure 1).

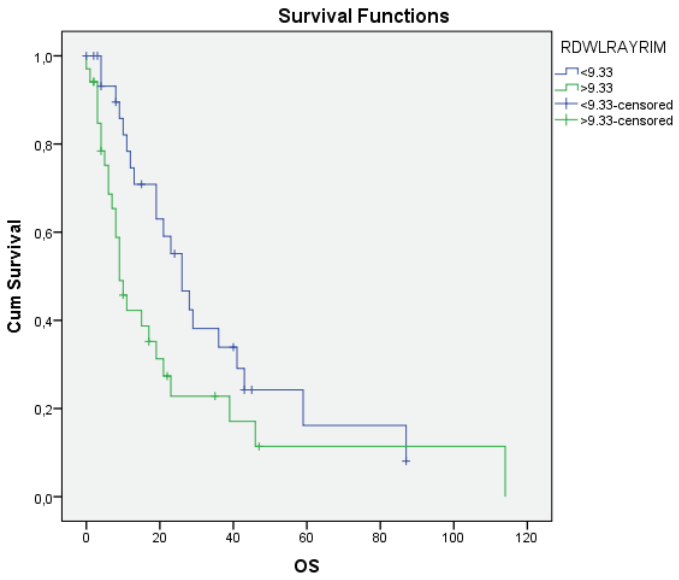

Figure 1.

However, the difference between these two groups was insignificant concerning progression-free survival (PFS) (p=0.501) (Figure 2).

Thus, PDWLR did not affect the PFS in mRCC patients (Figure 3).

Also, other parameters, including ECOG performance score, side of the renal tumor, presence or absence of LVI, and the number of metastatic sites, did not influence the PFS (p=0.117, p=0.317, p=0.345, p=0.269). As per ROC analysis, 200 was the optimal cut-off point in predicting OS (sensitivity: 59.6%; specificity: 52.6%).

Univariate and multivariate analyses were performed to investigate the effects of the demographic and clinical parameters on OS (Table 2).

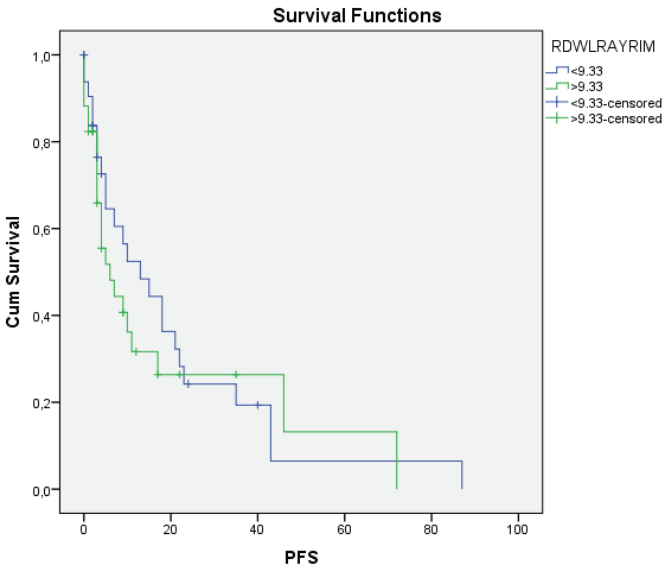

Figure 2.

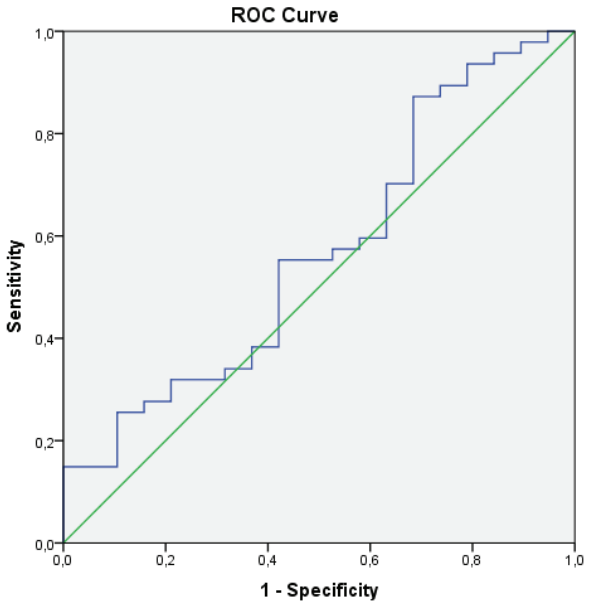

Figure 3.

The univariate analysis revealed that ECOG performance score and PDWLR had significantly affected the OS in patients with mRCC (HR: 0.489, HR: 1.851, p=0.047, p=0.04). However, only RDLWR emerged as an independent parameter affecting OS in multivariate analysis (HR: 2.047, p=0.026). In addition, analyses concerning the associations between PDWLR and other parameters showed a significant relationship between the ECOG performance score, PLR, and PDWLR (Table 3).

As per these results, RDWLR was not affected by patient age, gender, LVI status, side of the renal tumor, or the number of metastatic sites.

Discussion

Although there is consensus in the literature regarding the use of tyrosine-kinase inhibitors (TKI) as the first-line treatment in patients with mRCC, it is also accepted that response to treatment widely differs from patient to patient (12). Therefore, there is an ongoing search for novel markers to improve the prediction of outcomes such as treatment response, disease progression, and patient survival.

