Neutrophil-Lymphocyte Ratio in Predicting Infective Endocarditis: A Case-Control Retrospective Study

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1. Introduction

Infective endocarditis (IE) is a complex infectious disease with high morbidity and mortality [1]. The inflammation mechanism of IE is a complex network including interactions of inflammatory cytokines and other components of host response [2]. Previous studies indicated that inflammation markers such as monocyte to high-density lipoprotein cholesterol ratio (MHR) [3], Apolipoprotein A-I, HDL-C [4], and interleukin (IL)-17 [5] are favorable prognostic markers in IE. Elevated serum IL-6 and C-reactive protein (CRP) levels may suggest ongoing IE, and the former helps better and faster monitoring of treatment [6]. IL-8-containing cells in infected heart valves could be used as a marker of IE activity [7]. Rheumatoid factor (already a Duke minor criterion) is an inflammatory marker that helps in the diagnosis of patients with suspected IE [8, 9].

Leukocytes play a main role in infectious diseases [10]. As the predominant cells in white blood cells, neutrophils (NEU) and lymphocytes (LYM) carry a big weight in the inflammatory reaction of infection. Neutrophil leukocytosis (the gradual increase in neutrophil count and the simultaneous decrease in lymphocyte count) constitute a typical leukocyte change in response to acute bacterial infections [11]. The neutrophil-to-lymphocyte ratio (NLR) can reflect, in a synergistic manner, more about disease severity than...
either of the former leukocyte subgroups [12]. More and
more studies suggest that NLR, as an inexpensive and easily
accessible inflammatory marker, is an independent predictor
of unfavorable clinical outcomes in infectious [13–16] and
cardiovascular diseases [17–19], subclinical diabetic cardio-
myopathy, prediabetes and diabetes mellitus [20, 21], and
cancers [22–24]. The relationship between admission NLR
and IE was evaluated in only four studies. A retrospective
study enrolled in 121 IE patients found that high NLR at
admission is associated with in-hospital mortality and central
cerebrovascular system events [12]. Another study confirmed it
and further found that NLR showed no predictive indication of
mortality with long-term follow-up [25]. While Mishaal
et al. analyzed the data from 142 consecutive patients with
definitive IE and found that NLR is an independent predictor
of outcome in infective endocarditis; calculation of the NLR
upon admission may assist in early risk stratification of
patients with IE [26].

However, the relevant articles are small sample retrospec-
tive experiments, so the variety of NLR values during the
entire IE process cannot be accurately predicted. Moreover,
there is no comprehensive study on the IE caused by different
pathogens and in different populations. Whether NLR can
be used as an independent predictor of IE remains further
investigation. Herein, we carried out this study to evaluate
the ability of NLR to predict the occurrence and outcome
of IE.

2. Methods

2.1. Study Population. The IE patients were collected from
the Second Xiangya Hospital of Central South University
from 2015 to 2019. Inclusion criteria follow the modified
Duke criteria for the definitive diagnosis of IE [27]. The
exclusion criteria were as follows: (1) patients with malignant
tumor, blood system disease, receiving chemotherapy, gluco-
corticoid, or immunosuppressant treatment; (2) patients who
were interruption of treatment or automatic discharge and
no cause of death; (3) patients who had no NLR data before
the treatment. Healthy individuals from the medical exami-
nation center of our hospital were enrolled in our study. In-
hospital bad clinical outcome was defined and followed at
least one condition: (1) hospital death; (2) any clinically overt
central nervous system event, including embolic brain infarcti-
on, brain hemorrhage, transient ischemic attack, and men-
ingitis [12]. The Ethics Committees of the Second Xiangya
Hospital of Central South University approved the study pro-
tocol (yxblcys-201501).

2.2. Clinical Data Collection. The characteristic data of
patients including gender, age, risk factors, blood culture
results, pathogens, and body temperature were collected
from the medical system. The complete blood cell counts
and differential counts of leucocytes, NLR, CRP, and procal-
citomin (PCT) levels were measured in the clinical laboratory
department of our hospital. If the patient has multiple test
results, the first one before treatment was collected in our
study.

