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Original Article / Özgün Makale

Evaluation of preoperative neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients undergoing major vascular surgery

Majör vasküler cerrahi yapılan hastalarda ameliyat öncesi nötrofil-lenfosit oranı ve trombosit-lenfosit oranının değerlendirilmesi

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Background: This study aims to examine whether preoperative neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) had a preoperative prognostic role and its association with survival in patients undergoing major vascular surgery.

Methods: Between June 2005 and December 2012, 838 consecutive patients (593 males, 245 females; mean age 63 years; range, 10 to 99 years) who underwent major vascular surgery in our clinic were included. The NLR and PLR were determined by dividing the absolute neutrophil and platelet count by the absolute lymphocyte count.

Results: The mean mortality risk was 2.85 (range 1.67-4.87) in patients with a NLR of ≥5 and 3.76 (range 2.31-6.12) in patients with a PLR of ≥200. The proportion of diabetic patients was significantly higher for patients with NLR ≥5 (63.7%; p= 0.000) and PLR ≥200 (%53.8; p= 0.003).

Conclusion: Our study results showed that increased levels of NLR and PLR were directly correlated with mortality and inversely correlated with survival in the postoperative period and that diabetic patients were under a higher risk.

Key words: Neutrophil-lymphocyte ratio; platelet-lymphocyte ratio; vascular surgery.

Amaç: Bu çalışmada majör vasküler cerrahi yapılan hastalarda ameliyat öncesi nötrofil-lenfosit oranının (NLR) ve trombosit-lenfosit oranının (PLR) prognostik bir rolü olup olmadığı ve sağkalım ile olan ilişkisi araştırıldı.

Çalışma planı: Haziran 2005 ve Aralık 2012 tarihleri arasında majör vasküler cerrahi yapılan 838 ardışık hasta (593 erkek, 245 kadın; ort. yaş 63 yıl; dağılım 10-99 yıl) çalışmaya alındı. Mutlak nötrofil ve trombosit sayısının mutlak lenfosit sayısına bölünmesi ile NLR ve PLR hesaplandı.

Bulgular: Ortalama mortalite riski NLR ≥5 olan hastalarda 2.85 (dağılım 1.67-4.87), PLR ≥200 olan hastalarda 3.76 (dağılım 2.31-6.12) idi. Diyabet hastalarının oranı, NLR ≥5 (%63.7; p=0.000) ve PLR ≥200 olan hastalarda (%53.8; p=0.003) anlamlı düzeyde daha yüksekti.

Sonuç: Çalışma bulgularımız artmış NLR ve PLR'nin ameliyat sonrası mortalite ile doğrudan, sağkalım ile ters ilişkili olduğunu ve diyabetli hastaların daha yüksek risk altında olduğunu gösterdi.

Anahtar sözcükler: Nötrofil-lenfosit oranı; trombosit-lenfosit oranı; vasküler cerrahi.

The atherosclerotic process of the narrowing and hardening of arteries can occur in each artery of the human body.[1] There are numerous studies in literature that have documented the significance of low-grade inflammation in the pathogenesis of atherosclerosis and the acute complications associated with it.[2] As for the cardiovascular risk, the inflammation involves several biological markers.[3,4] Of these, total leukocyte count is foremost, and this serves as an indicator of cardiovascular events in unselected adults, patients

