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ORIGINAL ARTICLE – OPEN ACCESS

Role of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Prognostic Predictors Before Treatment for Metastatic Bladder Cancer Patients Receiving First-Line Chemotherapy

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ABSTRACT

Objective: The correlation between neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and the prognosis of different cancers has been determined by a series of studies. The role of these inflammatory markers as definitive prognostic factors in bladder cancer is controversial. This research was conducted to explore the prognostic worth of pretreatment inflammatory markers including NLR and PLR in metastatic bladder cancer (mBC) patients receiving first-line chemotherapy.

Materials and Methods: We retrospectively appraised 71 patients diagnosed with mBC from August 2005 to November 2017. According to the threshold values that were identified by receiver operating characteristic (ROC) curve analysis, the NLR and PLR were each divided into two groups: first, ≤2.93 and >2.93, and second, ≤168.9 and >168.9 respectively. The Cox proportional hazards model was applied to uncover the probable predictors of progression-free survival (PFS) and overall survival (OS).

Results: Findings obtained by univariate analysis determined that an elevated NLR, a high PLR, and the onset of anemia were significantly correlated with poorer OS. Additionally, a significant relationship was found between an elevated NLR and reduced PFS. In the multiple analysis, an elevated NLR was identified as an independent predictor for both, reduced OS (Odds Ratio (OR): 5.58, 95% Confidence interval (CI): 2.80–11.13, p<0.05) and PFS (OR: 3.43, 95% CI: 1.92–6.12, p<0.05).

Conclusion: Findings of this research revealed that NLR was an independent prognostic tool of PFS and OS in mBC patients undergoing first-line chemotherapy.

Keywords: Metastatic bladder cancer, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prognosis

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INTRODUCTION

Metastatic bladder neoplasm remains one of the most intractable oncological tumors. According to important guidelines, the 5-year overall survival (OS) rate stands at a troubling value of ~10% of all recorded survival rates (1, 2). In spite of receiving treatment with standard cisplatin-based chemotherapy, the median survival time is approximately 14 months and there is marked heterogeneity in the clinical consequences of mBC patients (3, 4). This poor process indicates the requirement of sustained improvements in understanding cancer biology and effective risk classification (5).

Recently, there has been an enhanced argument promoting the value of inflammation in malignant tumor improvement and progression (6). Emerging research has demonstrated that inflammatory tools including NLR and PLR play substantial roles in forecasting various outcomes of diverse malignant neoplasms including colorectal, ovarian, breast, prostate, gastric, and bladder cancer (7–13). The objective of the current research is to explore pretreatment inflammatory markers including NLR and PLR and determine their skill in predicting the outcome of metastatic bladder cancer patients undergoing first-line chemotherapy.

MATERIALS and METHODS

Patients with mBC who received first-line chemotherapy from August 2005 to November 2017 were considered eligible for this single-center retrospective study. The research was approved by the ethics board of Erciyes University Medical School, Melikgazi/Kayseri, Turkey (Approval number: 2018/630).

The criteria of inclusion for this study were: (I) patients with urothelial bladder cancer proven by histopathology, (II) patients who had undergone first-line chemotherapy, and (III) patients with existing clinical records including demographic data, pathologic properties of the tumor, therapeutic interventions, and laboratory data. The following exclusion criteria were considered: (I) patients with clinical confirmation of acute infection, systemic inflammation, or other autoimmune disturbances, (II) patients who previously had received immune suppressive therapy, (III) patients with hematological disorders, and (IV) patients with a second malignant tumor arising from different regions.

Data on neutrophil, thrombocyte, and lymphocyte levels were obtained from blood tests taken before the first cycle of chemotherapy. The NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. The PLR was calculated by dividing the absolute thrombocyte count by the absolute lymphocyte count.

All patients underwent preliminary screening and cancer staging using computed tomographic scans of the abdomen, pelvis, and thorax to verify the extent of the tumor. Additional assistive imaging methods, such as magnetic resonance imaging, bone scans, and positron emission tomography were contemplated, taking into account the patients' symptoms or if the method was deemed necessary by the attending clinician. After the second or third cycle of chemotherapy, the treatment response was appraised clinically and radiologically according to the Response Evaluation Criteria in Solid Tumors.

