Postprint: Predictive Value of a Lymphocyte Count-Based Multi-parameter Model for Prognosis in Patients with Acute Exacerbation of Interstitial Lung Disease Complicated by Pulmonary Infection

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Abstract

Background Patients with interstitial lung disease are prone to acute exacerbations, with infection being one of the important triggers. Patients experiencing acute exacerbation have high mortality rates and poor prognosis. Currently, there are limited domestic studies on this population.

Objective To investigate the clinical predictive value of dynamic changes in peripheral blood lymphocyte count for the prognosis of patients with acute exacerbation of interstitial lung disease (AE-ILD) complicated by pulmonary infection, and to establish a relevant predictive model.

Methods AE-ILD patients hospitalized in the Department of Respiratory Medicine, Affiliated Hospital of Xuzhou Medical University from January 2022 to June 2024 were retrospectively enrolled. Based on 28-day survival status, patients were divided into a death group and a survival group. General patient data were collected including: gender, age, diagnosis, ILD classification, underlying diseases; disease severity scores including: Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score; laboratory indicators including: white blood cell count (WBC), neutrophil count (NEU), lymphocyte count on days 1, 3, and 5 (LYM), hemoglobin (Hb), platelet count (PLT), procalcitonin (PCT), C-reactive protein (CRP), albumin (ALb), total bilirubin (T-bil), lactate dehydrogenase (LDH), creatinine (Scr), activated partial thromboplastin time (APTT), partial pressure of oxygen (PO2), partial pressure of carbon dioxide (PCO2), fraction of inspired oxygen (FIO2), oxygenation index (P/F), lactate (Lac). Differences between the two groups were compared, statistically significant indicators were screened, and receiver operating characteristic (ROC) curves for each indicator

predicting 28-day prognosis were plotted. R software was used to perform univariate and multivariate Cox proportional hazards regression analysis. Scores were assigned to each indicator based on hazard ratio (HR) to construct a nomogram prediction model. Risk stratification was established after calculating the sum of scores for all indicators, and the ROC curve of the prediction model was plotted to evaluate its predictive value. R software was used to plot 28-day survival curves for AE-ILD patients in different risk stratifications and compare the 28-day survival rates among different groups.

Results A total of 102 patients were enrolled, including 37 in the survival group and 65 in the death group. The APACHE II score, SOFA score, PCT, CRP, and LDH in the death group were higher than those in the survival group (P<0.05). LYM on days 3 and 5, Alb, and P/F in the death group were lower than those in the survival group (P<0.05). With the extension of treatment time, LYM in the death group gradually decreased, while LYM in the survival group gradually increased. ROC curve results showed that the AUCs for day 3 LYM, day 5 LYM, APACHE II score, and SOFA score in predicting 28-day prognosis of AE-ILD patients were 0.723, 0.764, 0.733, and 0.704, respectively. Multivariate Cox regression analysis showed that P/F (HR=2.01, 95%CI=1.08~3.75), PCT (HR=2.14, 95%CI=1.02~4.49), Hb (HR=2.34, 95%CI=1.22~4.48), and day 5 LYM (HR=2.40, 95%CI=1.01~5.70) were independent risk factors for 28-day death in AE-ILD patients. A nomogram model was constructed based on day 5 LYM, P/F, PCT, and Hb. The AUC value of this model for predicting 28-day death in AE-ILD patients was 0.853 (95%CI=0.781~0.925), with an optimal cutoff value of 2, sensitivity of 88.24%, and specificity of 82.35%. According to the optimal risk stratification results, 0~2 points were classified as the low-risk group and 3~6 points as the high-risk group. The comparison of 28-day survival rates between the two groups showed statistically significant differences (2=51, P<0.001).

Conclusion The decrease in LYM is associated with increased 28-day mortality in patients with AE-ILD complicated by pulmonary infection. The clinical prediction model established in this study based on four indicators (day 5 LYM, P/F, PCT, and Hb) provides a convenient method for judging patient prognosis.

