



Neutrophil to Lymphocyte Ratio May Be a Diagnostic Marker for Prosthetic Joint Infection

Nötrofil Lenfosit Oranı Protezli Eklem Enfeksiyonlarında Tanısal Belirteç Olabilir

Neutrophil to Lymphocyte Ratio Prosthetic Joint Infection

Umur Hatay Gölge¹, Burak Kaymaz¹, Özhan Pazarcı², Seyran Kılıç², Zekeriya Öztumur², Okay Bulut²

¹Department of Orthopaedics and Traumatology, Çanakkale Onsekiz Mart University School of Medicine, Çanakkale,

²Department of Orthopaedics and Traumatology, Cumhuriyet University School of Medicine, Sivas, Turkey

Özet

Amaç: Total diz protezi (TDP) etkin ve başarılı bir yöntem olup periprotetik eklem enfeksiyonu (PPI) gibi komplikasyonlar bu başarıyı gölgeleyebilir. Nötrofil lenfosit oranı (NLO) hemogramla kolayca elde edilebilen subklinik inflamasyonun basit bir belirteçidir. Bu çalışmanın amacı PPI tanısı için NLO'nun tahmin kabiliyeti incelendi. Gereç ve Yöntem: 2007-2014 yılları arasında evre 4 gonartroz tanısı ile total diz protezi yapılan hastalar değerlendirildi. PPI olan 30 hasta grup I olup bu gruptaki hastaların eritrosit sedimentasyon hızı (ESH), C-reaktif protein (CRP), nötrofil lenfosit oranı (NLO), Lökosit ve nötrofil dahil hematolojik testler çalışmaya dahil edilerek retrospektif olarak değerlendirildi. Hastaların preoperatif ve postoperatif 6. ay NLO karşılaştırıldı. Enfeksiyonu olmayan TDP ameliyatı yapılmış 103 hasta kontrol grubu (grup II) olarak alındı. Grup I ve grup II deki hastalar da NLO yönünden karşılaştırıldı. Bulgular: Grup I (PPI sonrası iki aşamalı revizyon cerrahisi ile tedavi edilenler) otuz hasta (17 kadın, 13 erkek) iken Grup II (TDP ameliyatı olup takip süresince hiçbir enfeksiyon belirtisi olmayanlar) ise 103 hasta olup (94 kadın, 9 erkek) idi. NLO'nun preoperatif ve postoperatif 6. aydaki karşılaştırılmasında 3.2 ± 0.7 den 2.2 ± 0.5 düştüğü görüldü ($p < 0.001$). Grup II deki NLO ise 2.1 ± 0.7 olup grup I preoperatif değeri ile karşılaştırılmasında da anlamlı fark izlendi ($p < 0.001$). Enfeksiyon için NLO'nunda 2.45 değeri sınır olarak bulundu. Tartışma: NLO, ESH ve CRP gibi enfeksiyon parametreleri ile birlikte PPI tanısında yardımcı olarak kullanılabilir.

Anahtar Kelimeler

Nötrofil Lenfosit Oranı; Eklem Enfeksiyonu; Total Diz Protez

Abstract

Aim: Total knee arthroplasty (TKA) is an effective and successful procedure but the outcome may occasionally be compromised by complications such as periprothetic joint infection (PJI). Blood neutrophil to lymphocyte ratio (NLR) is a simple marker of subclinical inflammation that can be easily obtained from the differential White Blood Cell count. This study aims to analyze the predictive ability of NLR for the diagnosis of PJI. **Material and Method:** Patients who were diagnosed as grade 4 gonarthrosis and operated for total knee arthroplasty between years 2007-2014 were evaluated. Thirty patients with PJI were included in the study as Group I and hematological tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC) and neutrophil to lymphocyte ratio (NLR) of the patients were evaluated retrospectively. Preoperative and postoperative 6th month NLR values of the patients were compared. Also 103 age matched patients operated for total knee arthroplasty with no sign of infection were included in the study as controls (Group II). Patients in Group I and Group II were also compared in terms of NLR. **Results:** Thirty patients (17 female, 13 male) were present in Group I (patients with PJI and treated with two staged revision surgery) and 103 patients (94 female, 9 male) were present in Group II (patients operated for total knee arthroplasty and had no sign of infection during the follow up period). NLR has been found to decrease from 3.2 ± 0.7 to 2.2 ± 0.5 when compared between the preoperative and postoperative 6th month period ($p < 0.001$). NLR has been found to be 2.1 ± 0.7 in Group II and 3.2 ± 0.7 in Group I at preoperative period. ($p < 0.001$). The value of 2.45 was found to be cut-off point for infection. **Discussion:** NLR can be used as marker for PJI together with the other markers as ESR and CRP to increase the accuracy of the diagnosis.

