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Araştırma Makalesi / Research Article

Prognostic Value of De Ritis Ratio (aspartate aminotransaminase/ alanine aminotransaminase) and Systemic Inflammatory Markers in Patients with Non-Metastatic Clear Cell Renal Cell Carcinoma

Non-Metastatik Berrak Hücreli Renal Karsinomalı Hastalarda De Ritis Oranı (aspartat aminotransaminaz/alanin aminotransaminaz) ve Sistemik İnflamatuar Belirteçlerin Prognostik Değeri

[1]Ali Furkan Batur, [1]Muhammed Furkan Aydogan, [2]Muslu Kazım Korez, [1]Murat Gul, [1]Mehmet Kaynar, [3]Murat Akand, [1]Ozcan Kilic, [1]Serdar Goktas

[1]Selçuk University School of Medicine , Department of Urology, Konya, Turkey

[2]Selçuk University School of Medicine , Department of Biostatistics, Konya, Turkey

[3]University Hospitals Leuven, Department of Urology, Leuven, Belgium

Abstract

This study evaluates whether the preoperative aspartate aminotransaminase/ alanine aminotransaminase (De Ritis Ratio - DRR) value affects the prognosis and has a relationship with histopathological variables of non-metastatic clear cell renal cell carcinoma (ccRCC) cases surgically treated. The second aim was to assess the association between neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and lymphocyte monocyte ratio (LMR) values with prognosis, and progression-free survival (PFS) in the same group of patients. We reviewed the medical records of 118 non-metastatic ccRCC cases that underwent partial or radical nephrectomy (2009-2019). Kaplan-Meier analysis with log-rank tests was performed to evaluate the difference in progression between DRR, NLR, PLR, and LMR and groups. Moreover, univariate and multiple Cox proportional hazard analyses were performed to identify the predictors of progression. Metastases and local recurrence were detected in 22.9% and 6% of the patients, respectively. Our median follow-up period was 26 months. The univariate Cox regression analysis was showed that the tumor size, invasion (presence), pathological stage (3+4), and NLR level (≥ 1.98)) were statistically significant predictors for PFS. However, DRR was no statistically significant predictor for PFS (p>.05). We did not find any significant value for the DRR value as a predictive parameter in ccRCC prognosis. The increase in NLR is associated with a poor prognosis. Therefore, the use of NLR in predictive nomograms may contribute positively to the determination of prognosis.

Keywords: De Ritis ratio; clear cell; renal cell cancer; kidney cancer; prognosis

Özet

Bu çalışmada cerrahi olarak tedavi edilen nonmetastatik berrak hücreli renal hücreli karsinom (bhRHK) olgularının preoperatif aspartat aminotransaminaz/alanin aminotransaminaz (De Ritis Oranı - DRO) değerinin prognozu etkileyip etkilemediği ve histopatolojik değişkenlerle ilişkisi değerlendirilmiştir. İkinci amaç da, aynı grup hastalarda nötrofil lenfosit oranı (NLO), trombosit lenfosit oranı (PLO) ve lenfosit monosit oranı (LMO) değerleri ile prognoz ve progresyonsuz sağkalım (PS) arasındaki ilişkiyi değerlendirmekti. Kliniğimizde 2009-2019 yılları arasında parsiyel veya radikal nefrektomi uygulanan 118 metastatik olmayan bhRHK vakasının tıbbi kayıtları incelenerek çalışmaya alındı. DRO, NLO, PLO ve LMO ve gruplar arasındaki progresyon farkını değerlendirmek için log-rank testleri ile Kaplan-Meier analizi yapıldı. Ayrıca, progresyon öngörücülerini belirlemek için tek ve çok değişkenli Cox regresyon analizleri yapıldı. Hastaların %22,9'unda metastaz ve %6'sında lokal nüks saptandı. Ortanca takip süresi 26 aydı. Tek değişkenli Cox regresyon analizi, tümör boyutunun, invazyon (varlığı), patolojik evre (3+4) ve NLO seviyesinin (≥ 1,98) PS için istatistiksel olarak anlamlı öngörücüler olduğunu gösterdi. Ancak DRO, PS için istatistiksel olarak anlamlı bir öngörücü değildi (p>.05). bhRHK prognozunda prediktif parametre olarak DRR değeri için anlamlı bir değer bulamadık. Ancak, NLO'deki artış kötü prognoz ile ilişkili bulundu. Bu nedenle prediktif nomogramlarda NLO kullanımı prognozun belirlenmesine olumlu katkı sağlayabilir.

