# RESEARCH ARTICLE

# Lack of Any Role of Systemic Inflammatory Responses in Predicting Muscle Invasion by Bladder Cancer

**Mehmet Solakhan[1], Ozlem Demirpence[2], Nuri Orhan[3], Omer Aydın Yıldırım[4], Ebru Guzel[5], Mustafa Yıldırım[6]\***

## Abstract

Background: The purpose of this study is to evaluate if there is a relation between platelet: lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) values and tumour histology and spread in bladder cancer cases. Materials and Methods: Bladder cancer patients undergoing TUR-M operation, with histopathologically verified diagnosis, followed-up and treated at the Private Medical Park Gaziantep Hospital between 2010 and 2015, have were included in the study. NLR and PLR values were calculated using complete blood count data obtained at the first presentation. Results: A total of 99 patients were included in the study, 7 (7.1%) women and 92 men (92.9%). When NLR was used as the indicator of systemic inflammatory response (SIR), it was determined that, 52 (52.5%) of the patients were SIR negative and 47 (47.5%) SIR positive. No significant relation could be detected between NLR and tumour grade and muscle invasion ($p=0.948$, $p=0.480$). When PLR was used as SIR indicator, it was determined that 71 (71.7%) of the patients were found as negative and 28 (28.3%) as positive. No significant relation could be detected between PLR and tumour grade and muscle invasion ($p=0.651$, $p=0.494$). Conclusions: In our study we did not detected a relation between tumour histological behavior and PLR and NLR in bladder cancer. However, NLR and PLR are easily calculated, accessible, inexpensive and simple-to-use laboratory data from whole blood counts.

Keywords: Neutrophil/lymphocyte ratio - platelet/lymphocyte ratio - bladder cancer - prognosis - muscle invasion

## Introduction

Bladder cancer is the 9th most frequently observed type of cancer around the world (Siegel et al., 2014) 75-85% of bladder cancers consist of non-muscle-invasive bladder cancers (NMIBC) (Babjuk et al., 2013).Today some prognostic factors, such as tumour grade, positive cytology, immunological and molecular characteristics have been defined for bladder cancer (Sylvester, 2006). Recently, changes in white blood cells such as neutrophil, lymphocyte, monocyte in the peripheral blood, values such as NLR (neutrophil lymphocyte ratio) PLR (platelet: lymphocyte ratio) have been determined as simple, applicable, inexpensive and reliable prognostic indices for determining systemic inflammatory response (SIR) (Atzpodien et al., 2003; Schmidt et al., 2005; Kaya et al., 2013; Gunaldi et al., 2015).

They can cause malign diseases or chronic inflammation, as well as benign diseases such as autoimmune disease and infection (Hussein et al., 2005; Aliustaoglu et al., 2010). Therefore the relation between changes in the micro-environment of the tumour and prognosis, has been examined in other studies. Immune cells such as granulocytes and lymphocytes, are important stroma components at the tumour micro-environment, that arrange carcinogenesis and metastasis. The correlation of granulocytes and lymphocytes in the peripheral blood and this immune cells in the tumour stroma, is very closely interrelated (Pollard, 2004).

Although the reason for SIR development in cancer patients is not known exactly, hypoxia related to tumour necrosis, changes in neuro-endocrine metabolism, interleukin synthesis and acute phase protein production are blamed (Forrest et al., 2003).

The purpose of this study is to evaluate if there is a relation between the PLR and NLR values obtained using parameters of complete blood count, used as a routine laboratory method, with tumour histology and spread in bladder cancer.

## Materials and Methods

Bladder cancer patients who had TUR-M operation, with histopathologically verified diagnosis, followed-up and treated, between 2010 and 2015 at the Private Medical Park Gaziantep Hospital, have been included in the study.

*[1]Department of Urology, [3]Department of Biochemistry, [4] Department of İnternal Medicine, [5]Department of Radiology, [6]Department of Medical Oncology, Medicalpark Gaziantep Hospital, Gaziantep, [2]Department of Biochemistry, Cumhuriyet University, Sivas, Turkey \*For correspondence: mustafayildirim7@yahoo.com*

Patient files have been searched retrospectively and age, gender, histopathologic sub-type, radiologic imaging results, metastasis development during stage and follow-up and survival information have been obtained. NLR and PLR values have been calculated using the complete blood count data obtained at the first application of the patients to the oncology clinic, prior to chemotherapy or radiotherapy.

Patient exclusion criteria have been determined as patients who have had blood transfusion in the last 2 months, with active haemorrhage, with hemorrhagic diathesis, with hyper or hypothyroidism, with infection, with dissemine intravascular coagulation, receiving heparin therapy or with connective tissue disease. NLR was obtained by dividing absolute neutrophil count with absolute lymphocyte count. SIR was accepted as positive in cases where NLR <2.56 and SIR was accepted as positive in cases where NLR ≥2.56 (Yamanaka et al., 2007).

PLR was obtained by dividing absolute thrombocyte count with absolute lymphocyte count. SIR was accepted as positive in cases where PLR <160 and SIR was accepted as positive in cases where PLR ≥160(Smith RA et al., 2008).

