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

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Abstract
Aim: Total knee arthroplasty (TKA) is an effective and successful procedure but the outcome may occasionally be compromised by complications such as periprosthetic 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 to analyze the predictive ability of NLR for the diagnosis of PJI. Material and Method: Patients who were diagnosed as grade 4 gonarthritis 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 6 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 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
Neutrophil to Lymphocyte Ratio Prosthetic Joint Infection

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 neutrophile 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 gonartrosis 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/µL 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 50 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 (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
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 cortisol-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].

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

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean±sd</td>
<td>median</td>
<td>mean±sd</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>48.4±29.6</td>
<td>21.9±11.1</td>
<td>5.9-20</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>27.5±16.4</td>
<td>1.7±2.9</td>
<td>0.4-13.0</td>
</tr>
<tr>
<td>WBC (&gt;103/μl)</td>
<td>8.0±1.8</td>
<td>6.6±1.4</td>
<td>2.3-8.8</td>
</tr>
<tr>
<td>HGB (mg/dl)</td>
<td>12.4±1.8</td>
<td>9.5-17.8</td>
<td>8.1-13.0</td>
</tr>
<tr>
<td>Lymphocytes (&lt;103/μl)</td>
<td>1.9±0.5</td>
<td>1.5±0.7</td>
<td>0.4-3.5</td>
</tr>
<tr>
<td>Neutrophil (&gt;103/μl)</td>
<td>6.0±1.2</td>
<td>3.1±1.1</td>
<td>1.0-5.2</td>
</tr>
<tr>
<td>N/L</td>
<td>3.2±0.7</td>
<td>1.2-5.2</td>
<td>1.2-3.7</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Non-Infected TKA (n=103)</th>
<th>Infected TKA (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean±sd</td>
<td>Median (min-max)</td>
<td>mean±sd</td>
</tr>
<tr>
<td>WBC (103/μl)</td>
<td>7.3±1.7</td>
<td>8.0-11.8</td>
<td>7.7</td>
</tr>
<tr>
<td>HGB (mg/dl)</td>
<td>12.3±1.5</td>
<td>12.4±1.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Lymphocytes (&gt;103/μl)</td>
<td>2.1±0.6</td>
<td>1.9±0.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Neutrophil (&gt;103/μl)</td>
<td>4.3±1.1</td>
<td>6.0±1.2</td>
<td>6.0</td>
</tr>
<tr>
<td>N/L</td>
<td>2.1±0.7</td>
<td>3.2±0.7</td>
<td>3.1</td>
</tr>
</tbody>
</table>

sd: standard deviation, min: minimum, max: maximum
p: Mann Whitney U Test, *: Independent 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.

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.
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.

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Competing interests

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