Anahtar Kelimeler: De Ritis oranı; berrak hücreli; renal hücreli kanser; böbrek kanseri; prognoz

Correspondence:
Ali Furkan BATUR
Selçuk University School of Medicine , Department of Urology, Konya, Turkey,
e-mail: alifurkanbatur@gmail.com

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1. Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all malignancies, with the highest incidence in western countries. Clear cell RCC(ccRCC) constitutes 70-80% of all RCCs. Roughly 70% of ccRCCs are localized at the time of diagnosis. However, 20% to 40% of patients who underwent nephrectomy due to localized RCC show recurrence, and this rate is also valid for ccRCC (1).

Several factors, including anatomical, histological, clinical, and molecular, and nomograms to predict localized RCC prognosis, have been identified and are currently used (1). Even though most of these prognostic factors and models have predictive accuracy, there is an urgent need to identify new prognostic factors to determine the patients under the risk of disease recurrence and progression more precisely.

Disease progression in malignancies depends on the complicated relationship between the tumor and the patient's inflammatory response. However, the synthesis of inflammatory cytokines triggered by the tumor microenvironment has been shown to alter hematological components, such as serum neutrophil and lymphocyte counts (2). Platelets have also been associated with tumor angiogenesis and metastasis (3). Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and lymphocyte monocyte ratio (LMR) are the most investigated ratios for this purpose. Mainly, NLR has been extensively studied in colorectal, stomach, ovarian, kidney, and bladder cancers. Many studies have shown that its elevation is associated with a poor prognosis (4–6). Publications exist to demonstrate that the increase in PLR value and decreased LMR value are related to poor RCC prognosis. However, most of these publications evaluating systemic inflammatory markers in RCC have focused on metastatic patients. The number of publications that primarily evaluate localized RCC is limited (7–11).

Aspartate aminotransaminase(AST) and alanine aminotransaminase(ALT) are used in many clinical branches to evaluate liver function. These aminotransferases are expressed in various compartments of malignant or non-malignant cells. While ALT is only found in the hepatocellular cytoplasm and mitochondria, AST can be expressed in many organs such as the heart, kidney, brain skeletal muscle, and liver. The ratio of these two liver function enzymes is known as the De Ritis Ratio (DRR)(12). The DRR increases in direct proportion to the increase in anaerobic glycolysis with the hypothesis called the Warburg effect and indicated a deterioration in the prognosis of the disease. DRR has been studied previously in testicular cancer, pancreatic cancer, prostate cancer, bladder cancer, and RCC. Although an actual cut-off value was not found in these studies, it was stated that prognosis and overall survival worsen with the increase of DRR(13,14). Considering the studies that specifically evaluated the relationship between DRR and RCC, it was seen that there were 9 studies in the literature (15–23). Five of these studies assess the relationship between localized RCC and DRR. In all of these, the relationship between increased DRR and poor prognosis has been demonstrated at different rates (15,17–19,23). Only 1 of these studies specifically evaluated cases of ccRCC. In this study, Lee et al. determined the DRR cut-off value as 1.5. In histopathological subgroup analysis, it was shown that the increase in DRR was associated with an unfavorable prognosis in patients with ccRCC (19).

Based on this literature information, we primarily aimed to evaluate whether the preoperative DRR value affects the prognosis and has a relationship with histopathological variables of our non-metastatic ccRCC cases surgically treated. In addition, our second goal was to assess the association between NLR, PMR, and LMR values with histopathological factors and prognosis in the same group of patients. Finally, we aimed to evaluate the correlation of these rates among themselves. In this sense, our study was the first study to assess all these ratios' relations with non-metastatic ccRCC patients' prognosis.