*Statistical analysis*

Statistical analysis was performed using SPSS 15.0 software. Frequency, percent ratio, arithmetic mean, standard deviation, 95% confidence intervals and mean values have been used in defining the variables. The Chi-square test was used compare these proportions in different groups. $p<0.05$ has been considered as statistically significant.

## Results

A total of 99 patients have been included in the study, with 7 (7.1%) women, 92 men (92.9%). The ages of patients was in the range 65.3 ± 12.8 (range 27-95) years. After evaluating patient histologies, low grade bladder cancer was detected in 46 (46.5%) patients and high grade bladder cancer was detected in 53 (53.5%) patients. No significant relation could be detected between age and tumour histology, NLR and PLR (p=0.505, p=071, p=0.602). 16 (16.2%) of the patients had muscle-invasive bladder cancer (MIBC) and 83 (83.2%) had NMIBC cancer. Significant relation has been detected between tumour grade and muscle invasion (p 0.001).

When NLR was used as SIR indicated, it was determined that 52 (52.5%) of the patients were found as SIR negative and 47 (47.5%) as SIR positive. No significant relation could be detected between NLR and tumour grade and muscle invasion (p=0.948, p=0.480). When PLR was used, it was determined that 71 (71.7%) of the patients were SIR negative and 28 (28.3%) positive. No significant relation could be detected between PLR and tumour grade and muscle invasion (p=0.651, p=0.494).

## Discussion

SIR is related to poor prognosis in many solid tumours

(Gunaldi M et al., 2015). In our study we determined that NLR and PLR positivity, among SIR indicators, was not related to tumour grade in bladder cancer.

In the neoplastic process, changes in cytokine and chemokine levels, increase in neutrophil counts, slight increase in thrombocyte count and decrease in lymphocytes can be detected with the help of triggered SIR (Ertas et al., 2013) . Malign tissues can be infiltrated with immune cells and these cells may play an important role in the growth and progression of certain tumours (Hussein et al., 2005) .

It has been indicated that increase of neutrophils to 50-60% level at the tumour micro-environment, increases angiogenesis, viability, motility and invasion. Therefore it has been argued that the excess number of neutrophils in the tumour stroma could be related to poor prognosis and could induce the development of a progression in the tumour by releasing cytokines and chemokines-(Xu et al., 2014).

Also, lymphocytes directed from tumour tissue to surrounding tissue cause decrease in T-4 helper and T-8 suppressor lymphocyte count and thus to decrease in cellular immunity; and as a result, cause lymphopenia, considered as a prognostic factor (Kim et al., 2010).

Based on these effects of neutrophils and lymphocytes in tumour progression, it has been determined that NLR, obtained from peripheral blood count data, indicate the inflammation degree of the tumour and the prognostic importance of immune cell response against tumour has been shown (Shimada et al., 2010).

Lee et. al. have examined factors predicting MIBC in 226 patients prior to TUR-M ( Lee et al., 2015). In this study they have shown that NLR and tumour diameter are independent factors predicating MIBC. No significant relation has been detected in this study between PLR and muscle invasion. In contrast with our study, Lee et al. have shown that NLR and muscle invasion are related.

NLR also predicts neoadjuvant treatment in muscle invasive bladder cancer. Seah et. al. have shown that NLR decreased in patients with response to the treatment and NLR increased in patients without any observed treatment response (Seah JA et al., 2015). Mano et al. have argued that NLR could have a role in predicting recurrence in patients without muscle invasion (Mano R et al., 2015). In this retrospective study, recurrence ratio has been determined to be higher in the group with high NLR.

Platelet count, as part of the inflammatory response, may increase in solid tumours. Interleukin-6 (IL-6), a thrombopoietic cytokine, may be released by tumour cells. Thrombocytes may ease metastasis by protecting tumour cells from natural killer cell-mediated lysis and may also contribute to tumour growth, invasion and angiogenesis with the biological factors they contain. PLR is related to the prognosis and tumour survival of many cancers, such as colorectal, ovarian, lung and hepatocellular cancer. However its specific mechanism has not been fully understood (Topcu et al., 2014; Zhou et al., 2014).

Platelets may increase tumour growth by increasing angiogenesis through vascular endothelial factor (VEGF), which is a cytokine (Bambace et al., 2011). Compared to the healthy control group, it has been shown that there has

been a significant increase in VEGF-A in the platelets in cancer patients (Wiesner et al., 2010). In the study by Lee et al., the role of PLR in MIBC could not be shown as in this study (Lee et al., 2015).

NLR and PLR prognostic markers have been used also in preoperative evaluation for surgical staging and it has been stated that they are directly related to nodal involvement in vulvar squamous cell carcinoma (Ertas et al., 2013). In another retrospective study, it has been stated that NLR and PLR were independent prognostic factors in predicting survival in gastrointestinal tumours (Goh et al., 2015). The fact that we have not performed surgical stating and survival evaluation is an important constraint of our study.

