Do neutrophil- lymphocyte, platelet-lymphocyte ratio correlate with pathological outcomes in localized renal tumors?

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Research article

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Abstract

Background: We investigated the association of the blood parameters such as neutrophil, platelet accounts and neutrophil/lymphocyte ratio (NLR) with tumor type, tumor size and Fuhrman grade in nonmetastatic renal cell carcinoma (RCC) cases.

Methods: A total of 343 patients with nonmetastatic (T1- 4N0M0) RCC were included into the study. The patients were divided into four groups: clear cell (group-1), papillary (group-2), chromophobes (group-3) and other pathologies (group-4). In each grouping systems, the NLR, white blood cell (WBC), platelet (PLT), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV) values were compared.

Results: There were 222 patients with clear cell (group-1), 62 papillary (group-2), 16 chromophobes (group-3) and 43 patients with other pathologies (group-4). There was a significant difference between the groups in group-1 and group-3 in terms of white blood cell (WBC), platelet (PLT), lymphocyte and neutrophil count. However, there was no significant difference between the groups by the surveys in terms of Neutrophil / Lymphocyte Ratio (NLR) values. There was no significantly difference between survival and NLR either.

Conclusion: NLR is a cheap and easy parameter to calculate but is not suitable to predict tumor prognosis and survival yet. NLR cut-off value is the biggest problem for now. But evidences show, we are too close to overcome this problem.

Background

Renal cell carcinoma (RCC) is about %85 of the renal masses and originates from the renal cortex (1). RCC accounts for 5% and 3% of all cancers in men and women respectively (2) and is generally diagnosed between 50 and 70 years of life (3). There has been a rapid increase in the incidence of RCC in the past 30 years due to improvements in imaging techniques (4). Surgical resection is the gold standard treatment for clinically localized disease but unfortunately, recurrence rate is 10–20% after the surgery (5–7).

Besides the inflammation and the tumor microenvironment play an important role in the development and progression of malignancies, it affects the response to therapies (8). Many laboratory parameters are changed according to systemic inflammation, like increased levels of C-reactive protein, some cytokines, neutrophils, platelets and decreased level of serum albumin level. But we still do not know completely how the inflammation worsen clinical outcome. One way, tumor cells produce some cytokines that increase the neutrophil levels and result neutrophilia may lead to suppression of cytolytic activity of immune cells such as lymphocytes, natural killer and T cells (9, 10). Another important cells are platelets that release vascular endothelial growth factor (VEGF), which provides neo-angiogenesis for tumor growth and secrete thrombospondin which facilitates tumor adhesion and extravasation (11).

One of the net index of the systemic inflammation status is an increased neutrophil-to-lymphocyte ratio (NLR), on this basis, there are studies showing that high NLR level indicates poor prognosis (12), especially in solid tumors such as small cell lung cancer (13), colorectal (14), hepatocellular carcinoma (15, 16) and ovarian cancer (17). Studies on RCC and NLR showed that inflammation plays an important role in the pathogenesis and progression of RCC (18) and also neutrophils and platelets have a prominent role in the tumor formation and development. So NLR, platelets and neutrophil levels are an easily available and cheap laboratory parameters that have the potential to become a cost effective biomarker to predict disease progression.

In this study, we aimed to investigate the association of the NLR and hematological components including serum neutrophil, lymphocyte, platelet, mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) with RCC subtypes.

Methods

This retrospective study, which was approved by the Ethics Committee of Clinical Research in Malatya, Turkey (protocol number 2018/14–20), was conducted in a single urology clinic to review the medical data of 343 patients who underwent radical nephrectomy surgery with nonmetastatic (T1–4N0M0) RCC were included in the study between January 1998 and December 2014. The demographic information of the patients, perioperative laboratory parameters, and pathology results were recorded (Table 1). The patients were branched out into four groups according to tumor subtype (Group 1 clear cell, Group 2 papillary, group 3 chromophobe and group 4 is other subtypes). In each grouping systems, the NLR, white blood cell (WBC), platelet (PLT), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV) values were compared.