Keywords

Neutrophil to Lymphocyte Ratio; Joint Infection; Total Knee Arthroplasty

DOI: 10.4328/JCAM.3918

Received: 01.10.2015 Accepted: 19.10.2015 Printed: 01.03.2016 J Clin Anal Med 2016;7(2): 218-21

Corresponding Author: Umur Hatay Gölge, Department of Orthopaedics and Traumatology, Çanakkale Onsekiz Mart University School of Medicine, 17000, Çanakkale, Turkey. GSM: +905059389994 F.: +90 2862183738 E-Mail: uhg31@hotmail.com

Introduction

Total knee arthroplasty (TKA) is an effective and successful procedure but the outcome may occasionally be compromised by complications. Periprosthetic joint infection (PJI) is one such complication that occurs after 1% to 3% of TKA [1,2]. Despite all efforts for prevention, PJI is still an important problem of the orthopaedic community. One of the problems associated with PJI relates to timely diagnosis of this complication [3,4]. Early and accurate diagnosis is the first step of the effective treatment modality for the patients with PJI. Today, diagnosis remains dependent on clinical judgement and reliance on standard clinical tests including serologic tests [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC)], analysis of aspirated joint fluid, and interpretation of intraoperative tissue and fluid test results. And the diagnosis is usually based on a combination of findings rather than a only one [5,6].

Blood neutrophil to lymphocyte ratio (NLR) is a simple marker of subclinical inflammation that can be easily obtained from the differential white blood cell count. There are relative changes in the circulating levels of WBCs in response to systemic inflammation and infection. The best known of these is a relative lymphopenia accompanying neutrophilia [7]. In recent years, WBC count and subtype count have been recognized as markers of inflammation in some rheumatic and nonrheumatic diseases and it has shown to be a good indicator of inflammation [7-11]. NLR has recently emerged as a prognostic marker in patients with cancer, coronary artery diseases and ischemic cerebrovascular diseases and has been reported to be an indicator of the overall inflammatory status of the body [12-15] and it has recently been begun to be studied in the orthopedics field. After surgery for hip fracture it was found to be related with postoperative mortality [16,17].

This marker has not yet been studied in patients with PJI. In the present study, we aimed to analyze the predictive ability of NLR for the diagnosis of PJI.

Material and Method

A consecutive series of patients who were diagnosed as grade 4 gonarthrosis and operated for total knee arthroplasty at Cumhuriyet University Department of Orthopaedics and Traumatology between years 2007-2014 were evaluated. A total of 1087 patients were found to be operated for total knee arthroplasty. Of these, thirty patients were found to be infected after the TKA surgery. The knee was considered infected if either preoperative or intraoperative cultures were positive. If cultures failed to isolate an organism, then PJI was diagnosed if both the leukocyte count was more than 1760 cells/ μ L and polymorphonuclear cells were more than 73% [4] or there was either a draining sinus tract or abscess present. The criteria used for an ESR to be considered elevated was more than 30 mm/h and for the CRP was more than 10 mg/L. All the patients with PJI were treated with two-staged revision surgery. In the first surgery all the components were removed and antibiotic impregnated cement were placed subsequent to a wide debridement. After the regression of the infection clinically and serologically, the patients were operated for the 2nd stage surgery and removal of the cement and implantation of the revision arthroplasty

components were performed.

