Kocaeli Med J 2019; 8; 3: 22-27

Nötrofil-Lenfosit Oranı, Parsiyel Nefrektomi Öncesinde 4 cm'den Büyük Renal Kitlesi Olan Hastaların Patoloji Sonucunu Tahmin Etmekte Faydalıdır

Neutrophil-Lymphocyte Ratio is Valuable in Predicting the Pathology Result in the Patients with Renal Mass > 4 cm Prior to the Partial Nephrectomy

Volkan Çağlayan, Efe Önen, Sinan Avcı, Murat Şambel, Metin Kılıç, Erdem Toprak, Sedat Öner

Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Üroloji Kliniği, Bursa, Türkiye

ÖZ

GİRİŞ ve AMAÇ: *Nötrofil-lenfosit oranının (NLR) parsiyel nefrektomi (PN) öncesi renal kitlelerin patoloji sonuçlarının öngörülmesindeki etkinliğini değerlendirmek.*

YÖNTEM ve GEREÇLER: *Mart 2012 ve Mart 2018 tarihleri arasında PN yapılan 76 hastanın verileri değerlendirildi. Hastalar patoloji sonuçlarına (malign grup benign grup), tümör evresine (T1a-T1b) ve tümör derecesine (Grade 1-Grade2-Grade3) ve kitle boyutuna (<4 cm-> 4 cm) göre gruplandı.*

BULGULAR: *Benign grup 17 hastadan, malign grup 59 hastadan oluşmaktaydı. Benign ve malign grupların preoperatif NLR'leri karşılaştırıldığında istatistiksel olarak anlamlı bir fark bulunmadı (p = 0.113). Malign grup tümör evresine göre (T1a-T1b) 2 gruba ayrıldığında, T1b grubunun NLR değeri benign grup ve T1a grubundan anlamlı olarak yüksekti (sırasıyla p= 0.007 ve p<0.001). Grade 3 tümör grubunda NLR, grade1 ve grade2 gruplarına göre anlamlı olarak daha yüksekti (sırasıyla, p<0.001 ve p = 0.02). Otuz dört hastada, 4 cm'den büyük böbrek kitleleri vardı. NLR 4 cm'den büyük malign böbrek kitlesi olan hastalarda anlamlı olarak yüksekti (p = 0,035). Maligniteyi tahmin etmek için cut-off değeri 2,31 idi ve % 65 özgüllük ve % 50 duyarlılığa sahipti.*

TARTIŞMA ve SONUÇ: *NLR, böbrek kitleleri 4 cm'den büyük olan hastalarda patoloji sonucunu öngörmede değerli bir parametredir. Daha yüksek NLR değeri yüksek dereceli tümörler ile ilişkilidir. NLR'nin etkinliğini doğrulamak için ileri çalışmalar yapılmalıdır.*

Anahtar Kelimeler: *parsiyel nefrektomi, nötrofil-lenfosit oranı, renal hücreli karsinom*

ABSTRACT

INTRODUCTION: *To assess the efficacy of neutrophil-lymphocyte ratio (NLR) in predicting the pathology results of renal masses prior to partial nephrectomy (PN).*

METHODS: *The data of 76 patients who underwent PN between March 2012 and March 2018 was evaluated. Patients were grouped according to pathology results (malign group-benign group), tumor stage (T1a-T1b) and tumor grade (Grade1-Grade2-Grade3) and mass size (≤4 cm->4 cm).*

RESULTS: *Benign group was consisted of 17 patients and malign group was of 59 patients. No statistically significant difference was found when preoperative NLR of benign and malign groups were compared (p=0.113). When malign group was divided into 2 groups according to tumor stage (T1a-T1b), NLR of T1b group was significantly higher than benign group and T1a group (p=0.007 and p<0.001, respectively). In grade3 tumor group, NLR was significantly higher when compared with grade1 and grade2 groups (p<0.001 and p=0.02, respectively). Thirty-four patients had renal masses >4 cm. NLR was significantly higher in the patients with >4 cm malign renal masses (p=0.035). The cut-off value to predict malignancy was 2.31 with 65% specificity and 50% sensitivity.*

DISCUSSION and CONCLUSION: *NLR is a valuable parameter at predicting pathology result in patients with renal masses >4 cm. Higher NLR value was associated high grade tumors. Further studies must be performed to certify the efficacy of NLR.*

Keywords: *partial nephrectomy, neutrophil-lymphocyte ratio, renal cell carcinoma*

