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Original Article

Predictive value of peripheral blood inflammatory indexes for blood stream infection in patients with urinary tract infection

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Abstract: Purpose: To investigate the predictive value of peripheral blood inflammatory indexes for blood stream infection (BSI) in patients with urinary tract infection. Materials and methods: Patients who were suspicious of blood stream infection and received blood culture and routine blood test simultaneously between January 2011 and June 2016 in our department were analyzed retrospectively. A total of 51 patients with positive blood culture were assigned to Group BSI. And the other 238 patients with negative blood culture were assigned to Group control. Peripheral blood inflammatory indexes including white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MON), percentage of neutrophil (NEU%), percentage of lymphocyte (LYM%), percentage of monocyte (MON%), neutrophil-to-lymphocyte ratio (NLR), and neutrophil-to-monocyte ratio (NMR) were compared between groups. Then predictive value of indexes that had statistical difference and integrated index of NLR and NMR were evaluated through Receiver Operating Characteristic (ROC) curve. Multivariate Logistic regression was done to identify indexes' contribution to BSI. Results: NEU%, NLR and NMR were significantly higher in Group BSI ($P<0.05$). However, LYM%, MON%, LYM and MON were significantly higher in Group control ($P<0.05$). No statistical difference could be seen in WBC and NEU between two groups ($P>0.05$). AUC of LYM, MON, NEU%, LYM%, MON%, NLR and NMR were 0.632, 0.700, 0.670, 0.633, 0.656, 0.630 and 0.703 respectively. Multivariate analysis showed NLR and NMR were independently related to BSI (OR = 2.463, 95% CI: 1.225~4.951, P = 0.011) (OR = 3.205, 95% CI: 1.617~6.351, P = 0.001). Conclusion: For patients with urinary tract infection who were suspicious of BSI, peripheral blood indexes should be supervised. MON and NMR were independent prognostic factors and had higher predictive value for BSI, combining NLR and NLR could improve accuracy.

Keywords: Blood stream infection, neutrophil, lymphocyte, monocyte, peripheral blood

Introduction

Blood stream infection (BSI) is defined as invasion of pathogens to blood and subsequent growth in blood. BSI could induce release of cytokines and then activate systemic inflammatory response, which could develop to severe sepsis and septic shock, even death with no timely and accurate treatment. On account of development of antibiotics, mortality results from BSI declines recently [1]. But ignorance, delayed diagnosis and inappropriate treatment of BSI are still common [2]. Positive blood culture is gold standard to diagnose BSI, but this test is time-consuming. Then quick and accurate tests are essential to the timely treatment of BSI. Recent studies showed some new tests and biomarkers such as DNA test of pathogens, procalcitonin and C-reactive protein could predict BSI earlier [3]. But the predictive value varied in different studies, and some hospitals are unable to conduct these tests due to high cost.

Routine blood test is the most common used test in clinical work due to its advantage of quickness, convenience and lower cost. Many of the recent studies have indicated that the neutrophil-to-lymphocyte ratio (NLR) is a significant inflammatory marker in various diseases. More and more evidence have showed correlation between NLR and poor prognosis, espe-

Table 1. The demographic features and clinical parameters of the subjects

	Group BSI	Group control	x^2/Z	*P* value
	n = 51	n = 238		
Gender			x^2 = 0.624	0.429
Male	32	135		
Female	19	103		
Age	58±16	59 (50-69)	Z = -0.219	0.827
History of lithotripsy			x^2 = 0.822	0.365
Yes	10	61		
No	41	177		
Malignancy			x^2 = 0.114	0.736
Yes	18	90		
No	33	148		
Use of glucocorticoid or immunosuppressant			x^2 = 2.697	0.101
Yes	5	8		
No	46	230		
Diabetes			x^2 = 1.474	0.225
Yes	12	39		
No	39	199		
Fever >38°C			x^2 = 1.783	0.182
Yes	42	212		
No	9	26		

cially in cardiovascular diseases and cancer [4]. We aimed to evaluate the predictive value of peripheral blood inflammatory indexes for BSI in patients with urinary tract infection.

Materials and methods

We retrospectively scanned files of patients who were suspicious of blood stream infection and received blood culture and routine blood test simultaneously between January 2011 and June 2016 in our department.

A total of 51 patients with positive blood culture (contaminated samples were excluded) were assigned as the study group (Group BSI). The other 238 patients with negative blood culture in the same period were considered as Group control.

