—Original—

Effects of Drug Therapy on T Lymphocyte Subsets and the Associations of These Subsets with Recurrent Chronic Bronchitis Attacks

Jing Zhang[1], Shan Wang[1], Yun Shi[1] and Chunting Tan[2]

[1]Department of Geriatric Medicine, Medical Health Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China
[2]Department of Respiratory Medicine, Beijing Friendship Hospital, Capital Medical University, Beijing, China

Background: We evaluated the effects of drug therapy on T lymphocyte subsets and their associations with recurrent chronic bronchitis (CB) attacks.

Methods: A total of 162 CB patients treated from April 2020 to April 2021 were selected. All patients underwent anti-infective, cough-relieving, and phlegm-eliminating treatment, as detailed in *Clinical Pathway for Chronic Bronchitis*. They were divided into a recurrent attack group (n=95) and a non-recurrent attack group (n=67). Changes in T lymphocyte subsets at different time points of treatment and their associations with the number of attacks were analyzed. Associated factors were analyzed in a multivariate logistic regression model, and their predictive value was validated using a nomogram prediction model and receiver operating characteristic (ROC) curves.

Results: The number of attacks at 1 year after treatment was positively correlated with $CD8^+$ and negatively correlated with $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$. A history of smoking, $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ were independent risk factors for recurrent attacks. The nomogram prediction model showed that the total risk value corresponding to smoking history, low $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$, and elevated $CD8^+$ was 0.86, and the concordance index and area under the ROC curve of the model was 0.896 (95% CI: 0.782-0.997, $P<0.05$) and 0.816 (95% CI: 0.803-0.847, $P<0.001$), respectively. There was an association between T lymphocyte subsets and recurrent attacks before and after treatment of CB.

Conclusions: Low $CD3^+$, $CD4^+/CD8^+$ and $CD4^+$, elevated $CD8^+$, and smoking history were risk factors for recurrent attack. (J Nippon Med Sch 2025; 92: 61–68)

Key words: chronic bronchitis, T lymphocyte subset, recurrent attack

Introduction

Chronic bronchitis (CB) is a form of chronic inflammation characterized by bronchial ciliary beat weakening, bronchial wall thickening and mucosal epithelial cell injury resulting from respiratory tract infection, allergy, or inhalation of dust, fumes, or harmful chemical gases, often involving lung tissues. CB manifests primarily as excessive phlegm, cough, chest distress, and shortness of breath, and may be accompanied by bronchospasm, dyspnea, wheezing, and other respiratory dysfunction in severe cases[1,2]. It is more frequent from late autumn to early spring and is moderately relieved in most patients after temperatures increase[3]. During an acute attack of CB, mainly caused by pathogenic bacteria, respiratory tract tissues of patients are in a long-term state of infection, and inflammatory cytokines secreted by T lymphocytes and other inflammatory cells are implicated in the immune response and structural remodeling of the respiratory system, coordinating cell differentiation, and apoptosis in immune stress[4]. Cluster of differentiation 4^+ ($CD4^+$) and $CD8^+$ T lymphocyte subsets help maintain cellular immunity to viral infection and change dramatically in chronic respiratory diseases such as asthma and lung disease[5]. With the recent decline in air quality due to industrial pollution, the annual incidence rate of CB has been increasing[6]. This refractory protracted disease is

Correspondence to Chunting Tan, Department of Respiratory Medicine, Beijing Friendship Hospital, Capital Medical University, 95 Yong'an Road, Xicheng District, Beijing 100050, China
E-mail: chuntingtan@ccmu.edu.cn
https://doi.org/10.1272/jnms.JNMS.2025_92-111
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Table 1 Characteristics of patients

Item	Recurrent attack group (n=95)	Non-recurrent attack group (n=67)	χ^2/t	P
Age (Y)	59.15±7.67	55.83±7.49	t=2.740	0.007
Male [n (%)]	49 (51.58)	35 (52.24)	χ^2=0.007	0.934
Hypertension [n (%)]	43 (45.26)	31 (46.27)	χ^2=0.016	0.899
Diabetes mellitus [n (%)]	18 (18.95)	10 (14.93)	χ^2=0.445	0.505
Cerebrovascular disease [n (%)]	26 (27.37)	18 (26.87)	χ^2=0.005	0.944
Coronary heart disease [n (%)]	27 (28.42)	15 (22.39)	χ^2=0.745	0.388
Smoking history [n (%)]	63 (66.32)	29 (43.28)	χ^2=8.494	0.004
WBC ($\times10^9$/L)	19.06±5.23	16.42±4.62	t=3.318	0.001
NEU ($\times10^9$/L)	8.84±2.67	7.71±1.59	t=3.097	0.002
GR (%)	78.27±9.89	77.46±8.73	t=0.538	0.591
LYM ($\times10^9$/L)	1.52±0.39	1.61±0.42	t=1.401	0.163
PLT ($\times10^9$/L)	125.96±30.12	133.28±33.21	t=1.460	0.146
NLR	5.53±1.45	4.89±1.39	t=2.814	0.006
ALT (U/L)	52.12±16.97	50.98±16.84	t=0.422	0.673
AST (U/L)	52.28±16.37	49.79±17.21	t=0.933	0.352
CRP (mg/L)	20.16±5.17	17.89±4.38	t=2.928	0.004