İletişim / Correspondence:
Dr. Efe Önen
Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Üroloji Kliniği, Bursa, Türkiye
E-mail:efe17@yahoo.com
Başvuru Tarihi: 22.08.2019
Kabul Tarihi: 04.11.2019

INTRODUCTION

Kidney cancer is the third most common diagnosed malign tumor of urogenitale system. It approximately has a worldwide incidence of 338000 new cases per year and constitutes 1.7 % of all cancer related deaths (1). In Europe, overall mortality rates for renal cell carcinoma (RCC), which is the most common type of kidney cancer (2), increased up to the early 1990s, and stabilised or declined thereafter (3). Due to increased use of imaging methods such as ultrasound (US) and computed tomography (CT), the rate of incidentally diagnosed RCC has increased (4-7). As a result, the incidence of smaller renal masses which are suitable for nephron-sparing treatments increased. Also, the published studies supported the partial nephrectomy (PN) versus radical nephrectomy (RN), as it could better preserve renal functions and prevent the development of metabolic or cardiovascular disorders subsequent to the surgery (8-10). However, imaging methods are still not sufficient for preoperatively decision-taking. Some benign hemorrhagic or inflammatory cysts may mimic like malignant tumors on CT images (11). Although most angiomyolipomas contain fat and can be diagnosed with unhanced CT alone, 5 % of angiomyolipomas may contain little or no fat and may be indistinguishable from a small RCC in CT (12,13). Additionally, preoperative identification of oncocytomas is an important problem. Although some imaging features of oncocytomas such as homogeneous enhancement and central scar at CT were defined, none of these are sufficient to rule out the presence of malignancy. In the literature, it was revealed that 20% of the resected masses were benign following PN (14,15).

Over the last decades, increasing evidences supported that systemic inflammation plays a crucial role in the development and progression of various cancers including RCC (16-19). Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are systemic inflammatory response markers which can easily be derived from complete blood count (CBC). In this study, considering the relatively low sufficiency of radiological methods we aimed to assess the efficacy of inflammation markers in predicting pathology results of renal masses prior to PN.

METHODS

The data of 76 patients who underwent PN between 2012 and 2018 were evaluated retrospectively. Preoperative CBC, blood biochemical analysis, contrast enhanced CT reports and detailed pathological results of the patients were recorded. Patients diagnosed with a kidney mass and who underwent PN treated by either open or laparoscopic methods in our institute were included in the study. The exclusion criteria included patients with other known malignancies, hematologic diseases, autoimmune diseases, active infections, those under anticoagulant treatment or prior steroid or anticancer therapy, or patients where perioperative routine laboratory tests were unavailable. Patients were grouped according to the pathology results (malign group- benign group), tumor stage (T1a group- T1b group) and tumor grade (Fuhrmann Grade 1-Fuhrman Grade 2- Fuhrman Grade 3 or 4) and mass size (renal masses ≤ 4 cm and renal masses >4 cm) and the predictive value of NLR and PLR were assessed.

Statistical Analysis

Distribution of variables was assessed with the One-Sample Kolmogorov-Smirnov test. The variables with normal distribution was reported as the mean ± standard deviation (SD) and those with abnormal distribution was reported as median (minimum–maximum) values. Comparisons between groups were evaluated using the Pearson's chi-square test for categorical variables and using the Mann–Whitney U test or independent sample t test for continuous variables. The area under curve (AUC), calculated by receiver operating charecteristics (ROC) curve, was used to assess the predictive accuracy. Youden Index method was used to find the cut-off value. The IBM SPSS software package version 21.0 (Statistical Package for Social Sciences™, Chicago, IL, USA) was used for statistical analysis and $p < 0.05$ was considered as significant.

RESULTS

Of 76 patients, 49 were male and 27 were female. The mean age of the patients was 54.1±10.6 years. Descriptives of total cohort were showed in table 1.

VTable 1. Descriptives of total cohort	
Age (years), (mean±SD)	54.1 ± 10.6
Hemoglobin (g/dl), (mean±SD)	14.15 (9.7-17)
Creatinin (mg/dl), [median (min-max)]	0.9 (0.5-1.4)
PLR (mean±SD)	128.3 ± 34.15
NLR, [median (min-max)]	2.3 (1.36-4.47)
NLR: neutrophil-lymphocyte ratio; PLR:platelet-lymphocyte ratio	

The patients were divided into two groups according to the pathology results. The benign group was consisted of 17 patients and the malign group was of 59 patients. In the benign group 9 patients had oncocytomas, 3 had angiomyolipomas, 3 had calcified cysts, 2 had renal cortical adenomas. All the patients in the malign group had clear cell carcinoma. No statistically significant difference was found when the preoperative NLR and PLR of the groups were compared (p=0.113 and p=0.380, respectively) (Table 2).