If common skin contaminant (ie, diphtheroids [Corynebacterium spp], Bacillus [not B anthracis] spp, Propionibacterium spp, coagulase-negative staphylococci [including S epidermidis], viridans group streptococci, Aerococcus spp, Micrococcus spp) was cultured from 2 or more blood cultures drawn on separate occasions, this kind of bacteria could be recognized as pathogen resulted in blood stream infection, otherwise this sample was classified as contaminated.

Blood samples used for blood culture and routine test were collected simultaneously. Peripheral blood indexes and other prognostic factors for BSI such as history of lithotripsy, malignancy, use of glucocorticoid or immunosuppressant, diabetes, fever >38°C were identified. Peripheral blood indexes included white cell count (WBC), percentage of lymphocyte (LYM%), percentage of monocyte (MON%), percentage of neutrophil (NEU%), lymphocyte count (LYM), monocyte count (MON), NLR and neutrophil-to-monocyte ratio (NMR) (Supplementary Table).

Statistical analyses were performed with SPSS 19.0 (SPSS, Version 20.0; Chicago, IL, USA) statistics software. Appropriateness of the variables to a normal distribution was analysed through the Kolmogorov-Smirnov test. Chi-square, and Mann-Whitney U tests were used to identify differences between the two groups.

Receiver Operating Characteristic (ROC) analysis was performed to identify cut-off value and Area Under the Curve (AUC) was calculated to evaluate predictive value of investigated indexes. Sensitivity and specificity were also determined by ROC analysis.

According to cut-off value, peripheral blood inflammatory indexes of each patient were con-

Table 2. Univariate analysis of peripheral blood indexes between two groups

Peripheral blood inflammatory index	Group BSI Median (Q25, Q75) (n = 51)	Group control Median (Q25, Q75) (n = 238)	Z	*P* value
WBC	9.59 (6.26, 13.63)	9.21 (6.9, 12.34)	-0.086	0.932
LYM%	6.9 (4, 12.1)	9.9 (6.07, 14.33)	-2.965	0.003[a]
MON%	3.17 (0.7, 5.4)	5.64 (2.98, 8.1)	-4.48	<0.001[a]
NEU%	86.4 (83.8, 92.8)	83.57 (77.63, 88.43)	-3.811	<0.001[a]
LYM	0.67 (0.39, 0.98)	0.87 (0.54, 1.21)	-2.988	0.003[a]
MON	0.24 (0.05, 0.56)	0.5 (0.28, 0.75)	-3.495	<0.001[a]
NEU	8.36 (4.9, 12.2)	7.48 (5.45, 10.41)	-0.715	0.474
NLR	13.29 (6.93, 21.02)	8.45 (5.48, 14.84)	-2.921	0.003[a]
NMR	28.94 (14.67, 119.75)	14.6 (9.98, 28.99)	-4.551	<0.001[a]

[a]P<0.05, statistically significant.

Table 3. Pathogen distribution and proportion

Pathogen	Number of strains	Proportion
Gram-negative bacteria		
Escherichia coli	30	57.69%
Klebsiella pneumonia	4	7.69%
Pseudomonas aeruginosa	3	5.77%
Proteus mirabilis	2	3.85%
Morganella morganii	1	1.92%
Total	40	76.92%
Gram-positive bacteria		
Staphylococcus epidermidis	3	5.77%
Staphylococcus aureus	1	1.92%
Staphylococcus warneri	1	1.92%
Enterococcus faecium	1	1.92%
Total	6	11.54%
Fungi		
Candida albicans	3	5.77%
Candida tropicalis	2	3.85%
Candida parapsilosis	1	1.92%
Total	6	11.54%

verted into binary variable. Logistic regression analysis was performed to identify their contribution to BSI.

Statistically, P<0.05 was deemed as significant.

Results

There were no statistical differences detected for basic information between two groups

A total of 51 patients with positive blood culture (Group BSI) and 238 patients with negative blood culture (Group control) were included in the study. No statistical differences could be detected in gender, age, history of lithotripsy, malignancy, use of glucocorticoid or immunosuppressant, diabetes and fever >38°C between two groups (**Table 1**).

All peripheral blood inflammatory indexes except WBC and NEU had significant differences in the BSI and Group control

NEU%, NLR and NMR were much higher in Group BSI, as LYM%, MON%, LYM and MON were much higher in Group control, all of the differences were statistically significant (P<0.05). There were no statistical differences of WBC, NEU detected between two groups (P>0.05) (**Table 2**).

Pathogen distribution of BSI patients

52 strains of bacteria and fungi were identified in 51 patients (one patient was double infection of klebsiella pneumonia and enterococcus faecium), 40 (76.92%) were gram-negative bacteria, 6 (11.54%) were gram-positive bacteria, and 6 (11.54%) were fungi (**Table 3**).