Laboratory Data

Hemoglobin (Hb), hematocrit (Htc), white blood cell (WBC), neutrophil, lymphocyte and platelet counts, mean platelet volume (MPV), and red blood cell distribution width (RDW) were obtained using Beckman Coulter LH780 and Beckman Coulter LH750 (California, USA) analyzers. Neutrophil-to-lymphocyte ratio and PLR values were calculated by dividing the total neutrophil and platelet counts by the total lymphocyte count, respectively.

Statistical analysis

The data were given as minimum and maximum. Kruskal-Wallis H test was used to compare preoperative whole blood counts and renal pathologies. The Mann-Whitney U test with Bonferroni correction was used for multiple comparisons. For all analyses, the p value of $p < 0.05$ was considered statistically significant. The data were analyzed using the SPSS software program for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The files were divided into four groups: 222 patients with clear cell (group–1), 62 papillary (group–2), 16 chromophobes (group–3) and 43 patients with other pathologies (group–4). The hematological results of the patients are given in the table 2. 46 of the operations were partial nephrectomy and 297 of them were radical nephrectomy. The mean tumor diameter was calculated as 6.14 cm (1,5–21 cm). Surgical margin was reported as positive in 30 (8,74%) patients at all and 11 (23,9%) patients with nephron sparing surgery.

There was a significant difference between the groups in group–1 and group–3 in terms of white blood cell (WBC), platelet (PLT), lymphocyte and neutrophil count (p = 0,005, p = 0,008, p = 0,004, p = 0,011 in respectively) (figure 1). Mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) values were significantly different between group–2 and group–4 (p = 0,006,p = 0,03 respectively) (figure 2), significant difference was found between group–2 and group–3 by lymphocyte count (p: 0,012). However, there was no significant difference between the groups by the surveys in terms of Neutrophil / Lymphocyte Ratio (NLR) values (when the threshold value for NLR is accepted as 2.5) (figure 3). The average of the patients' disease free survival was found 27,50 months (12 - 60) in five-year follow-up (figure 4).

Discussion

The incidence of RCC has been increasing in the last three decades (19). One of the reasons for this increase may be frequently introduction of radiological imaging methods. (20). The other reasons are increased environmental exposures, smoking, obesity, and changes in lifestyle. Surgery is still the gold standard treatment for patients with localized disease, but 10%–60% of them develop recurrence after surgery (19).

Until this time, several prognostic factors have been investigated and reported for RCC, the stage and grade of the tumor are the most important factors (20). Still some prognostic factors are also being investigated. One of them is systemic inflammatory markers. The mainstay of these studies is the tumor's effects on the inflammation system that the distribution of circulating inflammatory cells changes (21). The main change is thrombocytosis and increased neutrophil levels as well as relative decreased levels of lymphocytes. Neutrophils normally secrete some cytokines including interleukin 1 (IL–1), IL–6, tumor necrosis factor (TNF), and vascular endothelial growth factor VEGF, which is a proangiogenic factor (19). Besides they also release reactive oxygen species, nitric oxide, and arginase (22). Additionally the neutrophils aggregate tumor growth and metastasis by changing tumor microenvironment with remodeling the extracellular matrix and also suppressing the T-cell response. Another factor that decreases the cytotoxic T lymphocytes activity is immunosuppressive cytokines secreted by tumor cells (23). As a result, the decreased lymphocyte count and activity causes suboptimal defense in the T lymphocyte arm of defensive immune system against cancer. Furthermore, the platelets have an important role in cancer progression. They promote tumor growth and neo-angiogenesis by VEGF

cytokine secretion (22). So, VEGF facilitates metastasis by inducing new vessel formation (24). Solid tumor cells secrete IL 6 themselves (25). As a result of all these deadly circulation mechanisms, tumor cells can easily develop and metastases to the body. In conclusion, increasing evidence at this point supports the association between inflammation and cancer development, progression and progression (26). According to our results, increased neutrophil, platelet, lymphocyte and White blood cell account seen in group 1 and 3.