Thirty patients with PJI so that needed revision surgery were included in the study as Group I and hematological tests including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC) and neutrophil to lymphocyte ratio (NLR) of the patients were evaluated retrospectively. Preoperative and postoperative 6th month (the time that the patient had no sign of infection) NLR values of the patients were compared. Also 103 age matched patients operated for total knee arthroplasty with no sign of infection were included in the study as controls (Group II). Patients in Group I and Group II were also compared in terms of NLR.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences version 19.0 (IBM Corp. Released 2010; IBM SPSS Statistics for Windows, Version 19.0 Armonk, NY; IBM Corp.). The normality of the data was determined by the Kolmogorov-Smirnov test. According to the normality distribution, independent t-test or Mann-Whitney-U test was used in order to compare Group I and Group II; Paired Samples test or Wilcoxon Signed Rank Tests in order to compare the preoperative and postoperative values in Group I. Differences were considered to be significant at $p < 0.05$ for all tests (two-tailed).

Roc Curve Analysis was used to determine the cut-off point for the diagnostic potency of NLR.

Results

Thirty patients (17 female, 13 male) were present in Group I (patients with PJI and treated with two staged revision surgery) and 103 patients (94 female, 9 male) were present in Group II (patients operated for total knee arthroplasty and had no sign of infection during the follow up period). Mean age was 64.3 ± 9.3 years (48 to 82 y) in group I and 66.2 ± 7.4 years (45 to 85 y) in group II. There was no statistically significant difference between the groups in terms of age.

Table 1 summarizes the mean values of the hematological markers in Group I before the first operation (infected period) and after approximately 6th month (30.5 ± 4.01 weeks) of the second surgery in the period that infection regressed. NLR has been found to decrease from 3.2 ± 0.7 to 2.2 ± 0.5 when compared between the preoperative and postoperative 6th month period and this decrease in NLR was a statistically significant as well as ESR and CRP ($p < 0.001$) (Figure 1).

Table 2 summarizes the mean values of the hematological markers in Group II (patients without infection) and Group I before the first operation (infected period). NLR has been found to be 2.1 ± 0.7 in Group II and 3.2 ± 0.7 in Group I. There was a statistically significant difference between groups in terms of NLR ($p < 0.001$) (Figure 2).

Roc Curve Analysis to determine a cut-off point for infection was used and the value of 2.45 was found to be cut-off point for infection with 90% sensitivity and 72% specificity (Figure 3).

Discussion

Periprosthetic joint infection has ascended to the highest rank as the cause of failure following joint arthroplasty [5,18]. One of the problems associated with PJI relates to timely diagnosis

Table 1. Preoperative hemogram values of the infected knee arthroplasty with a comparison of hemogram values after the revision total knee replacement.

	Infected total knee arthroplasty				p
	Preoperative		Postoperative		
	mean±sd	min-max median	mean±sd	min-max median	
ESR(mm/h)	48.4±29.6	18-136 42	21.9±11.1	5-59 20	<0,001
CRP(mg/l)	27.5±16.4	9.8-90 21.0	3.7±2.9	0.4-13.0 3.0	<0,001
WBC (×103/μl)	8.0±1.8	4.1-11.9 7.7	6.6±1.4	2.3-8.8 6.7	<0,001
HGB(mg/dl)	12.4±1.8	9.5-17.8 12.5	10.3±1.2	8.1-13.0 10.2	<0,001
Lymphocytes (×103/μl)	1.9±0.5	1.0-2.9 1.9	1.5±0.7	0.4-3.5 1.4	0.003
Neutrophil (×103/μl)	6.0±1.2	4.1-8.7 6.0	3.1±1.1	1.0-5.2 3.3	<0,001
NLR	3.2±0.7	2.2-5.3 3.1	2.2±0.5	1.2-3.7 2.2	<0,001

sd: standart deviation, min: minimum, max: maximum
p: Wilcoxon Signed Ranks Test, Paired Samples Test