2.3. Statistical Analysis. Statistical analysis was performed
using SPSS Statistics, version18.0 (SPSS Inc., Chicago, IL). Measured data were expressed as mean ± standard deviation
(x ± s) or the median (interquartile range). The Student t-
test was used to compare data between the groups displaying
normal distribution. Nonparametric tests are used for com-
parison between the two groups with nonnormal distribution
data. The area under the receiver operating characteristic
curves (ROCs) was used to evaluate the value of NLR in pre-
dicting the prognosis of patients with IE. p < 0.05 was consid-
ered statistically significant.

3. Results

3.1. Characteristics. Following the inclusion criteria and
exclusion criteria, we enrolled 678 patients with IE and
2520 healthy controls from the Second Xiangya Hospital
during 2015 and 2019. The clinical characteristic description
of the patients and healthy controls was shown in Table 1 and
Table S1. The age of IE patients was 43.25 ± 17.60 years,
and the age of controls was 42.28 ± 15.85 years, which had no
difference (p = 0.86). There was also no statistical difference
in sex distribution between patients and healthy controls
(p = 0.08) (Table 1). The percentage of comorbidity and
predisposing factors were 14.01% rheumatic heart disease,
followed by 12.54% congenital heart disease and 5.16% sep-
sis. The positive rate of blood culture and cardiac valve
vegetation culture was 33.92%. The pathogens of patients
were 86.70% Gram-positive bacteria, 6.87% Gram-negative
bacteria, and 6.43% fungus, respectively. Among the Gram-
positive bacterial infections, the most common bacteria is α-
hemolytic streptococcus (58.41%), followed by Staphylococcus aureus (15.35%), Staphylococcus epidermidis
(4.46%), and Coagulase negative staphylococci (4.46%). Sixteen Gram-negative bacteria were isolated from culture.
Acinetobacter Baumannii, Escherichia coli, and Brucella
were the top three Gram-negative bacteria. Sixteen strains of fungi were isolated from culture, including 8 C.
parapsilosis, 5 Candida albicans, and 2 Candida glabrata.
The detailed pathogens of patients were shown in Table 1
and Table S1. The inflammatory markers of IE patients
before anti-infective drug treatment including NLR, PCT,
and CRP were 6.29 ± 9.36, 2.34 ± 9.53 μg/L, and 53.13 ±
55.76 mg/L, respectively. NLR and NEU values of controls
were significantly lower than those in IE patients (p < 0.001).

3.2. The Predictive Effect of NLR, NEU, and LYM in Patients
with IE. The ROC curves of NLR, NEU, and LYM for total IE
patients were plotted (Figure 1). For all IE patients, the area
under the ROC curve (AUC) of NLR was 0.817 (95% confi-
dential interval (CI) = 0.794 – 0.839); the standard deviation
was 0.012, and p < 0.001. The critical value of NLR for diag-
nosis of IE was 2.68, with a sensitivity of 69%, and a specifici-
ity of 88%. AUC of NEU and LYM was 0.66 (95% CI = 0.631 – 0.689) and 0.27 (95% CI = 0.247 – 0.293), and
p values were both less than 0.001. The critical value of
NEU for diagnosis of IE was 6.425, with a sensitivity of
47.6%, and a specificity of 97.6%. The critical value of LYM
for diagnosis of IE was 5.107, with a sensitivity of 1.9%, and a specificity of 98.8% (Table 2).

3.3. The Predictive Effect of NLR and Other Evaluation Indexes in IE Patients with Different Culture Results. In the ROC curve analysis, the critical value of NLR for diagnosis of IE with positive culture was 3.04, with a sensitivity of 79.6%, and a specificity of 92.9%; for diagnosis of IE with negative culture, the critical value was 2.675, with a sensitivity of 62.1%, and a specificity of 88.1% (Table 3, Figure 2).

