Predictive value of postoperative NLR, PLR and LMR for early periprosthetic joint infection after total joint arthroplasty: a pilot study

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Abstract

Background The purpose of this study was to evaluate the predictive value of the postoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) for early periprosthetic joint infection (PJI).

Methods : During the period from January 2008 to December 2016, 104 patients (26 early PJI cases and 78 non-PJI cases) who underwent total joint arthroplasty at the Department of Orthopedics in our hospital were enrolled in this study. All of the relevant clinical information and laboratory indexes were reviewed from our hospital follow-up system. The time when any abnormal symptoms or signs occurred, including fever, local swelling or redness around the surgical site between the 2nd and 4th weeks after surgery, was defined as the “suspect time”. We compared laboratory parameters, including NLR, PLR, LMR, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), between the two groups. The trends of NLR, LMR, PLR, CRP and ESR were also reviewed after surgery. The predictive ability of these parameters at the suspect time for early PJI was evaluated by multivariate analysis and receiver operating characteristic (ROC) curve analysis.

Results : NLR, PLR and LMR returned to preoperative levels within two weeks after surgery in the two groups. In the early PJI group, NLR and PLR were significantly increased during the incubation period of infection or infection, and LMR was significantly reduced, although 61.5% (16/26) of the patients had normal white blood cells. Interestingly, ESR and CRP were still relatively high two weeks after surgery, and the change in these two indexes was not obvious when infection occurred. NLR and PLR were significantly correlated with early PJI (Odds ratio (OR) N LR =88.36, OR PLR =1.12, P NLR =0.005, P PLR =0.01), and NLR had great predictive ability for early PJI, with a cut-off value of 2.77 (sensitivity=84.6%, specificity=89.7%, 95% CI=0.86-0.97) .

Conclusions: ESR and CRP are not sensitive for the diagnosis of early PJI due to their persistently high levels after arthroplasty. The postoperative NLR at the suspected time has a great ability to predict early PJI, and more attention should be paid to it.

Background

Osteoarthritis (OA) is one of the most common chronic degenerative diseases in middle-aged and elderly people. It is estimated that 10–15% of adults over the age of 60 years suffer from OA worldwide. In China, approximately 110 million elderly people are estimated to have symptomatic knee OA [1]. Total joint arthroplasty (TJA), including total knee arthroplasty (TKA) and total hip arthroplasty (THA), has become the most effective method for end-stage OA. However, the early diagnosis of periprosthetic joint infection (PJI), one of the most disastrous complications of TJA, is still a challenging task for surgeons. Early PJI, defined as PJI within 4 weeks after index arthroplasty, has been used by many studies[3, 4]. It is much more difficult to diagnose early postoperative PJI than chronic PJI, which can be assisted by infectious traits such as pain, redness, inflammatory exudation and sinus. The International Consensus

on PJI recommends C-reactive protein（CRP） >100 mg/L, synovial WBC count >10,000 cells/mL, and % polymorphonuclear neutrophils of 90% as diagnostic cut-offs for early postoperative PJI (<6 weeks from index surgery). However, due to the long duration of the return of ESR to normal levels after surgery (usually at least 3-8 weeks), it is not sensitive to early postoperative PJI. CRP levels return to preoperative levels within 3 weeks; however, it may be elevated by various causes in addition to postoperative infection because elderly patients with comorbid illnesses frequently undergo TJA [5, 6].

Recently, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) have been studied and found to be valuable in predicting the outcomes or prognosis of many diseases, such as oncological diseases, inflammatory diseases and some infectious diseases [7-11]. Moreover, Jiri Gallo[12] found that the white blood cell count and neutrophil/lymphocyte percentage in synovial fluid may have excellent AUCs for the detection of PJI. As far as we know, however, the predictive value of these parameters in serum for early PJI has not been reported.

The purposes of our study are (1) to observe the trends of NLR, PLR and LMR after TJA and (2) to evaluate the predictive value of these parameters for early PJI.