Table 2. Comparison of the pathological groups			
	Benign group (n=17)	Malign group (n=59)	*p* value
Age (years), (mean±SD)	53.52 ± 13.44	54.27 ± 9.77	0.801
Gender (male/female)	7/10	42/17	0.023
Hemoglobin (g/dl), [median (min-max)]	13.80 (9.7-16.9)	14.4 (9.7-17)	0.545
Creatinin (mg/dl), [median (min-max)]	0.8 (0.6-1.3)	0.9 (0.5-1.4)	0.062
PLR (mean±SD)	121.86 ± 27.45	130.17 ± 35.8	0.380
NLR [median (min-max)]	2.15 (1.36-2.73)	2.32 (1.78-4.47)	0.113
NLR: neutrophil-lymphocyte ratio; PLR:platelet-lymphocyte ratio			

The malign group was divided into 2 groups according to the tumor stage. T1a group (≤4 cm tumor) was consisted of 33 patients and T1b group (tumor > 4 cm but not > 7 cm) was of 26 patients. When the comparison of NLR and PLR were evaluated, NLR of the T1b group was significantly higher than benign group and T1a group (p=0.007 and p<0.001, respectively) (Table 3).

Table 3.Preoperative PLR and NLR by the tumor stage				
	Benign group (n=17)	T1a group (n=33)	T1b group (n=26)	*p*value
PLR (mean±SD)	121.86 ± 27.45	126.05 ± 35.3	135.4 ± 36.5	(B-T1a)=0.912 (B-T1b)=0.416 (T1a-T1b)=0.551
NLR [median (min-max)]	2.15 (1.36-2.73)	2.20 (1.78-3.11)	2.37 (2.14-4.47)	(B-T1a) =0.705 (B-T1b) =**0.007** (T1a-T1b) <**0.001**
NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; B: benign group				

The efficacy of Fuhrman grade on NLR and PLR was also assessed. Of the 59 patients with malign pathology result, 16 patients had Fuhrman grade 1 tumors, 30 had Fuhrman grade 2 tumors and 13 had Fuhrman grade 3 or 4 tumors. In Fuhrman grade 3-4 tumor group, NLR was significantly higher when compared with grade 1 and grade 2 groups (Table 4).

Table 4. Comparison of preoperative PLR and NLR values of the grades				
	Fuhrman Grade 1 (n=16)	Fuhrman Grade 2 (n=30)	Fuhrman Grade 3 or 4 (n=13)	*p* value
PLR (mean±SD)	125.1 ± 40.8	127.3 ± 29.2	143 ± 42.6	(G1-G2)=0.997 (G1-G3,4)=0.499 (G2-G3,4)=0.510
NLR [median (min-max)]	2.19 (1.78-3.11)	2.33 (2.11-3.07)	2.62 (2.23-4.47)	(G1-G2)=**0.041** (G1-G3,4)<**0.001** (G2-G3,4)=**0.02**
NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio				

The renal masses were divided into 2 groups according to the tumor size. Of 76 patients, 34 patients had renal masses >4 cm. NLR was significantly higher in the patients with >4 cm malign renal masses (p=0.035) (Table 5). The area under the ROC curve was 0.743. According to the Youden Index method, the cut-off value was 2.31 with 65% specificity and 50% sensitivity (Figure 1).

Table 5. Comparison of NLR according to the size of mass			
Comparsion of NLR for the patients with renal mass > 4 cm			
	Benign group (n=8)	Malign group (n=26)	*p* value
NLR [median (min-max)]	2.25 (1.36-2.240)	2.41 (2.14-4.47)	0.035
Comparsion of NLR for the patients with renal mass ≤ 4 cm			
	Benign group (n=9)	Malign group (n=33)	*p* value
NLR [median (min-max)]	2.15 (1.56-2.73)	2.20 (1.78-3.11)	0.806
NLR: neutrophil-lymphocyte ratio			

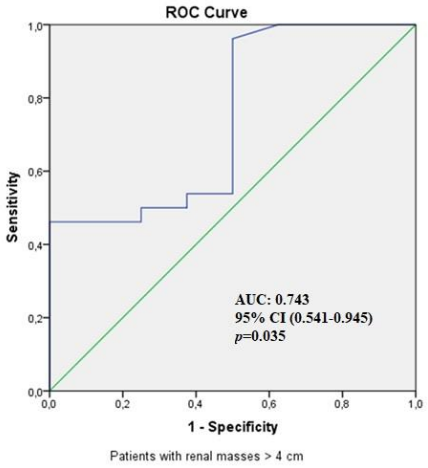

Figure 1. *NLR predictive accuracy for malign pathology in patients with > 4 cm renal masses*