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; GR: neutrophilic granulocyte; LYM: lymphocyte; NEU: neutrophil count; NLR: neutrophil/lymphocyte ratio; PLT: platelet; WBC: white blood cell count.

Data were compared by the *t*-test between two groups. Count data were compared by the χ^2 test between two groups.

treated mainly with anti-infective, phlegm-eliminating, and asthma-relieving drugs but cannot be cured clinically and has a poor prognosis; patients have a greatly diminished quality of life and their lives may be threatened by recurrent attacks[7]. Therefore, this study explored changes in peripheral blood T lymphocyte subsets after treatment and their associations with recurrent attacks in CB patients, thereby providing a diagnostic basis for clinical treatment and important information on improving patient quality of life.

Materials and Methods

Participants

A total of 162 CB patients treated in our hospital from April 2020 to April 2021 were selected as the participants, including 84 males and 78 females aged 43-82 years, with an average age of 57.69±7.58 years. The patients were divided into a recurrent attack group (n=95; ≥2 attacks from the end of treatment to the last follow-up) and a non-recurrent attack group (n=67) on the basis of recurrent acute attacks after treatment. Inclusion criteria were as follows: 1) patients meeting the diagnostic criteria and with clinical manifestations, as detailed in *Guidelines for the Prevention and Treatment of Chronic Bronchitis*[8], 2) those with complete clinical data, 3) those with acute attacks of <3 days, and 4) those whose acute attacks resolved after treatment. Patients were excluded if they had 1) a malignancy, 2) severe blood disease, 3) pulmonary tuberculosis or other bronchial diseases, such as bronchial asthma and bronchiectasis, or 4) an allergic constitution, or were 5) lactating or pregnant. The patients and their families were informed of this study in detail, and all patients signed an informed consent document. This study was approved by the ethics committee of our hospital.

Data Collection

General data on patients, including basic information, smoking history, and medical history, were collected from electronic medical records. About 10 mL of fasting peripheral blood was drawn within 24 h after admission and sent to the laboratory. Then C-reactive protein (CRP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured with a Siemens ADVIA XPT automatic biochemical analyzer, and white blood cell count (WBC), neutrophil count (NEU), neutrophilic granulocyte (GR), lymphocyte count (LYM), platelet count (PLT), and neutrophil/lymphocyte ratio (NLR) were measured with a Cellometer automatic cell counter (Beijing ZDC Biotech Co., Ltd.). About 5 mL of fasting peripheral blood was drawn from each patient and sent to the laboratory within 24 h after admission, at the fifth day of treatment, and at 24 h after 10-day treatment. Per-

centages of peripheral blood T lymphocyte subsets, including $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$, before and after treatment, were analyzed with a nanoflow cytometer (Xiamen NanoFCM Co., Ltd.). In detail, 10 μL of labeled fluorescent monoclonal antibody CD45-FITC/CD4-RD1/CD8-CD/CD3-PC5 was added to each test tube, followed by the addition of 100 μL of venous blood containing EDTA-K2, mixing, and incubation in the dark at room temperature for 20 min. After 500 μL of erythrocyte lysate was added to lyse red blood cells, the mixture was reacted at room temperature for 15 min in the dark, mixed with 500 μL of phosphate-buffered saline, and placed in the dark for 10 min at room temperature for flow cytometry. Quantitative analysis was performed, and the data were recorded.