Full Text

Study on the Predictive Value of a Multi-parameter Model Based on Lymphocyte Count for the Prognosis of Patients with Acute Exacerbation of Interstitial Lung Disease Complicated with Pulmonary Infection

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Abstract

Background: Patients with interstitial lung disease (ILD) are prone to acute exacerbation, with infection being one of the important triggers. Patients with acute exacerbation have high mortality rates and poor prognoses, and currently there are few domestic studies targeting this population. **Objective:** To investigate the clinical predictive value of dynamic changes in peripheral blood lymphocyte count (LYM) for the 28-day prognosis of patients with acute exacerbation of interstitial lung disease (AE-ILD) complicated with pulmonary infection, and to establish a relevant predictive model based on this. **Methods:** AE-ILD patients hospitalized in the Respiratory Department of the Affiliated Hospital of Xuzhou Medical University from January 2022 to June 2024 were retrospectively enrolled as study subjects. Patients were divided into a death group and a survival group based on their 28-day survival status. General patient data collected included: gender, age, diagnosis, ILD type, and underlying diseases; disease severity scores included: Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score; laboratory indicators included: white blood cell count (WBC), neutrophil count (NEU), lymphocyte count on days 1, 3, and 5 (LYM), hemoglobin (Hb), platelet count (PLT), procalcitonin (PCT), C-reactive protein (CRP), albumin (ALb), total bilirubin (T-bil), lactate dehydrogenase (LDH), creatinine (Scr), activated partial thromboplastin time (APTT), partial pressure of oxygen (PO2), partial pressure of carbon dioxide (PCO2), fraction of inspired oxygen (FIO2), oxygenation index (P/F), and lactate (Lac). Differences between the two groups were compared, and statistically significant indicators were screened. Receiver operating characteristic (ROC) curves were plotted to predict the 28-day prognosis of patients. Univariate and multivariate Cox proportional hazards regression analyses were performed using R software. Scores were assigned to each indicator based on the hazard ratio (HR), and a nomogram prediction model was constructed. After calculating the total score of each indicator, risk stratification was established, the ROC curve of the prediction model was plotted, and its predictive value was evaluated. R software was used to plot the 28-day survival curves of AE-ILD patients with different risk stratifications, and the 28-day survival rates of patients in different groups were compared. **Results:** A total of 102 patients were enrolled, including 37 in the survival group and 65 in the death group. The death group had higher APACHE II scores, SOFA scores, PCT, CRP, and LDH than the survival group ($P<0.05$). The death group had lower LYM on days 3 and 5, Alb, and P/F than the survival group ($P<0.05$). With the extension of treatment time, LYM in the death group gradually decreased, while LYM in the survival group gradually increased. ROC curve results showed

that the AUCs of day 3 LYM, day 5 LYM, APACHE II score, and SOFA score for predicting 28-day prognosis in AE-ILD patients were 0.723, 0.764, 0.733, and 0.704, respectively. Multivariate COX regression analysis showed that P/F (HR=2.01, 95%CI=1.08~3.75), PCT (HR=2.14, 95%CI=1.02~4.49), Hb (HR=2.34, 95%CI=1.22~4.48), and day 5 LYM (HR=2.40, 95%CI=1.01~5.70) were independent risk factors for 28-day death in AE-ILD patients. A nomogram model was constructed based on day 5 LYM, P/F, PCT, and Hb. The AUC value of this model for predicting 28-day death in AE-ILD patients was 0.853 (95%CI=0.781~0.925), with an optimal cut-off value of 2, sensitivity of 88.24%, and specificity of 82.35%. According to the optimal risk stratification results, 0~2 points were classified as the low-risk group, and 3~6 points as the high-risk group. The difference in 28-day survival rates between the two groups was statistically significant (^{2}=51, P<0.001). **Conclusion:** The decrease in LYM is associated with increased 28-day mortality in AE-ILD patients complicated with pulmonary infection. The clinical prediction model established in this study based on four indicators (day 5 LYM, P/F, PCT, and Hb) provides a convenient method for judging patient prognosis.