2. Material and Methods

Patient population

The files of 225 patients diagnosed with kidney cancer at the Selcuk University Medical Faculty hospital between 01.10.2009 and 20.05.2019 were retrospectively reviewed. Primary RCC patients who underwent partial or radical nephrectomy and whose pathology had ccRCC were included in our study. Exclusion criteria were as follows: being younger than 18 years of age(n=3), pregnancy status(n=2), patients with non-clear cell RCC(n=51), history of metastatic disease at the time of diagnosis(n=22), hematological disease or second malignancy at the time of diagnosis(n=10), history of liver diseases(n=7) or lack of data(n=12). Finally, a total of 118 patients were included in the analyses.

As is routine practice in the clinic, Tumor-Node-Metastasis classification(1) is used, and abdominal computed tomography or magnetic resonance imagination are routinely performed in the preoperative period for patients suspected of having a kidney mass at ultrasonography.

Complete blood count and liver function tests were routinely performed during preoperative anesthesia preparation. The tests were evaluated at the earliest 30 days before surgery. During this period, if the patient had more than one blood test, the test closest to the operation was evaluated. Patients with incomplete data were excluded. DRR was calculated by dividing the AST value by the ALT value. NLR was calculated by dividing the neutrophil count by the lymphocyte count. PLR and LMR were calculated by dividing the platelet count and lymphocyte count by the lymphocyte count and monocyte count, respectively.

Radical or partial nephrectomy was performed either by an open or laparoscopic technique by four different experienced urologists with standard surgical methodology. Open surgeries were performed transperitoneally or retroperitoneally, depending on the surgeon's preference. The laparoscopic method was always performed in a transperitoneal way per the clinical routine.

The demographic data, preoperative blood chemistry and complete blood count results, tumor size according to the preoperative radiologic investigation, and the patients' pathology results were recorded. Pathological features included tumor size and presence of renal vein and pelvic invasion, renal capsule invasion, lymph node invasion, and adrenal gland involvement. The grading was made according to the Fuhrmann nuclear grading system(24). The pathological evaluation was carried out by pathologists experienced in the uro-oncology field in our university's pathology department as required by routine practice.

Follow-up schedule and the definition of progression

In the post-operative period, patients were followed up every 6 months for the first 2 years and annually thereafter. Physical examination, laboratory tests (complete blood count, serum blood chemistry, erythrocyte sedimentation rate, and urinalysis), and thoracic, abdominal, and pelvic tomography were performed as required by routine practice. Distant metastasis detection and/or local recurrence were defined as progression. Mortality data of the patients were taken from the national population directorate system. Progression-free survival (PFS) was accepted as the time from the moment of surgery to progression at the last follow-up visit.

Outcomes

The primary outcome is comparing prognostic factors, progression status, metastasis status, and life status of the disease with values below and above DRR 1.24. The secondary outcomes are to evaluate the relation of NLR, PLR, and LMR values with histopathological factors and prognosis in the same group of patients. Tertiary outcomes are the evaluation of the correlations of these ratios (DRR, NLR, PLR, and LMR) among themselves.

Statistical analysis

All statistical analysis was performed using the IBM Statistical Package for the Social Sciences version 22 (IBM SPSS Statistics for Windows, Chicago, IL, USA). Shapiro-Wilk and Q-Q plots were used to check the normality of the variables. Data were expressed as mean ± standard deviation (range: min-max), or median (interquartile range) for continuous variables, and also described as counts (n) and percentages (%) for categorical variables. Independent t-test, Mann-Whitney U test, and chi-square test were used to evaluate the groups' differences in parameters. According to the studies performed, the 1.24 value determined for DRR was chosen as the cut-off value (16). Similarly, 1.98, 189, and 3 values were determined as cut-off values for NLR (25), PLR (9), and LMR (10), respectively, according to the performed studies. The correlations between stage, Fuhrman grade, invasion status metastases, progression, DRR, NLR, PLR, and LMR parameters were investigated by the Spearman correlation coefficient. Kaplan-Meier analysis with log-rank tests was performed to evaluate the difference in progression between DRR, NLR, PLR, and LMR and groups. Moreover, univariate and multiple Cox proportional hazard analyses were performed to identify the predictors of progression. A p-value less than 0.05 was considered statistically significant.