In 2012, Keizman et al. investigated the association of pre-treatment NLR with PFS and OS in 133 patients with mRCC who were prescribed a TKI (i.e., sunitinib) (13). They concluded that an NLR of 3 or lower was significantly associated with OS. Since NLR and PLR were suggested as markers of systemic inflammatory response, researchers continued to focus on these hematological indices to validate their prognostic significance in the setting of mRCC. Thus, in 2015, Gunduz and coworkers retrospectively reviewed the data of 100 patients with mRCC to assess the prognostic value of PLR in this disease (14). These authors demonstrated that a PLR level higher than 210 was significantly associated with reduced PFS and OS in patients with mRCC.

In line with Keizman et al., Chrom and colleagues analyzed the data of 266 mRCC patients and investigated the parameters that might affect the OS (13,15). These patients were received TKIs such as sunitinib, pazopanib, or sorafenib. These researchers concluded that the Fuhrman grade was significantly associated with the survival of these patients. Additionally, an NLR of 4 or higher was independently associated with an unfavorable prognosis in this study.

Park et al. analyzed the significance of PLR and NLR in the prognosis of mRCC patients (16). They worked on 63 patients who were on TKIs and found that a high PLR (i.e., PLR>150) was related to significantly shorter survival. Similarly, Wang et al. reported that an elevated PLR predicted poor OS in renal and prostate cancer patients (8).

Semeniuk-Wojtas et al. investigated the prognostic values of systemic inflammation indices such as NLR, PLR, and CRP for PFS and OS in patients with mRCC who were on TKIs (12). This meta-analysis concluded that NLR, PLR, and CRP could predict clinical outcomes in these patients. Huszno et al. evaluated the significance of hematological indices such as PLR and NLR in patients with mRCC (17). After reviewing the data of 141 mRCC patients retrospectively, these authors concluded that elevated (i.e., >3.68) NLR and PLR (i.e.,>144.4) were significantly associated with shorter OS and PFS and that NLR and PLR

Table 2. Results of univariate and multivariate analysis

Parameter	Hazard ratio (HR)	p value (univariate analysis)	Hazard ratio (HR)	p value (multivariate analysis)
Age <65 vs. >65	0.685 (0.371-1.265)	0.226		
Gender Male vs. female	1.931 (1.000-3.7289	0.05	0.426 (0.212-0.859)	0.017
History of radical nephrectomy Present vs. absent	0.368 (0 .088-1.543)	0.171		
ECOG performance score <1 ≥1	0.489 (0.241-0.992)	0.047	0.573 (0.278-1.184)	0.133
Number of metastatic sites 1,2 vs. 3	1.022 (0.560-1.865)	0.944		
Lymphovascular invasion Present vs. absent	1.348 (0.664-2.736)	0.408		
PLR ≤200 vs. >200	1.639 (0.903-2.974)	0.104		
PDWLR	1.851 (1.028-3.331)	0.04	2.047 (1.091-3.840)	0.026
RDW	1.422 (0.760-2.662)	0.271		

ECOG: Eastern Cooperative Oncology Group, PDWLR: Platelet Distribution Width Lymphocyte Ratio, RDW: Red cell distribution width

Table 3. Analysis of the relationship between PDWLR and study parameters

Parameters	PDWLR<9.33	PDWLR>9.33	pvalue
PLR <200 >200	 20(62.5) 12(37.5)	 9(26.5) 25(73.5)	0.003
AGE <65 >65	 22(68.8) 10(31.2)	 20(58.8) 14(41.2)	0.402
GENDER Female Male	 10(31.2) 22(68.8)	 7(20.6) 27(79.4)	0.322
ECOG performancescore <1 >1	 15(46.9) 17(53.1)	 6(17.6) 28(82.4)	0.011
LVI absent present	 26(81.2) 6(18.8)	 26(76.5) 8(23.5)	0.635
Tumorlocalization Right Left	 15(46.9) 17(53.1)	 15(44.1) 19(55.9)	0.822
Number of metastaticsites 1 or 2 ≥3	 21(65.6) 11(34.4)	 23(67.6) 11(32.4)	0.862

PDWLR: Platelet distribution width lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ECOG: Eastern Cooperative Oncology Group, LVI: Lymphovascular invasion

were independent prognostic factors for OS. In line with this study, Aktepe et al., who worked on 150 mRCC patients on TKI treatment, reported that PLR was an independent predictor for OS in these patients, and those with a PLR of higher than 204 had a significantly lower median OS than those with a PLR lower than this level (18).

Although several studies analyzed the roles of NLR and PLR in predicting the prognosis of mRCC, none investigated the role of PDWLR (8,12-18). Awadth et al. investigated this marker in systemic lupus erythematosus (SLE) patients and reported that PDWLR could be considered an adjunct biomarker in its diagnosis (19). In addition, they concluded that PDWLR

could be used to follow SLE patients' disease activity. As such, Kose et al. reported that relatively higher PDWLR levels were associated with severe envenomation in patients with snakebites (20). These researchers concluded that PDWLR could be used as an indicator of disease severity and a predictor of adverse outcomes.

To the best of our knowledge, our study was the first to investigate the role of PDWLR in predicting survival in mRCC patients. However, it has some limitations that should be considered while evaluating its findings. First, it is a retrospective study. Second, it has a small sample size. Third, the analysis did not include histopathological parameters such as Fuhrman grade and hematological indices such as NLR. However, despite these weaknesses, we conclude that PDWLR can be used in prognostic scoring systems for mRCC patients.

Compliance with Ethical Standards:All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval for this cross-sectional study was granted by Ankara Dışkapı Training and Research Hospital clinical research ethics committee decision date and number:28.06.2021 -114/17

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