Therapeutic Regimens

All patients underwent anti-infective, cough-relieving, and phlegm-eliminating treatment in accordance with *Clinical Pathway for Chronic Bronchitis*. Amoxicillin capsules (0.25 g × 12 s × 2 plates, Zhuhai United Laboratories [Zhongshan] Co., Ltd., NMPN H44021351) were taken (2 tablets/time, once every 6-8 h, daily dose ≤4 g). Ambroxol hydrochloride tablets (30 mg × 10 s × 2 plates, Sinopharm Shantou Jinshi Pharmaceutical Co., Ltd., NMPN H20083547) were taken after meals (1-2 tablets/time, 3 times/d). If dyspnea occurred during treatment, aminophylline sustained-release tablets (0.1 g × 24 s, Yantai Luyin Pharmaceutical Co., Ltd., NMPN H37020065) were also taken (1-3 tablets/time, 2 times/d). Treatment continued for 10 days for all patients.

Follow-Up

After discharge, the status of bronchitis attacks was monitored for 1 year in outpatient clinic and by telephone every 3 months. The result of follow-up was recorded as 0 attacks, 1 attack, 2 attacks, 3 attacks, etc.

Statistical Analysis

SPSS 23.0 software was used for statistical analysis. Measurement data were expressed as mean ± SD and analyzed with the *t* test for comparisons between 2 groups. Intergroup comparisons at different times points were performed by repeated-measures analysis of variance. First, differences between 2 groups and the time differences of measured values at each time point were compared. For intergroup comparison, differences between groups at each time point were compared using the independent samples *t* test, and time differences in each group were compared by the SNK-q test. Count data were expressed as percentages (%) and compared with the χ^2 test between two groups. Correlations between T lymphocyte subsets and number of attacks were investigated by Pearson's analysis. Factors associated with recurrent attack were analyzed in a multivariate logistic regression model, and their predictive value was assessed using receiver operating characteristic (ROC) curves. Model discrimination was assessed by area under the curve (AUC), concordance of the nomogram model was evaluated by the calibration curve, and net benefit at different threshold probabilities was evaluated using the decision curve to determine the clinical applicability of the nomogram model. A P value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Duration from discharge to recurrent acute attack during follow-up was 5.13±1.08 months in the recurrent attack group, and the number of attacks was 2.74±0.36. Comparison of the clinical and laboratory variables of the 2 groups revealed that in the recurrent attack group patients were older, the proportion of smokers was higher, and levels of WBC, NEU, NLR, and CRP were higher than in the non-recurrent attack group (P<0.05); other variables were not significantly different (P>0.05) (**Table 1**).

T lymphocyte Subsets at Different Time Points

After treatment, $CD3^+$ and $CD4^+$ levels rose in both groups, and the differences were significant in the non-recurrent attack group at 5 days and 10 days (P<0.05). After treatment, $CD8^+$ rose in the recurrent attack group but declined in the non-recurrent attack group, and there were significant differences at 5 days and 10 days (P< 0.05). $CD4^+/CD8^+$ decreased in the recurrent attack group but increased in the non-recurrent attack group after treatment, and the differences were significant at 5 days and 10 days (P<0.05). $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ did not significantly differ between the groups before treatment (P>0.05) but significantly differed at 5 days and 10 days after treatment (P<0.05) (**Table 2**).

Association between T Lymphocyte Subsets and Number of Attacks

Pearson correlation analysis showed that the number of attacks at 1 year after treatment was positively correlated with $CD8^+$ and negatively correlated with $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ (P<0.05) (**Table 3**).

Multivariate Logistic Regression Analysis of Recurrent Attacks

The multivariate logistic regression model included variables that significantly differed between groups as in-

Table 2 T lymphocyte subsets at different time points in the two groups (mean±SD)

Group		$CD3^+$ (%)	$CD4^+$ (%)	$CD8^+$ (%)	$CD4^+/CD8^+$ (%)
Recurrent attack group (n=95)	Before treatment	58.74±8.35	34.51±10.19	24.95±8.22	1.72±0.29
	5 d after treatment	59.46±8.79	34.87±9.56	25.69±8.15	1.68±0.31
	10 d after treatment	59.81±9.56	34.96±9.32	26.81±8.05	1.64±0.31
Non-recurrent attack group (n=67)	Before treatment	60.19±9.27	35.54±9.47	24.76±7.41	1.73±0.42
	5 d after treatment	62.49±9.16#	37.84±7.29#	22.84±7.16#	1.82±0.48#
	10 d after treatment	64.32±10.08*#	39.21±7.33*#	22.13±7.02*#	2.09±0.53*#
Healthy subjects		60-80	35-55	20-24	2.00-2.80

Intergroup comparisons at different times points were performed by repeated-measures analysis of variance. First, differences between two groups and time differences in measured values at each time point were compared. For intergroup comparison, differences between groups at each time point were compared using the independent samples *t* test, and time differences of each group were compared by the SNK-q test.