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with stable angina, and acute coronary syndromes.[5-9] In addition, total leukocyte count is an indicator with limitations in that the relationship between leukocytosis and patient outcomes is complex and nonlinear.[10,11] Moreover, there are several studies that have shown an independent association,[12] and this has led to a growing interest towards the analysis of white cell subtypes. For instance, the neutrophil component of the total leukocyte count endows it with a predictive role.[13-15] Similarly, a reduction in the lymphocyte count has been reported to be associated with a poor prognosis.[11,16,17] Compared with the total white blood cell (WBC) count or individual white cell subtypes, this value may be a better predictor of cardiovascular risk.[18-20] The neutrophil-lymphocyte ratio (NLR) provides an inexpensive index for systemic inflammation and also helps to predict survival after percutaneous coronary intervention[19] and coronary artery bypass grafting (CABG).[21] In order to effectively modify the risk factors and reduce the complications likely to occur in the postoperative period, high-risk patients need to be identified preoperatively. Furthermore, several studies have shown a relationship between the elevated peripheral blood platelet count and major adverse cardiovascular adverse outcomes.[22-25] On the other hand, other studies have determined that a low peripheral blood lymphocyte count indicates major adverse cardiovascular outcomes.[17,26-28] In our study, we examined whether the NLR and the platelet-lymphocyte ratio (PLR) had a preoperative prognostic role in patients undergoing major surgery and attempted to determine the effect that these ratios had on their survival.

PATIENTS AND METHODS

A total of 838 consecutive patients (593 males, 245 females; mean age 63 years; range 10 to 99 years) underwent major vascular surgery at our institution between June 2005 and December 2012, and their records regarding preoperative age, gender, hemoglobin and creatinine levels, white blood cell (WBC) lymphocyte, and platelet counts, hypertension, type of surgery, and duration of hospitalization are stored in our database. However, we excluded the clinical evidence of active infection, active cancer and hematological proliferative diseases along with active or chronic inflammatory or autoimmune diseases in our study. All analyses were conducted using blood samples obtained immediately before surgery. The NLR and PLR were calculated by dividing the absolute neutrophil and platelet count by the absolute lymphocyte count. In order to categorize patients into low- and high-NLR groups, a NLR of ≥5 was used since previous studies also used a similar cut off value.[29,30] The patients were also divided into two groups according to whether their PLR was <200 or ≥200. The primary end point was all-cause mortality, and cause of death was specified as cardiac if this was listed as the primary cause or a contributory factor on the death certificate. Our study was in compliance with the Declaration of Helsinki, and it was approved by the local research ethics committee.

Statistical analysis

Normally distributed continuous data was presented using mean values (including ± standard deviation). Survival rates were calculated utilizing the Kaplan-Meier method, and comparisons were made using the log-rank test. Risk estimations were performed using the Cox regression model. In addition, Breslow's generalized Wilcoxon test was employed to determine the clinical characteristics of the patients, and a chi-square test was then used to compare them with regard to the duration of the postoperative hospital stays of the patients and the differing quartiles of the NLR and PLR (categorical variables). All statistical analyses were completed using the SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) software program.

RESULTS

The patients underwent several major vascular procedures, and these are presented in Table 1.

There were 108 patient deaths within 30 days of the surgery. We found a significantly higher mean mortality risk of 2.85 (range 1.67-4.87) for the patients with a NLR of ≥5 and this risk was mean 3.76 (range, 2.31-6.12) for those with a PLR ≥200. Furthermore, the proportion of diabetic patients was significantly higher for the patients with an NLR of ≥5 (63.7%; p=0.000) and a PLR of ≥200 (53.8%; p=0.003).

Table 1. Surgical procedures

Surgical procedures	n	%
Carotid endarterectomy	94	11.2
Supra-aortic bypass	4	0.5
Abdominal aortic aneurysm repair	98	11.7
Aortoiliac/aortofemoral bypass	24	2.9
Upper extremity bypass surgery	21	2.5
Arterial embolectomy of the upper extremity	69	8.2
Lower extremity bypass surgery	226	27.0
Arterial embolectomy of the lower extremity	302	36.0
Total	838	100

The mean survival time for the patients with an NLR of ≥5 (13.5%) was 14.1 months [95% confidence interval (CI): 11.6-16.5) while it was 16.9 months for those with an NLR of <5 (0.8%) (95% CI: 14.9-18.9) (p=0.001) (Figure 1).