MON% and NMR had higher predictive value for BSI

Univariate analysis indicated that LYM%, MON%, NEU%, LYM, MON, NLR, and NMR were statistically different between two groups. So ROC analysis was done to evaluate the predictive value of these seven indexes. The results showed that AUCs of these indexes were 0.632, 0.700, 0.670, 0.633, 0.656, 0.630, and 0.703 respectively (**Figures 1** and **2**). Sensitivity and

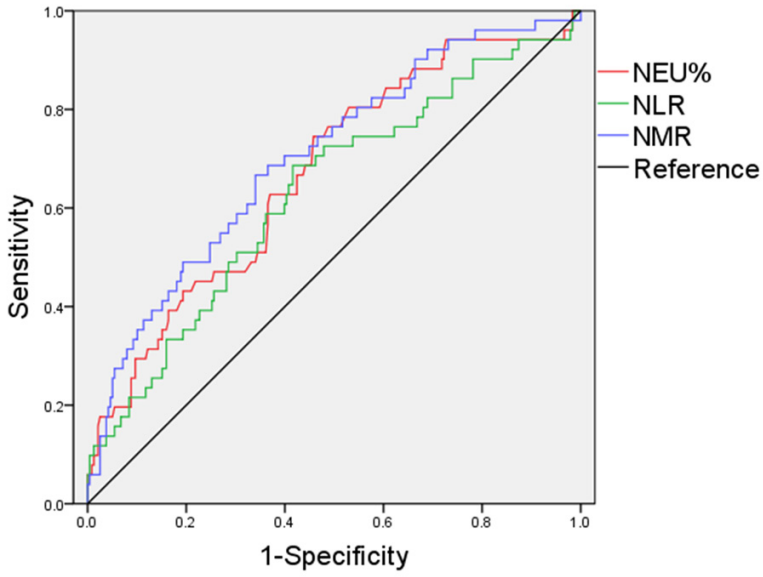

Figure 1. ROC curve of NEU%, NLR, and NMR.

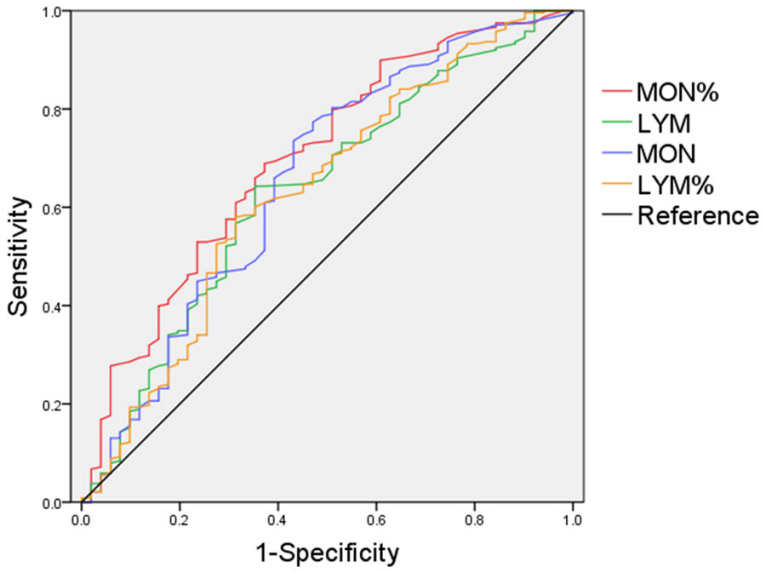

Figure 2. ROC curve of LYM%, MON%, LYM, and MON.

specificity of each index were 58.00%, 68.60%; 68.90%, 62.70%; 74.50%, 54.20%; 64.30%, 64.70%; 73.50%, 56.90%; 68.60%, 58.40%; 66.70%, 66.00%; respectively (**Table 4**).

Integration of NLR and NMR could improve predictive accuracy

We integrated NLR and NMR by Logistic Regression, and evaluated its predictive value. AUC of ROC was 0.714, cut-off value was estimated as 0.129 according to Youden index. With this value, sensitivity was 88.20% and specificity was 46.20% (**Figure 3**). Parallel and series tests were conducted with cut-off value of NLR and NMR, sensitivity and specificity were 90.20% and 45.40%; 45.10% and 79.00% (**Table 5**).

