Research Square

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Neutrophil to Lymphocyte Ratio as a predictor for diagnosis of early Periprosthetic Joint Infection

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Research article

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Abstract

Background: Periprosthetic joint infection (PJI) is a catastrophic complication after total joint arthroplasty (TJA). The diagnosis of PJI is very difficult, especially in the early postoperative period. The value of the neutrophil to lymphocyte ratio (NLR) is useful for the diagnosis of infection. The purpose of this study was to determine the accuracy of the NLR in the diagnosis of early PJI after total knee or hip joint arthroplasty.

Methods: We retrospectively reviewed consecutive primary total knee or hip arthroplasty and identified the patients who readmitted within the first 90 days postoperatively between January 2011 and October 2018. There were 20 cases diagnosed early PJI and 101 uninfected cases based on the modified Musculoskeletal Infection Society (MSIS) criteria. The serum parameters (C-reactive protein, erythrocyte sedimentation rate, white blood-cell count, NLR, interleukin-6 levels) were compared between the two groups. Receiver operating characteristic curves were generated to determine the optimal cutoff values for each parameter. Sensitivity, specificity, and positive and negative predictive values were calculated for each parameter.

Results: The CRP, ESR, WBC, NLR and IL-6 values were all elevated in the infected group compared to the uninfected group. The mean CRP (infected=59.06, uninfected=10.09), ESR (infected=35, uninfected=17), WBC(infected=7.95x109,uninfected=6.16x109), NLR (infected=4.89, uninfected=2.18), IL-6 (infected=40.68, uninfected=7.46). All values were significant difference between the two groups. The best test for the diagnosis of early PJI was IL-6 (AUC=81.4%; optimal cutoff value 8.07pg/ml) followed by the NLR (AUC =80.2%; optimal cutoff value 2.13), CRP (AUC =79.3%; optimal cutoff value 9.27mg/l), ESR (AUC =74.4%; optimal cutoff value 22mm/h) and WBC (AUC = 63.2%; optimal cutoff value 8.91x109).

Conclusions: This study is the first to show that NLR values are more accurate than CRP and may be considered as useful parameters for the diagnosis of early PJI because it is an easy, cheap and convenient parameters to be calculated in daily practice without extra costs.

Introduction

Periprosthetic joint infection (PJI) is a catastrophic complication after total joint arthroplasty (TJA) with high morbidity and mortality. The early and accurate diagnosis of PJI is of great clinical significance for the treatment of PJI [1–2]. A less invasive procedure to retain the prosthetic components may be adopted in the early postoperative stage. However, the diagnosis of PJI is very difficult due to the lack of an absolute diagnostic test. It remains even more challenging for the diagnosis of early PJI because the normal periincisional swelling and erythema make it difficult to distinguish an early postoperative infection from the normal postoperative course.

It is essential to diagnose early PJI based on a combination of clinical judgment, blood testing, synovial fluid aspiration, standard radiographs and microbiologic as well as histopathologic inspections. However, there are very few literatures regarding for the diagnosis of early PJI because of lack of a suitable control

group as the truly aseptic revisions are rare in the early postoperative period. Kim et al. [3] reported that the serum CRP may be an excellent screening test in the workup of early PJI after TKA. However, Bedair et al. [4] found that the sensitivity of serum CRP for diagnosing early PJI was only 53%. The synovial fluid aspiration is also an excellent test in the workup of early PJI. The sensitivity and specificity of synovial WBC counts are approximately 95%-98.9% and 91%-100% respectively [3–5]. But the synovial fluid aspiration is an invasive operation and sometimes it is very hard to obtain synovial fluid even though repeat joint aspiration, especially for the hip joint.

Among the various kinds of tests, it is very critical to find a simple and practical marker for the diagnosis of early PJI. The serum WBC count has very little utility due to the very low sensitivity as markers of PJI [6]. In recently, the value of the neutrophil to lymphocyte rate (NLR) that is derived from the absolute neutrophil and absolute lymphocyte counts of a complete blood count is a routinely available marker of predicting outcomes in oncology, cardiovascular diseases and infections [7–9]. Yombi et al. [10] reported that the NLR may be potentially a better biomarker for the detection of early PJI after TKA because it had a faster normalization than CRP. However, further studies are still required to determine the conclusions through a comparative study. To the best of our knowledge, there were no related studies. Therefore, the purpose of this study was to determine the accuracy of the NLR in the diagnosis of early PJI.

