

ORIGINAL ARTICLE

Neutrophil-to-Lymphocyte Ratio in Adult Community-Acquired Pneumonia Patients Correlates with Unfavorable Clinical Outcomes

Yan L. Ge¹, Hai F. Zhang¹, Qian Zhang¹, Xiao Y. Zhu¹, Cong H. Liu², Nan Wang³, Jia B. Zhang¹, Hao Chen³, Yi Chen¹, Wen Q. Li¹, Zhen Z. Li¹, Ai S. Fu¹, Hong Y. Wang¹

¹ Department of Respiratory Medicine, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, China

² Department of Internal Medicine, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, China

³ Department of Science and Education, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, China

⁴ Department of Cardiovascular Medicine, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei, China

SUMMARY

Background: Despite the extensive improvement in antibiotic treatment and medical care, severe adult community-acquired pneumonia (CAP) remains as the significant cause of death worldwide. Earlier prognosis assessment and timely treatment in adult CAP patients are useful for prognosis. The neutrophil-to-lymphocyte ratio (NLR) in blood routine has a broad application possibility in assessing inflammatory reaction and prognosis. The aim of this study was to examine the relationship between NLR and inflammatory reaction and to unravel the usefulness of NLR in the assessment of clinical outcomes in adult CAP patients.

Methods: This retrospective study was conducted based on adult patients with a primary diagnosis of CAP. All patients included received a routine blood test and calculated NLR. All of the measurement data were analyzed with paired *t*-test and the enumeration data were analyzed with χ^2 test. Multivariate analysis was performed to investigate the association between predictors (age, male, CURB-65 scores, comorbidity, NLR, and other inflammatory cells in blood routine) and unfavorable outcomes of CAP (ICU admission and 30-day mortality). Receiver operating characteristic curves (ROC) were used to evaluate the sensitivity and specificity of NLR in predicting unfavorable outcomes of CAP.

Results: One hundred fifty patients were included. Compared with favorable outcomes group, age, CURB-65 scores, WBC, neutrophil and lymphocyte counts, and NLR were elevated in unfavorable outcomes group ($p < 0.05$), gender and coexisting illness did not differ obviously. Multivariate logistic regression model analysis showed CURB-65 scores and NLR were independent predictors correlated with unfavorable outcomes ($p < 0.05$). The area under the ROC curve (AUC) of NLR was 0.81 (95% CI 0.73 to 0.89), the sensitivity was 81.00% and specificity was 72.8%. NLR is superior to CURB-65 in predicting unfavorable outcomes. NLR combined CURB-65 has better sensitivity and specificity (89.40% versus 91.30%).

Conclusions: NLR is a simple, cheap, and rapidly available measurement in blood routine and is associated with unfavorable clinical outcomes in adult CAP patients.

(Clin. Lab. 2019;65:xx-xx. DOI: 10.7754/Clin.Lab.2018.181042)

Correspondence:

Yan L. Ge
Department of Respiratory Medicine, North China University
of Science and Technology Affiliated Hospital
Jianshe Road 73, 063000 Tangshan, Hebei
China
Phone: +86 315-3725886
Fax: +86 315-2852195
Email: geyanlei1983@qq.com

Hong Y. Wang
Department of Respiratory Medicine, North China University
of Science and Technology Affiliated Hospital
Jianshe Road 73, 063000 Tangshan, Hebei
China
Email: tsmwhy@163.com

Manuscript accepted November 6, 2018

KEY WORDS

CAP, neutrophil-to-lymphocyte, clinical outcomes

INTRODUCTION

Despite the extensive improvement in antibiotic treatment and medical care, severe adult CAP remains a significant cause of death worldwide [1,2]. According to previous larger epidemiological investigations in China, CAP is the fourth leading cause of mortality, mostly occurring in elderly adults [3,4]. Patients with severe CAP usually survive with advanced support in intensive care unit (ICU), causing major socioeconomic burden. Earlier prognosis assessment and timely treatment in adult CAP patients are useful for prognosis [5]. In the pathophysiology of adult CAP, the imbalance between pro-inflammatory and anti-inflammatory systems plays a critical role in the outcomes of severe CAP. Roles of different inflammatory cells in blood routine, including neutrophils, lymphocytes, and other white blood cells have been studied thoroughly in previous investigations [6-9]. The neutrophil-to-lymphocyte ratio (NLR) attracts particular attention and has been proven to be an indicator of inflammation and prognosis in cerebral ischemia [10], carcinoma [11,12], severe traumatic brain injury [13], coronary artery disease [14,15], acute exacerbation of chronic obstructive pulmonary disease [16, 17], and so on. However, the relationship between NLR and adult CAP clinical outcomes was still unclear. The aim of this study was to examine the relationship between NLR and inflammatory reaction and to unravel the usefulness of NLR in assessment of clinical outcomes in adult CAP patients.