Methods

The study protocol was approved by the Institutional Review Board of our Hospital, and informed consent was obtained from all patients. The Hospital Follow-up System (HFS, an electronic database comprising complete medical records for inpatient and outpatient patients) was used in our study. We reviewed the patients diagnosed with early PJI (within 4 weeks after surgery) from February 2008 to December 2016 according to the criteria recently proposed by the Musculoskeletal Infection Society[13]. In total, 30 patients diagnosed with early PJI from February 2008 to December 2016 in our department were enrolled in this study. To make the results more reliable, we excluded PJI cases that occurred within 2 weeks after surgery and only included PJI cases that occurred between weeks 2 and 4. We defined “suspect time” as any abnormal symptoms or signs that occurred, including fever, local swelling or redness around the surgical site two weeks after the surgery and before the diagnosis was made. It is routine to observe laboratory tests at 1 and 3 days after surgery in our department during the hospital stay of the patient. ESR, CRP and routine blood examination were requested at 7 and 14 days when the patients left the hospital and went to a community hospital, and the data were uploaded by apps (WeChat). Patients’ basic information (including age, sex, height, weight, and body mass index (BMI)) and the results of preoperative laboratory tests (including neutrophil (N), lymphocyte (L), monocyte (M), and platelet (P) counts, ESR and CRP) were obtained. We excluded patients with incomplete data for CRP, ESR or routine blood examination. Finally, 26 patients were included in the final analyses. A control group was matched at a ratio of 1:3 by sex, BMI, year of surgery and Charlson-Deyo scores. All the included data were compared between the two groups. Moreover, the postoperative levels of ESR, CRP, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) were observed in the two groups after the operation. Pearson correlation analysis was conducted to evaluate the relationships between early PJI and the parameters at the suspected time. Receiver operating

characteristic (ROC) analysis and multivariate analysis were also performed to determine the predictive value of these hematological parameters at the suspected time for early PJI.

Statistical analysis

All the statistics are presented as the mean ± SD for continuous variables and the median (P25, P75) for discrete variables. Clinical characteristics were compared between the PJI group and the non-PJI group. The continuous variables of different groups were compared by using Student's t-test or the Mann–Whitney U test, and categorical variables were tested using Pearson's X^2 test. In ROC analysis, the optimal cut-off values of several markers, including NLR, PLR, and LMR, that best predict the possibility of early PJI were determined with the maximum value of Youden's index, which was calculated by sensitivity + 1-specificity. All statistical analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided, and statistical significance was defined as when the p-value was less than 0.05.

Results

A total of 104 patients (PJI group: N=26; non-PJI group: N=78) were included in this study. As shown in Table 1, the mean age was 65.47±10.23 years in the PJI group and 62.15±9.33 years in the non-PJI group. The preoperative NLR and PLR in the PJI group were higher than those in the non-PJI group, and the preoperative LMR was slightly lower in the PJI group. However, there was no significant difference in any of the preoperative parameters, including age, BMI, Charlson-Deyo score, WBC, neutrophil count, lymphocyte count, platelet count, NLR, PLR, LMR, ESR and CRP, between the two groups.

The trends of postoperative NLR, PLR, LMR, CRP and ESR at different time points in both groups are shown in Figure 1. In the two groups, the above indexes except LMR increased rapidly on the first day and reached a peak 1-3 days after the operation, while LMR decreased significantly and then elevated gradually. In addition, NLR, PLR and LMR returned to their preoperative levels within approximately two weeks. However, ESR and CRP remained higher (ESR>20 mm/h, CRP>20) two weeks after the operation. For the PJI group, the average suspected time point was 21.6 days; NLR, PLR and LMR were significantly different compared with those in the non-PJI group (P<0.01, Table 2), even with 61.5% (16/26) of patients with normal white blood cell levels at the suspected time.

In the association analysis (Table 3), the Pearson correlation coefficients for WBC, NLR, PLR and LMR at the suspected time were obtained (r_{WBC}=0.22, r_{NLR}=0.72, r_{PLR}=0.61, r_{LMR}=0.39). However, there was no correlation between early PJI and the other parameters. The results of multivariate analysis suggested that the increased NLR and PLR are independent predictive indexes for early PJI (Table 3, OR_{NLR}=88.36, OR_{PLR}=1.12, P_{NLR}=0.005, P_{PLR}=0.01).

The ROC curves of NLR, LMR, and PLR at the suspected time are shown in Fig 2. The results shown in Table 4 indicate that the areas under the ROC curve (AUCs) were all larger than the reference value (0.5).

NLR had the highest area under the ROC curve (AUC) (AUC_{NRL}=0.93, AUC_{PLR}=0.87, AUC_{LMR}=0.81). The cut-off value of NLR was 2.77 (sensitivity=84.6%, specificity=89.7%, 95% CI=0.86-0.97).

Discussion

The diagnosis of early PJI is challenging. Timely measures such as oral antibiotics or debridement are important for preserving implants and reducing patient suffering [14]. Our study shows that increased NLR at the suspected time (the time when any suspicious symptoms or signs of infection first occur after joint arthroplasty) is more valuable in predicting early PJI, while ESR and CRP remain at a relatively high level.