*P<0.05 *vs.* before treatment, #P<0.05 *vs.* control group at the same time points.

Table 3 Association between T lymphocyte subsets and number of attacks

Time point	Statistics	$CD3^+$ (%)	$CD4^+$ (%)	$CD8^+$ (%)	$CD4^+/CD8^+$ (%)
Before treatment	γ	–0.139	–0.087	0.097	–0.160
	P	0.085	0.517	0.443	0.072
At 1 year after treatment	γ	–0.340	–0.376	0.412	–0.527
	P	0.011	0.002	0.001	0.000

Correlations of T lymphocyte subsets with number of attacks were determined by Pearson's analysis.

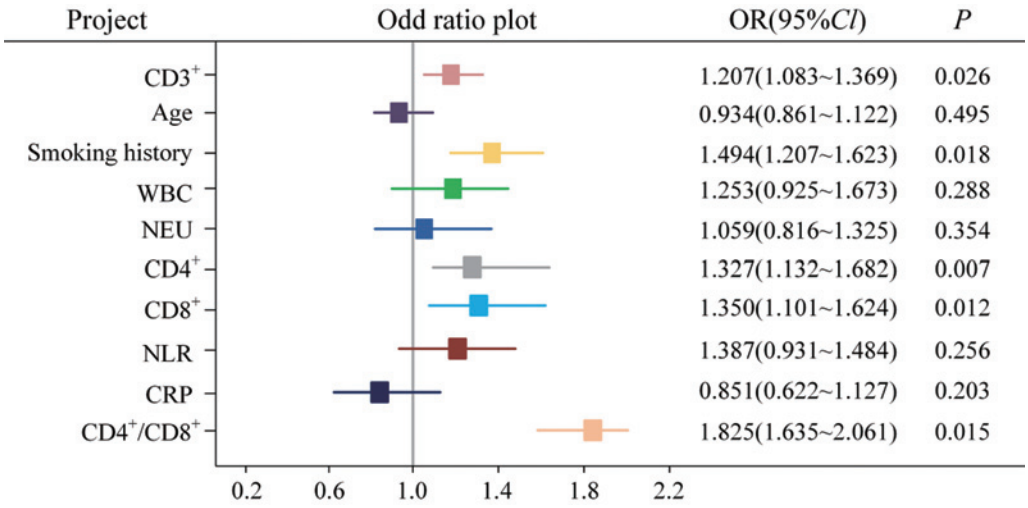

Fig. 1 Forest plot of multivariate logistic regression analysis of independent risk factors for recurrent attacks.

dependent variables and the presence of recurrent attacks after treatment (No=0, Yes=1) as the dependent variable. The results revealed that smoking history, $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ were independent risk factors for recurrent attack (P<0.05) (**Fig. 1**).

Nomogram Model for Predicting Recurrent Attacks

The nomogram model for predicting recurrent CB attacks was established using the 5 independent risk factors. The weight of each factor in the model differed. Scores corresponding to smoking history, low $CD3^+$, low $CD4^+$, elevated $CD8^+$, and low $CD4^+/CD8^+$ were 43.52, 61.93, 34.75, 39.64, and 64.52 points, respectively. The total score was 244.36 points, and the corresponding risk value for recurrent attack was 0.86. The prediction probability for recurrent attack was 85.76% (**Fig. 2**).