For Gram-positive bacteremia IE patients, the ROC was 0.913 (0.882 to 0.943; \( p < 0.001 \)), and the critical value of NLR was 3.055, with a sensitivity of 82.4%, and a specificity of 93.1%. For Gram-negative bacteremia IE, the ROC was 0.822 (0.672 to 0.973; \( p < 0.001 \)), and the critical value of NLR was 3.035, with a sensitivity of 75%, and a specificity of 92.9%. For fungus, the ROC was 0.625 (0.416 to 0.834); the standard deviation was 0.107, and \( p = 0.096 \). The critical value of NLR for the diagnosis of fungi infected IE was 3.91, with a sensitivity of 46.7%, and a specificity of 97.4% (Table 3, Figure 3).

The values of CRP in IE patients with Gram-positive and Gram-negative bacteria and fungi infected were 59.28 ± 54.79, 65.98 ± 65.88, and 78.23 ± 37.41 mg/L, respectively. The value of PCT in Gram-positive bacteria-infected IE patients was 2.34 ± 9.53 μg/L, which was higher than that in Gram-negative bacteria (1.42 ± 3.18 μg/L) and fungi (1.86 ± 2.93 μg/L), respectively (Table 4).

3.4. Comparison of Demographic and Laboratory Data between Different Outcome of IE Patients. After evaluating the clinical in-hospital outcome of IE patients, we defined 537 good-outcome and 141 bad-outcome IE patients.
was no difference about the age, comorbid conditions, and predisposing factors between the two groups. The male distribution was higher in good-outcome patients than bad-outcome group (70.2% vs. 60.99%, \( p = 0.036 \)). The proportion of culture-positive in good-outcome patients was less than that in bad-outcome patients (31.66% vs. 43.26%, \( p = 0.01 \)). The proportion of fungus-infected patients in the good-outcome group was less than that in the bad-outcome group (1.12% vs. 6.38%, \( p = 0.001 \)). And the inflammatory markers including NLR, PCT, and CRP were all different between the two groups (all \( p \) values were less than 0.001). NLR was higher in the bad-outcome group than that in the good-outcome group (3.8 ± 2.02 vs. 3.6 ± 2.61, \( p < 0.001 \) (Table 5). In the ROC curve analysis to predict the outcome of IE patients, using a cut point of 5.557, the AUC for the NLR was 0.647 (95% CI, 0.594-0.701; \( p < 0.001 \)) with a sensitivity of 39.0% and a specificity of 85.3%. Using a cut-point of 8.095, the AUC for the NEU was 0.625 (95% CI, 0.570-0.681;
Variability and atypicality in the clinical presentation of IE make the diagnosis a clinical challenge, especially for the early diagnosis [28]. Early diagnosis and effective treatment are essential to good patient outcome, which could reduce the morbidity and mortality of IE. The diagnostic strategy was currently recommended by the American Heart Association and the modified Duke criteria [27, 29]. The diagnosis of IE requires typical microorganisms grown from at least 2 separate blood cultures, which needs a relative long time [29]. Moreover, it also needs evidence of endocardial involvement, which has different symptoms due to different pathogens. Therefore, a simple blood test will help to predict IE and it is highly desirable [28].

As an inexpensive and easily accessible inflammatory marker, NLR is an independent predictor of unfavorable outcome.

\( p < 0.001 \) with a sensitivity of 52.5% and a specificity of 72.1%. (Figure 4, Table 2).

### 4. Discussion

Variability and atypicality in the clinical presentation of IE make the diagnosis a clinical challenge, especially for the early diagnosis [28]. Early diagnosis and effective treatment are essential to good patient outcome, which could reduce the morbidity and mortality of IE. The diagnostic strategy

![ROC curve](image1)

![ROC curve](image2)

![ROC curve](image3)

**Figure 3:** The ROC curves of NLR for predicting IE with different infectious pathogens. (a) Gram-positive bacteremia, (b) Gram-negative bacteremia, and (c) fungus.

