

Neutrophil Count to Lymphocyte Count Ratio is a Potential Diagnostic Index for Bacteremia in AdultYong Xia¹, Xu-Guang Guo¹, Tian-Xing Ji², Qiong Chen¹¹Department of Clinical Laboratory Medicine, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, 510150, People's Republic of China²Department of Clinical Laboratory Medicine, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, 510260, People's Republic of Chinagysyxy@gmail.com

Abstract: The neutrophil count to lymphocyte count ratio (NLCR) provides a fast indication of bacteremia. The goal of our research was to inspect the prognostic value of the neutrophil count to lymphocyte count ratio in bacteremia and determine an optimal ratio for the diagnosis of bacteremia. We studied 22 patients with bacteremia and 118 without bacteremia retrospectively. NLCR calculated from the white blood cell differential count. We retrospectively evaluated the ability of the C-reactive protein (CRP) level, procalcitonin (PCT) level, white blood cell (WBC) count, neutrophil count, lymphocyte count and neutrophil count to lymphocyte count ratio to predict bacteremia in adult patients with suspected bacteremia. These data were compared between patients with bacteremia and patients without bacteremia. One hundred and forty patients managed were included in this study, 22 patients with bacteremia and 118 patients without bacteremia. The data of NLCR in bacteremia group was higher than in the group without bacteremia (10.58±1.99 vs. 5.61±0.61). Increased NLCR was associated with a highly potential diagnosis of bacteremia, as shown by the AUC 95% confidence interval (CI) of 0.67(0.55-0.81). The optimal cut-off of NLCR from ROC curves was 11.34, giving sensitivities of 40.91 %, specificities of 93.22 %, negative likelihood ratio of 0.63, positive likelihood ratio of 6.03. Elevation of the NLCR is significantly associated with bacteremia. Neutrophil count to lymphocyte count ratio is a potential prognostic index for the diagnosis of bacteremia.

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1. Introduction

There is evidence that the neutrophil count to lymphocyte count ratio (NLCR) has prognostic value in a variety of tumor types such as colorectal cancer (Walsh et al. 2005), stomach cancer (Gwak et al. 2007), hepatocellular carcinoma (Halazun et al. 2009), lung cancer (Sarraf et al. 2009), pancreatic ductal adenocarcinoma (Bhatti et al. 2010), gastric cancer (Ubukata et al. 2010), esophageal cancer (Sharaiha et al. 2011), cervical carcinoma (Lee et al. 2012), breast cancer (Azab et al. 2013) and upper urinary tract urothelial carcinoma, et al. It is reported that NLR could be used in the diagnosis of appendicitis (Bialas et al. 2006), acute pancreatitis (Azab et al. 2011), ulcerative colitis (Celikbilek et al. 2013), and bacterial community-acquired pneumonia (Yoon et al. 2013). A recent report from De Jager et al. (de Jager et al. 2010) found that lymphocytopenia and neutrophil-lymphocyte count ratio prognosticate bacteremia better than ordinary infection markers in an emergency care unit. However, the clinical significance of NLR compared to procalcitonin in the diagnosis of bacteremia and NLR in the diagnosis of hospital acquired bacteremia remains unknown.

In this research, we assessed the ability of the neutrophil count to lymphocyte count ratio,

compared with conventional parameters such as C-reactive protein (CRP) level, the white blood cell (WBC) count, neutrophil cell count, lymphocyte count and procalcitonin (PCT) level, to predict bacteremia in patients with suspected bacteremia. We compared these indexes between patients with bacteremia and patients without bacteremia.

2. Material and Methods**2.1 Subjects**

Patients admitted to the third affiliated hospital of Guangzhou medical university in Guangzhou, a 1000-bed teaching hospital in Guangdong province, China, with a first episode of hospital-related bacteremia between May to July in 2009. Bacteremia was interpreted as the positive blood culture.

The exclusion criteria of this study were as follows: 1) Patients aged smaller than eighteen years old; 2) patients with hematological disease; 3) patients with HIV infection; 4) patients with a second bacteremia in a single admission; 5) patients receiving glucocorticoids or chemotherapy; 6) Blood cultures considered contaminated. Coagulase-negative Staphylococcus considered contaminated (Terradas et al. 2012); 6) patients detected with C-

reactive protein level in serum, procalcitonin level in serum, WBC count, neutrophil cell count and lymphocyte count not at the same time.

All data were drawn from clinical practice. Patients with bacteremia (positive blood cultures) were compared with control patients with suspected hospital acquired bacteremia but had a negative blood cultures.

