European Review for Medical and Pharmacological Sciences 2016; 20: 1467-1473

The predictive effect of initial complete blood count of intensive care unit patients on mortality, length of hospitalization, and nosocomial infections

L. KUTLUCAN[1], A. KUTLUCAN[2], B. BASARAN[1], M. DAGLI[2], A. BASTURK[2], B. KOZANHAN[1], M. GUR[3], E. SENOCAK[3], M. KOS[3]

[1]Department of Anesthesiology, Konya Training and Research Hospital, Konya, Turkey
[2]Department of Internal Medicine, Selcuk University, School of Medicine, Konya, Turkey
[3]Department of Internal Medicine, Duzce University, School of Medicine, Düzce, Turkey

Abstract. – OBJECTIVE: The mean platelet volume (MPV) can be used as an indicator of platelet activation. However, it has been shown that the platelet/lymphocyte ratio (PLR) can provide useful predictive information about inflammation and aggregation pathways. The neutrophil/lymphocyte ratio (NLR) may also be helpful as a marker of systemic or local inflammation. The main objective of this study evaluated to unselected critically ill patients the relationship of initial MPV, NLR, and PLR with mortality, length of hospitalization, and the risk of developing nosocomial infections in ICU patients.

PATIENTS AND METHODS: In this retrospective study, we evaluated consecutive patients at our tertiary nine-bed ICU. One hundred seventy-three patients who were followed up during a 1-year period were included.

RESULTS: MPV levels were found to be higher in patients who died in the hospital ($p = 0.05$). In addition, there was a significant positive correlation between expected mortality rate and MPV among non-survivors ($p = 0.009$). NLR levels were higher among non-survivors, but this difference was not statistically significant ($p = 0.435$). PLR levels were similar between non-survivors and survivors ($p = 0.173$). The initial NLR and PLR were significantly higher in patients with nosocomial infections. NLR and PLR had a significant positive correlation with length of hospitalization ($p = 0.006$ and $p = 0.027$, respectively).

CONCLUSIONS: In our study, we found that high PLR and NLR may be indicators for the development of nosocomial infections. Moreover, the length of hospitalization may be prolonged in patients with high PLR and NLR.

Key Words:
Platelet/lymphocyte ratio, Neutrophil/lymphocyte ratio, Mean platelet volume, Prognosis, Length of hospitalization, Nosocomial infections.

Introduction

The average life expectancy is increasing with advances in medicine. The number of patients in the older age groups, along with age-associated comorbidities and need for intensive care, is rising. Every year, more than 5 million patients in the United States are being admitted to intensive care units (ICUs); however, survival success can be achieved only in 10-29% of these patients[1]. Various causes, including sepsis, may lead to continuing systemic inflammatory conditions among patients in ICU. Among its many negative impacts, inflammation leads to endothelial dysfunction. As a result of endothelial dysfunction and platelet activation and consumption, organ dysfunction may occur[2]. Therefore, to assess the inflammation status of patients in the ICU, various biomarkers, such as acute phase reactants and cytokines, are widely used routinely during clinical practice or for scientific studies.

The mean platelet volume (MPV) may be used as an indicator of platelet activation. Elevated MPV is related to an increase in prothrombotic processes[3]. Although the platelet volume index can be used in the differential diagnosis of thrombocytopenia[4,5], most published studies have emphasized the relationship between systemic inflammatory state and infectious response[6-8]. In ICU patients, endothelial dysfunction generated by inflammation may cause platelet activation and consumption in the microcirculation. Therefore, diffuse thrombosis and multiorgan failure may occur. MPV has been used as a marker of mortality in the ICU in some studies. Increased MPV was found to be a predictor of the higher mortality rates in two of these three studies[2,9,10].