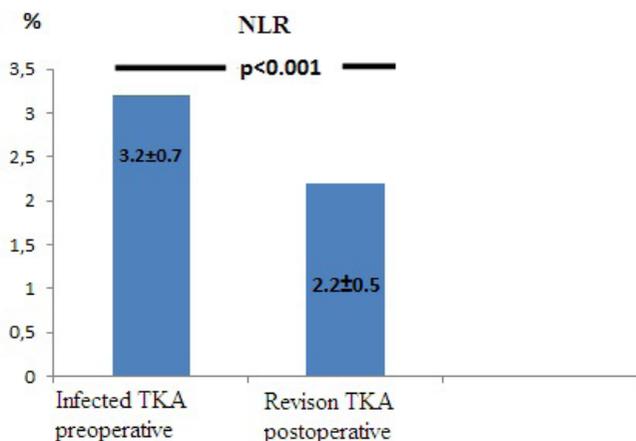


Figure 1. Infected total knee arthroplasty in patients with neutrophil lymphocyte ratio with neutrophil lymphocyte ratio patients who underwent revision total knee replacement. Also the comparison of the two groups.

of this complication [3,4]. Despite availability of various diagnostic modalities, confirmation of PJI can be difficult in some patients [19-22]. Further, there is no consensus as to what constitutes a PJI, making its diagnosis very challenging [23]. Although literature abounds with reports on the accuracy of various tests for diagnosis of PJI [1,4,20-22], the small sample size and the conflicting findings of studies hinder the interpretation of the available data.

As screening tools ESR and CRP are excellent and they should be obtained in every patient with a painful TKA. Elevated ESR and/or CRP were highly predictive of PJI and should prompt further evaluation such as joint aspiration [24].

According to recent publications the neutrophils included in the N/L ratio reflect the inflammatory response as they mediate inflammation by various biochemical mechanisms, such as release of arachidonic acid metabolites and platelet-aggravating factors. Relative lymphopenia on the other hand reflect the cor-

Table 2. The patient infected total knee prosthesis comparison of with non-infected total knee prosthesis blood values

	Non-Infected TKA (n= 103)		Infected TKA (n=30)		p
	mean±sd	Median (min-max)	mean±sd	Median (min-max)	
WBC (103/μl)	7.3±1.7	7.3 (3.4-11.6)	8.0±1.8	7.7 (4.1-11.9)	0.063
HGB (mg/dl)	12.3±1.5	12.2 (8.2-15.7)	12.4±1.8	12.5 (9.5-17.8)	0.774*
Lymphocytes (×103/μl)	2.1±0.6	2.1 (0.8-4.3)	1.9±0.5	1.9 (1.0-2.9)	0.192*
Neutrophil (×103/μl)	4.3±1.1	4.3 (1.7-8.6)	6.0±1.2	6.0 (4.1-8.7)	<0.001
N/L	2.1±0.7	1.9 (1.1-4.6)	3.2±0.7	3.1 (2.2-5.3)	<0.001

sd: standart deviation, min: minimum, max: maximum
p: Mann Whitney U Test, *:IndependentSamples Test

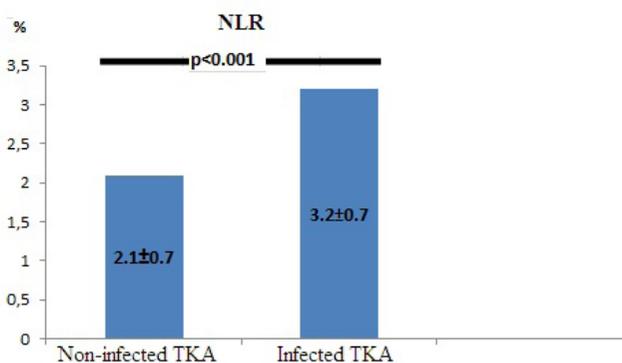


Figure 2. Total knee arthroplasty is infected and non-infected patients neutrophil lymphocyte ratio. Also the comparison of the two groups.