2.2 Infection markers

White blood cell count (WBC), neutrophil counts and lymphocyte counts were tested on a Sysmex XE-2100 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). The neutrophil count to lymphocyte count ratio was calculated as the neutrophil counts to lymphocyte counts. CRP levels were detected with an enzyme-linked immunoassay Equipment Reader i-CHROMA (Boditech medicine incorporation, SantaClara, Chuncheon, Korea). Procalcitonin levels were tested with a fully automated immunochemistry testing system (cobas E 601 module) (F. Hoffmann-La Roche Ltd, New Jersey, USA).

2.3 Ethics

The study was approved by the Ethics Committee of the third affiliated hospital of Guangzhou medical university and all aspects of the study comply with the Declaration of Helsinki. Ethics Committee of the third affiliated hospital of Guangzhou medical university specifically approved that not informed consent was required because data were going to be analysed anonymously. Bacterial strains were isolated from human clinical samples which were collected following the third affiliated Hospital of Guangzhou medical university approved procedures.

2.4 Statistical analysis

Data were reported as mean \pm standard deviation (SD). The difference between mean or median values was tested by using the Mann-Whitney or Student's t-test test, while the differences between rates were tested by χ^2 - or Fisher exact tests. The predictive values of neutrophil count to lymphocyte count ratio were estimated by receiver operating characteristic curve analysis, reporting the area under the curve. Area under the curves were compared according to the method by DeLong et al (DeLong et al. 1988).

The optimal cut-off for each test was determined when the Youden index achieved the highest value. On the basis of optimal threshold given by receiver operating characteristic curve analysis, all the analyses were performed using SigmaPlot Version 12.2 (Systat Software, San Jose, CA) and SPSS17.0 (SPSS Inc., Chicago, IL, USA). The statistical level was set at $p < 0.01$ as a significance.

3. Results

3.1 Subjects inclusion, exclusion criteria and the study population.

During the study period, 524 patients were screened: 242 patients who detected with C-reactive protein level, procalcitonin level, white blood cell count, neutrophil cell count and lymphocyte count not at the same time were excluded; 137 patients with ages under 18 years old were excluded; 5 with hematological disease were excluded. Finally, there were 22 patients with a bacteremia and 118 patients without bacteremia were included (Table 1).

Table 1. Clinical Characteristic of the Subjects in the Bacteremia Group and Control Group

	Bacteremia group (n = 22)	Control group (n = 118)	P value
Age	48 \pm 5	32 \pm 1	NA
Female	18 (81.8)	114 (96.6)	NA
Previous antibiotic usage	3 (13.6)	7 (14.4)	0.198
COPD	5 (22.7)	29 (24.6)	0.853
Diabetes	5 (22.7)	27 (22.9)	0.987
Renal disease	2 (9.1)	12 (10.2)	0.877
Smoking	2 (9.1)	16 (13.6)	0.565
Alcohol abuse	3 (13.5)	19 (16.1)	0.771

Data presented as number (percentage) of patients or mean (\pm SD).NA: not applicable, COPD:Chronic obstructive pulmonary disease

3.2 Microorganism isolates analyzed

As shown in Table 2, microorganisms (n = 22) isolated from the 22 patients in bacteremia group included 13 gram-negative isolates and 9 gram-positive isolates. The highest isolates of gram-negative isolates were Escherichia coli and gram-positive isolates were Staphylococcus aureus.

Table 2. Microorganisms (n = 22) isolated from the 22 Patients in the Study Cohort

Gram-negative isolates	n	Gram-positive isolates	n
Escherichia coli	11	Staphylococcus aureus	3
Acinetobacter baumannii	1	Enterococcus faecalis	2
Actinobacillus	1	Viridans streptococci	2
		Streptococcus agalactiae	2
Total	13		9

3.3 Clinical characteristics of the participants

As shown in Table 3, significant increases in C-reactive protein level, procalcitonin level, white blood cell count, neutrophil cell count, lymphocyte count and neutrophil cell count to lymphocyte count ratio were observed in patients who diagnosed of bacteremia ($p < 0.05$). Consistent with previous studies, we found that the patients with bacteremia had a higher neutrophil count to lymphocyte count ratio ($p < 0.05$ for all) (de Jager et al. 2010; Terradas et al. 2012).