**Table 4:** Infection markers in IE patients with different pathogen culture results.

| Infection markers | Negative culture \((N = 448)\) | Positive culture \((N = 230)\) | Gram-positive bacteria \((N = 202)\) | Gram-negative bacteria \((N = 16)\) | Fungus \((N = 15)\) | \( p \) value |
|-------------------|-------------------------------|-----------------------------|---------------------------------|---------------------------------|-----------------|-----------|
| PCT (μg/L)        | 2.37 ± 10.40                  | 2.30 ± 7.96                 | 2.41 ± 8.51                     | 1.42 ± 3.18                    | 1.86 ± 2.93     | 0.766     |
| CRP (mg/L)        | 49.00 ± 55.77                 | 60.85 ± 54.91               | 59.28 ± 54.79                   | 65.98 ± 65.88                  | 78.23 ± 37.41   | 0.288     |
| NLR               | 5.76 ± 8.61                   | 7.93 ± 10.14                | 7.27 ± 6.78                     | 13.44 ± 16.95                  | 11.59 ± 25.39   | 0.021     |
clinical outcomes in infectious diseases. NLR is indicative of an impaired cell-mediated immunity associated with systemic inflammation [30]. A previous study about NLR focused on its role of predicting the outcome as a simple prognostic marker [10, 12, 25]. The predictive value of the NLR is important in many tumors, infectious, and cardiovascular diseases [31–33]. In order to investigate the role of NLR in predicting the occurrence of IE, we enrolled 678 IE patients and 2520 healthy controls in our study. To the best of our knowledge, this is the first evaluation study of NLR in predicting the early diagnosis of IE. We found that NLR values of IE patients were significantly higher than NLR values of controls. The critical value of NLR for diagnosis of IE with positive culture has a higher sensitivity and specificity than the diagnosis of IE with negative culture. The predictive effect of NLR in IE patients with Gram-positive bacteria is better than IE patients with Gram-negative bacteria. While the NLR has no predictive effect in IE patients with fungus-infected. This result implies that the predictive effect of NLR in IE depends on the culture results and different pathogens of infection. We also carried out the ROC analysis, and the cut-off values for Gram-positive, Gram-negative, and fungal pathogens are very similar, thus NLR does not seem suitable to discriminate on admission patients with IE by different pathogens. Further larger-sample clinical investigation should perform to confirm it and find other inflammatory markers to discriminate patients with IE by different pathogens.

Studies found that PCT and CRP might be valuable additional diagnostic markers in patients with suspected IE [5, 9]. One study found the area under the ROC curve that used PCT to predict IE was 0.856 (95% CI 0.750 to 0.962), compared with 0.657 (95% CI 0.511 to 0.802) for CRP [28]. Especially noteworthy is that this study compared the suspected IE patients and confirmed IE patients. Because of the lack of tests of PCT and CRP in healthy control, we did not analyze their predictive role.

Up to now, several studies have investigated the relationship between admission NLR and IE [10, 12, 25, 26]. Turak et al. showed that NLR was associated with in-hospital mortality and central nervous system events in IE patients [12]. A total of 121 IE patients were evaluated, and the study found that NLR ≥ 7.1 predicted in-hospital mortality and unfavorable outcomes [12]. Bozbay et al. also investigated 171 IE

Table 5: Clinical and hematologic data compared between different clinical outcomes of IE patients.