CRP and ESR are regarded as signals of inflammation or infection. At present, ESR and CRP are also common serum biomarkers for the diagnosis of PJI [15]. However, they may not be suitable for early PJI[16]. In this study, we reviewed the trend of the postoperative CRP, ESR, NLR, LMR and PLR levels within two weeks. The persistent high level of ESR and CRP (Fig. 1) after surgery greatly limited their implementation in the screening or prediction of early PJI, which was consistent with the findings of published literature [5, 17]. Yombi JC [18] found that CRP values rose abruptly after surgery, with peak values reached on day 2 or 4. Subsequently, CRP levels remained elevated for approximately 2 weeks in the immediate postoperative phase and returned to normal levels 3–6 weeks after surgery. Moreover, Herrero FA et al [19] also reported that elevated CRP after TKA can persist for 150 days. Other serum biomarkers, such as D-dimer[20], interleukin-6[21], tumor necrosis factor-a[22] , procalcitonin (PCT) and α-defensin[23, 24], have been researched for diagnosing PJI, but these parameters are not easily accessible in some remote areas, and larger-scale studies are still needed to validate their effectiveness.

NLR, PLR, and LMR, which can be easily obtained by routine blood tests, have been demonstrated as stable and cost-effective biomarkers for the diagnosis or prognosis of many diseases, including cardiovascular, autoimmune, neoplastic and inflammatory diseases[8, 25, 26]. Dogruel F et al [27] reported that patients with severe dental infection whose pretreatment NLR was more than 5.19 may need a higher dose of antibiotics and to stay more than 1 day in the hospital, so they suggested that the pretreatment NLR may be used as a prognostic marker for patients with odontogenic infections. Yapıcı O et al [28] found that NLR could be used as an inexpensive and simple biomarker to predict the development of osteomyelitis and/or amputation risk in patients with diabetic foot infection. Wu Y [29] showed that NLR and PLR were two useful inflammatory markers for the assessment of disease activity in patients with systemic lupus erythematosus .

In our study, the results of Pearson’s correlation and multivariable analysis showed that NLR and PLR at the suspected time are independent factors associated with early PJI. According to the ROC analysis, NLR may be more valuable than PLR, and the cut-off value for predicting early PJI was 2.77. This means that early PJI could be predicted if NLR is >2.77 at the suspect time defined in our study.

There are several limitations in our study. First, the major drawback of our study is that we did not include data on any probable effect of antibiotic use or the type of pathogens found in PJI cultures on the ratios. Second, the sample size in our study was relatively small, and this was a retrospective study. Third, only the perioperative period (within 7 days) and the first follow-up point (two weeks) were analyzed in patients without early PJI because postoperative follow-up is routinely conducted at two weeks, 3 months and 6 months after discharge in our department. In addition, NLR and PLR also increased significantly due to the surgery and returned to the preoperative level within two weeks, so we chose patients diagnosed with PJI two weeks after the operation. Moreover, whether there is a difference in the threshold value of NLR between TKA and THA could not be obtained from the present study. Therefore, larger-scale, prospective studies and subgroup analyses are needed to further investigate the ability of NLR to predict early PJI.

Conclusion

In conclusion, we found that the neutrophil-to-lymphocyte ratio may be more sensitive and credible in predicting the early periprosthetic joint infection when any potential infectious symptoms or signs occur two weeks after total joint arthroplasty.

Abbreviations

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PJI: periprosthetic joint infection; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ROC: receiver operating characteristic; OR: Odds ratio; OA: Osteoarthritis; TJA: total joint arthroplasty; TKA: total knee arthroplasty; THA: total hip arthroplasty; HFS: Hospital Follow-up System; BMI: body mass index; ROC: receiver operating characteristic.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Huashan Hospital. The informed consent was written by each of the patients and their guardians.

Consent to publish

Not applicable.

Availability of data and material

The raw data will be made available from the authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

GLZ and JC were involved in all the work of the article. JW, YBW and JX were involved in the data collection and analysis. SQW, GYH, FYC, JSS and HW were involved in data collection. All authors have read and approved the manuscript, and ensure that this is the case.