Keywords: Lymphocyte count; Dynamic change; Infection; Acute exacerbation of interstitial lung disease; Prognosis

Introduction

Interstitial lung disease (ILD) is a group of diseases involving the lung interstitium, encompassing more than 200 disease entities. The etiology and pathogenesis of ILD are complex and diverse, and have not yet been fully elucidated [1]. Acute exacerbation of interstitial lung disease (AE-ILD) is one of the leading causes of death in ILD patients [2]. The etiology of AE-ILD is complex, with high mortality rates [3]. The concept of acute exacerbation was initially described in idiopathic pulmonary fibrosis (IPF) [4], but with increasing understanding of ILD, acute exacerbation has been increasingly recognized in other types of ILD [5-7]. In previous diagnostic criteria, the diagnosis of AE-ILD required exclusion of infectious factors, but with in-depth research, infection has been regarded as the primary trigger of acute exacerbation [8-9]. Lymphocyte count (LYM) is an important indicator for measuring immune function and is also a relatively inexpensive and easily obtainable clinical parameter. During severe infection, lymphocytes undergo massive apoptosis [10-11]. Studies have found that lymphocytes are involved in the regulation of fibrosis [12-14]; therefore, it is speculated that LYM plays an important role in the occurrence of AE-ILD. Previous studies [15] have found that low peripheral blood LYM levels are associated with poor short-term prognosis in AE-ILD patients. Further analysis revealed that baseline LYM in AE-ILD patients with infection was not significantly different from that in non-infected patients, but the prognosis of the two groups was significantly different, suggesting that this may be related to the delayed reduction of LYM during the inflammatory period, which limits

the role of LYM in evaluating the inflammatory progression of AE-ILD [16]. Considering that AE-ILD patients have long hospital stays, advanced age, and severe conditions, which differ from ordinary patients with acute pulmonary infection, this study aimed to further explore the relationship between early dynamic changes in LYM and infection-related indicators and prognosis in AE-ILD patients. Through Cox regression analysis, we sought to establish a prognostic prediction model for AE-ILD patients complicated with pulmonary infection, identify predictive factors for prognosis in infection-related AE-ILD, and provide new insights for clinical diagnosis and treatment of AE-ILD.

Methods

1.1 Study Subjects

A retrospective cohort study was conducted, selecting patients hospitalized in the Department of Respiratory and Critical Care Medicine at the Affiliated Hospital of Xuzhou Medical University from January 2022 to June 2024 as study subjects. Patients were divided into survival and death groups based on their 28-day survival status. All patient treatment protocols were in accordance with the Expert Consensus on Diagnosis and Treatment of AE-ILD [17]. This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (approval number: XYFY2024-KL214-01), strictly adhered to ethical requirements in medical clinical research, and was exempted from informed consent.

1.2 AE-ILD Diagnostic Criteria

The latest AE-ILD diagnostic criteria were referenced [17-18]: (1) previous or current diagnosis of ILD; (2) acute deterioration or progression of dyspnea usually occurring within 1 month; (3) high-resolution CT of the chest showing newly emerged diffuse ground-glass nodules and/or consolidation shadows on the original ILD background; (4) exclusion of heart failure or fluid overload.

1.3 Inclusion and Exclusion Criteria

Inclusion criteria: (1) met AE-ILD diagnostic criteria; (2) clearly complicated with infection (having infection symptoms, elevated inflammatory markers, imaging infection manifestations, and etiological results); (3) AE-ILD patients aged 18-80 years; (4) patients with normally recorded follow-up data.

Exclusion criteria: (1) history of organ transplantation; (2) history of acquired immunodeficiency; (3) history of malignant tumors; (4) use of immunotherapy drugs during treatment; (5) hospital stay <72 hours; (6) pregnant or lactating patients; (7) patients with missing medical data.