3.4 Predictive efficiency of infection makers in diagnosis of bacteremia

Infection markers for the bacteremia group and the control group (non-bacteremia group) are

shown in Table 3. The C-reactive protein level in serum of the bacteremia group was significantly higher compared with the non-bacteremia group (mean \pm standard deviation 97.51 ± 18.51 mg/l vs. 46.43 ± 5.93 mg/l; $P = 0.016$). A C-reactive protein level in serum of 36.10 mg/l or more has been indicated bacteremia based on the Youden index calculated from sensitivity and specificity. Using 36.10 mg/l as the optimum cut-off point, the sensitivity and specificity for the diagnosis of bacteremia was 72.73% and 67.80%, and the positive predictive value and negative predictive value of C-reactive protein in the diagnosis of bacteremia was 29.63% and 93.02%, respectively.

Table 3. Infection Markers in the Group with Patients of Positive Blood Cultures and Group with Patients of Negative Blood Cultures

Infection markers	Bacteremia group (n=22)	Control group (n=118)
C-reactive protein level (mg/l)	97.51 ± 18.51	46.43 ± 5.93
Procalcitonin (ng/ml)	7.996 ± 2.968	0.078 ± 0.996
White blood cell count (/l)	$14.12 \pm 2.31 \times 10^9$	$10.06 \pm 0.34 \times 10^9$
Neutrophil count (/l) Lymphocyte count (/l)	$11.84 \pm 2.14 \times 10^9$ $0.8 \pm 0.5 \times 10^9$	$7.62 \pm 0.34 \times 10^9$ $1.2 \pm 0.7 \times 10^9$
Lymphocyte count (/l)	$1.47 \pm 0.17 \times 10^9$	$1.74 \pm 0.06 \times 10^9$
Neutrophil-lymphocyte count ratio	10.58 ± 1.99	5.61 ± 0.47
Data displayed as mean \pm SD SD standard deviation.		

The procalcitonin level in serum of the bacteremia group was significantly higher than the non-bacteremia group (mean \pm standard deviation 7.996 ± 2.968 mg/l vs. 0.078 ± 0.966 mg/l; $P < 0.0001$). A procalcitonin level in serum of 0.232 mg/l or more has been indicated bacteremia based on the Yoden index. Using 0.232 mg/l as the optimal cut-off point, the sensitivity and specificity in diagnosing bacteremia was 68.18% and 99.15%, and the positive predictive value and negative predictive value of procalcitonin in the diagnosis of bacteremia was 93.75% and 94.35%, respectively.

The white blood cell count in bacteremia group differ significantly from the white blood cell count in the non-bacteremia group ($14.12 \pm 2.31 \times 10^9/l$

vs. $10.06 \pm 0.34 \times 10^9/l$; $P = 0.0016$). In the bacteremia group, 1/22 patients had a white blood cell count above $17.88 \times 10^9/l$ (sensitivity 5.19%). In the non-bacteremia group, there were 116/118 patients had a white blood cell count above $17.88 \times 10^9/l$ (specificity 98.31%). Using criteria as the optimum cut-off point, the positive predictive value of white blood cell count in the diagnosis of bacteremia was 71.42% against a negative predictive value of 87.22%.

The difference of neutrophil cell count between the bacteremia group and the non-bacteremia group was significant ($11.84 \pm 2.14 \times 10^9/l$ vs. $7.62 \pm 0.34 \times 10^9/l$; $P = 0.006$). In the study cohort, 4/22 patients had a neutrophil count above a cut-off point of $15.24 \times 10^9/l$ (sensitivity 19.05%) against

115/118 patients in the control group (specificity 97.46%). Using this cut-off point, the positive predictive value of neutrophil count in the diagnosis of bacteremia was 62.50% against a negative predictive value of 87.12%.

The lymphocyte count in the bacteremia group was significantly lower than the non-bacteremia group ($0.8 \pm 0.5 \times 10^9/l$ vs. $1.2 \pm 0.7 \times 10^9/l$; $P < 0.0001$). In the bacteremia group, 5/22 patients had a lymphocyte count above $2.42 \times 10^9/l$ (sensitivity 23.81%) versus 104/118 patients in the non-bacteremia group (specificity 88.14%). According to Youden index of lymphocyte count in the diagnosis of bacteremia, we use an optimal cut-off point below $1.0 \times 10^9/l$, the positive predictive value of lymphocyte count in the diagnosis of bacteremia was 63.6% against a negative predictive value of 68.8%.