| Parameters                          | Good outcome (N = 537)     | Bad outcome (N = 141)     | p value |
|-------------------------------------|----------------------------|---------------------------|---------|
| Age                                 | 42.56 ± 16.81              | 45.89 ± 20.26             | 0.074   |
| Sex (male)                          | 377 (70.2%)                | 86 (60.99%)               | 0.036   |
| Comorbid conditions                 |                            |                           |         |
| Coronary artery disease             | 58 (10.81%)                | 16 (11.34%)               | 0.853   |
| Nephropathy                         | 62 (11.55%)                | 22 (15.6%)                | 0.193   |
| Diabetes                            | 77 (14.34%)                | 18 (12.76%)               | 0.632   |
| Pulmonary infection                 | 9 (1.68%)                  | 3 (2.13%)                 | 0.721   |
| Cardiac insufficiency               | 103 (19.18%)               | 21 (14.89)                | 0.241   |
| Hypertension                        | 29 (5.4%)                  | 10 (7.09%)                | 0.443   |
| Brain disease                       | 7 (1.3%)                   | 2 (1.42%)                 | 1       |
| Predisposing factors                |                            |                           |         |
| Rheumatic heart disease             | 78 (14.53%)                | 17 (12.06%)               | 0.452   |
| Congenital heart disease            | 68 (12.66%)                | 17 (12.06%)               | 0.847   |
| Prosthetic valve                    | 105 (19.55%)               | 28 (19.86%)               | 0.935   |
| Degenerative valve disease          | 75 (13.97%)                | 14 (9.93%)                | 0.206   |
| Implantable cardiac devices         | 32 (5.96%)                 | 10 (7.09%)                | 0.619   |
| Pathogens                           |                            |                           |         |
| Culture positive                    | 170 (31.66%)               | 61 (43.26%)               | 0.010   |
| Culture negative                    | 367 (68.24%)               | 80 (56.74%)               | —       |
| Gram-positive bacteria              | 152 (28.31%)               | 47 (33.33%)               | 0.243   |
| Gram-negative bacteria              | 12 (2.23%)                 | 5 (3.55%)                 | 0.375   |
| Fungus                              | 6 (1.12%)                  | 9 (6.38%)                 | 0.001   |
| Inflammatory markers                |                            |                           |         |
| NEU                                 | 6.84 ± 4.60                | 9.07 ± 5.60               | <0.001  |
| LYM                                 | 2.23 ± 1.68                | 2.22 ± 1.90               | 0.961   |
| NLR                                 | 3.62 ± 2.61                | 5.80 ± 6.02               | <0.001  |
| PCT (μg/L)                          | 1.94 ± 9.67                | 3.15 ± 7.18               | <0.001  |
| CRP (mg/L)                          | 50.14 ± 50.23              | 64.24 ± 63.02             | <0.001  |
patients and found that patients in the high NLR group had a higher incidence of in-hospital mortality, while NLR cannot be a useful prognostic marker during long-term follow-up [25]. Meshaal et al. found that a higher NLR, TLC, neutrophil percentage, creatinine level, and CRP level upon admission were associated with increased in-hospital mortality and morbidity in IE patients [26]. We also evaluate the role of NLR and clinical outcome of IE patients. In our study, we defined 537 good-outcome patients and 141 bad-outcome IE patients and found NLR could predict the clinical outcome of IE to the largest extent, compared with NEU and LYM. Our relative large-sample case-control study results provide more stronger evidences that NLR is a reliable predictive biomarker of IE infection, not only in the early diagnosis but also in the outcome of IE than those already reported diseases including cerebral hemorrhage [34, 35] and ischemic stroke [36, 37].

5. Limitations
The limitations of our study were as follows: first, retrospective data have many uncontrollable confounding factors that limit data consistency. For instance, complicated diseases such as pneumonia and meningitis would influence the value of NLR; second, the true state of illness and treatment before their admission, such as the use of oral antibiotics before admission, also affects the accuracy of NLR value in our statistics; third, the small sample from single study center may also limit our research. Moreover, it would be more informative to evaluate mortality rather than poor clinical course, while for the limit sample-size, this study did not perform it. Further follow-up investigation is needed to conduct a mortality-related analysis.

6. Conclusions
In summary, our study suggests that NLR is an effective diagnostic indicator of IE. Moreover, we also found that NLR value could predict the clinical outcome of IE patients. Therefore, NLR is a useful predictive marker for IE patients. In the future, prospective studies with a larger sample-size from multicenters about the prediction ability of NLR in occurrence and clinical outcome of IE patients will be carried out to confirm our retrospective study results.

Data Availability
The data used to support the findings of this study are included within the article and within the supplementary information file.

Conflicts of Interest
The authors declare that they have no conflict of interest.

Authors’ Contributions
All authors contributed to study design and data acquisition, analysis or interpretation, and drafting of this manuscript. All the authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of data analysis.

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Supplementary Materials
Table S1: the details of pathogenic microorganisms of infective endocarditis. (Supplementary Materials)

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Mediators of Inflammation

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