Corresponding Author: Leyla Kutlucan, MD; e-mail: leylakutlucan@hotmail.com

White blood cell count (WBC), a classical inflammation marker, is also used in many scoring systems during routine daily clinical practice. Recent studies have shown increased ratios of WBC subsets in stress conditions such as inflammation[11-13]. Therefore, we proposed the use of the neutrophil/lymphocyte ratio (NLR) as a marker of systemic or local inflammation. The NLR is a marker that can be measured inexpensively and easily with a simple complete blood count (CBC). Increased NLR has been shown to be a predictor of morbidity and mortality. The relationships between NLR and prognosis and mortality in patients with chronic inflammatory disease, sepsis, cardiovascular, pulmonary, and neoplastic diseases have been reported in the literature[14-20]. However, evidence of the importance of NLR among ICU patients is very limited, with only a relationship with mortality assessed to date[1,11].

It has been shown that the platelet/lymphocyte ratio (PLR) can provide more useful predictive information than platelets or lymphocytes alone concerning the inflammation and aggregation pathways[21]. PLR is a negative prognostic marker, particularly for cardiovascular and malignant diseases. PLR also is a new marker for hospital and post hospital mortality due to cardiovascular diseases[22-24]. To the best of our knowledge, no study to date has evaluated the relationship between PLR and prognosis, length of hospitalization, and the risk of developing nosocomial infections in the ICU.

In this study, we aimed to evaluate the relationship between complete blood count parameters that are inexpensive to measure during initial evaluations (e.g., MPV, NLR, and PLR) and mortality, length of hospitalization, and the risk of development of nosocomial infections in ICU patients. In this way, we tried to identify the markers of prognosis in critically ill patients. In addition, we assessed the predictive effect of WBC, vitamin B12, lactate, hemoglobin (Hb), platelets, albumin, high-sensitivity C-reactive protein (hs-CRP), creatine kinase-MB (CK-MB), and lactate dehydrogenase (LDH) upon admission regarding mortality.

Patients and Methods

This retrospective study was performed in a tertiary nine-bed ICU at our Department of Internal Medicine. Unselected critically ill patients, who were monitored for less than 2 days, were pregnant, had received chemotherapy or immunosuppressive therapy, were previously diagnosed with hematologic malignancies or HIV, and were younger than 18 years of age were excluded. Demographic data, first diagnoses, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE) scores, Glasgow Coma Scale (GCS) scores, and mortality rates were noted on admission.

Peripheral blood samples were collected upon admission for the evaluation of CBC; biochemical, hormonal, and serologic parameters; and acute phase reactants. A blood sample for CBC was collected into a tube containing ethylenediaminetetraacetic acid. Hematologic parameters were analyzed within 30 min after sample collection using a hematology analyzer (Abbott CELL-DYN 3700; Abbott Diagnostics, Lake Forest, IL, USA). The counts for leukocytes (103/□L), neutrophils (103/□L), lymphocytes (103/□L), and platelets (103/□L) were recorded. NLR and PLR were calculated using the results of these counts. Hb levels (g/dL) and MPV (fL) were determined. Hormonal and biochemical levels were assayed using a solid-phase competitive chemiluminescent enzyme immunoassay, a solid-phase chemiluminescent immunometric assay, a colorimetric method, and a competitive immunoassay (IMMULITE 2000, Siemens Healthcare Diagnostics, Tarrytown, NY, USA; and cobas 6000 c 501, Roche Diagnostics, Indianapolis, IN, USA). We also noted nosocomial infections diagnosed according to the nosocomial infection criteria as well as hospitalization period and discharge conditions.

Statistical Analysis

All data relevant to the study were analyzed using SPSS Statistics 19 software (IBM, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation, and categorical variables are presented as percentages. The analyses were performed with the Mann-Whitney U test, *t*-test, and bivariate correlation test. The level of statistical significance was set at $p < 0.05$.

Ethics

The patient data were obtained from medical records in our hospital's registry. Ethical approval was obtained from the Ethics Committee of our institute. The procedures followed were in accordance with the ethical standards of the re-

sponsible committee on human experimentation (institutional or regional) and with the 1975 Declaration of Helsinki as revised in 1983.