Statistical Analysis

Histograms and q-q plots were used to assess the data normality. A two-sided independent samples t-test was implemented to compare distinctions between continuous variants, while the Fisher exact test and the Pearson chi-square test were applied to determine the relationship between categorical variables. Receiver operating characteristic (ROC) curves were used to detect the discriminative impact of NLR and PLR in predicting the survival rate in bladder cancer patients. The area under the ROC curves was calculated with 95% confidence intervals. The DeLong test was used to compare the area under the ROC curves between NLR and PLR markers. The Youden index was calculated to detect the optimal cut-off value for each marker. Specificity, sensitivity, negative and positive predictive values were calculated with 95% confidence intervals.

Survival probabilities were predicted with the Kaplan-Meier method and group comparisons were applied with the Log-rank test. Furthermore, univariate and multiple Cox regression analyses were used to determine the most substantial risk elements. The cumulative sum of Schoenfeld residuals was used to assess the proportional hazard assumption. Significant variables at a value of $p<0.25$ on univariate analysis were taken into multiple models and forward stepwise selection was performed using a likelihood ratio statistic at a stringency level of $p<0.10$. Hazard ratios were also obtained with 95% confidence intervals. The calibration of the model was assessed using the Hosmer-Lemeshow goodness of fit test. A p-value of less than 5% was considered statistically significant. Analyses were conducted using TURCOSA (Turcosa Analytics Ltd. Co., www.turcosa.com.tr, Melikgazi, Kayseri, Turkey) and easyROC (14) software.

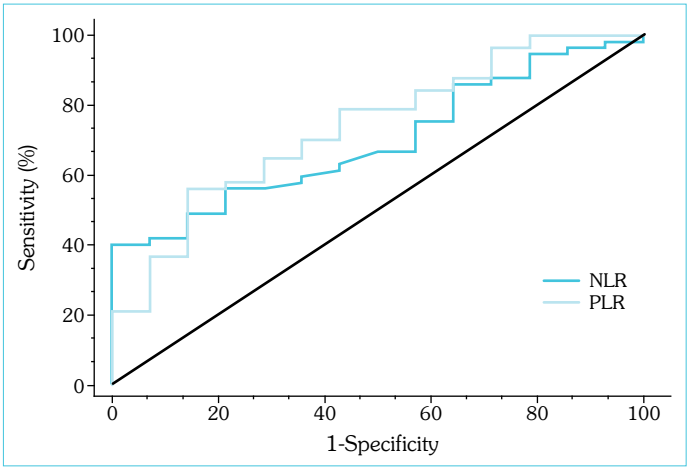

Figure 1. The predictive value of NLR and PLR for survival

RESULTS

In this study, the median patient age was 65 years (range: 36–79 years), and the total enrolment of 71 patients included 63 men (88.7%) and 8 women (11.3%). The most frequent location of metastasis was seen in the lymph nodes (64.8%) in 46 patients, followed by the lungs (52.1%) in 37 patients, and the liver (18.3%) in 13 patients. According to the chemotherapy response, patients were grouped as exhibiting; partial response (32.4%), stable disease (42.3%), progressive disease (23.9%), and complete response (1.4%). Regarding the chemotherapy regimen, 49 patients (69%) received platinum-based combination chemotherapy, 11 patients (15.5%) received single-agent gemcitabine, and 11 patients (15.5%) received taxane-based chemotherapy.

According to the threshold levels that were detected by ROC curve analysis, the NLR and PLR were each divided into two groups: ≤2.93 and >2.93, ≤168.9 and >168.9, respectively (Fig. 1, Table 1).

Table 1. ROC curve results and statistical diagnostic measures for NLR and PLR in predicting exitus in bladder cancer patients

Statistics	NLR>2.93	PLR>168.91
ROC curve statistics		
Area under curve	0.697 (0.576–0.800)	0.738 (0.620–0.835)
p-value	0.004	0.001
Diagnostic measures		
Sensitivity	0.404 (0.276–0.542)	0.561 (0.424–0.693)
Specificity	1.000 (0.768–1.000)	0.857 (0.572–0.982)
Positive predictive value	1.000 (0.852–1.000)	0.941 (0.803–0.993)
Negative predictive value	0.292 (0.170–0.441)	0.324 (0.180–0.498)