Methods

After Institutional Review Board approval, we retrospectively reviewed the cases of consecutive primary total knee or hip arthroplasty in our institutions between January 2011 and October 2018. A total of 245 cases readmitted within the first 90 days postoperatively were identified. These patients were admitted to hospital again in 90 days for the following reasons: (1) staged bilateral total knee or hip arthroplasty, (2) dislocation, (3) patellar ligament rupture, (4) persistent wound drainage, (5) fever, (6) fracture, (7) erythema, (8) superficial infection, (9) postoperative infection was suspected. Blood samples for CRP, ESR, IL-6 and other markers were taken on the morning following readmission as part of our routine work-up and were then sent to the medical laboratory center for testing as soon as possible. All data including CRP, ESR, white blood cell (WBC) count, IL-6, neutrophil count and lymphocyte count were obtained from electronic medical records by manual chart review. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

One hundred and twenty-four cases were excluded for the following reasons: inflammatory arthritis, such as rheumatoid and ankylosing spondylitis etc(45), superficial infection(24), postoperative fever due to urinary tract infection, upper-respiratory infection etc(12), a history of malignancy(4), missing critical data (39). These exclusions left 121 cases were analyzed. There were 20 infected cases and 101 uninfected according to the Musculoskeletal Infection Society (MSIS) criteria [11] (Table 1). 18 cases that satisfied one of two major criteria: a sinus tract communicating with the prosthesis(16), Two positive periprosthetic cultures with phenotypically identical organisms(2); 2 cases that satisfied three of five minor criteria: a single positive intraoperative periprosthetic tissue culture, a positive histologic analysis

of periprosthetic tissue (> 5 neutrophils per high power field) and elevated synovial fluid white blood cell (WBC) count (Fig. 1).

There were 19 cases that underwent debridement, antibiotics and implant retention (DAIR) and one case was managed with one-stage revision in the infected group. An aspiration was intraoperatively performed just before opening the joint capsule for the synovial white blood cell count, differential and culture. Four to six tissue samples for culture and three to five samples for histology analysis were taken from the periprosthetic tissues in which infection was suspected. The visibly infected and necrotic tissue is excessively debrided, the wound is thoroughly irrigated and mobile components are exchanged if possible. The same manage for one-stage revision, with the addition that the whole prosthesis is removed and exchanged for a new implant. Subsequent antimicrobial therapy is prescribed for a minimum of six weeks. Three cases in the infected group failed and no cases were diagnosed and reoperated for PJI in the uninfected group with at least 1-year follow-up.

Statistical Analysis

All of the statistical analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Empower Stats (http://www.empowerstats.com, X&Y Solution). The parametric data were analyzed using t tests and categorical variables were assessed using chi-square tests. The results of the diagnostic tests were compared between the groups using the Mann-Whitney test. A p value of 0.05 was considered significant. Receiver operating characteristic (ROC) curves were generated to determine the diagnostic value of each parameter for the assessment of early PJI. The area under the curve (AUC) was calculated. The optimal threshold for each parameter as a diagnostic tool for early PJI was determined using the Youden index. The sensitivity and specificity of the diagnostic tests were calculated.

Results

There were 20 cases in infected group and 101 cases in uninfected group based on the MSIS criteria. There was no significant difference in age, BMI, time interval, joint (hip or knee) between two groups. The characteristics of each cohort are shown in (Table 2).

The CRP, ESR, WBC, NLR and IL-6 values were significantly higher in the infected group compared to the uninfected group. The mean CRP (infected = 59.06, uninfected = 10.09), ESR (infected = 35, uninfected = 17), WBC (infected = 7.95×10^9, uninfected = 6.16×10^9), NLR (infected = 4.89, uninfected = 2.18), IL-6 (infected = 40.68, uninfected = 7.46) (Table 3).

The ROC curve analysis demonstrated the IL-6 was the best test for diagnosis of early PJI (AUC = 81.4%) followed by the NLR (AUC = 80.2%), CRP (AUC = 79.3%), ESR (AUC = 74.4%) and WBC (AUC = 63.2%) (Fig. 2). We identified the cutoff values for the IL-6 at 8.07 pg/ml. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was 80%, 76.2%, 40%, and 95.1%, respectively.