3. Results

The average age of 118 patients included in the study was 63.44 years. The mean tumor size was 5.1 cm. A total of 78% of the patients were stage 1, 4.2% stage 2, 13.6% stage 3, and 16.1% stage 4 without metastases. Pathological characteristics of the patients were 8.5%, 45.8%, 38.1%, and 9% of the Fuhrmann grade 1, 2, 3, 4 ccRCC, respectively. Metastases and local recurrence were detected in 22.9% and 6% of the patients, respectively. Our median follow-up period was 26 months, and 8 patients died during this period. The median PFS was 23 months.

For DRR, a value of ≥ 1.24 was taken as the cut-off point. According to this value, no statistically significant difference was found in tumor stage, invasion status, Fuhrmann grade, metastasis, and progression parameters(Table 1).

Table 1. The demographic and clinicopathological characteristics according to the De ritis ratio (>1.24 vs ≥ 1.24) groups

Variables	Total (*n*=118)	DRR < 1.24	DRR ≥ 1.24	*p*-value
Age (years)	63.44 ± 11.46 (29 – 86)	62.96 ± 12.56	63.86 ± 10.49	.674
Gender				.381
Male	69 (58.5%)	35 (63.6%)	34 (54%)	
Female	49 (41.5%)	20 (36.4%)	29 (46%)	
Stage				.533
Stage 1	78 (66.1%)	7 (67.3%)	41 (65.1%)	
Stage 2	5 (4.2%)	1 (1.8%)	4 (6.3%)	
Stage 3	16 (13.6%)	9 (16.4%)	7 (11.1%)	
Stage 4	19 (16.1%)	8 (14.5%)	11 (17.5%)	
Surgical TreatmentChoice				.783
Radical Nephrectomy	92 (78%)	44 (80%)	48 (76.2%)	
Partial Nephrectomy	26 (22%)	11 (20%)	15 (23.8%)	
Size (mm)	5.160 ± 2.55	5.297	5.028	.571
Fuhrmann grade				.768
Fuhrmann 1	10 (8.5%)	6 (10.9%)	4 (6.3%)	
Fuhrmann 2	54 (45.8%)	26 (47.3%)	28 (44.4%)	
Fuhrmann 3	45 (38.1%)	19 (34.5%)	26 (41.3%)	
Fuhrmann 4	9 (7.6%)	4 (7.3%)	5 (7.9%)	
Invasion Status				.469

None	85 (72%)	42 (72.4%)	43 (71.7%)	
Renal vein and pelvic	15 (12.7%)	7 (12.1%)	8 (13.3%)	
Renal capsule	10 (8.5%)	7 (12.1%)	3 (5.0%)	
Lymph node	5 (4.2%)	4 (1.7%)	1 (6.7%)	
Adrenal gland	3 (2.5%)	2 (1.7%)	1 (6.7%)	
ECOG				.797
ECOG 1	87 (73.7%)	41 (74.5%)	46 (73%)	
ECOG 2	25 (21.2%)	12 (21.8%)	13 (20.6%)	
ECOG 3	6 (5.1%)	2 (3.6%)	4 (6.3%)	
Metastasis				.516
None	98 (83.1%)	47 (85.5%)	51 (81%)	
Lungs	6 (5.1%)	2 (3.6%)	4 (6.3%)	
Bone	7 (5.9%)	2 (3.6%)	5 (7.9%)	
Liver	1 (0.8%)	0 (0%)	1 (1.6%)	
Multipl	6 (5.1%)	4 (7.3%)	2 (3.2%)	
Progression				.688
Negative	98 (83.1%)	47 (85.5%)	51 (81%)	
Positive	20 (16.9%)	8 (14.5%)	12 (19%)	
Survival status				.999
Alive	110 (93.2%)	51 (92.7%)	59 (93.7%)	
Ex	8 (6.8%)	4 (7.3%)	4 (6.3%)	
Follow-up duration	26 (12 – 49) (*n*=118)	26 (15.50 – 59.50)	27 (10 – 37.75)	.098
Overall Survival	26.50 (12 – 48.75)	26 (16 – 59.50)	27 (9.50 – 36.50)	.077
Progression Free Survival	23.50 (6 – 38.75)	24 (12 – 43.50)	23 (5 – 33)	.278

a Values are presented as mean±standard deviation, or number(%)
b DRR De Ritis Ratio, ECOG Eastern Cooperative Oncology Group Performance Status

For NLR, statistically significant differences were found regarding the gender, stage, tumor size, Fuhrmann grade, invasion status, metastases, and progression parameters between the groups(<1.98 vs. ≥1.98) (Table 2).