Additionally, the mean survival time for the patients with a PLR of ≥200 was 12.9 months (16.7%) (95% CI: 9.9-15.8) and 16.7 months for those with a PLR of <200 (2.1%) (95% CI: 14.9-18.5) (p= 0.002) (Figure 2).

DISCUSSION

In our study, we examined the preoperative blood count of the patients who underwent major surgery and discovered that having an NLR of ≥5 or a PLR of ≥200 increased the mortality rates five- to six-fold and that the survival times of these patients were decreased. We also showed that both of these parameters were significantly higher in the patients with diabetes. Bhutta et al.,[29] who conducted one of the two studies that used the same cut-off values for the NLR as our study, found that the NLR was crucial for predicting medium-term mortality and for two-year-survival rates that were predicted dependent on diabetes. In another recent study, Spark et al.[30] showed that the NLR could be used to identify poor-risk patients within a group receiving treatment for critical limb ischemia. The NPR reflects the balance of the neutrophilia between the inflammation and the relative lymphopenia of the cortisol-induced stress response. Neutrophilia also has the potential to indicate maladaptive processes.[31] Additionally, atherogenesis does not represent simply passive injury with infiltration of the lipids but an active, inflammatory process. Leukocytes play an essential role in these inflammatory processes, which may be either acute or chronic. Gennari et al.[32] and Dionigi et al.[33] revealed that lymphocytopenia that occurs after major surgery stems from neuroendocrine stress and leads to cortisol production, which ultimately causes lymphocytopenia in the peripheral blood. Additionally, decreased lymphocytes observed after myocardial infarction (MI) have been linked to injuries connected with ischemia-reperfusion (IR).[34]

The NLR has been shown to significantly reflect the likely outcomes of percutaneous coronary intervention (PCI) and CABG.[19,21] In a recent study, Chung et al.[35] examined 252 patients who underwent thoracic endovascular aneurysm repair (TEVAR) over a period of 11 years in order to identify the risk factors for late mortality and found that preoperative leukocytosis was an independent factor for late mortality, regardless of the clinical presentation. They also showed that preoperative leukocytosis may assist in risk stratification. Neutrophilia springs from the demargination of neutrophils, delayed apoptosis, and the stimulation of stem cells by growth factors [interleukin 6 and granulocyte colony stimulating factor (GCSF)]. Neutrophils promote plaque rupture as a result of the release of proteolytic enzymes, arachidonic acid derivatives, and superoxide radicals. Therefore, neutrophilia reflects the exaggerated

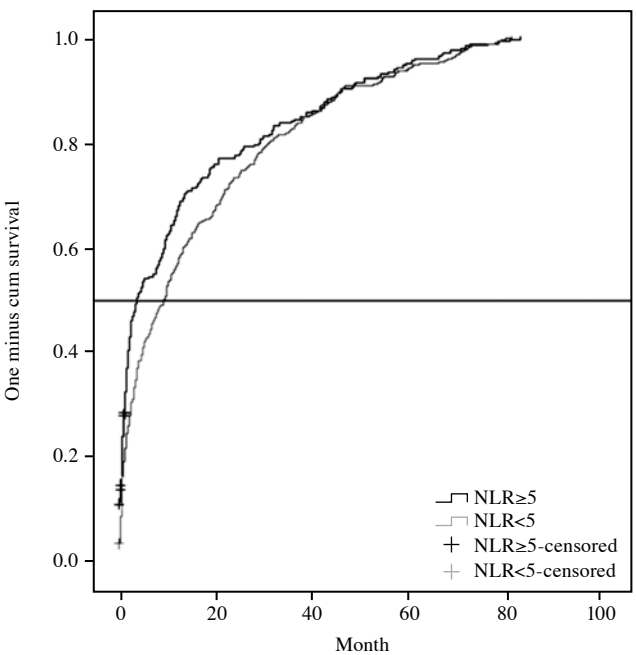

Figure 1. Survival curves for patients with an neutrophil-lymphocyte ratio of ≥5 and an neutrophil-lymphocyte ratio of <5.