NLR and NMR were independently related to BSI

Peripheral blood inflammatory indexes were converted to binary variables according to cut-off value. Then multivariate logistic regression analysis was done to identify their contribution to BSI. History of lithotripsy, malignancy, use of glucocorticoids or immunosuppressant, diabetes, fever >38°C were also investigated by logistic regression. The results showed that NLR and NMR were independently related to BSI (OR = 2.463, 95% CI: 1.225~4.951, P = 0.011) (OR = 3.205, 95% CI: 1.617~6.351, P = 0.001) (**Table 6**).

Discussion

With the development of antibiotics, treatment of BSI is more and more effective. But due to abuse of antibiotics, use of immunosuppressant, glucocorticoids, and chemotherapy drug, morbidity of BSI is rising. Rodriguez-Creixems M ect. reported morbidity of BSI was 1.6% in 1986, and increased to 3.1% in 2006 [5]. Gold standard to diagnose BSI is still blood culture, but the results will be waited for 5 to 7 days. Patient's state would change a lot during this period. Thus in most situations doctors would decide the use of antibiotics empirically, and then adjusted therapy referring to result of blood culture. But sometimes antibiotics empirically used could not cover the pathogens, or superinfection would occur due to dysbacteriosis resulted from

Table 4. Predictive values of LYM%, MON%, NEU%, LYM, MON, NLR, and NMR

Peripheral blood inflammatory index	Cut-off value	Sensitivity	Specificity	Youden index	AUC (95% CI)
LYM%	8.85	58.00%	68.60%	0.266	0.632 (0.543, 0.721)
MON%	3.85	68.90%	62.70%	0.316	0.700 (0.619, 0.781)
NEU%	83.95	74.50%	54.20%	0.287	0.670 (0.588, 0.752)
LYM	0.715	64.30%	64.70%	0.29	0.633 (0.547, 0.719)
MON	0.295	73.50%	56.90%	0.304	0.656 (0.566, 0.746)
NLR	9.81	68.60%	58.40%	0.27	0.630 (0.543, 0.717)
NMR	20.38	66.70%	66.00%	0.327	0.703 (0.624, 0.783)

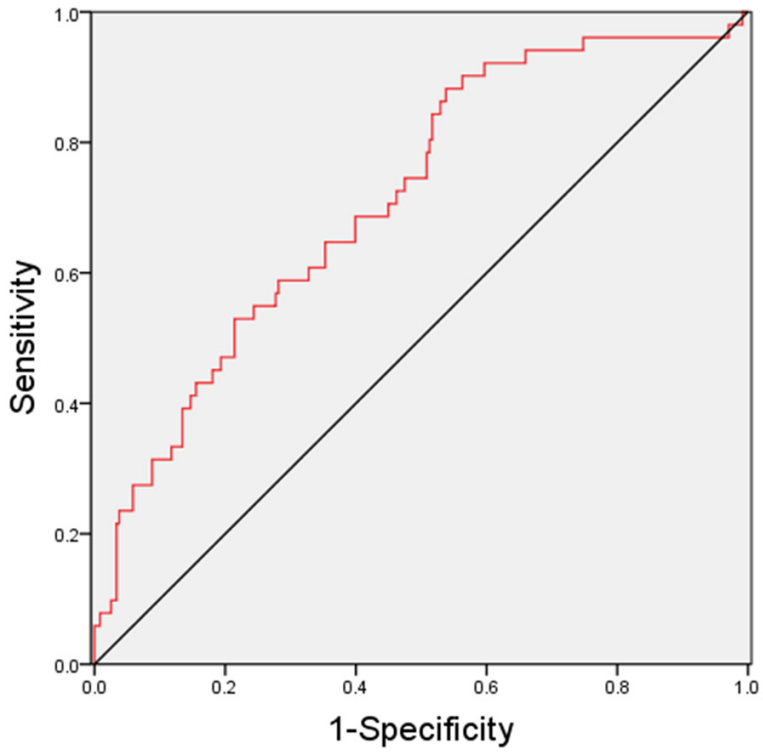

Figure 3. ROC curve of integrated NLR and NMR. Logistic regression model: Logit (P) = -2.237+0.028*NLR+0.005*NMR.

Table 5. Sensitivity and specificity of 3 methods to integrated NLR and NMR

Method	Sensitivity	Specificity	Youden Index
Integrated with Logistic regression	88.20%	46.20%	0.344
Parallel test	90.20%	45.40%	0.356
Series test	45.10%	79%	0.241

usage of multiple antibiotics. Some other tests or biomarkers were investigated to predict BSI early and accurately, most of the tests and biomarkers are expensive and require special equipment.