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Tables

Table 1. Patient basic characteristics

	PJI group (N=26)	non-PJI group (N=78)	t/X^2	P value
Age (years)	65.47±10.23	62.15±9.33	1.53	0.13
male (% total)	14 (53.8%)	40 (51.3%)	0.39	0.53
BMI (kg/m2)	24.15±2.37	23.32±2.75	1.38	0.17
White blood cell (WBC×10^9)	6.32±1.66	6.61±2.12	0.63	0.53
Neutrophil count (NE×10^9)	3.75±1.18	3.84±2.08	0.21	0.83
Lymphocyte count (LM×10^9)	1.72±0.57	1.82±0.63	0.71	0.48
monocyte counts (MO×10^9)	0.45±0.20	0.46±0.35	0.14	0.89
Platelet count	220.83±56.96	214.18±61.69	0.48	0.63
ESR (mm/h)	18.13±14.88	15.62±12.96	0.82	0.41
CRP (mg/L)	9.27±15.41	7.10±10.93	0.79	0.43
NLR	2.17±0.40	2.11±0.43	0.42	0.68
PLR	129.10±51.68	114.42±35.83	1.34	0.18
LMR	3.88±1.60	3.96±1.59	0.22	0.82

PJI, periprosthetic joint infection; BMI, Body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio；PLR；platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio.

Table 2. The parameters at the suspect time point

variable	PJI group	Non-PJI group	t	P value
ESR	38.80±5.60	36.96±5.04	1.57	0.12
CRP	32.77±4.45	31.51±7.19	0.84	0.4
NLR	3.52±0.67	2.38±0.38	10.76	<0.01
LMR	2.96±0.36	3.93±1.09	4.45	<0.01
PLR	150.69±19.35	124.11±13.34	7.8	<0.01

Table 3. Pearson Correlation relevant analysis and multivariate analysis between the PJI and the parameters at the suspect time

	Pearson Correlation		Multivariate Analysis		
Variable	r	P-vlaue	OR	95% CI	P-value
White blood cell (WBC×10^9)	0.22	0.02*	0.98	0.64-1.50	0.93
Neutrophil count (NE×10^9)	0.20	0.04*	1.12	0.81-1.54	0.49
Age (years)	0.17	0.09	1.04	0.93-1.17	0.46
BMI (kg/m2)	0.14	0.15	1.02	0.67-1.55	0.93
ESR (mm/h)	0.15	0.12	1.08	0.89-1.32	0.42
CRP (mg/L)	0.08	0.41	0.98	0.81-1.19	0.81
NLR	0.72	<0.01*	88.36	3.89-2004.61	0.005*
PLR	0.61	<0.01*	1.12	1.03-1.23	0.01*
LMR	0.39	<0.01*	0.41	0.09-1.83	0.24

*r, Pearson correlation coefficient; OR, odds ratio; CI, confidence interval; * means statistical difference; BMI, Body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio；PLR，platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio*

Table 4. AUC of the NLR，PLR and LMR at suspect time

Variable	AUC	cut-off	Sensitivity (%)	Specificity (%)	95% CI
NLR	0.93	2.77	84.6	89.7	0.86-0.97
PLR	0.87	139.22	88.5	87.2	0.79-0.93
LMR	0.81	3.40	88.5	78.2	0.72-0.88

AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio；PLR，platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio

Figures

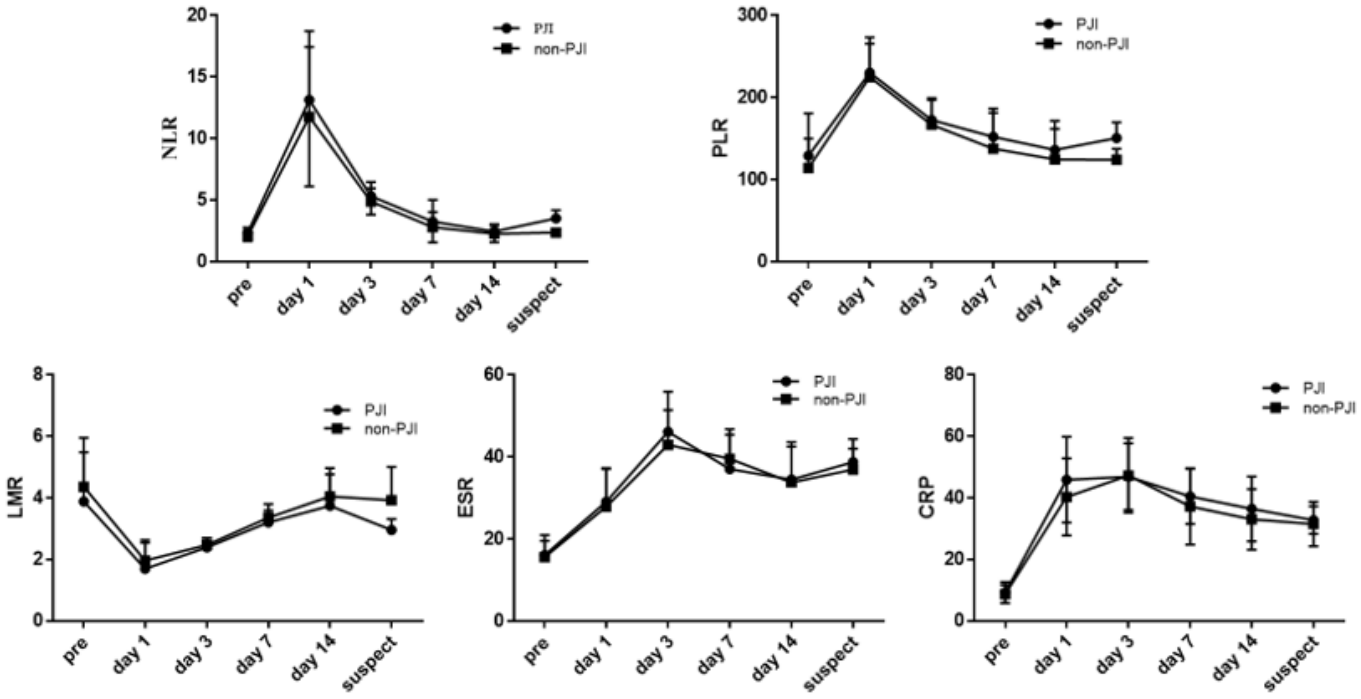

Figure 1

The overall trend of NLR、PLR、LMR、ESR and CRP in the non-PJI and PJI group after the operation

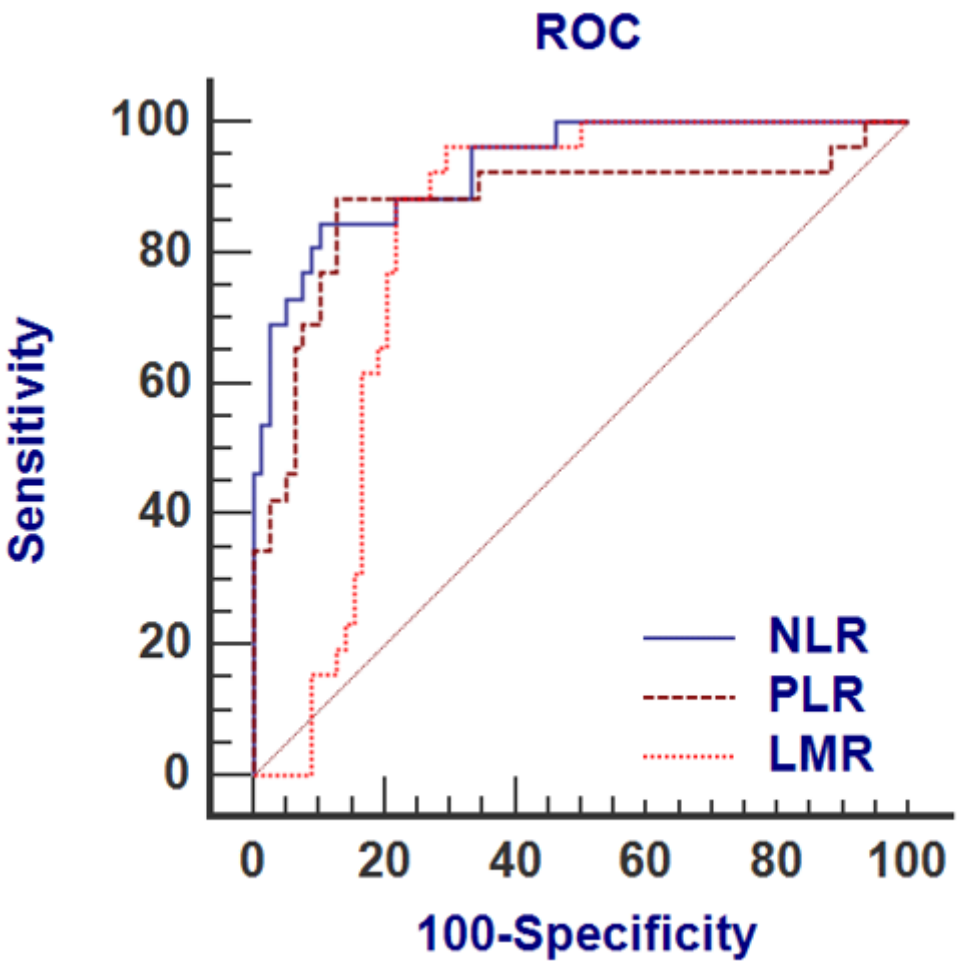

Figure 2

ROC curve of the NLR、PLR、LMR at the suspect time