Results

One hundred seventy-three patients who were hospitalized in our ICU during a 1-year period were included in this study. Ninety (52%) of the patients were men, and 83 (48%) were women. The mean age of all patients was 68.6 years (range, 20-93 year). The mean age of the female patients was 67.9 years, and the mean age of the male patients was 69.3 years. One hundred sixty-four patients had, at least, one comorbidity upon admission.

Eighty-one (51 male and 30 female; 46.8%) of all included patients died during their ICU stay, and 92 (39 male and 52 female; 53.2%) of all included patients were discharged to the wards. According to the hospital admission data, the 81 patients who died were older ($p < 0.001$), had lower GCS scores ($p < 0.001$), had a higher expected mortality rate ($p < 0.001$), and had higher APACHE II scores ($p < 0.001$) than patients who remained alive at the end of the study period (Table I).

Evaluation of all the blood parameters of all accepted patients revealed that the WBC values were significantly higher ($p = 0.019$) and Hb levels were significantly lower ($p = 0.001$) among non-survivors than among survivors (Table II). However, the platelet counts were similar between the two groups ($p = 0.156$). Although the MPV levels were within the normal range among all patients, significantly higher MPV levels were found among non-survivors ($p < 0.05$). Also, a significant positive correlation between the expected mortality rate and MPV was observed among non-survivors ($p = 0.009$). NLR levels were higher among the non-survivors, but this difference was not statistically significant ($p = 0.435$). PLR levels were similar between the survivors and non-survivors ($p = 0.173$). The vitamin B12 levels were lower than normal in 51 patients; of these patients, 14 (27%) were non-survivors and 37 (73%) were survivors. The mean vitamin B12 level was twofold higher among the non-survivors than among survivors ($p = 0.001$). The levels of lactate, LDH, hs-CRP, and CK-MB were significantly higher, and albumin was significantly lower among non-survivors than among survivors. The D-dimer and troponin levels were higher among the non-survivors, but this difference was not statistically significant (Table II).

During follow-up, nosocomial infections occurred in 42 patients (24.2%). When we evaluated the relationship between initial laboratory parameters and the incidence of nosocomial infection, we found that the 42 patients with nosocomial infections had significantly higher levels of thrombocytes and vitamin B12, as well as higher NLR and PLR ($p = 0.031$, $p = 0.050$, $p = 0.002$, and $p = 0.009$, respectively) (Table III).

At the end of follow-up, the mean ICU length of hospitalization was 11.9 ± 18.7 days for all patients. The mean hospitalization periods were 15 ± 22.7 days and 9.2 ± 13.9 days for non-survivors and survivors, respectively ($p = 0.039$). NLR and PLR ($p = 0.006$ and $p = 0.027$, respectively) showed significant positive correlations with the length of hospitalization. In contrast, Hb, WBC, PLT, MPV, and vitamin B12 levels did not show significant correlations with the length of hospitalization.

Discussion

In recent studies, relationships have been demonstrated between thrombosis, aggregation, inflammation, and CBC parameters. MPV, NLR, and PLR calculated using CBC laboratory values

Table I. Comparison of the average age and prognostic predictors between survivors and non-survivors.

Evaluation of hospital admissions	All patients (n = 173)	Survivors (n = 92)	Non-survivors (n = 81)	*p*-value
The average age (SD)	68.6 ± 15.5	64.6 ± 17.7	73.2 ± 11.5	< 0.001
GKS (SD)	8.83±4.4	10.7 ± 4.2	7 ± 4	< 0.001
APACHE II score (SD)	25.2 ± 10.5	19.6 ± 8.7	31.5 ± 8.5	< 0.001
Expected mortality rate (%) (SD)	54.8 ± 24.7	42.4± 19.6	68.9 ± 22.2	< 0.001

SD: Standart Deviation; GKS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table II. Comparison of laboratory tests between survivors and non-survivors.