DISCUSSION

The markers of the systemic inflammatory response derived from CBC are achieved from composite ratios of different circulating blood cells. The main approach is to take the ratio of different white blood cells or platelets and then apply a prognostic threshold that outcome is effectively stratified. NLR based on the ratio of neutrophil and lymphocyte counts and PLR based on the ratio of platelet and lymphocyte counts are the most frequently used parameters to evaluate systemic inflammatory response. In the systemic reviews, the presence of higher values of NLR and PLR were associated with poor overall survival (OS) (20,21). Increased neutrophil count and decreased lymphocyte count were both associated with tumor invasion, metastasis, recurrence and poor survival. The presence of neutrophilia inducts the production of circulating vascular endothelial growth factor, angiogenesis-regulating chemokines and tissue inhibitors of metalloproteinases which are associated with tumor invasion, recurrence and metastasis (21). Also, the presence of lymphopenia may reduce the production of cytokines and inhibit the cytotoxic cell death which is important to suppress the tumor proliferation and metastasis (16).

In the most of previous studies evaluating the prognostic value of preoperative NLR in patients with RCC, increased NLR was found to be associated with recurrence and poor survival. Ohno et al. revealed that increased preoperative NLR was an independent risk factor for recurrence (22). In another study, NLR was defined as an independent factor for disease free survival after surgery for patients with localized nonclear cell RCC (23). Nevertheless, there are limited studies assessing the diagnostic value of preoperative NLR in predicting renal mass pathology.

In the study performed by Viers et al., the data of 2402 patients who underwent RN or PN was evaluated retrospectively. They reported that NLR value was significantly higher in RCC group (p=0.037). However, when patients were grouped according to the size of mass, significancy was revealed in only the patients who had renal masses larger than 7 cm (p<0.001). Also, an elevated pre-treatment NLR was more often associated with RCC as well as higher grade tumors (p<0.001) and more aggressive histologic subtypes (p=0.002) (24). Bazzi et al. assessed the clinicopathologic characteristics of 1004 patients with ≤4 cm small renal masses undergoing nephrectomy. No association was found between preoperative NLR and pathology of the renal mass (25). Consistently with the studies mentioned above, according to our results no relationship was demonstrated between preoperative NLR and malign pathology result in patients with < 4 cm renal masses.

In the study performed by Widz et al, high NLR (≥2,69) significantly correlated with worse survival outcome and higher tumor stage (26). Kısa et al reported that higher NLR (>2,6) was associated with increased risk of pT 3–4 tumors (27). In our study, a cut-off value of 2,31 was associated with increased risk of tumors > 4 cm and it was compatible with the literature.

As far as we know, there is only one study in the literature similiar to the current study. Gorgel et al. evaluated the data of 79 patients who underwent PN. Preoperative NLR of the patients with clear cell RCC was significantly higher (p<0.001). However, NLR

was not associated with the tumor grade as well as the size of the mass (28).

In the current study, compatible and controversial results with literature both existed. According to our analysis, NLR is a valuable parameter for predicting malign lesions only in the patients with >4 cm renal masses. Also, higher NLR value was associated high grade tumors.

There are several limitations of this study. First, the data was conducted from retrospective cohort. Second, the number of patients was low. Third, NLR can be effected by various conditions such as anti-inflammatory drug use, chronic infection and smoking.

CONCLUSION

NLR is a valuable parameter at predicting the pathology results in patients with renal masses > 4 cm. Higher NLR value was associated high grade tumors. Further studies must be performed to certify the efficacy of NLR.