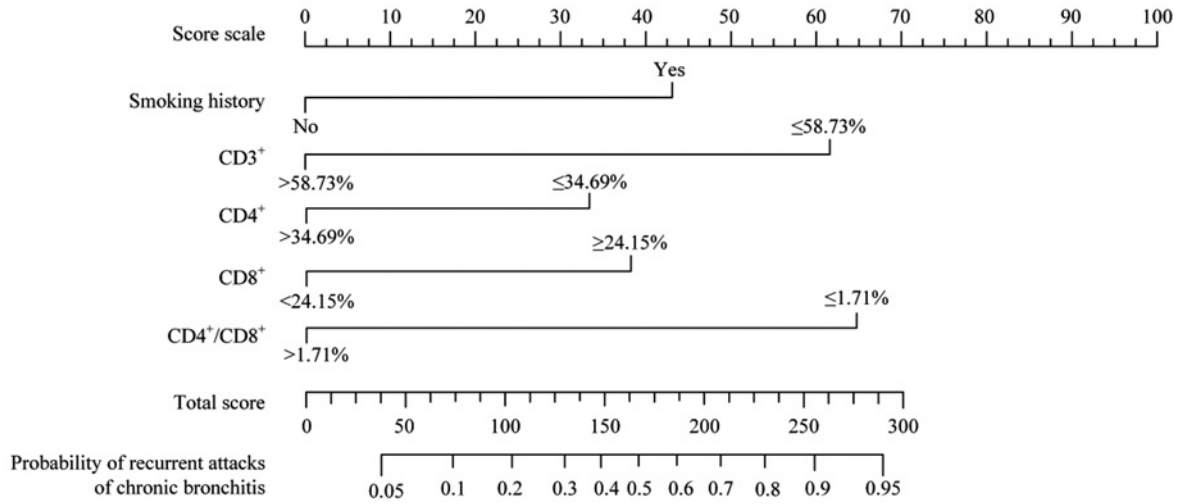

Fig. 2 Nomogram model for predicting recurrent attacks.

Model Validation

The discrimination of the model was assessed using the ROC curve. The model had an AUC of 0.816 (95% CI: 0.803-0.847, P<0.001), a sensitivity of 0.922, and a specificity of 0.641, suggesting good discrimination (**Fig. 3A**). The concordance index of the model was 0.896 (95% CI: 0.782-0.997, P<0.05), and the internal validation results showed that the standard curve fitted well with the prediction curve in the calibration curve, indicating that the risk of recurrent attack predicted by the model conformed well to the actual risk (**Fig. 3B**).

Recurrence-Free Curves

The recurrence-free curves were plotted in relation to change in T lymphocyte subsets. The results showed that recurrence-free status was significantly better in patients with elevated $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ and low $CD8^+$ values after treatment (P<0.05) (**Fig. 4**).

Discussion

Respiratory system symptoms such as cough, expectoration, chest distress, and shortness of breath are frequent at night and before dawn[9]. The incidence and recurrence rates for CB remain high, despite recent advances in treatment[10]. CB can cause recurrent attacks that seriously threaten the quality of life and even the lives of affected persons and greatly decrease sustainable development of global public health[11]. Therefore, to improve assessment of CB prognosis, it is important to identify biomarkers with high sensitivity and specificity for CB and factors associated with recurrent CB attack.

Many inflammatory cells, including neutrophils, T lymphocytes, and macrophages, are implicated in abnormal respiratory inflammatory response. These cells secrete inflammatory cytokines that drive the airway immunopathological response while eliminating viruses[12]. CRP is an inflammatory factor produced by the human body in response to pathogenic microbial infection. As an index of bacterial infection, CRP is important in the diagnosis and treatment of respiratory infectious diseases[13]. In this study, CRP level was significantly higher in the recurrent attack group than in the non-recurrent attack group, suggesting that the former had more severe inflammation.

Patients with acute attacks of CB have weak immune function, and T lymphocyte subsets vary with respect to expression level and regulatory effect in airway inflammation[14]. Miura *et al.*[15] used flow cytometry to determine expression of T lymphocyte subsets in peripheral blood of patients with airway inflammation and found that $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ exhibited significant differences. In a rat experiment, Huang *et al.*[16] found that rats with non-asthmatic eosinophilic bronchitis had an increased level of circulating $CD4^+CD25^+CD127^{low/-}$ regulatory T cells. Barnes *et al.*[17] argued that the $CD8^+$ T lymphocyte subset was the major active marker in airway inflammation. Through expression of pro-inflammatory cytokines, $CD8^+$ T cells induce airway inflammation and lung disease, and those isolated from the lungs of CB patients tend to be more cytotoxic[18]. The present results showed that $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ were all independent risk factors for recurrent CB attack. As compared with the non-recurrent attack group, the recurrent attack group had higher $CD4^+$ and $CD8^+$ levels and a lower $CD4^+/CD8^+$ level after treatment, suggesting that $CD8^+$ has a greater impact than $CD4^+$ on recurrent attacks of CB, and that elevation of $CD4^+$ and $CD8^+$ causes