With the calculated threshold of NLR set at 2.13, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was 85%, 68.3%, 34.7%, and 95.8%, respectively (Table 4).

Discussion

It is very difficult to identify an early postoperative infection after total knee or total hip arthroplasty due to the lack of an absolute diagnostic test. In this study, we determined interleukin-6(IL-6) in serum was associated with a high accuracy as a marker for the diagnosis of early PJI, followed by the NRL, the C-reactive protein, the erythrocyte sedimentation rate, and the white blood cell count.

Interleukin-6(IL-6) is an inflammatory cytokine produced by activated monocytes and macrophages and induces the production of major acute-phase proteins, including CRP [12]. Some studies have showed that the IL-6 in serum was a valuable marker for diagnosis of PJI. Di Cesare et al. [13] showed serum IL-6 was more accurate marker than either ESR or the CRP level for the detection of chronic PJI. A meta-analysis [14] published serum Il-6 as a potential superior diagnostic test compared with the conventional ESR and CRP, the pooled sensitivity and specificity were 97% and 91%, respectively. At present there were not reports about IL-6 in serum as a useful marker for diagnosis of early PJI. Maniar et al. [15] found the normal trajectory of interleukin-6 had a more rapid increase and quicker return to normal than CRP after uncomplicated TKA. Although the author cannot comment specifically on their value in detecting infection, any deviation from a known normal trajectory can facilitate a quicker decision to perform knee aspiration to diagnose early PJI more promptly. However, in our study, when we identified the cutoff values for the IL-6 at 8.07 pg/ml, the sensitivity, specificity was 80%, 76.2%, respectively. IL-6 in serum may be a useful marker for the diagnosis of early PJI. This is the first to investigate the use of serum IL-6 to diagnose early PJI.

The serum IL-6 was not often detected because of expensive costs. Interestingly, another indicator, NLR performed very well and had the high AUC (0.804). The accuracy of the value of NLR was less than Il-6 but greater than CRP. It may be more suitable for screening to diagnose early PJI because it is convenient to be obtained in daily practice without extra costs.

The value of the NRL had been shown a significant association with infection. Dogruel et al. [16] demonstrated there were statistically significant correlations between NLR and prolonged hospital stay and postoperative antibiotic doses for the treatment of odontogenic infection. Josse et al. [17] showed that the preoperative NLR $\geq$ 2.3 was found to be an independent predictor of major surgical complications such as wound infection in patients undergoing colorectal surgery. Bolat et al.[18] investigated the relationship between NLR and early postoperative infection as a complication of penile prosthesis implantation (PPI). And the NLR value could be a potential laboratory parameter for predicting early postoperative infectious complications in patients undergoing PPI. de Jager et al.[19] described the NLR had the highest AUC of 0.73 and differed significantly from the CRP level of 0.62. The NLR was better value in predicting bacteremia than routine parameters like CRP. Yombi et al. [10] reported that the NLR had a distribution pattern with a faster return to normal values than CRP in a standard post-operative

period after TKA. It was potentially a better biomarker to follow post-operative inflammation or early infection after TKA. On the basis of our data, with the calculated threshold of NLR set at 2.13, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was 85%, 68.3%, 34.7%, and 95.8%, respectively. To the best of our knowledge, this is the first study to investigate the NLR in diagnosing early PJI.

Although there were some literatures that elaborate possible explanations about the association between elevated NLR and the development of postoperative infection [20–22]. However, the exact mechanism remains unclear. But the most important finding of this study was that NLR may be a useful parameter for the diagnosis of early PJI.

There are several limitations of this study that should be considered. First, this is retrospective study and the inherent limitations exist. There may be some selection bias because several potential cases were excluded due to no record of the serum ESR, CRP, or IL-6. Although this study has a retrospective design, it provides clinically useful information. Second, there is no consensus on definition of the early PJI. We defined 90 days as early PJI and shorter time needed to be detected. Finally, we recruited 121 cases to the study. Although the total sample size was relatively sufficient, there was a small sample size in infected cases that limited the statistical power of our conclusions. Therefore, our findings should be confirmed in a larger study and at multiple institutions.

