Limited value of serum neutrophil-to-lymphocyte ratio in the diagnosis of chronic periprosthetic joint infection

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Abstract

Background: Diagnosing chronic periprosthetic joint infection (PJI) is challenging. No single biomarker can accurately recognize PJI preoperatively in a timely manner. Therefore, the aim of the present study was to investigate the usefulness of the serum neutrophil-to-lymphocyte ratio (NLR) in aiding the diagnosis of chronic PJI.

Materials and methods: We retrospectively evaluated the medical records of 158 patients who had undergone revision arthroplasty (104 with aseptic mechanic failure and 54 with chronic PJI) from July 2011 to July 2020. Univariate analysis followed by multivariate logistic regression was applied to compare NLR, C-reactive protein (CRP), and erythrocyte sedimentation ratio (ESR) between the two groups. The receiver operating characteristic (ROC) curve was used to assess the diagnostic performance of NLR alone and in combination with CRP and ESR.

Results: NLR, CRP, and ESR were significantly higher in patients with chronic PJI than in the aseptic revision group (p < 0.05). ROC curve analysis revealed that NLR had a sensitivity of 57.41% and a specificity of 77.88% with an optimal threshold of 2.56. The optimal threshold for CRP and ESR was 7.00 mg/L (sensitivity 62.50% and specificity 83.12%) and 43 mm/h (sensitivity 59.38% and specificity 80.52%), respectively. The combined diagnostic value of NLR with CRP and ESR was shown to have no additional diagnostic value in predicting chronic PJI.

Conclusion: Compared with traditional inflammatory biomarkers (ESR and CRP), the value of serum NLR alone or combined with CRP and ESR for diagnosing chronic PJI is limited.

Level of evidence: Level 3.

Keywords: Chronic periprosthetic joint infection, Neutrophil-to-lymphocyte ratio, Diagnosis

Introduction

Although significant progress has been made in total joint arthroplasty (TJA), periprosthetic joint infection (PJI) remains one of the most disastrous postoperative complications. It leads to a lengthy hospital stay, creates a substantial economic burden, and increases morbidity and mortality rates [1–3]. It has been claimed that approximately 1–2.5% of orthopedic patients undergoing primary TJA will develop PJI [3–5]. The timely and accurate diagnosis of PJI continues to be a challenge. Despite the suggestion of several biomarkers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), for the diagnosis of chronic PJI, as recommended by the Musculoskeletal Infection Society (MSIS), there are still no well-documented and reliable biomarkers that could help surgeons obtain the right and timely preoperative diagnosis [1, 6]. Both CRP and ESR could be within the normal range in some patients with PJI, particularly in those with chronic and low-virulence infections [7].
Additionally, the guideline requires the performance of an invasive procedure (joint aspiration and synovial fluid analysis/culture) or intraoperative exploration. Therefore, the requirement for easily accessible, noninvasive, and cost-effective biomarkers to assist with the timely and correct diagnosis of PJI is warranted.

The serum neutrophil-to-lymphocyte ratio (NLR), an easily accessible, cost-effective, and reproducible marker, is calculated from the complete blood count (CBC), which is recognized as a well-established biomarker of the systemic inflammatory response [8]. The NLR has been demonstrated to be a crucial biomarker for solid tumors and systemic rheumatic diseases, such as rheumatoid arthritis [9–11]. Recently, studies have shown that NLR was related to postoperative pain and surgical site infection in orthopedic surgery and might be a predictive biomarker for deep vein thrombosis after total knee arthroplasty [12–14]. Additionally, Golge reported that NLR might be useful in the diagnosis of PJI in the event of redness, swelling, or any other evidence of infection in the wound or surgical site, antibiotics will be continued or upgraded to high-level antibiotics. The diagnosis of chronic PJI in our institution was defined by the MSIS criteria [1, 6]. After the comprehensive evaluation of patients, those for which clinical suspicion of PJI existed, who had significantly elevated serological infection-related biomarkers, or who had positive imaging findings were subjected to aspiration and subsequent bacterial culture. Moreover, analysis of the synovial fluid (color, clarity, Rivalta test [19], white blood cell count, polymorphonuclear differential, and Gram stain as needed) was also required. Preoperative antibiotics were not generally provided for PJI patients unless we were given specific instructions based on the findings of the bacterial culture. Additionally, cultures were obtained from different sites intraoperatively before the irrigation of iodine fluid. Recently, pathologic periprosthetic tissues were biopsied during surgery and sent for histologic analysis (43% of revised patients). Empirical second-generation cephalosporins was routinely initiated during and continued after revision surgery. Sensitive antibiotics would be further prescribed according to the sensitivity test of bacterial culture. All patients received prophylactic heparin or other antithrombotic therapy to prevent deep vein thrombosis within 24 h postoperatively and for continuous 28 days. Lastly, CBC and infection-related biomarkers were regularly reexamined to monitor their fluctuations.