Parameter (normal range)	All patients (n = 173)	Survivors (n = 92)	Non-survivors (n = 81)	*p*-value
WBC (3.5-10.5 × $10^3/\mu$L)	15.2 ± 16.8	12.4 ±7.2	18.4 ± 23	0.019
Neu (1.7-7 × $10^3/\mu$L)	11.7 ± 10.7	11.3 ± 10.8	12.1 ± 10.7	0.639
Lym (0.9-2.9 × $10^3/\mu$L)	1.3 ± 1.3	1.24 ± 0.75	1.25 ± 1.82	0.982
Hb (13.5-17.5 g/dL)	10.6 ± 2.1	11.2 ± 2.2	9.8 ± 1.8	< 0.001
Plt (150-450 × $10^3/\mu$L)	205.2 ± 122.6	217.6 ±128.8	191.1 ± 114.4	0.156
MPV (9-13 fL)	9.3 ± 1.2	9.1 ± 1.7	9.5 ± 1.2	0.05
Vitamin B12 (191-663 pg/mL)	550.5 ± 487.4	374.2±362.9	750.7 ± 533.5	< 0.001
NLR	12.9 ± 12.5	12.2±12.9	13.7 ± 12.08	0.435
PLR	252.0 ± 201.8	232.4 ±168.6	274.3 ± 233.1	0.173
D-dimer (0-0.5 mcg/ml)	4.2 ± 7.9	3.2 ± 4.1	5.4 ± 10.6	0.068
Lactate (0.5-1.6 mmol/L)	2.9 ± 2.9	2 ± 1.5	3.9 ± 3.8	< 0.001
LDH (240-480 U/L)	447.9 ± 409.8	383.2 ± 292.9	521.4 ± 503.2	0.027
Albumin (3.5-5.2 g/dL)	2.8 ± 0.6	3 ± 0.6	2.6 ± 0.52	< 0.001
Troponin (< 0.1 ng/mL)	0.3 ± 0.8	0.17 ± 0.4	0.4 ± 1.1	0.064
hs-CRP (0-5 mg/L)	206.3 ± 191.4	151.8 ± 164.5	268.2 ± 201.8	< 0.001
CK-MB (< 12 U/L)	53 ± 47.4	44.1 ± 39.3	63.1 ± 53.6	0.008

WBC: White Blood Cell; Neu: Neutrophils; Lym: Lymphocytes; Hb: Hemoglobin; Plt: Platelets; MPV: Mean Platelet Volume; NLR: Neutrophil/lymphocyte Ratio; PLR: Platelet/lymphocyte Ratio; LDH: Lactate dehydrogenase; hs-CRP: high-sensitivity C-reactive protein; CK-MB: Creatine kinase-MB.

are simple and inexpensive markers of these processes. To the best of our knowledge, this study is the first evaluation of all of these parameters and their possible relevance to mortality, nosocomial infection, and length of hospitalization among ICU patients. We researched the utility of the PLR, which has been used before in patients with cardiovascular disease and malignancy, as a marker of inflammation in patients in ICU. MPV values upon ICU admission were significantly higher among non-survivors, but no association with mortality was shown for NLR or PLR. In addition, non-survivors had higher WBC, vitamin B12, lactate, LDH, hs-CRP, and CK-MB, as well as lower of Hb and albumin levels than survivors. Also, for the first time to the best of our knowledge, we have demonstrated that patients who developed nosocomial infections during follow-up had higher NLR and PLR calculated on the basis of CBC values taken upon admission. We also found a positive correlation between NLR and PLR with the length of ICU hospitalization.

Few studies have shown that MPV was higher in ICU non-survivors than survivors. Gao et al[10] reported high MPV levels in patients diagnosed with septic shock who died in the ICU. Zampieri et al[2] showed that high levels of MPV were associated with mortality in 84 ICU patients. Zhang et al[9] reported that high MPV levels were associ-

Table III. Comparison of laboratory tests between patients with or without nosocomial infection.