As a result of these evidences, some prognostic factors like NLR have been thought as valuable biomarkers to predict the tumor prognosis and survival (27). NLR is cheap and easily acquired when compared with other markers (28). Otunctemur et al. reported that NLR was significantly higher in patients with advanced stage tumor and high grade (T3–4, G3–4) than the others (3). A study by Arda et al. showed significant difference between NLR and tumor size (p: 0,029) but there is not relationship between Fuhrman grade and NLR (29). In contrast to our study, Viers et al. showed that the NLR had a significant association with Fuhrman grade and they 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 ($p < 0.01$) (19).

One of the major problems in this regard is cut-off value of the NLR. Indeed, although higher NLR has been related to worse OS and DFS/PFS in several solid tumors, the optimal cut-off is far from being detected (12). Very recently, PROCHE study results could add some contribution in this line (30). According to the study, authors find a linearly correlation between NLR and mortality risk; HR values had no significant at a cut-off of 3,0, but significant when the cut-off was 4.0 (30). According to the results of this study, NLR seems to be related to survival regardless tumor types. However, no prospective large trials have explored which NLR cut-off is the best in RCC, so this issue still remaining unanswered.

Ohno et al. said that 10-year recurrence-free survival rate for patients with a preoperative NLR ≥ 2.7 was significantly lower than NLR< 2.7 patients with 64.4% to 83.7%, respectively ($p = 0.0004$) (31). In a meta-analysis performed by Nunno et al included 24 studies and 10,034 patients, they investigate the prognostic role of NLR in RCC patients and found that: higher NLR was related to worse survival and PFS/DFS, higher NLR associated with worse OS in both metastatic and non-metastatic patients (32). Unfortunately, we couldn't find any relationship between disease free survival and NLR when the cut off value is accepted as 2.5.

Conclusions

Inflammatory parameters such as NLR can be used to get an idea about the prognosis of patients with RCC in theory. Nevertheless, there are currently no recommendations on the use of the NLR for RCC follow-up or estimated survival. Besides, optimal NLR cut off value is not yet determined. Further randomized studies are required to validate the inclusion of the NLR in RCC nomograms.

Declarations

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Abbreviations

NLR: Neutrophil/lymphocyte ratio

RCC: Renal cell carcinoma

WBC: White blood cell

PLT: Platelet

MCH: Mean corpuscular hemoglobin

MCV: Mean corpuscular volume

Hb: Hemoglobin

Htc: Hematocrit

RDW: Red blood cell distribution width

TNF: Tumor necrosis factor

VEGF: Vascular endothelial growth factor

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Contributions

Conception: AC, IT. Design: AC, IT. Acquisition: AC, IT. Analysis: AC, IT. Interpretation of data: AC, IT. Drafted the manuscript: AC, IT. All authors read and approved the final manuscript.

Corresponding author

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Ethics declarations

Ethics approval and consent to participate

This retrospective study, which was approved by the Ethics Committee of Clinical Research in Malatya, Turkey (*protocol number 2018/14–20)*„ was conducted in a single urology clinic to review the medical data of 343 patients who underwent radical nephrectomy surgery with nonmetastatic (T1–4N0M0) RCC were included in the study between January 1998 and December 2014.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