Table 2. The demographic and clinicopathological characteristics according to the Neutrophil lymphocyte ratio (<1.98 vs ≥ 1.98) groups

Variables	NLR < 1.98	NLR ≥ 1.98	*p*-value
Age (years)	62.2 ±9.7	64.8 ±12.7	.228
Gender			**.021**
Male	21 (44.7)	47 (66.2)	
Female	26 (55.3)	24 (33.8)	
Stage			**.043**
Stage 1	41 (87.2%)	47 (66.2%)	
Stage 2	3 (6.4%)	5 (7.0%)	
Stage 3	1 (2.1%)	7 (9.9%)	
Stage 4	2 (4.3%)	12 (16.9%)	
Size	4.1 (1.5-8.5)	5 (1.5-14)	**.030**
Fuhrmann grade			**,040**
Fuhrmann 1	6 (12.8%)	4 (5.6%)	
Fuhrmann 2	20 (42.6%)	34 (47.9%)	
Fuhrmann 3	21 (44.7%)	25 (35.2%)	
Fuhrmann 4	0 (0.0%)	8 (11.3%)	
Invasion Status			**,025**
None	41 (87.2%)	46 (64.8%)	

Renal vein and pelvic	5 (10.6%)	10 (14.1%)	
Renal capsule	0 (0.0%)	8 (11.3%)	
Lymph node	1 (2.1%)	4 (5.6%)	
Adrenal gland	0 (0%)	3 (4.2%)	
Metastasis			,097
Negative	43 (91.5%)	57 (80.3%)	
Positive	4 (8.5%)	14 (19.7%)	
Progression			**.007**
Negative	41 (87.2%)	46 (64.8%)	
Positive	6 (12.8%)	25 (35.2%)	
Follow-up duration	26 (11-113)	26 (6-116)	.897
Progression Free Survival	22 (8-113)	24 (6-116)	.854

a Values are presented as mean±standard deviation, median(min-max) or number(%)
b NLR Neutrophil lymphocyte ratio

For PLR, statistically significant differences were found regarding the stage, Fuhrmann grade, and invasion status parameters between the groups(<189 vs. ≥189) (Table 3).

For LMR, according to the cut-off value statistically significant difference was only found regarding the stage parameter between the groups (>3 vs. ≤3) (Table 4).

Table 3. The demographic and clinicopathological characteristics according to the platelet lymphocyte ratio (<189 vs ≥ 189) groups

Variables	PLR < 189	PLR ≥ 189	*p*-value
Age (years)	63±11.4	66.10±12.8	.342
Gender			.219
Male	54 (55.1%)	14 (70.0%)	
Female	44 (44.9%)	6 (30.0%)	
Stage			**.006**
Stage 1	77 (78.6%)	11 (55.0%)	
Stage 2	8 (8.2%)	0 (0.0%)	
Stage 3	4 (4.1%)	4 (20.0%)	
Stage 4	9 (9.2%)	5 (25.0%)	
Size (mm)	4.7 (1.5-14)	4.7 (1.8-9.5)	.849
Fuhrmann grade			.059
Fuhrmann 1	10 (10.2%)	0 (0.0%)	
Fuhrmann 2	45 (45.9%)	9 (45.0%)	
Fuhrmann 3	39 (39.8%)	7 (35.0%)	
Fuhrmann 4	4 (4.1%)	4 (20.0%)	
Invasion Status			.053
None	76 (77.6%)	11 (55.0%)	
Renal vein and pelvic	12 (12.2%)	3 (15.0%)	
Renal capsule	4 (4.1%)	4 (20.0%)	
Lymph node	4 (4.1%)	1 (5.0%)	
Adrenal gland	2 (2.0%)	1 (5.0%)	
Metastasis			.972
Negative	83 (84.7%)	17 (85.0%)	
Positive	15 (15.2%)	3 (15.3%)	
Progression			.126
Negative	75 (76.5%)	12 (60.0%)	
Positive	23 (23.5%)	8 (40.0%)	
Follow-up duration	28 (6-116)	21 (6-105)	.948
Progression Free Survival	23.50 (6-116)	18 (6-105)	.951

a Values are presented as mean±standard deviation, median(min-max) or number(%)
b PLR platelet lymphocyte ratio