Values are expressed as estimates and 95% confidence intervals. According to the DeLong test results, the differences between the area under ROC curves of NLR and PLR markers were not found to be statistically significant (p>0.05). NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; ROC: Receiver operating characteristic

Table 2. Characteristics of participants according to NLR and PLR

Variable	NLR		p	PLR		p
	≤2.93	>2.93		≤168.91	>168.91	
Age (years)	68.88±8.19	65.09±9.72	0.602	63.86±9.81	64.71±8.30	0.699
Gender						
Male	45 (93.80)	18 (78.30)	0.102	33 (89.20)	30 (88.20)	0.999
Female	3 (7.50)	5 (16.10)		4 (10.80)	4 (11.80)	
Age (years)						
<60	14 (29.20)	10 (34.80)	0.785	13 (35.10)	9 (26.50)	0.455
≥60	34 (70.80)	15 (65.20)		24 (64.90)	25 (73.50)	
ECOG performance status						
0–1	33 (68.80)	9 (39.10)	0.022	24 (64.90)	18 (52.90)	0.340
2	15 (31.30)	14 (60.90)		13 (35.10)	16 (47.10)	
Number of metastatic sites, n (%)						
Single site	21 (52.5)	21 (67.7)	0.230	23 (62.2)	19 (55.9)	0.630
Multiple	19 (47.5)	10 (32.3)		14 (37.8)	15 (44.1)	
Site of metastatic, n (%)						
Lymph node	34 (70.80)	12 (52.20)	0.184	26 (73.10)	20 (60.00)	0.333
Lung	23 (47.90)	14 (60.90)	0.325	19 (51.40)	18 (52.90)	0.999
Liver	10 (20.80)	3 (13.00)	0.529	4 (10.80)	9 (26.50)	0.126
Hemoglobina[a]						
Normal	22 (45.80)	13 (56.50)	0.454	14 (37.80)	21 (61.80)	0.590
Anemia	26 (54.20)	10 (43.50)		23 (62.20)	13 (38.20)	
Lactate dehydrogenase[b]						
≥ULN	12 (27.90)	7 (33.30)	0.772	9 (27.30)	10 (32.30)	0.786
<ULN	31 (72.10)	14 (66.70)		24 (72.70)	21 (67.70)	
Albumin						
≥4 g/d	30 (63.80)	17 (73.90)	0.433	23 (63.90)	24 (70.60)	0.616
<4 g/d	17 (36.20)	23 (26.10)		13 (36.10)	10 (29.40)	

n (%): Number and percent; mean±SD: Mean and standard deviation; [a]Lower limits of reference range: men, 13.0 g/dL; women, 11.5 g/dL; [b]Upper limit of reference range: 450 U/L; ULN: Upper limit of normal; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; ECOG: Eastern Cooperative Oncology Group