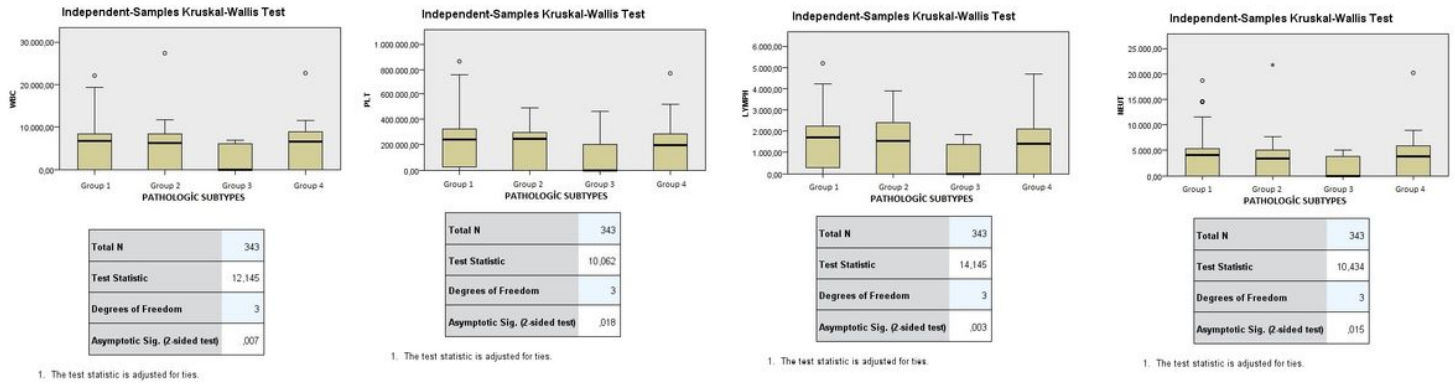
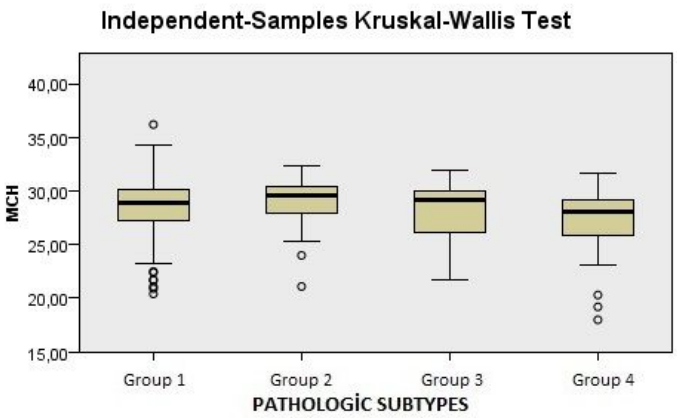


Figure 1

There was a significant difference between the groups in group-1 and group-3 in terms of white blood cell (WBC), platelet (PLT), lymphocyte and neutrophil count (p=0,005, p=0,008, p=0,004, p=0,011 in respectively)



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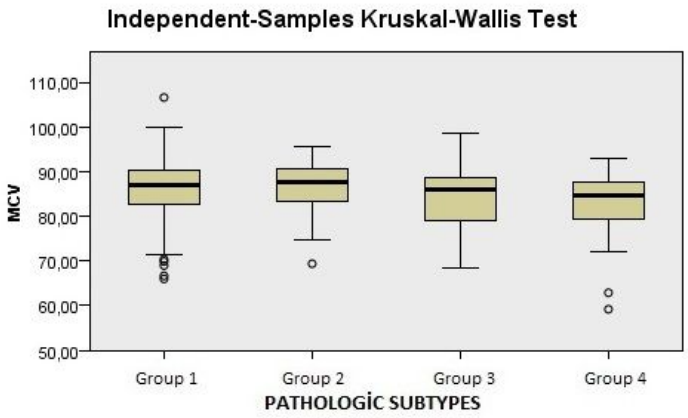
Degrees of Freedom	3
Asymptotic Sig. (2-sided test)	,012