Although sensitivity and specificity of routine blood test are not very high, but due to its convenience, quickness, and lower cost, it is still the most commonly used test to diagnose BSI. For a long time, physicians have taken WBC and NEU as the most important indexes for the prediction and evaluation of the treatment of BSI, but been ignorant of other peripheral blood inflammatory indexes, especially the ratio of different white blood cells.

Patients of BSI were at the state of immunosuppression, large amount of lymphocytes were induced to apoptosis, neutrophil count increased simultaneously, so NLR could be the reflection of systemic inflammation [6]. The prognostic value of NLR in cardiovascular diseases and cancer has been investigated [7, 8]. And its predictive value in BSI has been investigated recently [9]. Jilma ect. [10] investigated alteration of different kinds of white blood cells after inflammation, found that neutrophil count increased by 300%, lymphocyte count decreased by 85% and monocyte count decreased by 96% after 4 to 6 hours of inflammation. So we took NMR into investigation.

Univariate analysis showed that the predictive value of commonly used indexes such as WBC

Table 6. Multivariate Logistic regression combined with ROC curve

	B	S.E.	Wals	df	Sig.	Exp (B)	EXP (B) 95% C.I.	
							Lower	Upper
History of lithotripsy	-.705	.443	2.533	1	.112	.494	.207	1.177
Malignancy	-.454	.370	1.507	1	.220	.635	.307	1.311
Use of glucocorticoid or immunosuppressant	.883	.654	1.826	1	.177	2.419	.672	8.707
Diabetes	.260	.407	.408	1	.523	1.296	.584	2.877
Fever >38°C	-.364	.453	.646	1	.421	.695	.286	1.688
NLR	.901	.356	6.401	1	.011[a]	2.463	1.225	4.951
NMR	1.165	.349	11.142	1	.001[a]	3.205	1.617	6.351

[a]P<0.05, statistically significant.

and NEU was poor, because we found no difference of WBC and NEU among two groups. Other indexes especially indexes associated with monocyte and lymphocyte were significantly different among two groups, which indicated that these indexes had the predictive value for BSI, and this founding accorded with other articles.

NMR had the highest comprehensive predictive value, cut-off value was estimated as 20.38 according to Youden index. With this value, sensitivity was 66.70% and specificity was 68.60%. NEU% had the highest sensitivity, which was 74.50%; LYM% had the highest specificity, which was 68.60%. Every index had its own advantages and disadvantages, but generally their predictive value was lower than some other studies [9]. This may be the result of specific characteristics and bacterial spectrum of patients with urinary tract infection.

Also, different indexes could be combined to improve the predictive value. We integrated NLR and NMR with logistic regression, AUC was 0.714, sensitivity was 88.20%, which were higher than any single indexes. Sensitivity of parallel test was 90.20%, specificity of series test was 79.00%, also higher than any single indexes.

BSI of patients with urinary tract infection had specific bacterial spectrum, proportion of Gram-negative bacterium was much higher than Gram-positive bacterium. Of Gram-negative bacterium, the most common pathogens were Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, and Klebsiella pneumonia [11]. This accorded with our statistical data. Alteration of white blood cells could be different upon different bacterial spectrum. Vandijck ect. [12] reported significant difference of peripheral white blood cells between infection of Gram-positive bacterium and Gram-negative bacterium. This may be the reason why our finding was a little different from other articles. But this hypothesis needs support from investigation of larger sample. Equally, due to specific bacterial distribution, empirically used antibiotics for BSI patients with urinary tract infection should cover common pathogens such as Escherichia coli, Pseudomonas aeruginosa and so on.

Recent studies have found predictive value of procalcitonin and C-reactive protein for BSI. But those tests are expensive and require special equipment, so they are difficult for some local hospitals to conduct. But future investigation could combine peripheral blood inflammatory indexes and other tests or biomarkers to improve accuracy.

This study had several limitations. This was a retrospective study, and the sample was small. So further studies need to be prospective and larger samples are essential. Mechanisms about the elevation of NLR in BSI have been researched, but we found the elevation of NMR was more significant than NLR, and few studies reported the mechanism of alteration of NMR, this also needs further investigation.

Conclusion

Peripheral blood indexes were associated with blood stream infection in patients with urinary tract infection. Indexes associated with monocytes had higher predictive value for BSI. MON and NMR were independent prognostic factors and had higher predictive value for BSI, combining NLR and NLR could improve accuracy.

But underlying mechanism for the elevation of NMR is yet to be fully elucidated and should be the focus of future study.

Disclosure of conflict of interest

None.

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