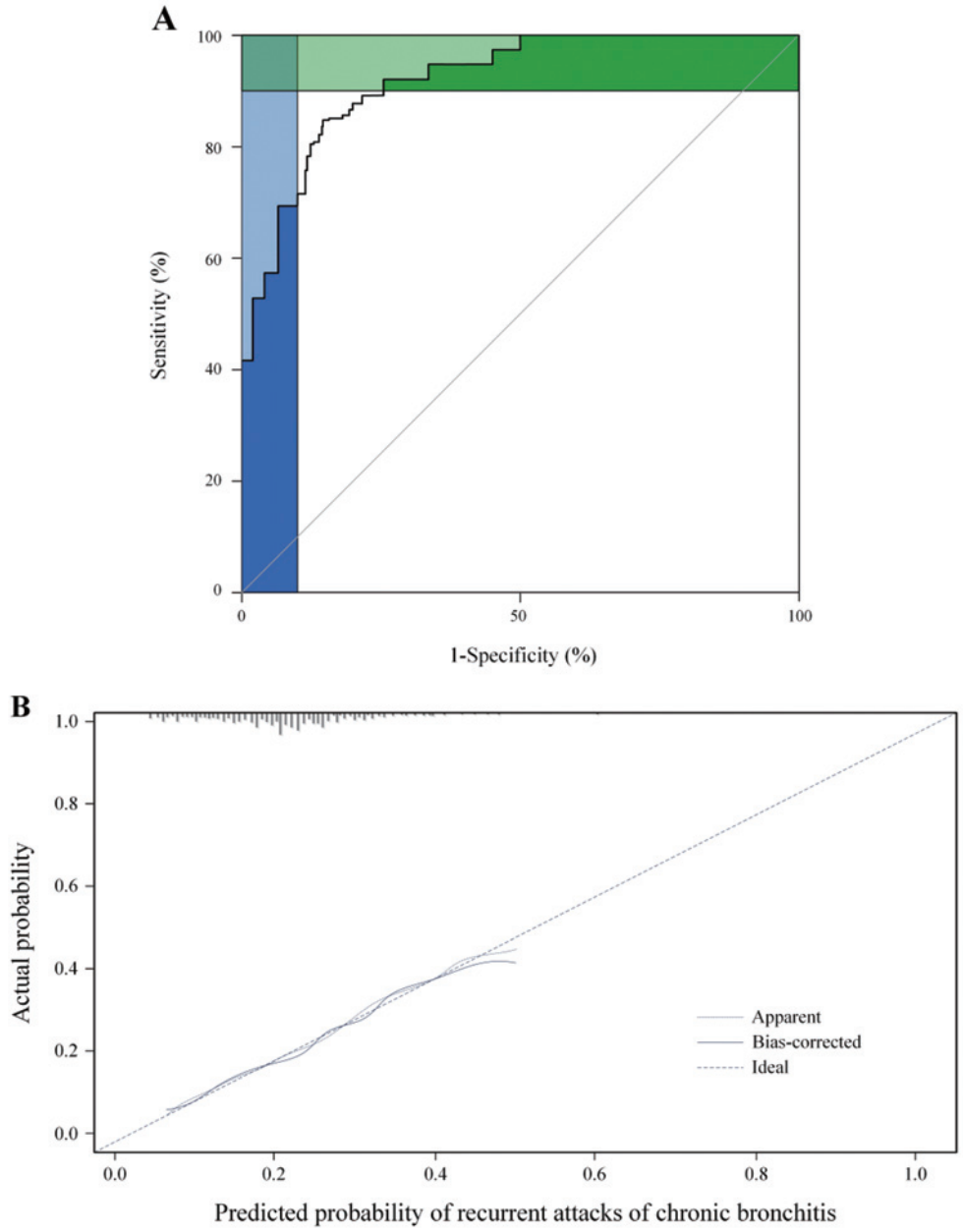

Fig. 3 Validation of nomogram prediction model. A) ROC curve of model. B) Calibration curve of internal validation.

greater pathological damage to the respiratory system. Kaveh *et al*.[19] proved that $CD4^+$ and $CD8^+$ T lymphocyte subset count was a major marker of the severity and complications of respiratory virus infection. Another study[20] showed that upon stimulus of bronchial mucosal epithelial tissues by pathogenic inhalants in the case of respiratory inflammation, $CD8^+$ T cells are activated and proliferate, and that vascular endothelial growth factors are activated to increase vascular permeability, thereby contributing to exudation and spread of inflammation. Inflammatory injury in CB can be effectively alleviated by strictly controlling inhalation of cigarette smoke and dust and inhibiting activation of $CD8^+$ T cells. As in the above studies, we found that a history of smoking was an independent risk factor for recurrent attack of CB, as was deficient $CD3^+$. The reason for low $CD3^+$ T cell counts in the peripheral blood of patients with virus infection-induced CB is unclear. One hypothesis is that $CD3^+$ T cells are depleted by severe infection, so that the number of these cells is lower in blood. Another possibility is that $CD3^+$ T cells migrate from peripheral blood circulation to lung and airway tissues during severe infection. Nevertheless, respiratory disease can alter $CD3^+$ T cell count. Ose *et al*.[21] found that respiratory virus infection led to a decline in $CD3^+$ T cell count in mouse models. Gul *et al*.[22] confirmed that change in $CD3^+$ T cell