Table 4. The demographic and clinicopathological characteristics according to the lymphocyte monocyte ratio (> 3 vs ≤ 3) groups

Variables	LMR > 3	LMR ≤ 3	*p*-value
Age (years)	63 (39-86)	69 (29-83)	.221
Gender			**.004**
Male	37 (48.1%)	31 (75.6%)	
Female	40 (51.9%)	10 (24.4%)	
Stage			**.035**
Stage 1	62 (80.5%)	26 (63.4%)	
Stage 2	6 (7.8%)	2 (4.9%)	
Stage 3	2 (2.6%)	6 (14.6%)	
Stage 4	7 (9.1%)	7 (17.1%)	
Size (mm)	4.7 (1.5-11)	4.9 (1.5-14)	.154
Fuhrmann grade			.840
Fuhrmann 1	7 (9.1%)	3 (7.3%)	
Fuhrmann 2	33 (42.9%)	21 (51.2%)	
Fuhrmann 3	32 (41.6%)	14 (34.1%)	
Fuhrmann 4	5 (6.5%)	3 (7.3%)	
Invasion Status			.131
None	62 (80.5%)	25 (61.0%)	
Renal vein and pelvic	7 (9.1%)	8 (19.5%)	
Renal capsule	5 (6.5%)	3 (7.3%)	
Lymph node	2 (2.6%)	3 (7.3%)	
Adrenal gland	1 (1.3%)	2 (4.9%)	
Metastasis			.140
Negative	68 (88.3%)	32 (78.0%)	
Positive	9 (11.7%)	9 (22.0%)	
Progression			.156
Negative	60 (77.9%)	27 (65.9%)	
Positive	17 (22.1%)	14 (34.1%)	
Follow-up duration	29 (6-116)	26 (11-108)	.684
Progression Free Survival	23 (6-116)	24 (6-108)	.876

a Values are presented as mean±standard deviation, median(min-max) or number(%)
b LMR ymphocyte monocyte ratio

When we evaluated the correlation of stage, presence of invasion, Fuhrmann grade, metastasis, progression, DRR, NLR, PLR, and LMR parameters, a significant correlation was not found with DRR. However, NLR was statistically significantly correlated with stage, invasion status, progression, PLR, and LMR parameters. Similarly, PLR and LMR parameters were statistically significantly associated with the stage and presence of invasion parameters.

Kaplan-Meier analysis showed no significant difference between high (≥1.24) and low (<1.24) DRR for PFS (Log-rank=0.836, p=.361). There was a statistically significant difference between high (≥1.98) and low (<1.98) NLR for PFS (Log-rank=5.738, p=.017) (Figure 1). Kaplan-Meier analysis performed according to cut-off values for PLR(≥198 vs. <198) and LMR(>3 vs. ≤3) values did not find any statistically significant difference between the groups for PFS (p=.214 and p=.208).

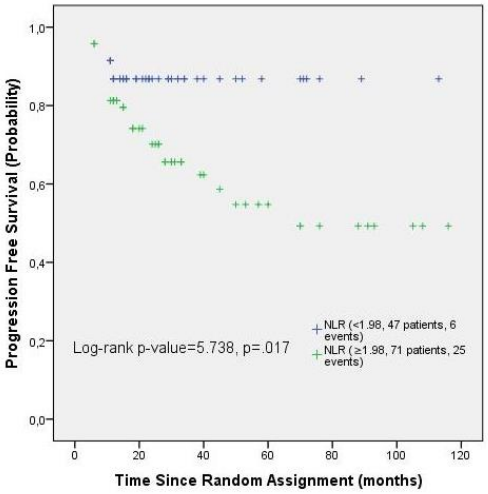

Figure 1. Kaplan-Meier analysis of the patients between high (≥1.98) and low (<1.98) neutrophil lymphocyte ratio (NLR) for Progression Free Survival

The univariate Cox regression analysis was showed that the tumor size, invasion (presence), pathological stage (3+4), and NLR level (≥ 1.24)) were statistically significant predictors for PFS (Table 5). However, DRR was no statistically significant predictor for PFS (p>.05). Besides, only the pathological stage (3+4) was a statistically significant predictor for PFS in multiple analyses (Table 5).