The difference of neutrophil count to lymphocyte count ratio between the bacteremia group and the non-bacteremia group was significant (10.58 ± 1.99 vs. 5.61 ± 0.47 ; $P = 0.0005$). According to Youden index calculated from sensitivity and specificity, we used an optimal cut-off point of 11.34 for the neutrophil count to lymphocyte count ratio in the diagnosis of bacteremia. In the study cohort, 9/22 patients had a neutrophil count to lymphocyte count

ratio higher than 11.34 (sensitivity 40.91%) versus 110/118 patients in the non-bacteremia group (specificity 93.22%). And the positive predictive value of neutrophil count to lymphocyte count ratio in diagnosing bacteremia was 50.00% versus a negative predictive value of 89.34%. The sensitivity, specificity, positive predictive value and negative predictive value for the before-mentioned infection index in diagnosing bacteremia are listed in Table 4.

Receiver operating characteristic curves of the six infection markers for differentiating bacteremia from non-bacteremia are presented in Figure 1. The area under the curve for the C-reactive protein level in serum was 0.65 (confidence interval = 0.51 to 0.80). The area under the curve for the white blood cell count and the neutrophil count was 0.56 (confidence interval = 0.42 to 0.70) and 0.60 (confidence interval = 0.46 to 0.74), respectively. The lymphocyte count and the neutrophil count to lymphocyte count ratio had an area under the curve of 0.42 (confidence interval = 0.27 to 0.57) and 0.68 (confidence interval = 0.55 to 0.81), respectively. The area under the curve for the procalcitonin level in serum for the diagnosis of bacteremia was 0.89 (confidence interval = 0.82 to 0.97).

Table 4. Receiver Operating Characteristics Curves of Infection Markers for Diagnosing Bacteremia

Infection markers	AUC(95%CI)	Optimal threshold	Sensitivity(95%CI)	Specificity(95%CI)
White blood cell	0.56(0.42-0.70)	17.88	5.19(5.19-19.05)	98.31(94.01-99.79)
Neutrophil count	0.60(0.46-0.74)	15.24	19.05(5.19-40.28)	97.46(92.75-99.47)
Lymphocyte count	0.42(0.27-0.57)	2.42	23.81(7.82-45.37)	88.14(80.90-93.36)
NLCR	0.68(0.55-0.81)	11.34	40.91(20.71-63.65)	93.22(87.08-97.03)
C-reactive protein	0.65(0.51-0.80)	36.10	72.73(49.78-89.27)	67.80(58.57-76.10)
Procalcitonin	0.89(0.82-0.97)	0.232	68.18(45.13-86.14)	99.15(99.15-99.98)

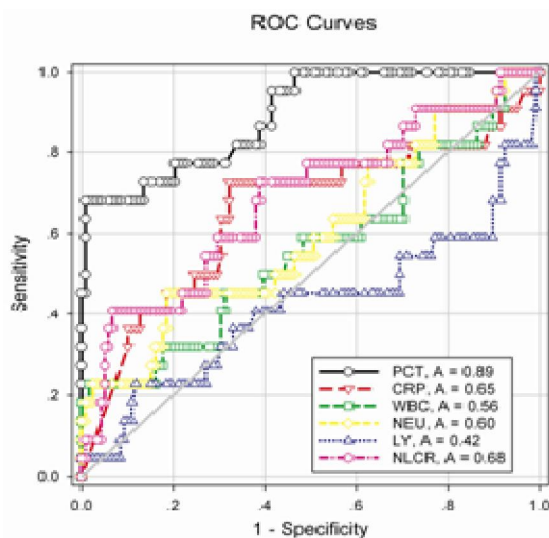


Fig1. AUC, Sensitivity and Specificity for Infection Markers in Diagnosing of Bacteremia

The area under the curve of receiver operating characteristic curve differed significantly ($P < 0.1$) from those for the C-reactive protein level in serum ($P = 0.0040$), white blood cell count ($P < 0.0001$), neutrophil cell count ($P = 0.0003$), lymphocyte count ($P < 0.0001$) and neutrophil count to lymphocyte count ratio ($P = 0.0063$). The area under the curve of the C-reactive protein receiver operating characteristic curve did not differ from those for white blood cell count ($P = 0.3661$), neutrophil cell count ($P = 0.5917$), lymphocyte count ($P = 0.2923$) and neutrophil count to lymphocyte count ratio ($P = 0.7775$). The area under the curve of the white blood cell receiver operating characteristic curve did not differ from those for neutrophil count ($P = 0.7008$), lymphocyte count ($P = 0.1902$) and neutrophil count to lymphocyte count ratio ($P = 0.2194$). The area under the curve of the neutrophil count receiver operating characteristic curve differed from those for lymphocyte count ($P = 0.0888$) but did not differ from

neutrophil count to lymphocyte count ratio ($P = 0.3950$). The area under the curve of the lymphocyte count in whole blood receiver operating characteristic curve differed from that for neutrophil count to lymphocyte count ratio ($P = 0.0110$).