Declarations

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:359–86.
2. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008;34(3):193–205.
3. Levi F, Ferlay J, Galeone C, Lucchini F, Negri E, Boyle P, La Vecchia C. The changing pattern of kidney cancer incidence and mortality in Europe. BJU Int. 2008;101(8):949-58.
4. Patard JJ, Rodriguez A, Rioux-Leclercq N, Guillé F, Lobel B. Prognostic significance of the mode of detection in renal tumours. BJU Int. 2002;90(4):358-63.
5. Kato M, Suzuki T, Suzuki Y, Terasawa Y, Sasano H, Arai Y. Natural history of small renal cell carcinoma: evaluation of growth rate, histological grade, cell proliferation and apoptosis. J Urol. 2004;172(3):863-6.
6. Tsui KH, Shvarts O, Smith RB, Figlin R, de Kernion JB, Belldegrun A. Renal cell carcinoma: prognostic significance of incidentally detected tumors. J Urol. 2000;163(2):426-30.
7. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The Role of Tobacco Smoke in Bladder and Kidney Carcinogenesis: A Comparison of Exposures and Meta-analysis of Incidence and Mortality Risks. Eur Urol. 2016;70(3):458-66.
8. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC, Blute ML. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. J Urol. 2008;179(2):468-71.
9. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? J Urol. 2009;181(1):55-61.
10. Miller DC, Schonlau M, Litwin MS, Lai J, Saigal CS. Renal and cardiovascular morbidity after partial or radical nephrectomy. Cancer. 2008;112(3):511-20.
11. Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. Urology 2005;66:484–8.
12. Jinzaki M, Tanimoto A, Narimatsu Y, Ohkuma K, Kurata T, Shinmoto H, Hiramatsu K, Mukai M, Murai M. Angiomyolipoma: imaging findings in lesions with minimal fat. Radiology 1997;205: 497–502.
13. Sant GR, Ayers DK, Bankoff MS, Mitcheson HD, Ucci AA Jr. Fine needle aspiration biopsy in the diagnosis of renal angiomyolipoma. J Urol 1990;143:999–1001.
14. Mullins JK, Feng T, Pierorazio PM, Patel HD, Hyams ES, Allaf ME. Comparative analysis of minimally invasive partial nephrectomy techniques in the treatment of localized renal tumors. Urology 2012; 80: 316–21.
15. Kutikov A, Fossett LK, Ramchandani P, Tomaszewski JE, Siegelman ES, Banner MP, Van Arsdalen KN, Wein AJ, Malkowicz SB. Incidence of benign pathologic findings at partial nephrectomy for solitary renal mass presumed to be renal cell carcinoma on preoperative imaging. Urology 2006; 68: 737–40.
16. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860-7.

17. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436-44.
18. Luo Y, She DL, Xiong H, Fu SJ, Yang L. Pretreatment neutrophil to lymphocyte ratio as a prognostic predictor of urologic tumors: a systematic review and meta-analysis. Medicine (Baltimore). 2015;94(40):e1670
19. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, Seruga B, Ocaña A, Tannock IF, Amir E. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23(7):1204-12.
20. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju124
21. Petrie HT, Klassen LW, Kay HD. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. J Immunol. 1985;134(1):230-4.
22. Ohno Y, Nakashima J, Ohori M, Hatano T, Tachibana M. Pretreatment neutrophil-to-lymphocyte ratio as an independent predictor of recurrence in patients with nonmetastatic renal cell carcinoma. J Urol. 2010;184(3):873–8.
23. de Martino M, Pantuck AJ, Hofbauer S, Waldert M, Shariat SF, Belldegrun AS, Klatte T. Prognostic impact of preoperative neutrophil-to-lymphocyte ratio in localized nonclear cell renal cell carcinoma. J Urol. 2013;190(6):1999–2004.
24. Viers BR, Thompson RH, Lohse CM, Cheville JC, Leibovich BC, Boorjian SA, Tollefson MK. Pre-treatment neutrophil-to-lymphocyte ratio predicts tumor pathology in newly diagnosed renal tumors. World J Urol. 2016;34(12):1693-9.
25. Bazzi WM, Dejbakhsh SZ, Bernstein M, Russo P. Neutrophil-lymphocyte ratio in small renal masses. ISRN Urol. 2014;2014:759253.
26. Widz D, Mitura P, Buraczyński P, Płaza P, Bar M, Cabanek M, Nowak G, Ostrowska A, Bar K. Preoperative neutrophil-lymphocyte ratio as a predictor of overall survival in patients with localized renal cell carcinoma. Urol J. 2019 May 13. doi: 10.22037/uj.v0i0.4541. [Epub ahead of print]
27. Kisa E, Yucel C, Keskin MZ, Karabicak M, Yalcin MY, Cakmak O, Ilbey YO. The Role of Hematological Parameters in Predicting Fuhrman Grade and Tumor Stage in Renal Cell Carcinoma Patients Undergoing Nephrectomy. Medicina (Kaunas). 2019 Jun 18;55(6). pii: E287.
28. Gorgel SN, Ozer K, Kose O, Dindar AS. Can preoperative neutrophil lymphocyte ratio predict malignancy in patients undergoing partial nephrectomy because of renal mass? Int Braz J Urol. 2018;44(3):461-6.