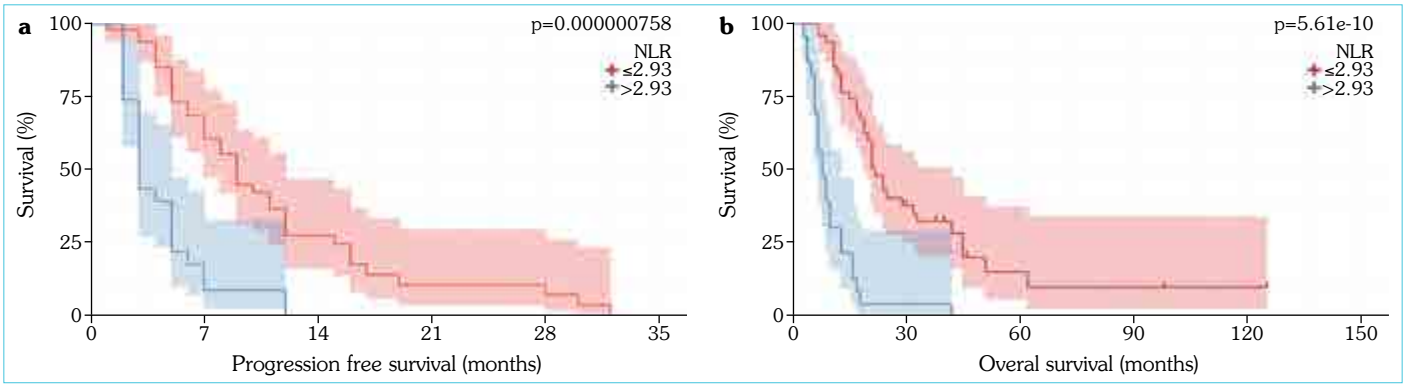

Figure 2. a, b. (a) Kaplan–Meier curves of PFS based on pre-treatment neutrophil-to-lymphocyte ratio (NLR). (b) Kaplan–Meier curves of OS based on pre-treatment neutrophil-to-lymphocyte ratio (NLR)

Except of performance status, there were no significant differences seen in the baseline characteristics between a high NLR (>2.93) and a low NLR (≤2.93) (Table 2). The median progression-free survival (PFS) was 3 months (95% Confidence interval (CI): 2.33–3.66) in the group with an elevated NLR and 9 months (95% CI: 7.53–10.4) in the group with a low NLR (p<0.001) (Fig.

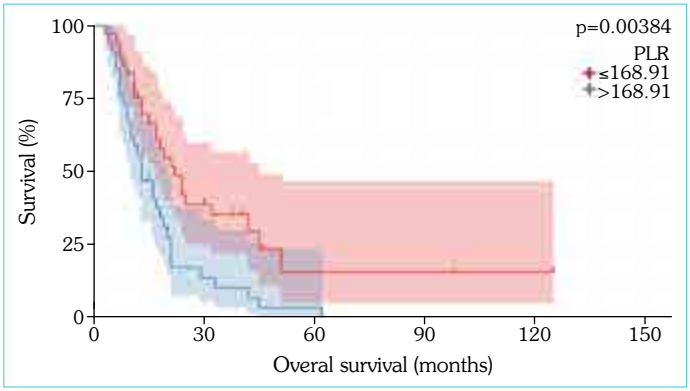

Figure 3. Kaplan–Meier curves of OS based on pre-treatment platelet-to-lymphocyte ratio (PLR)

2a). The median OS was 8 months (95% CI: 5.65–10.34) in the group with an elevated NLR and 22 months (95% CI: 18.5–25.4) in the group with a low NLR (p<0.001) (Fig. 2b).

There was no significant association between PLR groups and clinical parameters (Table 2). Median PFS was 5 months (95% CI: 3.06–6.93)in the group with an elevated PLR and 8 months (95% CI: 4.99–11.0) in the group with a low PLR (p=0.355). The median OS was 13 months (95% CI: 8.67–17.3) in the group with an elevated PLR and 22 months (95% CI: 15.5–28.4) in the group with a low PLR (p=0.003) (Fig. 3).

The global test or the Schoenfeld residuals showed a result as χ^2=4.31, p=0.505 to estimate the overall survival and showed a result of χ^2=0.54, p=0.464 to estimate the progression-free survival. Based on this result, it can be stated that the proportional hazard assumption was met. Univariate results were significant to predict the OS. Thus, a multiple model was created to estimate the OS by using only the NLR and Hemoglobin variable (Odds Ratio (OR)=5.58, p<0.05), (OR=0.43, p<0.05) (Table 3). None of the univariate results were significant enough to predict the PFS and only NLR was found to be significant (OR=3.43, p<0.05) in predicting the PFS of the patients (Table 3). Thus, a multiple model was created to estimate the PFS using only the NLR variable.

The Hosmer-Lemeshow test resulted as χ^2=36.49, p<0.001, which revealed that the built multiple Cox regression model in order to predict the OS of the patients was an appropriate tool. Similarly, the Hosmer-Lemeshow test resulted as χ^2=17.52, p<0.001, which revealed that the built multiple Cox regression model in order to predict the PFS of the patients was appropriate as well.