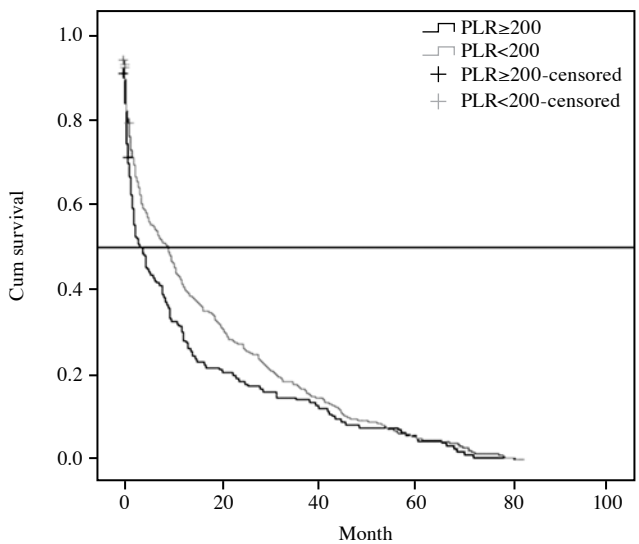

Figure 2. Survival curves for patients with a platelet-lymphocyte ratio of ≥200 and a platelet-lymphocyte ratio of <200.

inflammatory condition observed in atherosclerotic patients and is also associated with the cells involved in atherosclerotic plaque instability. Ischemic conditions lead to increased vasculogenesis, and this subsequently implies a chronic adaptation process with neutrophilia. In a study conducted by Haumer et al.,[36] they argued that altered endothelial cells promote the activation of neutrophils, which accelerates the build up of either microvascular or macrovascular occlusive plugs. Previous studies have also shown a relationship between the high values of peripheral thrombocytes and cardiovascular diseases.[9,23,37] In spite of this, Mueller et al.[37] were not able to prove an association between platelet counts and mortality in patients with acute coronary syndrome (ACS). In our study, we found an inverse correlation between high PLRs and survival times. Higher platelet counts may indicate an underlying inflammation because there are several inflammatory mediators which stimulate megakaryocytic proliferation and produce relative thrombocytosis. Furthermore, other studies have shown that patients with coronary artery diseases (CADs) have high levels of platelet monocyte aggregates in their bloodstream, which is correlated with plaque stability.[38]

Diabetic patients run a higher risk of having diffuse disease microvascular dysfunction. Lee et al.[39] determined that a high NLR was an independent predictive factor for major adverse cardiac events in post-MI diabetic patients and that the NLR was also an important predictor of macrovascular disease in diabetic patients in general. We also found significantly higher NLRs and PLRs in diabetic patients compared with those without this disease. It is well known that several metabolic and immunological changes occur in diabetic patients, which may be due to the different roles that neutrophils and lymphocytes have in the inflammatory response in diabetic patients. Several mechanisms, including increased levels of plasma, cortisol, leptin, and insulin, contribute to neutrophilia in diabetic patients. Other factors which may also play a part are advanced glycation end products, oxygen free radicals, and other cytokines, all of which possibly aid in the priming of neutrophils. In addition, the activated neutrophils secrete numerous inflammatory mediators which contribute to the increased levels of oxidative stress (OS), inflammation, necrosis with the resultant worsening prothrombotic states, endothelial dysfunction, plaque rupture, and infarct size.[40]

Conclusion

Determining the preoperative NLR and PLR can be done via easy, inexpensive tests. In this study, we showed that increased levels of these two parameters were directly correlated with mortality and inversely correlated with survival in the postoperative period. Furthermore, we identified that patients with diabetes were at a higher risk because of higher levels of PLR and NLR, which resulted in higher mortality and decreased survival in the postoperative period. It is our hope that these results may contribute toward the risk analysis of patients who undergo major vascular surgery.