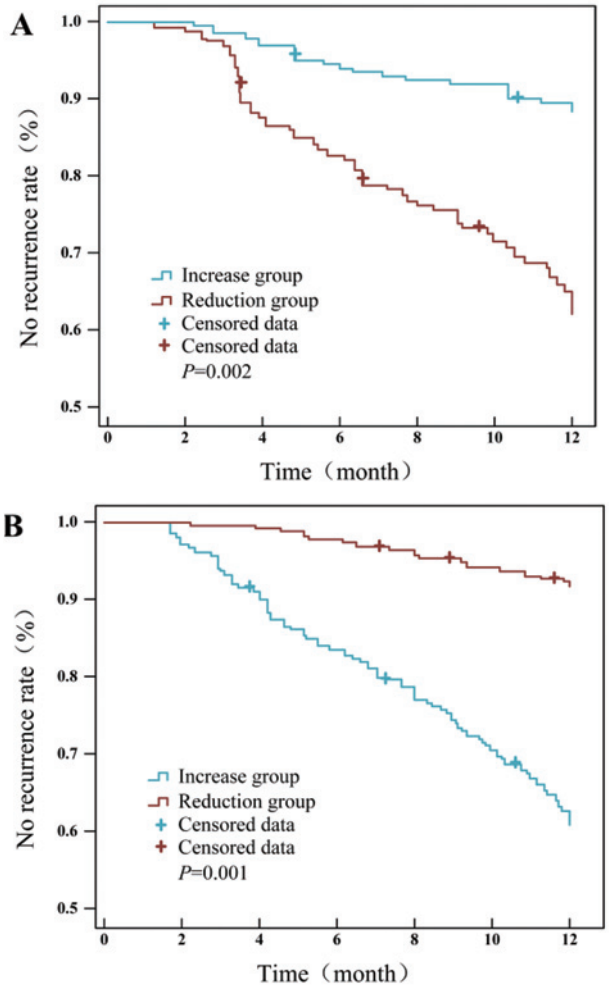

Fig. 4 Recurrence-free curves based on characteristics of changes in T lymphocyte subsets. A) Characteristics of changes in CD3+, CD4+, and CD4+/CD8+. B) Characteristics of changes in CD8+.

count in respiratory virus infection was as an important immunological marker for evaluating the severity of virus infections. The above findings further demonstrate a strong association between $CD3^+$ and recurrent attacks of CB. The inflammatory response worsens, and T lymphocyte subsets are strongly activated during recurrent CB attacks, so that the number of $CD3^+$, $CD4^+$, and $CD8^+$ cells is altered, in which case there are changes in patient clinical variables. In this study, the nomogram prediction model for recurrent attacks of CB comprised 5 independent risk factors ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$, and smoking history) and confirmed that the model had good discrimination and accuracy and could provide information for clinical assessment of prognosis of CB patients.

This study has limitations. First, the sample size was small and the data were from a single center, thus increasing the risk of selection bias. Second, only the difference in cell surface CDs was considered, and T lymphocyte subsets classified by function were not studied. Third, recurrence was not analyzed in relation to treatment type. Fourth, changes in T lymphocyte subsets were significant only after a short period of treatment. Multicenter studies with larger sample sizes and longer treatment times are ongoing in our group.

In conclusion, CB patients with recurrent attacks have elevated levels of $CD3^+$, $CD4^+$, and $CD8^+$ and a low $CD4^+/CD8^+$. A history of smoking, $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ are independent risk factors for recurrent CB attacks. The number of attacks is positively correlated with $CD8^+$ and negatively correlated with $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$. These findings suggest that T lymphocyte subset data may help predict recurrence after CB treatment.

Acknowledgements: None.

Funding: None.

Conflict of Interest: None.