Diagnostic criteria and protocol
To prevent infections after primary surgery, second-generation cephalosporins were frequently recommended intraoperatively and postoperatively within 24 h. In the event of redness, swelling, or any other evidence of infection in the wound or surgical site, antibiotics will be continued or upgraded to high-level antibiotics. The diagnosis of chronic PJI in our institution was defined by the MSIS criteria [1, 6]. After the comprehensive evaluation of patients, those for which clinical suspicion of PJI existed, who had significantly elevated serological infection-related biomarkers, or who had positive imaging findings were subjected to aspiration and subsequent bacterial culture. Moreover, analysis of the synovial fluid (color, clarity, Rivalta test [19], white blood cell count, polymorphonuclear differential, and Gram stain as needed) was also required. Preoperative antibiotics were not generally provided for PJI patients unless we were given specific instructions based on the findings of the bacterial culture. Additionally, cultures were obtained from different sites intraoperatively before the irrigation of iodine fluid. Recently, pathologic periprosthetic tissues were biopsied during surgery and sent for histologic analysis (43% of revised patients). Empirical second-generation cephalosporins was routinely initiated during and continued after revision surgery. Sensitive antibiotics would be further prescribed according to the sensitivity test of bacterial culture. All patients received prophylactic heparin or other antithrombotic therapy to prevent deep vein thrombosis within 24 h postoperatively and for continuous 28 days. Lastly, CBC and infection-related biomarkers were regularly reexamined to monitor their fluctuations.

Laboratory evaluation
Routine blood samples, such as CBC, were drawn in the morning after patients had fasted for at least 8 h. In revision patients, CRP and ESR were also requested. Samples were sent to our hospital’s medical laboratory as soon as possible, in accordance with accepted standards and
guidelines. Neutrophils and lymphocytes were extracted from CBC retrospectively. The NLR was calculated as the proportion of the absolute count of neutrophils to the absolute count of lymphocytes.

**Statistical analysis**

Mean and standard deviation (SD) were used to describe the quantitative data, while the number and percentage were calculated for categorical variables. An independent *t*-test was performed to detect differences in age between groups. The categorical variables of demographic features were calculated with the use of a χ² test. To evaluate the differences of each serologic biomarker between aseptic and septic groups, we used a Mann–Whitney *U* test for comparisons. To decrease the effect of confounding factors, the adjusted *p*-value was assessed by multivariate logistic regression (forward likelihood ratio method) regarding age, sex, operative joint, diabetes mellitus, and hypertension. The above analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 22, IBM Corporation, Armonk, NY, USA). MedCalc software (version 19.0.7, Ostend, Belgium) was employed to analyze the receiver operating characteristic (ROC) curves. Area under the curve (AUC), sensitivity, specificity, and other related parameters were used to investigate the diagnostic performance of NLR, CRP, ESR, and combination of biomarkers. The Youden index was applied to determine the optimal threshold for the diagnosis of PJI. Variables with *p* < 0.05 were considered statistically significant.

**Results**

**Demographic features of patients undergoing revision surgery**

The demographic features of both groups are presented in Table 1. Among patients with PJI, the average age was 64.5 years, with 31.5% being male. The baseline characteristics of age, sex ratio, and status of diabetes mellitus between the two groups did not exhibit significant differences. In the aseptic revision group, the percentage of patients with hip problems was significantly higher than in the PJI group (81.7% versus 50.0%, *p* < 0.001). Additionally, the two groups differed regarding the status of blood pressure, with the PJI group suffering more from hypertension (44.4% versus 21.2%, *p* = 0.002).

| Group and variable | Aseptic revision | PJI | *p*-Value | Adjusted *p*-Value |
|--------------------|-----------------|-----|-----------|-------------------|
| No. of patients    | 104             | 54  |           |                   |
| Age               | 63.40 ± 12.70   | 64.48 ± 10.83 | 0.596<sup>c</sup> |                   |
| Sex               | 0.453<sup>d</sup> |     |           |                   |
| Female            | 65 (62.5%)      | 37 (68.5%) | <0.001<sup>d</sup> |                   |
| Male              | 39 (37.5%)      | 17 (31.5%) |           |                   |
| Joint             |                 |     |           |                   |
| Hip               | 85 (81.7%)      | 27 (50.0%) |           |                   |
| Knee              | 19 (18.3%)      | 27 (50.0%) |           |                   |
| Diabetes mellitus | 0.557<sup>d</sup> |     |           |                   |
| Diabetic          | 12 (11.5%)      | 8 (14.8%) |           |                   |
| Nondiabetic       | 92 (88.5%)      | 46 (85.2%) |           |                   |
| Blood pressure    | 0.002<sup>d</sup> |     |           |                   |
| Hypertension      | 22 (21.2%)      | 24 (44.4%) |           |                   |
| Nonhypertension   | 82 (78.8%)      | 30 (55.6%) |           |                   |