Declaration of conflicting interests

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REFERENCES

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5-67.
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-95.
3. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998;279:1477-82.
4. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.
5. Phillips AN, Neaton JD, Cook DG, Grimm RH, Shaper AG. Leukocyte count and risk of major coronary heart disease events. Am J Epidemiol 1992;136:59-70.
6. Kannel WB, Anderson K, Wilson PW. White blood cell count and cardiovascular disease. Insights from the Framingham Study. JAMA 1992;267:1253-6.
7. Hajj-Ali R, Zareba W, Ezzeddine R, Moss AJ. Relation of the leukocyte count to recurrent cardiac events in stable patients after acute myocardial infarction. Am J Cardiol 2001;88:1221-4.
8. Schlant RC, Forman S, Stamler J, Canner PL. The natural history of coronary heart disease: prognostic factors after recovery from myocardial infarction in 2789 men. The 5-year findings of the coronary drug project. Circulation 1982;66:401-14.
9. Sabatine MS, Morrow DA, Cannon CP, Murphy SA, Demopoulos LA, DiBattiste PM, et al. Relationship between baseline white blood cell count and degree of

coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy- Thrombolysis in Myocardial Infarction 18 trial)substudy. J Am Coll Cardiol 2002;40:1761-8.

10. Gurm HS, Bhatt DL, Lincoff AM, Tcheng JE, Kereiakes DJ, Kleiman NS, et al. Impact of preprocedural white blood cell count on long term mortality after percutaneous coronary intervention: insights from the EPIC, EPILOG, and EPISTENT trials. Heart 2003;89:1200-4.
11. Coller BS. Leukocytosis and ischemic vascular disease morbidity and mortality: is it time to intervene? Arterioscler Thromb Vasc Biol 2005;25:658-70.
12. Folsom AR, Wu KK, Rosamond WD, Sharrett AR, Chambless LE. Prospective study of hemostatic factors and incidence of coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 1997;96:1102-8.
13. Kawaguchi H, Mori T, Kawano T, Kono S, Sasaki J, Arakawa K. Band neutrophil count and the presence and severity of coronary atherosclerosis. Am Heart J 1996;132:9-12.
14. Grau AJ, Boddy AW, Dukovic DA, Buggle F, Lichy C, Brandt T, et al. Leukocyte count as an independent predictor of recurrent ischemic events. Stroke 2004;35:1147-52.
15. Sweetnam PM, Thomas HF, Yarnell JW, Baker IA, Elwood PC. Total and differential leukocyte counts as predictors of ischemic heart disease: the Caerphilly and Speedwell studies. Am J Epidemiol 1997;145:416-21.
16. Ommen SR, Hodge DO, Rodeheffer RJ, McGregor CG, Thomson SP, Gibbons RJ. Predictive power of the relative lymphocyte concentration in patients with advanced heart failure. Circulation 1998;97:19-22.
17. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol 1997;79:812-4.
18. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005;45:1638-43.
19. Duffy BK, Gurm HS, Rajagopal V, Gupta R, Ellis SG, Bhatt DL. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. Am J Cardiol 2006;97:993-6.
20. Upadhya B, Applegate RJ, Sane DC, Deliargyris EN, Kutcher MA, Gandhi SK, et al. Preprocedural white blood cell count and major adverse cardiac events late after percutaneous coronary intervention in saphenous vein grafts. Am J Cardiol 2005;96:515-8.
21. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J 2007;154:995-1002.
22. Thaulow E, Erikssen J, Sandvik L, Stormorken H, Cohn PF. Blood platelet count and function are related to total and cardiovascular death in apparently healthy men. Circulation 1991;84:613-7.