DISCUSSION

There has been increasing documentation of the fact that inflammation has a significant effect on the development and progression of malignant neoplasms, owing to the release of chemokines and cytokines, facilitating proliferation and angiogenesis, and allowing suppression apoptosis (15). In the tumor microenvironment, neutrophils can promote the progression of cancer by means of production of cytokines such as tumor necrosis factor, interleukin (IL)-6, and IL-1. Additionally, neutrophils support the adherence and seeding of remote organ areas of the tumor by secretion of proteases and circulating vascular endothelial growth factor (VEGF) (16, 17). Thrombocytes stimulate the epithelial-mesenchymal transition in circulating tumor cells and encourage extravasation into metastatic areas (18). Lymphocytes perform a considerable effect on the cancer-specific immune response by inducing inhibiting tumor cell reproduction and migration and cytotoxic cell death. It has been clarified that enhanced tumor-infiltrating lymphocytes are related to a good prognosis in this tumor microenvironment (19, 20). In the current research, we examined the possible value of NLR and PLR as prognostic tools by assessing their efficacy in patients with mBC undergoing first-line chemotherapy.

The impact of NLR on predicting survival results was initially defined in different cancers including gastric, hepatic, and lung cancer (21–23). Although pretreatment NLR has been proved to be correlated with high survival rates in non-mBC patients undergoing curative resection (24), the prognostic importance of NLR has not been widely explored in mBC patients receiving chemotherapy. In a meta-analysis of 100 studies involving 40.559 patients, Templeton et al. found that the relationship between NLR and worsened prognosis was stronger in patients with metastatic disease than

Table 3. Univariate and multiple cox regression analysis of variables for OS and PFS

Variables	OS		PFS	
	Univariate HR (95% CI)	Multiple HR (95% CI)	Univariate HR (95% CI)	Multiple HR (95% CI)
Age, years (60≥, 60<)	1.23 (0.69–2.19)	–	1.00 (0.57–1.76)	–
Gender (Male/ Female)	1.74 (0.82–3.73)	–	1.20 (0.57–2.54)	–
Albumin (≥4 g/d, <4 g/d)	0.62 (0.34–1.14)	–	0.75 (0.41–1.35)	–
Hemoglobina (Normal/Anemia)	0.49 (0.29–0.85)	0.43 (0.23–0.81)*	0.78 (0.47–1.31)	–
Number of metastatic sites (Single/Multiple)	1.32 (0.78–2.23)	–	1.01 (0.60–1.69)	–
EGOG PS (0–1/ 2)	1.18 (0.69–2.02)	–	1.40 (0.82–2.39)	–
NLR (High/Low)	5.19 (2.90–9.28)	5.58 (2.80–11.13)*	3.51 (1.99–6.17)	3.43 (1.92–6.12) *
PLR (High/ Low)	2.10 (1.24–3.58)	–	1.19 (0.71–2.00)	–

*Only variable that remained in the multiple model; CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio

those without metastatic cancer, which could perchance reflect a weakened immune reaction to tumor cells and a larger tumor burden (25). Several recent research studies have appraised the importance of NLR in advanced stage urothelial neoplasms. Rossi et al. indicated that a high NLR was related to worse PFS and OS in urothelial cancer (26). Additionally, they evaluated the importance of changes in NLR after chemotherapy and determined that permanently high NLR had the worst prognosis whereas consistently low NLR had the best outcome (26).

A pooled analysis demonstrated that an elevated pre-therapy NLR was related to a poorer OS rate in unresectable or metastatic urothelial malignancy in patients (27). Tan et al. retrospectively explored 150 patients with metastatic or advanced bladder cancer (BC) to determine the prognostic effect of NLR (5). They showed that a high pre-therapy NLR was independently correlated with a poorer therapeutic response and worse OS in these patients (5).

Ohtake et al. appraised the effect of NLR on survival outcomes in BC patients who were treated with nedaplatin and gemcitabine. They determined that higher NLR significantly correlated with poor PFS and OS in patients who received chemotherapy for mBC (28).

Our study indicated that an elevated NLR correlates with worse PFS and OS in univariate analysis and an elevated NLR was identified to be an independent predictor of OS (OR: 5.58, 95% CI: 2.80–11.13, $p<0.05$) and PFS (OR: 3.43, 95% CI: 1.92–6.12, $p<0.05$) in the multiple analysis.

Except for hemostasis and thrombosis, it has been reported that platelets are responsible for cancer cell proliferation and metastasis owing to their action of releasing a great deal of pro-angiogenic molecules including VEGF, platelet-derived growth factors, and proteases (29, 30).