In the study we have not detected a relation between tumour histological behavior and PLR and NLR in bladder cancer. However, NLR and PLR are easily calculated, accessible, inexpensive and simple-to-use laboratory methods from blood count. We believe that new studies should be conducted to clarify the role of these methods in bladder cancer.

## References

Atzpodien J, Royston P, Wandert T, et al (2003). Metastatic renal carcinoma comprehensive prognostic system. *Br J Cancer*, **88**, 348-53.

Aliustaoglu M, Bilici A, Ustaalioglu BB, et al (2010). The effect of peripheral blood values on prognosis of patients with locally advanced gastric cancer before treatment. *Med Oncol*, **27**, 1060-5.

Bambace NM, Holmes CE (2011). The platelet contribution to cancer progression. *J Thromb Haemost*, **9**, 237-49.

Babjuk M, Burger M, Zigeuner R, et al (2013). EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol*, **64**, 39-53.

Ertas IE, Gungorduk K, Akman L, et al (2013). Can preoperative neutrophil: lymphocyte and platelet: lymphocyte ratios be used as predictive markers for lymph node metastasis in squamous cell carcinoma of the vulva? *Eur J Obstet Gynecol Reprod Biol*, **171**, 138-42.

Forrest LM, McMillan DC, McArdle CS, et al (2003). Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer*, **89**, 1028-30.

Gunaldi M, Goksu S, Erdem D, et al (2015). Prognostic impact of platelet/lymphocyte and neutrophil/lymphocyte ratios in patients with gastric cancer: a multicenter study. *Int J ClinExp Med*, **8**, 5937-42.

Goh BK, Chok AY, Allen JC Jr, et al (2015). Blood neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are independent prognostic factors for surgically resected gastrointestinal stromal tumours. *Surg*.

Hussein MR, Ahmed RA (2005). Analysis of the mononuclear inflammatory cell infiltrates in the non-tumourigenic, pre-tumourigenic and tumourigenic keratinocytic hyperproliferative lesions of the skin. *Cancer Biol Ther*, **4**, 819-21.

Kim HS, Han KH, Chung HH, et al (2010). Neutrophil to lymphocyte ratio for preoperative diagnosis of uterine sarcomas: a case-matched comparison. *Eur J Surg Oncol*, **36**, 691-8.

Kaya V, Yildirim M, Demirpence O, et al (2013). Prognostic significance of basic laboratory methods in non- small-cell-lung cancer. *Asian Pac J Cancer Prev*, **14**, 5473-6.

Lee SM, Russell A, Hellawell G (2015). Predictive value of pretreatment inflammation-based prognostic scores (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio) for invasive bladder carcinoma. *Korean J Urol*, **56**, 749-55.

Mano R, Baniel J, Shoshany O, et al (2015). Neutrophil-to-lymphocyte ratio predicts progression and recurrence of non-muscle-invasive bladder cancer. *Urol Oncol*, **33**, 1-7.

Pollard JW (2004). Tumour-educated macrophages promote tumour progression and metastasis. *Nat Rev Cancer*, **4**, 71-8.

Schmidt H, Bastholt L, Geertsen P,et al (2005). Elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma: a prognostic model. *Br J Cancer*, **93**, 273-8.

Sylvester RJ (2006). Natural history, recurrence, and progression in superficial bladder cancer. *Scientific World J*, **6**, 2617-25.

Shimada H, Takiguchi N, Kainuma O et al (2010). High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. *Gastric Cancer*, **13**, 170-6.

Siegel R, Ma J, Zou Z, Jemal A (2014). Cancer statistics. *CA Cancer J Clin*, **64**, 9–29.

Seah JA, Leibowitz-Amit R, Atenafu EG, et al (2015). Neutrophil-lymphocyte ratio and pathological response to neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer. *Clin Genitourin Cancer*, **13**, 229-33.

Smith RA, Ghaneh P, Sutton R, et al (2008). Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19–9 levels and platelet-lymphocyte ratio. *J Gastrointest Surg*, **12**, 1422–8.

Topcu HO, Guzel AI, Ozer I, et al (2014). Comparison of neutrophil/lymphocyte and platelet/ lymphocyte ratios for predicting malignant potential of suspicious ovarian masses in gynecology practice. *Asian Pac J Cancer Prev*, **15**, 6239-41.

Wiesner T, Bugl S, Mayer F, et al (2010). Differential changes in platelet VEGF, Tsp, CXCL12, and CXCL4 in patients with metastatic cancer. *Clin Exp Metastasis*, **27**, 141-9.

Xu AM, Huang L, Zhu L, Wei ZJ (2014). Significance of peripheral neutrophil-lymphocyte ratio among gastric cancer patients and construction of a treatment-predictive model: a study based on 1131 cases. *Am J Cancer Res*, **4**, 189-95.

Yamanaka T, Matsumoto S, Teramukai S, et al (2007). The baseline ratio of neutrophils to lymphocytes with patient prognosis in advanced gastric cancer. *Oncol*, **73**, 215-20.

Zhou X, Du Y, Huang Z, et al (2014). Prognostic value of PLR in various cancers: a meta-analysis. *PLoS One*, **9**, 101119.