1. The test statistic is adjusted for ties.

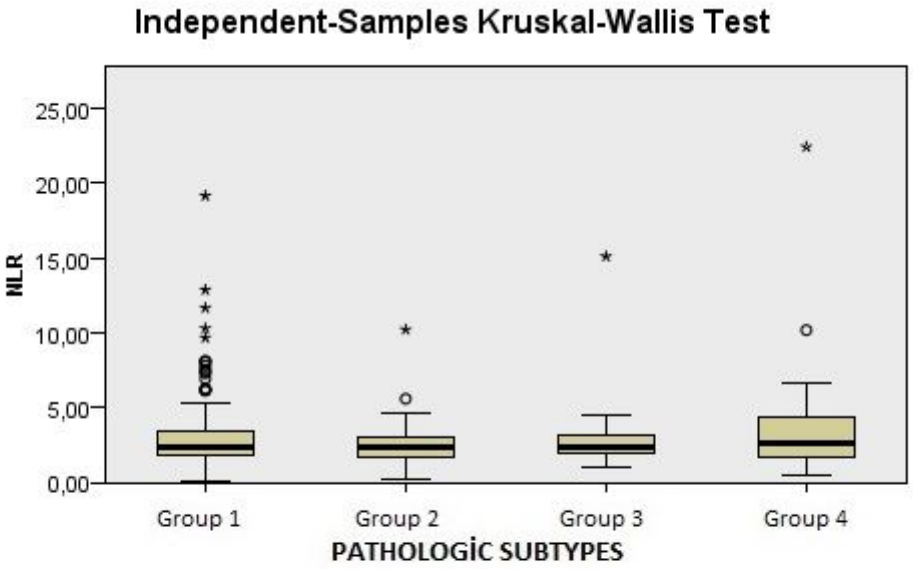


Total N	343
Test Statistic	9,743
Degrees of Freedom	3
Asymptotic Sig. (2-sided test)	,021

1. The test statistic is adjusted for ties.

Figure 2

Mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) values were significantly different between group-2 and group-4 (p=0,006,p=0,03 respectively)

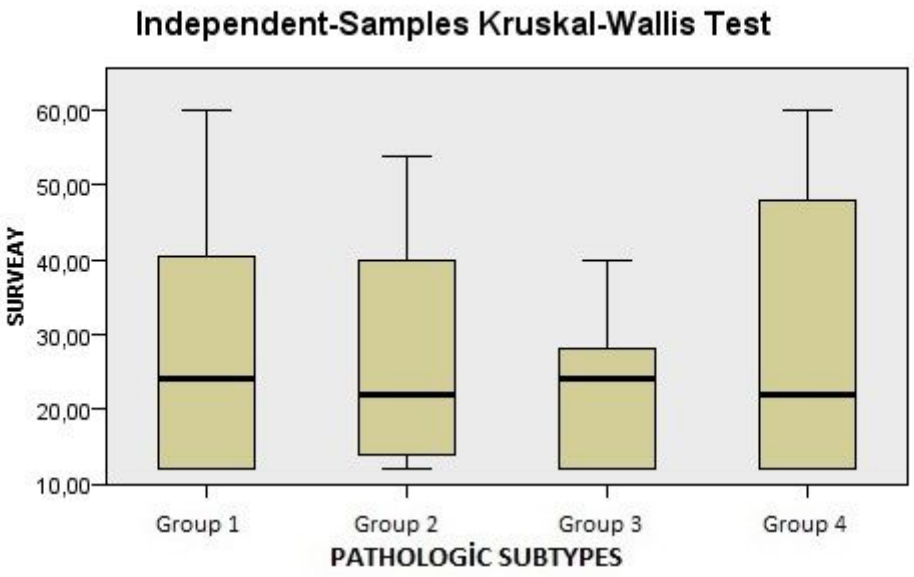


Total N	343
Test Statistic	1,932
Degrees of Freedom	3
Asymptotic Sig. (2-sided test)	,587

1. The test statistic is adjusted for ties.
2. Multiple comparisons are not performed because the overall test does not show significant differences across samples.

Figure 3

There was no significant difference between the groups by the surveys in terms of Neutrophil / Lymphocyte Ratio (NLR) values (when the threshold value for NLR is accepted as 2.5.



Total N	102
Test Statistic	1,357
Degrees of Freedom	3
Asymptotic Sig. (2-sided test)	,716

1. The test statistic is adjusted for ties.
2. Multiple comparisons are not performed because the overall test does not show significant differences across samples.

Figure 4

The average of the patients' disease free survival was found 27,50 months (12 - 60) in five-year follow-up.

Supplementary Files

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- Table2.docx
- Table1.docx