MATERIALS AND METHODS

Patients

This retrospective study was based on patients admitted into respiratory department or emergency department in a regional teaching general hospital in China between January 2016 and September 2018 for adult CAP. Diagnosis of CAP was confirmed by clinical manifestations and radiological studies. Patients in long-term care facilities or a recent stay in a hospital (less than a week) and with a known immune deficiency, hematological diseases and a known cause for leukopenia were excluded. Age, gender, CURB-65 score, serum inflammatory markers (WBC, neutrophils, lymphocytes, NLR) and prognostic indexes (ICU admission and 30-day mortality) were documented.

The measurement of inflammatory markers

Venous blood for neutrophil and lymphocyte counts was drawn from patients upon admission; this was day 1 NLR.

Neutrophil and lymphocyte count in routine blood test was measured by electrical impedance method on a HORIBA ABX Pentra 80 analyzer (HORIBA ABX SAS, Montpellier cedex, France) according to the manufacturer's instructions, and a value of $1.8 \times 10^9/L$ to $6.3 \times 10^9/L$ was used as the biological reference for neutrophil count and $1.1 \times 10^9/L$ to $3.2 \times 10^9/L$ for lymphocyte count.

Statistical analyses

We performed the statistical analysis using SPSS 20.0, and the significance level was set as a p-value < 0.05 . Continuous variables were expressed as mean \pm standard deviation (SD) or median and inter quartile range (IQR) when the distribution was not satisfied by the Kolmogorov-Smirnov test. All of the measurement data were analyzed with paired *t*-test and the enumeration data were analyzed with χ^2 test. This retrospective study was conducted based on adult patients with a primary diagnosis of CAP. All patients included received routine blood test and calculated NLR. All of the measurement data were analyzed with paired *t*-test and the enumeration data were analyzed with χ^2 test. Multivariate analysis was performed to investigate the association between predictors (age, male, CURB-65 scores, comorbidity, NLR, and other inflammatory cells in routine blood tests) and unfavorable outcomes of CAP (ICU admission and 30-day mortality). Receiver operating characteristic curves (ROC) were used to evaluate the sensitivity and specificity of NLR in predicting unfavorable outcomes of CAP.

RESULTS

Comparison of predictors in two groups (unfavorable outcome group and favorable outcome group)

One hundred fifty patients were included. Compared with the favorable outcome group, age, CURB-65 scores, WBC, neutrophil count, lymphocyte count, and NLR were elevated in the unfavorable outcome group ($p < 0.05$), gender and coexisting illness did not differ obviously ($p > 0.05$) (Table 1).

Multivariate analysis of the association between predictors and unfavorable outcomes of CAP

Multivariate logistic regression model analysis showed CURB-65 scores and NLR were independent predictors correlated with unfavorable outcomes ($p < 0.05$). (Table 2).

NLR for unfavorable outcomes of CAP

The area under the ROC curve (AUC) of NLR was 0.81 (95% CI 0.73 to 0.89), the sensitivity was 81.00% and specificity was 72.8%. The AUC of ROC curve of CURB-65 was 0.94 (95% CI 0.90 to 0.98), the sensitivity was 78.70% and specificity was 94.20%. The AUC of ROC curve of NLR combined CURB-65 was 0.96

Table 1. Comparison of clinical characteristics of CAP with favorable and unfavorable outcomes.

Characteristic	Patients with favorable outcome (n = 103)	Patients with unfavorable outcome (n = 47)	p-value
Age (years), median IQR	51 (35 - 64)	78 (69 - 84)	0.00
Male gender, n (%)	51 (49.51%)	32 (68.09%)	0.19
CURB-65 Scores			
0 - 1 Score n (%)	97 (94.17%)	10 (21.28%)	0.00
2 Scores n (%)	5 (4.85%)	16 (34.04%)	0.00
3 - 5 Scores n (%)	1 (0.98%)	21 (44.68%)	0.00
Peripheral blood routine			
WBC (x 10 ⁹ /L)	8.44 ± 3.44	13.40 ± 12.90	0.01
Neutrophil count (x 10 ⁹ /L)	5.43 ± 3.12	9.19 ± 6.18	0.00
Lymphocyte count (x 10 ⁹ /L)	1.71 ± 0.99	1.19 ± 0.66	0.00
NLR	3.19 ± 3.04	8.88 ± 5.81	0.00
Coexisting illness, n (%)	35 (33.98%)	43 (91.49%)	0.62

Abbreviations: IQR - interquartile range, WBC - white blood cell.