*PJI* periprosthetic joint infection

* Data are presented as the mean ± standard deviation

* Data are presented as the number (percentage) of patients

* *p*-Value was calculated by the independent *t*-test

* *p*-Value was calculated by the χ² test. *p* < 0.05 indicates a significant difference between groups

**Comparisons of serum biomarkers between patients in aseptic and septic groups**

For all three biomarkers (NLR, CRP, and ESR), significant differences were noted between the aseptic and septic groups, as shown in Table 2 and Fig. 1. The NLR for patients with previous diagnosis of chronic PJI was 3.22 compared with 2.13 among patients in the aseptic revision group (*p* = 0.001, adjusted *p* = 0.008). The mean value of CRP in the PJI group was 36.25 mg/L, which was significantly higher than that of the aseptic revision group with a mean value of 5.57 mg/L (*p* and adjusted *p* < 0.001). Similarly, the level of ESR in patients with PJI was significantly different in comparison with that of the aseptic revision group (63.35 versus 28.66 mm/h, *p* and adjusted *p* < 0.001).

**Table 2** Comparison of biomarkers between the aseptic and septic revision

| Biomarker    | Aseptic revision<sup>a</sup> | PJI<sup>a</sup> | *p*-Value | Adjusted *p*-Value |
|--------------|-----------------------------|---------------|-----------|--------------------|
| NLR (mg/L)   | 2.13 ± 0.97                 | 3.22 ± 2.37   | 0.001     | 0.008              |
| CRP (mg/L)   | 5.57 ± 9.27                 | 36.25 ± 38.79 | <0.001    | <0.001             |
| ESR (mm/h)   | 28.66 ± 22.17               | 63.35 ± 34.81 | <0.001    | <0.001             |

* *Data are presented as the mean ± standard deviation. *p*-Value was calculated by the Mann–Whitney *U* test. Adjusted *p*-value was assessed by the multivariate logistic regression (forward likelihood ratio method) regarding age, sex, joint, diabetes mellitus, and hypertension. *p* < 0.05 indicates a significant difference between groups.

| Group and variable | Aseptic revision<sup>a</sup> | PJI<sup>a</sup> | *p*-Value | Adjusted *p*-Value |
|--------------------|-----------------------------|---------------|-----------|--------------------|
| Demographic features of patients who underwent revision surgery | | | | |

**The diagnostic performance of NLR, CRP, and ESR in detecting chronic PJI**

Consecutively, ROC curves were used to depict the discriminatory performance of NLR, CRP, and ESR between
the aseptic mechanic failure group and the chronic PJI group. The respective AUC values for NLR, CRP, and ESR were demonstrated to be 0.66 [95% confidence interval (CI) 0.58–0.73, \( p = 0.001 \)], 0.84 (95% CI 0.77–0.89, \( p < 0.001 \)), and 0.79 (95% CI 0.72–0.85, \( p < 0.001 \)). The sensitivity and specificity of NLR in detecting PJI were 57.41% and 77.88%, with an optimal threshold > 2.56. The optimal threshold with regard to CRP and ESR was evaluated to be 7.00 mg/L (sensitivity 72.22% and specificity 82.69%) and 43.00 mm/h (sensitivity 68.52% and specificity 81.73%), respectively. The diagnostic performance of NLR was therefore shown to be inferior to that of CRP and ESR. Additionally, we further evaluated the combined diagnostic value of NLR, CRP, and ESR for predicting chronic PJI. The resulting AUC for the combination of NLR with CRP and ESR was shown to have no additional diagnostic value. On the other hand, as opposed to using CRP and ESR alone, the specificity and diagnostic performance of CRP in conjunction with ESR (92.31 versus 82.69%, 81.73%) were significantly improved, enhancing the ability to detect PJI (Table 3; Fig. 2).