Parameter (normal range)	Nosocomial infection		*p*-value
	Present (n = 42)	Absent (n = 131)	
Hb (13.5-17.5 g/dL)	10.4 ± 1.9	10.7 ± 2.2	0.470
WBC (3.5-10.5 × $10^3/\mu$L)	15.1 ± 7.8	15.2 ± 18.2	0.986
Plt (150-450 × $10^3/\mu$L)	241.9 ± 148.3	196.0 ± 108.3	0.031
MPV (9-13 fL)	9.2 ± 1.3	9.3 ± 1.2	0.650
Vitamin B12 (191-663 pg/mL)	677.9 ± 535.6	509.7 ± 465.8	0.050
NLR	18.1 ± 16.3	11.2 ± 10.6	0.002
PLR	322.6 ± 248.7	229.4 ± 179.6	0.009

Hb: Hemoglobin; WBC: White Blood Cell; Plt: Platelets; MPV: Mean Platelet Volume; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

ated with increased mortality in 443 of 1556 patients. Similarly, we have demonstrated an association between high MPV and mortality. Thus, MPV can be used as a sensitive marker for mortality in patients in ICU. In contrast, there was no significant relationship between MPV values and nosocomial infection or length of hospitalization. These associations were not addressed in the previous studies.

NLR has been investigated as a marker for prognosis in a limited number of studies of ICU patients. In an observational cohort study, Salciccioli et al[1] identified a positive correlation between NLR and mortality among consecutive critically ill patients, but no such association was found for patients with sepsis. High levels of NLR were attributed to high risk of in-hospital and 6-month mortality in one prospective study that included 373 patients in an Emergency Department[11]. NLR was shown to be a more useful indicator than WBC or CRP for the prediction of acute renal failure in 118 patients with severe sepsis[20]. Although NLR values among ICU nonsurvivors were high in our study, this finding was not statistically significant. We found no study in the literature in which researchers assessed the relationship between NLR upon admission with nosocomial infections or length of hospitalization. We found that NLR upon admission was significantly higher in patients diagnosed with nosocomial infections and those who had increased length of hospitalization.

PLR is now commonly used as a marker for aggregation and inflammation pathways in patients with coronary artery disease[22-24]. PLR is also used as a marker for other inflammatory conditions such as malignancies and liver and kidney diseases that are associated with high mortality rates[25-28]. Kundi et al[29] reported a relationship between mortality and high PLR in patients with acute pulmonary emboli; however, they did not assess PLR as a marker to show any relationship between mortality, length of hospitalization, or the risk of developing nosocomial infections in patients in ICU. In our research, PLR was 274.3 among non-survivors and 232.2 among survivors. Although this difference was not statistically significant, non-survivors had higher PLR values than survivors. We think that PLR and its connection with mortality can be better evaluated if a larger group of patients is studied.

Another important result of our study is that vitamin B12 level was twofold higher in nonsurvivors. Renal failure, cancer, and liver failure may result in increased vitamin B12 levels[30-32]. Numerous mechanisms are used to explain this rise of vitamin B12 levels. The most accepted one is pathologic changes in the liver and myeloid cells that lead to the accumulation of vitamin B12. Researchers in two studies reported conflicting results regarding mortality and vitamin B12 levels. Sviri et al[33] reported that the mortality risk increased with of vitamin B12 levels, particularly in patients with chronic disease. In contrast, Callaghan et al[34] did not find any connection between high vitamin B12 levels and mortality. They proposed the use of liver function tests instead of vitamin B12 levels to predict mortality. Our results correlate with the first study conducted by Sviri. Although 95% of patients in our study had a chronic disease, the follow-up to evaluate increases in vitamin B12 levels may be important among ICU patients. In addition, our results point to elevated vitamin B12 levels as a risk factor for the development of nosocomial infections. We could not find any similar study on this topic in our search of the literature.

Conclusions

Hemoglobin, WBC, and MPV are important parameters to predict prognosis in critically ill patients, but the measurement of PLR and NLR for prognosis is not clearly defined. According to our results, we found that high PLR, NLR, and vitamin B12 levels may be indicators for the development of nosocomial infections. Also, hospitalization may be prolonged in patients with high PLR and NLR. These parameters can be assessed as cut-off points for future research. These simple parameters that are inexpensive to measure can help physicians in decision-making about ICU patients' prognosis, length of hospitalization, and risk of developing nosocomial infections.