Table 2. Multivariate analysis for predictors associated with unfavorable outcomes of CAP.

Predictor	OR	95% CI	p-value
Age (years)	0.987	0.945 - 1.031	0.560
CURB-65 Scores	0.129	0.051 - 0.325	0.000
WBC (x 10 ⁹ /L)	0.978	0.902 - 1.080	0.987
Neutrophil count (x 10 ⁹ /L)	1.060	0.766 - 1.466	0.727
Lymphocyte count (x 10 ⁹ /L)	0.885	0.224 - 3.502	0.862
NLR	0.678	0.464 - 0.991	0.045

Table 3. The ROC analysis of NLR in predicting unfavorable outcomes of CAP.

Item	Sensitivity (%)	Specificity (%)	Younden's index (%)	SE	AUC (95% CI)	p-value
NLR	81.00	72.80	54.00	0.04	0.81 (0.73 - 0.89)	0.00
CURB-65 scores	78.70	94.20	73.00	0.20	0.94 (0.90 - 0.98)	0.00
Combined	89.40	91.30	81.00	0.02	0.96 (0.93 - 0.99)	0.00

(95% CI 0.93 to 0.99), the sensitivity was 89.40% and specificity was 91.30%. NLR is superior to CURB-65 in predicting unfavorable outcomes. NLR combined with CURB-65 has a better sensitivity and specificity. (Table 3, Figure 1-3).

DISCUSSION

CAP is a major infectious disease worldwide. According to previous larger epidemiological investigations in the United States, every year about 500,000 adults are hospitalized for CAP [18], of whom 50,000 to 100,000 patients are admitted to ICU to receive advanced support [19] causing major socioeconomic burden. Earlier

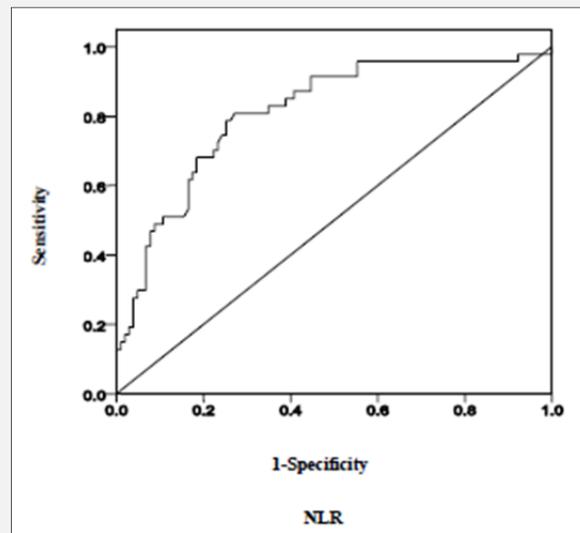


Figure 1. ROC curve of NLR in predicting unfavorable outcomes of CAP.

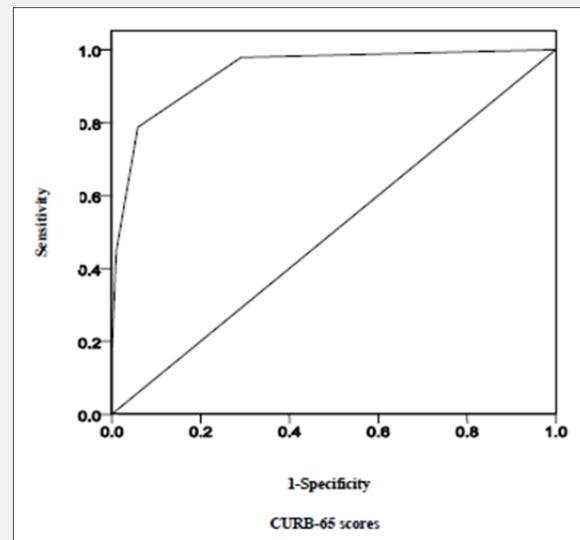


Figure 2. ROC curve of CURB-65 scores in predicting unfavorable outcomes of CAP.

prognosis assessment to identify patients with high mortality risk who need to be admitted as inpatients and receive timely treatment is useful for prognosis. Nowadays, many clinical prediction rules, such as CURB-65 and pneumonia severity index (PSI) have been devel-

oped [20,21], just focus on the specificity and sensitivity of CURB-65 and PSI. The performance of those prediction rules is quite good, while each has its weakness. CURB-65 sometimes overestimates in elderly patients [22-24] and PSI is time-intensive. NLR in routine blood