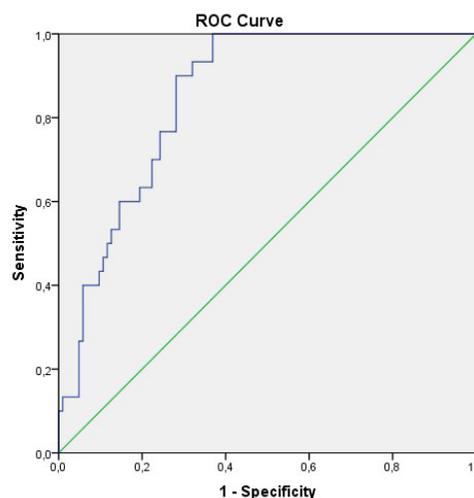


Figure 3. The evaluation of each of the two groups cut-off value for Roc Curve Analysis, this ratio was 2.45.

tisol-induced stress response [25]. In various studies the NLR correlates with markers of a proinflammatory state and an elevated NLR is associated with an increase in vascular end-points and with a worse outcome after oncologic surgery [26-28]. Also it has been associated with a high mortality in critical limb ischemia patients and has been found to be a prognostic marker in patients with cancer and coronary artery disease [25,29,31].

In the study NLR was investigated if it could be a marker as ESR or CRP and found to be a predictive marker for PJI and the patients with NLR value higher than 2.45 had more risk for PJI. We believe that NLR can be a marker for PJI as ESR, CRP. Also NLR can be used in the follow-up period of the infection to observe the effectiveness of the treatment as ESR and CRP.

The main drawback of our study is the retrospective study design and that we used a single blood sample to calculate NLR. Prospective design and blood samples in different periods of the infection and the correlation of NLR with the other serological markers like ESR, CRP could be more useful for the follow-up of the infection.

In conclusion NLR can be used as marker for PJI together with the other markers as ESR and CRP to increase the accuracy of the diagnosis.

Declaration of conflicting interests: The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

Competing interests

The authors declare that they have no competing interests.