**Discussion**

The association between preoperative levels of NLR and chronic PJI is yet to be elucidated. In the present study, we investigated the diagnostic performance of the cost-effective and easily accessible NLR biomarker in facilitating the diagnosis of chronic PJI. We found that the level of NLR was significantly higher in the PJI group than in the aseptic mechanic failure group. However, the diagnostic value of NLR alone was demonstrated to not be a superior biomarker to those of CRP and ESR in

![Fig. 1](image)

Comparisons of NLR, CRP, and ESR between aseptic mechanic failure and PJI patients. **A** NLR, **B** CRP, **C** ESR. The asterisks indicate a significant difference between groups. The \( p \)-values were calculated by the Mann–Whitney \( U \) test, \( p < 0.05 \) indicates a significant difference between groups. NLR neutrophil-to-lymphocyte ratio, CRP C-reactive protein, ESR erythrocyte sedimentation rate. The black line represents the mean value of each group.

**Table 3** Performance of serum NLR, CRP, ESR, and combination in the diagnosis of PJI

|        | NLR | CRP | ESR | NLR + CRP | NLR + ESR | CRP + ESR | NLR + CRP + ESR |
|--------|-----|-----|-----|-----------|-----------|-----------|-----------------|
| AUC    | 0.66| 0.84| 0.79| 0.84      | 0.79      | 0.83      | 0.83            |
| 95% CI | 0.58–0.73| 0.77–0.89| 0.72–0.85| 0.77–0.89| 0.72–0.85| 0.76–0.88| 0.76–0.88       |
| \( p \)-Value | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001          |
| Threshold | 2.56 | 7.00 | 43.00 | –         | –         | –         | –               |
| Sensitivity (%) | 57.41 | 72.22 | 68.52 | 72.22 | 68.52 | 64.81 | 64.81           |
| Specificity (%) | 77.88 | 82.69 | 81.73 | 82.69 | 81.73 | 92.31 | 92.31           |
| PPV (%) | 57.4 | 68.4 | 66.1 | 68.4 | 66.1 | 81.4 | 81.4            |
| NPV (%) | 77.9 | 85.1 | 83.3 | 85.1 | 83.3 | 83.5 | 83.5            |
| +LR | 2.60 | 4.17 | 3.75 | 4.17 | 3.75 | 8.43 | 8.43            |
| −LR | 0.55 | 0.34 | 0.39 | 0.34 | 0.39 | 0.38 | 0.38            |
| Accuracy (%) | 70.88 | 79.11 | 77.22 | 79.11 | 77.22 | 82.91 | 82.91           |
| DOR | 4.75 | 12.42 | 9.74 | 12.42 | 9.74 | 22.11 | 22.11           |

PJI periprosthetic joint infection, NLR neutrophil-to-lymphocyte ratio, CRP C-reactive protein, ESR erythrocyte sedimentation rate, AUC area under the curve, CI confidence interval, PPV positive predictive value, NPV negative predictive value, +LR positive likelihood ratio, −LR negative likelihood ratio, DOR diagnostic odds ratio
diagnosing chronic PJI. Moreover, when we combined NLR with CRP and ESR, this combination was shown to have no additional diagnostic value. Nonetheless, the combination of CRP and ESR enhanced specificity and diagnostic performance, and thus improved the ability to detect chronic PJI.

NLR is calculated directly from the commonly ordered and readily available count of neutrophils and lymphocytes in CBC, making it easily accessible and cost effective. More importantly, NLR has been recognized as a biomarker of the systemic inflammatory response [8]. As such, NLR has been reported to reflect a heightened inflammatory reaction and has gained increasing attention as a prognostic biomarker in many conditions, such as solid tumors, inflammatory diseases, and postoperative infection [10, 11, 14]. A previous study reported that NLR was significantly higher in patients with polymyalgia rheumatica and was shown to be associated with disease activity and specific clinical features [10]. Inose et al. retrospectively investigated the association of NLR with surgical site infection in patients who underwent spinal instrumentation surgery. They found that the level of NLR postoperatively was significantly related to surgical site infection with a cutoff of 3.87 [14]. Regarding the role of NLR in TJA, Yombi et al. investigated the distribution and fluctuation of NLR compared with that of CRP in patients who underwent total knee arthroplasty and found that NLR had a faster normalization and was more stable than CRP, demonstrating that NLR might be utilized as a potential biomarker to monitor postoperative inflammation or infection [20]. In terms of the diagnostic value of NLR in predicting early PJI, Zhao et al. and Yu et al. both revealed that NLR was sensitive and has a potential ability to diagnose early PJI, even superior to CRP [16, 17]. However, for chronic PJI, although the level of NLR was significantly higher in patients with PJI in comparison with aseptic patients in our study, the alone or combined diagnostic value of NLR in predicting chronic PJI was limited. Our present study addressed that NLR had poor diagnostic performance with a sensitivity of 57.41% and specificity of 77.88%. In comparison, the study conducted by Golge [15] revealed that the sensitivity and specificity of NLR in detecting PJI were 90% and 72%, respectively, that is, the sensitivity was much higher than that of our study. However, the study involved patients with either PJI or primary total knee arthroplasty, with the primary arthroplasty patients being considered as the control group, which would have a great impact on the diagnostic performance of NLR because of the larger heterogeneity between the two groups. As the selection of patients is crucial for exploring the diagnostic value of biomarkers, patients should be generalized under consistent conditions to decrease the confounding effect [21]. Hence, future studies might need to clarify the diagnostic value of serum NLR in predicting PJI, especially for the chronic condition.