Mutually, malignant cells could stimulate the aggregation of thrombocytes and manipulate thrombocyte activity to ease cancer progression (29, 31). Elevated serum platelets even for a brief period could lead to a worse outcome, therefore, elevated PLR, which displays high thrombocyte levels and low lymphocyte levels and is linked to a poor outcome. A few previous studies have declared the value of PLR as a prognostic tool in different cancers (8–10). However, the prognostic importance of PLR has not been appraised in mBC. In the current research, findings of univariate analysis uncovered that higher pretreatment PLR was related to worse OS. However, findings of the multiple analysis showed that high PLR was not an independent prognostic determinant of survival. Hence, the prognostic importance of PLR is still contentious and therefore should be further studied.

Anemia has an elevated incidence of almost 50% among patients with BC and is usually linked to metastatic cancer (32). A few studies have indicated that anemia predicts poorer OS in patients receiving first-line chemotherapy for metastatic disease (33, 34). We found that anemia was significantly correlated with worse OS, but not for PFS.

The main limitation of this research was that the sample size was relatively small, retrospective, non-randomized, and came from our single center in Turkey, which might be the cause of generalization of the results. In addition, we could not evaluate all the factors that would affect the results of NLR and PLR.

In conclusion, the current research discovered that high PLR and anemia were significantly related to worse OS in univariate analysis. A high NLR was significantly correlated with poorer PFS and OS in mBC patients receiving first-line chemotherapy. Additionally, findings of multiple analysis detected that a high pretreatment NLR was an independent prognostic determinant of PFS and OS. We opine that pretreatment inflammatory markers, particularly NLR, could be accurate prognostic tools for predicting the outcome of mBC patients undergoing first-line chemotherapy. However, further large prospective studies should be performed to verify whether pretreatment NLR has prognostic and predictive markers in patients with mBC.

Ethics Committee Approval: The research was approved by the ethics board of Erciyes University Medical School, Melikgazi/Kayseri, Turkey (Approval number: 2018/630).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – OB; Design – OB, ED; Supervision – OB, ED; Resource – OB, Mİ; Materials – OB; Data Collection and/or Processing – STF, ED, RÇ; Analysis and/or Interpretation – GEZ; Literature Search – STF, RÇ; Writing – OB, MO; Critical Reviews – Mİ, MÖ.

Conflict of Interest: The authors have no conflict of interest to declare.

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REFERENCES

1. Cancer Research UK. Bladder cancer survival by stage at diagnosis. 2016. [Cited May 2017.] Available at: URL; https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer. Accessed August 19, 2019.
2. American Cancer Society. Cancer Facts and Figures 2016. Atlanta, GA: American Cancer Society, 2016.
3. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005; 23(21): 4602–8. [CrossRef]
4. Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006; 42(1): 50–4. [CrossRef]
5. Tan YG, Eu EWC, Huang HH, Lau WKO. High neutrophil-to-lymphocyte ratio predicts worse overall survival in patients with advanced/metastatic urothelial bladder cancer. Int J Urol 2018; 25(3): 232–8.
6. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008; 454(7203): 436–44. [CrossRef]
7. Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol 2011; 13(7): 499–503. [CrossRef]
8. Azab B, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013; 30(1): 432. [CrossRef]
9. Feng JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio

(PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. World J Surg Oncol 2014; 12: 58. [CrossRef]
10. Lee S, Oh SY, Kim SH, Lee JH, Kim MC, Kim KH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 2013; 13: 350. [CrossRef]
11. Shin JS, Suh KW, Oh SY. Preoperative neutrophil to lymphocyte ratio predicts survival in patients with T1-2N0 colorectal cancer. J Surg Oncol 2015; 112(6): 654–7. [CrossRef]
12. Siddiqui A, Heinzerling J, Livingston EH, Huerta S. Predictors of early mortality in veteran patients with pancreatic cancer. Am J Surg 2007; 194(3): 362–6. [CrossRef]
13. Hermanns T, Bhindi B, Wei Y, Yu J, Noon AP, Richard PO, et al. Pre-treatment neutrophil-to-lymphocyte ratio as predictor of adverse outcomes in patients undergoing radical cystectomy for urothelial carcinoma of the bladder. Br J Cancer 2014; 111(3): 444–51. [CrossRef]
14. Goksuluk D, Korkmaz S, Zararsiz G, Karaagaoglu E. easyROC: An Interactive Web-tool for ROC Curve Analysis Using R Language Environment. The R Journal 2016; 8: 213–30. [CrossRef]
15. Moses K, Brandau S. Human neutrophils: Their role in cancer and relation to myeloid-derived suppressor cells. Semin Immunol 2016; 28(2): 187–96. [CrossRef]
16. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357(9255): 539–45. [CrossRef]
17. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010; 140(6): 883–99. [CrossRef]
18. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011; 20(5): 576–90. [CrossRef]
19. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003; 348(3): 203–13. [CrossRef]
20. Leffers N, Gooden MJ, de Jong RA, Hoogeboom BN, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009; 58(3): 449–59. [CrossRef]
21. Jung MR, Park YK, Jeong O, Seon JW, Ryu SY, Kim DY, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. J Surg Oncol 2011; 104(5): 504–10. [CrossRef]
22. Gomez D, Farid S, Malik HZ, Young AL, Toogood GJ, Lodge JP, et al. Preoperative neutrophil-to-lymphocyte ratio as a prognostic predictor after curative resection for hepatocellular carcinoma. World J Surg 2008; 32(8): 1757–62. [CrossRef]
23. Tomita M, Shimizu T, Ayabe T, Yonei A, Onitsuka T. Preoperative neutrophil to lymphocyte ratio as a prognostic predictor after curative resection for non-small cell lung cancer. Anticancer Res 2011; 31(9): 2995–8.
24. Viers BR, Boorjian SA, Frank I, Tarrell RF, Thapa P, Karnes RJ, et al. Pretreatment neutrophil-to-lymphocyte ratio is associated with advanced pathologic tumor stage and increased cancer-specific mortality among patients with urothelial carcinoma of the bladder undergoing radical cystectomy. Eur Urol 2014; 66(6): 1157–64. [CrossRef]
25. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014; 106(6): dju124. [CrossRef]
26. Rossi L, Santoni M, Crabb SJ, Scarpi E, Burattini L, Chau C, et al. High neutrophil-to-lymphocyte ratio persistent during first-line chemotherapy predicts poor clinical outcome in patients with advanced urothelial cancer. Ann Surg Oncol 2015; 22(4): 1377–84. [CrossRef]
27. Wu S, Zhao X, Wang Y, Zhong Z, Zhang L, Cao J, et al. Pretreatment Neutrophil-Lymphocyte Ratio as a Predictor in Bladder Cancer and Metastatic or Unresectable Urothelial Carcinoma Patients: a Pooled Analysis of Comparative Studies. Cell Physiol Biochem 2018; 46(4): 1352–64. [CrossRef]
28. Ohtake S, Kawahara T, Kasahara R, Ito H, Osaka K, Hattori Y, et al. Pretreatment Neutrophil-to-Lymphocyte Ratio Can Predict the Prognosis in Bladder Cancer Patients Who Receive Gemcitabine and Nedaplatin Therapy. Biomed Res Int 2016; 2016: 9846823. [CrossRef]
29. Nieswandt B, Aktas B, Moers A, Sachs UJ. Platelets in atherothrombosis: lessons from mouse models. J Thromb Haemost 2005; 3(8): 1725–36. [CrossRef]
30. Sharma D, Brummel-Ziedins KE, Bouchard BA, Holmes CE. Platelets in tumor progression: a host factor that offers multiple potential targets in the treatment of cancer. J Cell Physiol 2014; 229(8): 1005–15.
31. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 2012; 17(3): 216–22. [CrossRef]
32. Joynson CP, Sundar S, Symonds P. Anaemia is associated with poor overall survival but not with inferior local control in patients with muscle invasive bladder carcinoma treated by radical external beam radiotherapy. A retrospective study. Clin Oncol (R Coll Radiol) 2006; 18(10): 728–34. [CrossRef]
33. Bamias A, Efstathiou E, Moulopoulos LA, Gika D, Hamilos G, Zorzou MP, et al. The outcome of elderly patients with advanced urothelial carcinoma after platinum-based combination chemotherapy. Ann Oncol 2005; 16(2): 307–13. [CrossRef]
34. Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999; 17(10): 3173–81. [CrossRef]