Table 5. Cox proportional hazard analysis of prognostic factors for progression free survival in patients undergoing surgery for non-metastatic clear cell renal cell carcinoma

	Univariate		Multiple	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Tumor size	1.22 (1.07 - 1.39)	**.002**	.997 (,84 – 1.17)	.975
Invasion* (vs none)	4.00 (1.97 – 8.14)	**.000**	1.47 (.52 – 4.09)	.462
Pathological stage ≥ 3 (vs ≤ 2)	***.153 (0.75 - 0.31)***	***.000***	***5.95 (1,97 - 17,9)***	***.002***
Fuhrman grade ≥ 3 (vs ≤ 2)	1.83 (0.89 – 3.74)	.098	1.14 (.50 – 2.63)	.745
DRR ≥ 1.24 (vs < 1.24)	.719 (0.35 – 1.47)	.367	.894 (.41 – 1.90)	.771
NLR ≥ 1.98 (vs < 1.98)	.356 (0.14 – 0.86)	**.023**	1.94 (.71 – 5.33)	.194
PLR ≥ 189 (vs < 189)	1.65 (0.73 – 3.69)	.223	.402 (.12 – 1.26)	.118
LMR ≤ 3 (vs > 3)	1.56 (0.77 – 3.17)	.216	.916 (.39 – 2.14)	.840

a Invasion indicates renal vein and pelvic, renal capsule, lymph node, or adrenal gland invasion
b DRR De Ritis Ratio, NLR Neutrophil Lymphocyte Ratio, PLR Platelet Lymphocyte Ratio, LMR Lymphocyte Monocyte Ratio

4. Discussion and Conclusion

We did not find a significant effect of DRR in predicting the progression and prognosis of patients operated for ccRCC in this study. On the other hand, we found statistically significant differences between the risk groups according to the accepted cut-off limits of NLR and PLR in terms of metastases and progression.

In one of the 9 studies evaluating the DRR relationship in RCC patients, Canat et al. retrospectively assessed 298 patients who underwent nephrectomy for non-metastatic RCC. Although a relation was found between DRR and renal vein invasion, capsule invasion, and pelvis infiltration, no association with prognosis has been determined in this study (17). On the contrary, Hakmin Lee et al. found a significant relationship between post-operative survival and DRR values in patients who underwent nephrectomy due to non-metastatic clear cell RCC (19). In the study conducted by Bezan et al, preoperative DRR was an independent prognostic factor in patients with non-metastatic RCC (15). A recent study

examining the dynamics of DRR showed that non-metastatic RCC patients with low DRR before the operation who had higher DRR rates postoperatively were associated with worse cancer-specific survival (18).

From another point of view, Laukhtina et al. was concluded that DRR would not be applicable in predicting the prognosis of patients in the metastatic RCC group who underwent cytoreductive surgery(21). However, Ishihara et al. stated that DRR may be useful without determining the prognosis of patients undergoing cytoreductive surgery (16). The relationship between RCC in patients with end-stage renal disease and DRR has also been investigated. It has been stated that DRR has a prognostic value in these patients (26). In our study, no statistically significant difference was found with DRR regarding histopathological changes that could affect progression and prognosis. Also, when evaluated in terms of PFS, no statistically significant difference was found in terms of the accepted cut-off limit of 1.24 in Kaplan-Meier analysis. Also, in the Cox regression analysis, it was seen that there was no significant relationship between the DRR value.