4. Discussions

The most determinate way to confirm bacterial infections is the positive blood culture. However, several factors including practical antibiotic usage can influence this reference standard, furthermore, it is time consuming. Currently the C-reactive protein level in serum, the white blood cell count in the whole blood and the erythrocyte sedimentation rate have relatively low discriminatory ability in distinguishing patients with bacteremia and non-bacteremia. Increasing the diagnostic yield of bacteremia possibly depends on the combination of good markers or the introduction of more new infection indexes.

Recently, a systematic review and meta-analysis proved that procalcitonin is an advantageous biomarker for early diagnosis of bacteremia in critically ill patients with a mean sensitivity of 0.77 (95% CI 0.72-0.81) and specificity of 0.79 (95% CI 0.74-0.84). The area under the receiver operating characteristic curve was 0.85 (Wacker et al. 2013). According to our research, using 0.232 mg/l as the cut-off point, the sensitivity and specificity of procalcitonin in diagnosing bacteremia was 68.18% and 99.15%, and the area under the receiver operating characteristic curve is 0.89 (0.82-0.97). This observation coincides with the results of the Meta analysis.

Lymphocyte count could not be a specific infection index of bacteremia. This speculation is clinically appropriate because if the specificity of lymphocyte count were demonstrated, this infection index could be used to guide the choice of clinical examinations. It is reported that lymphocyte is associated with chronic infection of hepatitis B virus (Xu et al. 2013).

In a prospective study, Jager et al. evaluated the clinical capacity of lymphocyte count and neutrophil count to lymphocyte count ratio in the diagnosis of bacteremia. They found that the difference of C-reactive protein level in serum between the bacteremia group and the non-bacteremia group was different significantly (mean \pm standard deviation 176 ± 138 mg/l vs. 116 ± 103 mg/l; $P = 0.042$) (de Jager et al. 2010). Our study indicated that the C-reactive protein level in the bacteremia group was also significantly higher versus to the non-bacteremia group (mean \pm standard deviation 97.51 ± 18.51 mg/l vs. 46.43 ± 5.93 mg/l; $P = 0.016$).

Total leukocyte count and neutrophil cell count has been widely used as an infection index historically. In 1995, Goodman et al. highlighted that neutrophil cell count to lymphocyte count ratio could be used in the diagnosis of appendicitis (Goodman et al. 1995). Later, Walsh et al. reported neutrophil cell count to lymphocyte count ratio as a prognostic factor in the patients with colorectal cancer. Furthermore, some study indicated that predictive ability of elevated neutrophil cell count to lymphocyte count ratio on cardiac mortality in patients with stable coronary artery disease (Walsh et al. 2005). A recent study by Terradas et al. indicated that neutrophil cell count to lymphocyte count ratio as a prognostic marker in patients who diagnosed with bacteremia (Terradas et al. 2012). They found that a neutrophil cell count to lymphocyte count ratio of below 7 was indicative of a good outcome. Consistent with their research results, this study suggested that increased neutrophil count to lymphocyte count ratio was associated with a highly potential diagnosis of bacteremia. The optimal cut-off of neutrophil count to lymphocyte count ratio from receiver operating characteristic curves of the diagnosis of bacteremia was 11.34, giving sensitivities of 40.91 %, specificities of 93.22 %, negative likelihood ratio of 0.63, positive likelihood ratio of 6.03.

Different microorganisms isolated is shown in Table 2, the highest isolates of gram-negative isolates is *Escherichia coli*. It is in accordance with Jager's study (de Jager et al. 2010) but the highest isolates of gram-positive isolates of our research are *Staphylococcus aureus*.

One limitation of our study is that the data are retrospectively collected from clinical practice. Another limitation is the number of patients was small. Although our study was retrospective, neutrophil cell count to lymphocyte count ratio was compared with other infection markers, such as C-reactive protein or procalcitonin.

Absolute procalcitonin can be used in the diagnosis of infectious diseases for example bacteremia. Moreover, the ratio of neutrophil cell count and lymphocyte counts has great ability in the diagnosis of bacteremia. This infection marker is simple to integrate in daily practice and without extra costs. Furthermore, it is easily obtained and calculated quickly in clinical. In conclusion, the present study suggests that neutrophil cell count to lymphocyte count ratio is an interesting prognostic parameter for the diagnosis of bacteremia. Due to the small sample size and the retrospective data collection, further research will be needed to confirm the prognostic ability of neutrophil cell count to lymphocyte count ratio in the diagnosis of bacteremia.

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