Notes

The results of this study were presented in part at the VIth International Eurasian Hematology Congress, Antalya, Turkey (October 13, 2015).

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in this report.

References

1) Salciccioli JD, Marshall DC, Pimentel MA, Santos MD, Pollard T, Celi LA, Shalhoub J. The association between the neutrophil-to-lymphocyte ratio and mortality in critical illness: an observational cohort study. Crit Care 2015; 19: 13.
2) Zampieri FG, Ranzani OT, Sabatoski V, de Souza HP, Barbeiro H, da Neto LM, Park M, Da Silva FP. An increase in mean platelet volume after admission is associated with higher mortality in critically ill patients. Ann Intensive Care 2014; 4: 20.
3) de Gaetano G, Santimone I, Gianfagna F, Iacoviello L, Cerletti C. Variability of platelet indices and function: acquired and genetic factors. Handb Exp Pharmacol 2012; 210: 395-434.
4) Bowles KM, Cooke LJ, Richards EM, Baglin TP. Platelet size has diagnostic predictive value in patients with thrombocytopenia. Clin Lab Haematol 2005; 27: 370-373.
5) Ntaios G, Papadopoulos A, Chatzinikolaou A, Saouli Z, Karalazou P, Kaiafa G, Girtovitis F, Kontoninas Z, Savopoulos C, Hatzitolios A, Alexiou-Daniel S. Increased values of mean platelet volume and platelet size deviation width may provide a safe positive diagnosis of idiopathic thrombocytopenic purpura. Acta Haematol 2008; 119: 173-177.
6) Ozturk ZA, Dag MS, Kuyumcu ME, Cam H, Yesil Y, Yilmaz N, Aydinli M, Kadayifci A, Kepekci Y. Could platelet indices be new biomarkers for inflammatory bowel diseases? Eur Rev Med Pharmacol Sci 2013; 17: 334-341.
7) Küçükbayrak A, Ta T, Tosun M, Akta G, Alçelik A, Necati Hakyemez I, Kocoglu E, Akdeniz H. Could thrombocyte parameters be an inflammatory marker in the brucellosis? Med Glas (Zenica) 2013; 10: 35-39.
8) Rondina MT, Brewster B, Grissom CK, Zimmerman GA, Kastendieck DH, Harris ES, Weyrich AS. In vivo platelet activation in critically ill patients with primary 2009 influenza A(H1N1). Chest 2012; 141: 1490-1495.
9) Zhang Z, Xu X, Ni H, Deng H. Platelet indices are novel predictors of hospital mortality in intensive care unit patients. J Crit Care 2014; 29: 885.e1-6.
10) Gao Y, Li Y, Yu X, Guo S, Ji X, Sun T, Lan C, Lavergne V, Ghannoum, Li L. The impact of various platelet indices as prognostic markers of septic shock. PLoS One 2014; 9: e103761.
11) Akilli NB, Yortanli M, Mutlu H, Günaydin YK, Koylu R, Akca HS, Akinci E, Dundar ZD, Cander B. Prognostic importance of neutrophil-lymphocyte ratio in critically ill patients: short- and long-term outcomes. Am J Emerg Med 2014; 32: 1476-1480.
12) Galus MA, Stern J. Extreme lymphocytopenia associated with toxic shock syndrome. J Intern Med 1998; 244: 351-354.
13) Jilma B, Blann A, Pernerstorfer T, Stohlawetz P, Eichler HG, Vondrovec B, Amiral J, Richter V, Wanger OF. Regulation of adhesion molecules during human endotoxemia. Am J Respir Crit Care Med 1999; 159: 857-863.
14) Turkmen S, Dogru O, Tekin K, Kucukdurmaz Z, Cagliyan CE, Sarikaya S, Yucel H, Karapinar H, Ozkan B, Uysal OK, Basara A, Sancaktar E, Yilmaz A. The relationship between neutrophil/lymphocyte ratio and the TIMI flow grade in patients with STEMI undergoing primary PCI. Eur Rev Med Pharmacol Sci 2013; 17: 2185-2189.
15) Uthamalingam S, Patvardhan EA, Subramanian S, Ahmed W, Martin W, Daley M, Capodilupo R. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol 2011; 107: 433-438.
16) Yasar Z, Buyuksirin M, Ucsular FD, Kargi A, Erdem F, Talay F, Kurt OK. Is an elevated neutrophil-to-lymphocyte ratio a predictor of metabolic syndrome in patients with chronic obstructive pulmonary disease? Eur Rev Med Pharmacol Sci 2015; 19: 956-962.
17) Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001; 102: 5-14.
18) Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg 2009; 137: 425-428.
19) Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, Lee K. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother 2009; 58: 15-23.
20) Yilmaz H, Cakmak M, Inan O, Darcin T, Akcay A. Can neutrophil-lymphocyte ratio be independent risk factor for predicting acute kidney injury in patients with severe sepsis? Ren Fail 2015; 37: 225-229.
21) Yüksel M, Yildiz A, Oylumlu M, Akyüz A, Aydin M, Kaya H, Acet H, Polat N, Bilik MZ, Alan S. The association between platelet/lymphocyte ratio and coronary artery disease severity. Anatol J Cardiol 2015; 15: 640-647.
22) Akboga MK, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, Aras D. Association of platelet to lymphocyte ratio with inflammation and severity of coronary atherosclerosis in patients with stable coronary artery disease. Angiology 2016; 67: 89-95.
23) Kurtul A, Murat SN, Yarlioglues M, Duran M, Ergun G, Acikgoz SK, Demircelik MB, Cetin M, Akyel A, Kasapkara HA, Ornek E. Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. Am J Cardiol 2014; 114: 972-978.
24) Demircelik MB, Kurtul A, Ocek H, Cakmak M, Ureyen C, Eryonucu B. Association between