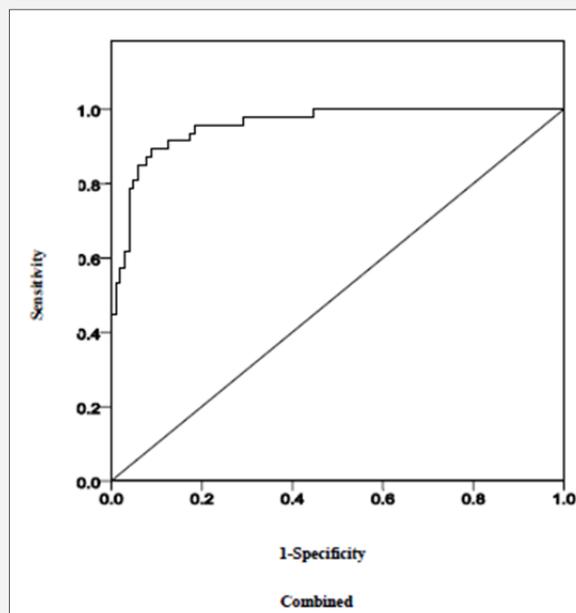


Figure 3. ROC curve of NLR combined CURB-65 scores in predicting unfavorable outcomes of CAP.

tests, which can reveal the imbalance between pro-inflammatory and anti-inflammatory systems, has broad application possibility in assessing inflammatory reaction and prognosis, such as in cerebral ischemia [10], carcinoma [11,12], severe traumatic brain injury[13], coronary artery disease [14,15], acute exacerbation of chronic obstructive pulmonary disease [16,17], and so on. However, the relationship between NLR and adult CAP clinical outcomes is still unclear. This study investigates the association between predictors (age, male, CURB-65 scores, comorbidity, NLR and other inflammatory cells in routine blood tests) and unfavorable outcomes of CAP (ICU admission and 30-day mortality). We also examine the relationship between NLR and inflammatory reaction and unravel the usefulness of NLR in assessment of clinical outcomes in adult CAP patients.

Our study found age, CURB-65 scores, WBC, neutrophil count, lymphocyte count and NLR were elevated in the unfavorable outcome group ($p < 0.05$), multivariate logistic regression model analysis showed CURB-65 scores and NLR were independent predictors correlated with unfavorable outcomes ($p < 0.05$). NLR is superior to CURB-65 in predicting unfavorable outcomes. NLR combined with CURB-65 has better sensitivity and specificity (89.40% versus 91.30%). All of these results indicated NLR is associated with an unfavorable clinical outcome in adult CAP patients, and it is a simple, cheap, and rapidly available measurement.

The main limitation of the study is only 150 patients were included in this retrospective study, so we have the possibility of selection bias. The major strength is that we employ a simple, cheap, and rapidly available index which correlates with unfavorable clinical outcomes in CAP patients.

CONCLUSION

In summary, the current study showed NLR as a simple, cheap, and rapidly available measurement in blood routine. It is associated with an unfavorable clinical outcome in adult CAP patients. Elevated NLR in adult CAP patients is associated with an increased ICU admission and lower survival.

Acknowledgment:

I thank all the patients in this study.

Ethical Approval:

This study was approved by ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in these studies were in accordance with the ethical standards. Informed consent was obtained from all individual participants included in this study.

Financial Support:

This work was supported by the Hebei Province Science Development Program [20191124].

Declaration of Interest:

No conflicts of interest.

References:

1. Adamuz J, Viasus D, Jimenez-Martinez E, et al. Incidence, timing and risk factors associated with 1-year mortality after hospitalization for community-acquired pneumonia. *J Infect* 2014;68:534-41 (PMID: 24534605).
2. Ewig S, Torres A. Severe community-acquired pneumonia. *Clin Chest Med* 1999;20:575-87 (PMID: 10516905).
3. Chen YS, Lin XH, Li HR, et al. [Etiological analysis and establishment of a discriminant model for lower respiratory tract infections in hospitalized patients]. *Zhong Hua Jie He He Hu Xi Za Zhi* 2017;40:909-14 (PMID: 29224300).
4. Li HY, Guo Q, Song WD, et al. Mortality among severe community-acquired pneumonia patients depends on combinations of 2007 IDSA/ATS minor criteria. *Int J Infect Dis* 2015;38:141-5 (PMID: 26255891).
5. Franco J. Community-acquired Pneumonia. *Radiol Technol* 2017;88:621-36 (PMID: 28900048).
6. De Jager CP, Wever PC, Gemen EF, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS One* 2012;7:e46561 (PMID: 23049706).
7. Kim MW, Lim JY, Oh SH. Mortality prediction using serum biomarkers and various clinical risk scales in community-acquired pneumonia. *Scand J Clin Lab Invest* 2017;77(7):486-92 (PMID: 28678546).
8. Hohenthal U, Hurme S, Helenius H, et al. Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia. *Clin Microbiol Infect* 2009;15:1026-32 (PMID: 19548923).
9. Zhou H, Guo S, Lan T, Ma S, Zhang F, Zhao Z. Risk stratification and prediction value of procalcitonin and clinical severity scores for community-acquired pneumonia in ED. *Am J Emerg Med* 2018, 36:2155-60 (PMID: 29691103).
10. Qun S, Tang Y, Sun J, et al. Neutrophil-To-Lymphocyte Ratio Predicts 3-Month Outcome of Acute Ischemic Stroke. *Neurotox Res* 2017;31:444-52 (PMID: 28181171).
11. Marchioni M, Primiceri G, Ingrosso M, et al. The Clinical Use of the Neutrophil to Lymphocyte Ratio (NLR) in Urothelial Cancer: A Systematic Review. *Clin Genitourin Cancer* 2016;14:473-84 (PMID: 27209348).
12. Ahn BK, Lee YS, Kim YJ, et al. Prediction model for mortality in cancer patients with pneumonia: comparison with CURB-65 and PSI. *Clin Respir J* 2018;12:538-46 (PMID: 27663181).
13. Rhind SG, Crmko NT, Baker AJ, et al. Prehospital resuscitation with hypertonic saline-dextran modulates inflammatory, coagulation and endothelial activation marker profiles in severe traumatic brain injured patients. *J Neuroinflammation* 2010;7(1):5 (PMID: 20082712).
14. Fan Z, Li Y, Ji H, Jian X. Prognostic utility of the combination of monocyte-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with NSTEMI after primary percutaneous coronary intervention: a retrospective cohort study. *BMJ Open* 2018;8:e023459 (PMID: 30341133).
15. Pinheiro Machado G, Araujo GN, Carpes CK, et al. Elevated neutrophil-to-lymphocyte ratio can predict procedural adverse events in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Coron Artery Dis* 2018 Oct 16 doi: 10.1097/MCA.0000000000000671 (PMID: 30334819).
16. Teng F, Ye H, Xue T. Predictive value of neutrophil to lymphocyte ratio in patients with acute exacerbation of chronic obstructive pulmonary disease. *PLoS One* 2018;13:e0204377 (PMID: 30265703).
17. Dai RX, Kong QH, Mao B, et al. The mortality risk factor of community acquired pneumonia patients with chronic obstructive pulmonary disease: a retrospective cohort study. *BMC Pulm Med* 2018;18:12 (PMID: 29357862).
18. Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med* 1997;157:1709-18 (PMID: 9250232).
19. Ewig S, Torres A. Severe community-acquired pneumonia. *Clin Chest Med* 1999;20:575-87 (PMID: 10516905).
20. Varshochi M1, Kianmehr P, Naghavi-Behzad M, Bayat-Makoo Z. Correspondence between hospital admission and the pneumonia severity index (PSI), CURB-65 criteria and comparison of their predictive value in mortality and hospital stay. *Infez Med* 2013;21:103-10 (PMID: 23774973).
21. Usui K, Tanaka Y, Noda H, Ishihara T. Comparison of three prediction rules for prognosis in community acquired pneumonia: Pneumonia Severity Index (PSI), CURB-65, and A-DROP. *Nihon Kokyuki Gakkai Zasshi* 2009;47:781-5 (PMID: 19827581).
22. Heppner HJ, Sehlhoff B, Niklaus D, Pientka L, Thiem U. [Pneumonia Severity Index (PSI), CURB-65, and mortality in hospitalized elderly patients with aspiration pneumonia]. *Z Gerontol Geriatr* 2011;44:229-34 (PMID:21769515).
23. Ge YL, Liu CH, Xu J, et al. Serum High-Sensitivity C Reactive Protein Improves Sensitivity of CURB-65 in Predicting ICU Admission and Mortality in Community-Acquired Pneumonia Patients. *Clin Lab* 2018;64(10):1749-54 (PMID: 30336524).
24. Gonzalez C, Johnson T, Rolston K, Merriman K, Warneke C, Evans S. Predicting pneumonia mortality using CURB-65, PSI, and patient characteristics in patients presenting to the emergency department of a comprehensive cancer center. *Cancer Med* 2014;3:962-70 (PMID: 24802800).