References

1. Puddu PE, Menotti A, Kromhout D, Kafatos A, Tolonen H. Chronic bronchitis in the 50-year follow-up of the European cohorts of the Seven Countries Study: prevalence, mortality and association with cardiovascular diseases. Respir Med. 2021;181:106385.
2. Cazzola M, Calzetta L, Page C, et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. Eur Respir Rev. 2015;24(137):451–61.
3. Bhatt SP, Bodduluri S, Kizhakke Puliyakote AS, et al. Structural airway imaging metrics are differentially associated with persistent chronic bronchitis. Thorax. 2021;76(4):343–9.
4. Cruz T, Lopez-Giraldo A, Noell G, et al. Multi-level immune response network in mild-moderate Chronic Obstructive Pulmonary Disease (COPD). Respir Res. 2019;20(1):152.
5. Huang J, Liu J, Xian Y, et al. Elevated circulating $CD4^+CD25^+CD127^{-/low}$ regulatory T cells in patients with non-asthmatic eosinophilic bronchitis. Lung. 2020;198(3):491–7.
6. Kelly F. Air pollution and chronic bronchitis: the evidence firms up. Thorax. 2021;76(8):744–5.
7. Wang G, Hallberg J, Um Bergstrom P, et al. Assessment of chronic bronchitis and risk factors in young adults: results from BAMSE. Eur Respir J. 2021;57(3):2002120.
8. Narsingam S, Bozarth AL, Abdeljalil A. Updates in the management of stable chronic obstructive pulmonary disease. Postgrad Med. 2015;127(7):758–70.
9. Landt E, Colak Y, Lange P, Laursen LC, Nordestgaard BG, Dahl M. Chronic cough in individuals with COPD: a population-based cohort study. Chest. 2020;157(6):1446–54.

10. Malesker MA, Callahan-Lyon P, Madison JM, Ireland B, Irwin RS; CHEST Expert Cough Panel. Chronic cough due to stable chronic bronchitis: CHEST Expert Panel Report. Chest. 2020;158(2):705–18.
11. Lai K, Long L. Current status and future directions of chronic cough in China. Lung. 2020;198(1):23–9.
12. Ramos-Ramirez P, Malmhall C, Johansson K, Adner M, Lotvall J, Bossios A. Lung regulatory T cells express adiponectin receptor 1: modulation by obesity and airway allergic inflammation. Int J Mol Sci. 2020;21(23):8990.
13. Perez L. Acute phase protein response to viral infection and vaccination. Arch Biochem Biophys. 2019;671:196–202.
14. Sharapova SO, Pashchenko OE, Guryanova IE, Migas AA, Kondratenko IV, Aleinikova OV. Recent thymic emigrants, T regulatory cells, and BAFF level in children with X-linked agammaglobulinaemia in association with chronic respiratory disease. Allergol Immunopathol (Madr). 2018;46(1):58–66.
15. Miura K, Inoue K, Ogura A, Kaminuma O. Role of $CD4^+$ T cells in allergic airway diseases: learning from murine models. Int J Mol Sci. 2020;21(20):7480.
16. Huang J, Liu J, Xian Y, et al. Elevated circulating $CD4^+CD25^+CD127^{-/low}$ regulatory T cells in patients with non-asthmatic eosinophilic bronchitis. Lung. 2020;198(3):491–7.
17. Barnes NC, Saetta M, Rabe KF. Implementing lessons learned from previous bronchial biopsy trials in a new randomized controlled COPD biopsy trial with roflumilast. BMC Pulm Med. 2014;14:9.
18. Nejad-Moghaddam A, Panahi Y, Abdollahpour Alitappeh M, Borna H, Shokrgozar MA, Ghanei M. Therapeutic potential of mesenchymal stem cells for the treatment of airway remodeling in pulmonary diseases. Iran J Allergy Asthma Immunol. 2015;14(6):552–68.
19. Kaveh DA, Garcia-Pelayo MC, Bull NC, Sanchez-Cordon PJ, Spiropoulos J, Hogarth PJ. Airway delivery of both a BCG prime and adenoviral boost drives CD4 and CD8 T cells into the lung tissue parenchyma. Sci Rep. 2020;10(1):18703.
20. Xu W, Yang H, Liu H, et al. Bronchoalveolar lavage T cell cytokine profiles and their association with lung function in children with Mycoplasma pneumoniae -associated bronchiolitis obliterans. Pediatr Pulmonol. 2020;55(8):2033–40.
21. Ose R, Weigmann B, Schuppan D, Waisman A, Saloga J, Bellinghausen I. Depletion of $CD56^+CD3^+$ invariant natural killer T cells prevents allergen-induced inflammation in humanized mice. J Allergy Clin Immunol. 2021;148(4):1081–1087.e2.
22. Gul A, Khan S, Arshad M, et al. Peripheral blood T cells response in human parainfluenza virus-associated lower respiratory tract infection in children. Saudi J Biol Sci. 2020;27(10):2847–52.

(Received, December 9, 2022)
(Accepted, October 30, 2024)