Conclusions

The findings of this study have shown that the IL-6 was the best test for diagnosis of early PJI. But it was not often detected because of expensive costs. However, the NLR that has the higher accuracy for the diagnosis of early PJI than CRP may be considered as a useful parameter for the diagnosis of early PJI because it is easy, cheap and convenient to be calculated in daily practice without extra costs. However, further studies evaluating the accuracy of NLR in more patients are needed to confirm the findings of the present study.

Abbreviations

PJI:Periprosthetic joint infection ; TJA:total joint arthroplasty; NLR:neutrophil to lymphocyte ratio; TKA:total knee arthroplasty; AUC:The area under the ROC curve; BMI:Body mass index; CRP:C-reactive protein; ESR:Erythrocyte sedimentation rate; IL-6:interleukin-6; LE:Leukocyte esterase; MSIS:Musculoskeletal Infection Society; NPV:Negative predictive value; PMN%:Percentage of polymorphonuclear cells; PPV:Positive predictive value; ROC:Receiver operating characteristic;WBC:White blood cell; PPI:penile prosthesis implantation.

Declarations

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Availability of data and materials
We do not wish to share our data, because some of the patient's data regarding individual privacy, and according to the policy of our hospital, the data could not be shared with others without permission.
Authors' contributions
BZY performed data collection and data analysis. BZY and JF drafted the manuscript. BZY, WC, LBH and JYC conceived of the study, participated in the design of the study, performed data interpretation, and participated in coordination. All authors read and approved the final manuscript.
Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital and in accordance with the standards of the National Research Council. Written informed consent was obtained from all participants.
Consent for publication
Not applicable.
Competing interests
The authors declare that they have no competing interests.

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Tables

Due to technical limitations, all tables are only available for download from the Supplementary Files section.

Figures

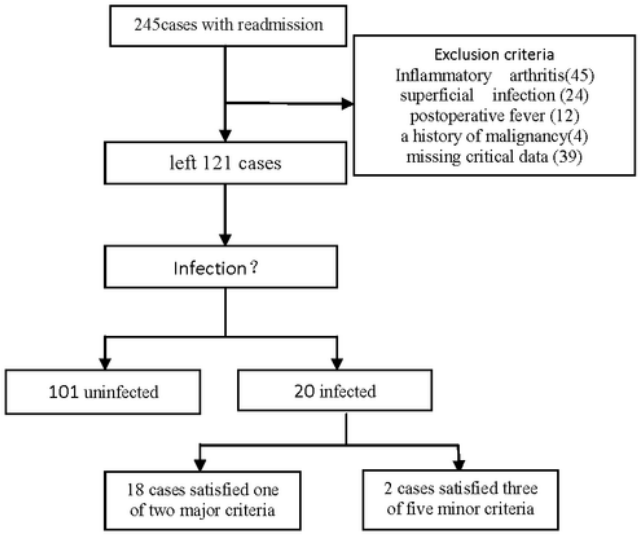

Fig.1 Flowchart

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Figure 1

Flowchart

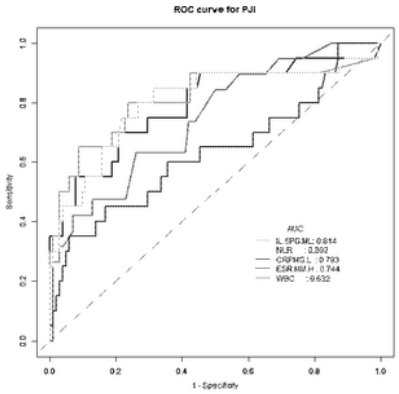

Fig 2
Receiver operating characteristic (ROC) curves for C-reactive protein(CRP), erythrocyte sedimentation rate(ESR), white blood-cell count(WBC), neutrophil to lymphocyte ratio (NLR) and interleukin-6(IL-6) in predicting early PJI

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Figure 2

Receiver operating characteristic (ROC) curves for C-reactive protein(CRP), erythrocyte sedimentation rate(ESR), white blood-cell count(WBC), neutrophil to lymphocyte ratio (NLR) and interleukin-6(IL-6) in predicting early PJI

Supplementary Files

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