The systemic inflammatory response is associated with survival in cancer patients. This inflammatory response can be measured by looking at the concentration of specific serum proteins (albumin, C-reactive protein) and the number of blood cells (neutrophils, lymphocytes, and platelets). The ratios of cell numbers, lymphocyte count, and serum albumin have been evaluated and compared in cancer studies many times(27).

Mainly, increasing NLR was associated with histopathological parameters that may lead to poor prognosis, metastasis, and progression in our study. These findings were consistent with the literature. Besides, there was a statistically significant difference between high (≥1.98) and low (<1.98) NLR for PFS according to the Kaplan-Meier analysis. Lastly, NLR was a statistically significant predictor for PFS according to the univariate cox regression analysis results but not for the multivariate analysis.

In our study, statistically significant differences were found regarding the stage, Fuhrmann grade, and invasion status parameters between PLR groups (<189 vs. ≥189). However, we did not find any statistically significant results regarding PLR value according to the univariate and multivariate cox regression analyses.

Few studies specifically evaluate the effects of NLR and PLR on recurrence in non-metastatic ccRCC in the literature. The study of Kim et al. evaluated 309 patients with a relatively long average follow-up period of 93 months. This study stated that post-operative evaluation of NLR is also effective in showing recurrences after 5 years. Similar to our research, when Kim et al. used 1.9 as the cut-off value in their study, the results were significant in univariate analysis but not in multivariate analysis (25). Also, Ohno et al. evaluated the effects of dynamic changes in NLR on non-metastatic ccRCC patients. They showed that lower NLR had better recurrence-free survival rates (27). In another study evaluating the effect of NLR on prognosis in non-metastatic ccRCC cases, Pichler et al. found no effect for cancer-specific survival and metastasis-free survival (28). Viers et al. found that higher NLR is associated with larger tumor size, higher nuclear grade, histologic tumor necrosis, and sarcomatoid differentiation. An NLR ≥ 4.0 was found to be significantly associated with worse 5-year cancer-specific and overall survival in this study (29). Albissini et al. found that increased PLR was significantly associated with reduced recurrence-free survival in their non-metastatic RCC patients (9). Besides, PLR>160 value was an independent risk factor for recurrence in Kim et al.'s study (25).

In our study, only the stage parameter was statistically meaningful between groups according to LMR values (>3 vs. ≤3). Besides, decreasing LMR was not significant in terms of PFS, according to Kaplan-Meier and cox regression analyses. In a meta-analysis conducted by Li et al., low LMR was statistically significant with poor overall survival, recurrence-free survival, and cancer-specific survival in RCC patients (30). Hutterer et al. stated that lower LMR was statistically significant with were statistically

significantly associated with older patients (≥65 y), high tumor grade (G3+G4), advanced pathologic T category (pT3+pT4), the presence of histologic tumor necrosis, and male gender (P<0.05). Besides, they found that low LMR as an independent prognostic factor for patients′ cancer-specific survival according to the multivariate analysis results (10).

Our study's limitations include the relatively small size of our patient group, the lack of patient data, the evaluation of only ccRCC patients, and the retrospective evaluation of the data. However, we think that it is our study's strength to evaluate all the ratios including the DRR, NLR, PLR, and LMR in the same specific group of non-metastatic ccRCC patients and the relationships among. Mainly, there are many studies in the literature showing the relationship between the increase of NLR with the negative prognosis and the factors affecting it. Our research in this direction has provided a natural control of our data group.

When studies examining the effect of DRR on the prognosis and metastasis of RCC are evaluated, it is impossible to give a definite cut-off value regarding this ratio and say that its increase is definitely related to poor prognosis. In this present study, DRR was not associated with prognosis and histopathological features related to prognosis in our non-metastatic ccRCC patient group. On the other hand, statistically significant results were found in our study regarding NLR, PLR, and LMR parameters, which have been studied much more in the literature and have more evidence. However, we could not prove that any of these ratios could affect the prognosis independently. When we evaluate all these together, we think that much more robust evidence is needed to include such ratios in the prognostic nomograms of RCC.

Ethics approval and consent to participate: *This retrospective chart review study involving human participants followed the institutional and national research committee's ethical standards and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained by the local ethics committee (approval number: 2019/158). All the procedures being performed were part of the routine care.*

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