platelet-to-lymphocyte ratio and contrast-induced nephropathy in patients undergoing percutaneous coronary intervention for acute coronary Syndrome. Cardiorenal Med 2015; 5: 96-104.

25) Lai Q, Castro Santa E, Rico Juri JM, Pinheiro RS, Lerut J. Neutrophil and platelet-to-lymphocyte ratio as new predictors of drop out and recurrence after liver transplantation for hepatocellular cancer. Transpl Int 2014; 27: 32-41.

26) Smith RA, Ghaneh P, Sutton R, Raraty M, Campbell F, Neoptolemos JP. Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19-9 levels and platelet-lymphocyte ratio. J Gastrointest Surg 2008; 12: 1422-1428.

27) Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, Jamaris S, Taib NA. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer 2015; 113: 150-158.

28) Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, Foulis AK, Horgan PG, Mc Millan DC. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer 2011; 47: 2633-2641.

29) Kundi H, Balun A, Cicekcioglu H, Cetin M, Kiziltunc E, Cetin ZG, Mansuroglu C, Ornek E. The relation between platelet-to-lymphocyte ratio and Pulmonary Embolism Severity Index in acute pulmonary embolism. Heart Lung 2015; 44: 340-343.

30) Ermens AA, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. Clin Biochem 2003; 36: 585-590.

31) Salles N, Herrmann F, Sakbani K, Rapin CH, Sieber C. High vitamin B12 level: a strong predictor of mortality in elderly inpatients. J Am Geriatr Soc 2005; 53: 917-918.

32) Carmel R. Extreme elevation of serum transcobalamin I in patients with metastatic cancer. N Engl J Med 1975; 292: 282-284.

33) Sviri S, Khalaila R, Daher S, Bayya A, Linton DM, Stav I, Heerden PVV. Increased Vitamin B12 levels are associated with mortality in critically ill medical patients. Clin Nutr 2012; 31: 53-59.

34) Callaghan FM, Leishear K, Abhyankar S, Demner-Fushman D, McDonald CJ. High vitamin B12 levels are not associated with increased mortality risk for ICU patients after adjusting for liver function: a cohort study. ESPEN J 2014; 9: e76-e83.