23. Iijima R, Ndrepepa G, Mehilli J, Bruskina O, Schulz S, Schömig A, et al. Relationship between platelet count and 30-day clinical outcomes after percutaneous coronary interventions. Pooled analysis of four ISAR trials. Thromb Haemost 2007;98:852-7.
24. Nikolsky E, Grines CL, Cox DA, Garcia E, Tcheng JE, Sadeghi M, et al. Impact of baseline platelet count in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction (from the CADILLAC trial). Am J Cardiol 2007;99:1055-61.
25. Vidwan P, Lee S, Rossi JS, Stouffer GA. Relation of platelet count to bleeding and vascular complications in patients undergoing coronary angiography. Am J Cardiol 2010;105:1219-22.
26. Ommen SR, Hammill SC, Gibbons RJ. The relative lymphocyte count predicts death in patients receiving implantable cardioverter defibrillators. Pacing Clin Electrophysiol 2002;25:1424-8.
27. Acanfora D, Gheorghiade M, Trojano L, Furgi G, Pasini E, Picone C, et al. Relative lymphocyte count: a prognostic indicator of mortality in elderly patients with congestive heart failure. Am Heart J 2001;142:167-73.
28. Zouridakis EG, Garcia-Moll X, Kaski JC. Usefulness of the blood lymphocyte count in predicting recurrent instability and death in patients with unstable angina pectoris. Am J Cardiol 2000;86:449-51.
29. Bhutta H, Agha R, Wong J, Tang TY, Wilson YG, Walsh SR. Neutrophil-lymphocyte ratio predicts medium-term survival following elective major vascular surgery: a cross-sectional study. Vasc Endovascular Surg 2011;45:227-31.
30. Spark JI, Sarveswaran J, Blest N, Charalabidis P, Asthana S. An elevated neutrophil-lymphocyte ratio independently predicts mortality in chronic critical limb ischemia. J Vasc Surg 2010;52:632-6.
31. Ott I, Neumann FJ, Gawaz M, Schmitt M, Schömig A. Increased neutrophil-platelet adhesion in patients with unstable angina. Circulation 1996;94:1239-46.
32. Gennari R, Dominioni L, Imperatori A, Bianchi V, Maroni P, Dionigi R. Alterations in lymphocyte subsets as prognosticators of postoperative infections. Eur J Surg 1995;161:493-9.
33. Dionigi R, Dominioni L, Benevento A, Giudice G, Cuffari S, Bordone N, et al. Effects of surgical trauma of laparoscopic vs. open cholecystectomy. Hepatogastroenterology 1994;41:471-6.
34. Pechan I, Holoman M, Zahorec R, Rendekova V, Kalnovicova T, Hola J, et al. Parameters of energy metabolism in patients after vascular reconstructive surgical procedures. Bratisl Lek Listy 1999;100:439-44. [Abstract]
35. Chung J, Corriere MA, Veeraswamy RK, Kasirajan K, Milner R, Dodson TF, et al. Risk factors for late mortality after endovascular repair of the thoracic aorta. J Vasc Surg 2010;52:549-54.
36. Haumer M, Amighi J, Exner M, Mlekusch W, Sabeti S, Schlager O, et al. Association of neutrophils and future cardiovascular events in patients with peripheral artery disease. J Vasc Surg 2005;41:610-7.
37. Mueller C, Neumann FJ, Hochholzer W, Trenk D, Zeller T, Perruchoud AP, et al. The impact of platelet count on mortality in unstable angina/non-ST-segment elevation myocardial infarction. Am Heart J 2006;151:1214.e1-7.

38. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis 2012;34:326-34.
39. Lee GK, Lee LC, Chong E, Lee CH, Teo SG, Chia BL, et al. The long-term predictive value of the neutrophil-to-lymphocyte ratio in Type 2 diabetic patients presenting with acute myocardial infarction. QJM 2012;105:1075-82.
40. Tsai JC, Sheu SH, Chiu HC, Chung FM, Chang DM, Chen MP, et al. Association of peripheral total and differential leukocyte counts with metabolic syndrome and risk of ischemic cardiovascular diseases in patients with type 2 diabetes mellitus. Diabetes Metab Res Rev 2007;23:111-8.