Many studies have delineated the value and established an optimal threshold of CRP and ESR in diagnosing chronic PJI. Both CRP and ESR, which are considered as specific indicators of infection, were shown to be highly

Fig. 2 ROC curve of NLR, CRP, ESR, and combination to predict PJI. a The diagnostic performance of each biomarker alone. b The diagnostic performance of the combination of biomarkers. NLR neutrophil-to-lymphocyte ratio, CRP C-reactive protein, ESR erythrocyte sedimentation rate, AUC area under the curve, PJI periprosthetic joint infection.
elevated in the PJI group and to gradually decline postoperatively [22, 23]. The sensitivity of CRP for diagnosing PJI has been reported to range from 74% to 94%, whereas its specificity ranged from 20% to 100%, with different predictive cutoffs [22–26]. On the other hand, the sensitivity and specificity of ESR were reported to vary from 42% to 94%, and 33% to 90%, respectively [23–25, 27, 28]. In our study, the diagnostic performance of CRP and ESR in predicting PJI was consistent with previous studies, showing high effectiveness for diagnosing PJI. Additionally, when CRP combined with ESR in predicting PJI, the specificity and diagnostic performance were significantly improved, which was in line with previous studies demonstrating that combinations of biomarkers have been addressed to enhance diagnostic performance [22, 28–30]. Abdelbary et al. conducted a systematic review to assess the combined diagnostic performance of various serum, synovial, and tissue-based tests for PJI. They demonstrated that the combination of CRP and ESR enhanced the diagnostic performance dramatically in detecting PJI [29]. Paziuk et al. demonstrated that the ratio of the platelet count to mean platelet volume was inferior to CRP and ESR when employed as a single index. However, when the ratio was used in combination with CRP and ESR, a statistically significant increase in the diagnostic performance of the combination of biomarkers in predicting PJI was observed [28]. Qin et al. revealed that the combination of D-dimer and CRP improved the diagnostic performance in predicting PJI [30]. Therefore, CRP and ESR, as traditional inflammatory markers, using alone or combined, exhibited promising value for diagnosing chronic PJI.

Our study has several limitations that should be considered when interpreting the results. First, this was a retrospective study and therefore might have introduced selection bias. Second, not all confounding variables were taken into account in the study. Third, the study only included patients who needed revision arthroplasty. As a result, it is possible that patients with asymptomatic infections or mild clinical manifestations were left out of the study. Finally, this was a single-center study with a small number of patients, particularly in the chronic PJI group. Recruiting more patients from multiple centers in a prospective study would allow for better representation.

**Conclusion**

Our study revealed that serum NLR was significantly higher in patients with chronic PJI than in those with aseptic mechanical failure. Nevertheless, in comparison with traditional inflammatory markers, the alone or combined value of serum NLR for diagnosing chronic PJI is limited. More large-scale and prospective studies might be needed to further elucidate the value of NLR in the diagnosis of chronic PJI.

**Abbreviations**

TJA: Total joint arthroplasty; PJI: Periprosthetic joint infection; NLR: Neutrophil-to-lymphocyte ratio; CBC: Complete blood count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation ratio; ROC: Receiver operating characteristic; SD: Standard deviation; AUC: Area under the curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; +LR: Positive likelihood ratio; −LR: Negative likelihood ratio; DOR: Diagnostic odds ratio.

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**Authors’ contributions**

YY, WC, ZZ, and PS contributed to the idea and design of the study. YY, WC, MG, QL, GX, BP, LZ, and XC contributed to data collection and data analysis, and drafted the manuscript. All authors contributed to the interpretation of results and manuscript revision. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the institutional review board of the first affiliated hospital of Sun Yat-sen University. The requirement for informed consent was waived due to the retrospective design of our study.

**Consent for publication**

Not applicable.

**Competing interests**

There are no conflicts of interest to declare.

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