References

- Della Valle CJ, Zuckerman JD, Di Cesare PE. Periprosthetic sepsis. *Clinical Orthopaedics and Related Research* 2004;420:26-31
- Phillips J, Crane T, Noy M, Elliott T, Grimer R. The incidence of deep prosthetic infections in a specialist orthopaedic hospital. A 15-year prospective survey. *Journal of Bone & Joint Surgery* 2006;88(7):943-8.
- Bauer TW, Parvizi J, Kobayashi N, Krebs V. Diagnosis of periprosthetic infection. *The Journal of Bone & Joint Surgery* 2006;88(4):869-82.
- Parvizi J, Ghanem E, Menashe S, Barrack RL, Bauer TW. Periprosthetic infection: what are the diagnostic challenges? *The Journal of Bone & Joint Surgery* 2006;88(suppl 4):138-47.
- Austin MS, Ghanem E, Joshi A, Lindsay A, Parvizi J. A simple, cost-effective screening protocol to rule out periprosthetic infection. *The Journal of arthroplasty* 2008;23(1):65-8.
- Spangehl MJ, Masri BA, O'CONNELL JX, Duncan CP. Prospective Analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. *The Journal of Bone & Joint Surgery* 1999;81(5):672-83.
- Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratislavské Lekárske Listy* 2001;102(1):5-14.
- Ahsen A, Ulu MS, Yuksel S, Demir K, Uysal M, Erdogan M, et al. As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. *Inflammation* 2013;36(6):1357-62.
- Uslu AU, Deveci K, Korkmaz S, Aydin B, Senel S, Sancakdar E, et al. Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? *Biomed Res Int* 2013;2013:185317.
- Walsh S, Cook E, Goulder F, Justin T, Keeling N. Neutrophil/lymphocyte ratio as a prognostic factor in colorectal cancer. *Journal of Surgical Oncology* 2005;91(3):181-4.
- Ozgoemren S, Godekmerdan A, Ozkurt-Zengin F. Acute-phase response, clinical measures and disease activity in ankylosing spondylitis. *Joint Bone Spine* 2007;74(3):249-53.
- Celikbilek A, Ismailogullari S, Zarsarsiz G. Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. *Journal of Clinical Laboratory Analysis* 2014;28(1):27-31.
- Sen N, Afsar B, Ozcan F, Buyukkaya E, Isleyen A, Akcay AB, et al. The neutrophil to lymphocyte ratio was associated with impaired myocardial perfusion and long term adverse outcome in patients with ST-elevated myocardial infarction undergoing primary coronary intervention. *Atherosclerosis* 2013;228(1):203-10.
- Gary T, Pichler M, Belaj K, Eller P, Hafner F, Gerger A, et al. Lymphocyte-to-monocyte ratio: a novel marker for critical limb ischemia in PAOD patients. *Int J Clin Pract* 2014;68(12):1483-7.
- 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(5):995-1002.
- Forget P, Moreau N, Engel H, Cornu O, Boland B, De Kock M. The neutrophil-to-lymphocyte ratio (NLR) after surgery for hip fracture (HF). *Arch Gerontol Geriatr* 2015;60(2):366-71.
- Sedlář M, Kvasnička J, Krška Z, Tománková T, Linhart A. Early and subacute inflammatory response and long-term survival after hip trauma and surgery. *Archives of Gerontology and Geriatrics* 2015;60(3):431-6.
- Vessely MB, Whaley AL, Harmsen WS, Schleck CD, Berry DJ. The Chitranjan Ranawat Award: Long-term survivorship and failure modes of 1000 cemented condylar total knee arthroplasties. *Clinical Orthopaedics and Related Research* 2006;452:28-34.
- Ghanem E, Parvizi J, Clohisy J, Burnett S, Sharkey PF, Barrack R. Perioperative antibiotics should not be withheld in proven cases of periprosthetic infection. *Clinical Orthopaedics and Related Research* 2007;461:44-7.
- Mumme T, Reinartz P, Alfer J, Müller-Rath R, Buell U, Wirtz D. Diagnostic values of positron emission tomography versus triple-phase bone scan in hip arthroplasty loosening. *Archives of Orthopaedic and Trauma Surgery* 2005;125(5):322-9.
- Pandey R, Berendt A, Athanasou N, Group OCS. Histological and microbiological findings in non-infected and infected revision arthroplasty tissues. *Archives of Orthopaedic and Trauma Surgery* 2000;120(10):570-4.
- Spangehl MJ, Masri BA, O'CONNELL JX, Duncan CP. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. *The Journal of Bone & Joint Surgery* 1999;81(5):672-83.
- Patel R, Osmon DR, Hanssen AD. The diagnosis of prosthetic joint infection: current techniques and emerging technologies. *Clinical Orthopaedics and Related Research* 2005;437:55-8.
- Parvizi J, Ghanem E, Sharkey P, Aggarwal A, Burnett RSJ, Barrack RL. Diagnosis of infected total knee: findings of a multicenter database. *Clinical Orthopaedics and Related Research* 2008;466(11):2628-33.
- Tamhane UU, Aneja S, Montgomery D, Rogers E-K, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *The American Journal of Cardiology* 2008;102(6):653-7.
- Mohri Y, Tanaka K, Ohi M, Yokoe T, Miki C, Kusunoki M. Prognostic significance of host-and tumor-related factors in patients with gastric cancer. *World Journal of Surgery* 2010;34(2):285-90.
- 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.
- Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. *European Journal of Surgical Oncology (EJSO)* 2008;34(1):55-60.
- Spark JI, Sarveswaran J, Blest N, Charalabidis P, Asthana S. An elevated neutrophil-lymphocyte ratio independently predicts mortality in chronic critical limb ischemia. *Journal of Vascular Surgery* 2010;52(3):632-6.
- Walsh S, Cook E, Goulder F, Justin T, Keeling N. Neutrophil/lymphocyte ratio as a prognostic factor in colorectal cancer. *Journal of Surgical Oncology* 2005;91(3):181-4.

How to cite this article:

Gölge UH, Kaymaz B, Pazarcı Ö, Kılınc S, Öztemur Z, Bulut O. Neutrophil to Lymphocyte Ratio May Be a Diagnostic Marker for Prosthetic Joint Infection. *J Clin Anal Med* 2016;7(2): 218-21.