1.4 General Data Collection

General patient information was collected, including gender, age, diagnosis, ILD type, and underlying diseases (including chronic diseases such as diabetes, cardiovascular disease, and renal disease).

1.5 Admission Condition Scoring

Sequential Organ Failure Assessment (SOFA) Score: Based on oxygenation index, platelet count, serum total bilirubin level, mean arterial pressure, dose of vasoactive drugs, Glasgow Coma Scale score, and creatinine level, each system is scored according to specific physiological parameters (0-4 points, total score 0-24 points).

Acute Physiology and Chronic Health Evaluation II (APACHE II): Based on acute physiology score (including body temperature, mean arterial pressure, heart rate, respiratory rate, and other indicators), age, and chronic health status score (whether there is severe organ dysfunction or immunosuppression, scored according to whether surgery was performed), with a total score of 0-71 points, where higher scores indicate more severe condition and poorer prognosis.

1.6 Laboratory Indicators

Laboratory test indicators collected at the time of patient admission included: white blood cell count (WBC), neutrophil count (NEU), lymphocyte count on days 1, 3, and 5 (LYM), hemoglobin (Hb), platelet count (PLT), procalcitonin (PCT), C-reactive protein (CRP), albumin (ALb), total bilirubin (T-bil), lactate dehydrogenase (LDH), creatinine (Scr), activated partial thromboplastin time (APTT), partial pressure of oxygen (PO2), partial pressure of carbon dioxide (PCO2), fraction of inspired oxygen (FIO2), oxygenation index (PaO2/FiO2, P/F), and lactate (Lac).

1.7 Statistical Methods

SPSS 25.0 software was used for statistical analysis. Normally distributed data were expressed as ($\bar{x}\pm s$) and compared between groups using independent samples t-test; non-normally distributed data were expressed as M(P25, P75) and compared between groups using rank-sum test; categorical data were expressed as relative numbers and compared between groups using ^{2} test. Receiver operating characteristic (ROC) curves were plotted to predict the 28-day prognosis of infection-related AE-ILD patients, and the area under the ROC curve (AUC) was calculated to compare the predictive value of different clinical indicators for infection-related AE-ILD prognosis. R software "ezcox" was used for univariate and multivariate Cox regression analysis to establish proportional hazards assumptions, visually interpret the impact of covariates on risk, and analyze the effects of multiple confounding factors. Multicollinearity was tested by calculating VIF values to evaluate whether there was collinearity between variables. A

nomogram prediction model was constructed based on influencing factors from multivariate Cox regression analysis. After calculating the total score of each indicator, risk stratification was established. Based on the established prediction model, R software "survminer" package was used to plot survival curves predicting 28-day prognosis in AE-ILD patients complicated with pulmonary infection, and the "pROC" package was used to plot ROC curves of the prediction model. $P<0.05$ was considered statistically significant.

Results

2.1 Comparison of Baseline Indicators Between Death and Survival Groups

This study collected data from 523 ILD patients, of which 351 met AE-ILD diagnostic criteria. According to exclusion criteria, 87 non-infection AE-ILD patients were excluded, 51 patients with missing medical data, 3 with organ transplantation history, 6 with malignant tumor history, 21 using immunotherapy drugs, 2 with hospital stay <72 hours, and 0 pregnant or lactating patients. A total of 102 patients met inclusion criteria, with complete and reliable data; no imputation was performed. Among the 102 enrolled patients, 62 were male (60.8%) and 40 were female (39.2%); median age was 69 (57, 83) years; 65 were in the 28-day death group (63.7%) and 37 in the survival group (36.3%). The death group had significantly higher rates of comorbid cardiovascular disease and renal insufficiency, as well as higher APACHE II scores, SOFA scores, PCT, CRP, and LDH than the survival group. The death group had significantly lower LYM on days 3 and 5, Alb, and P/F than the survival group (all $P<0.05$). There were no significant differences between groups in gender, age, diabetes comorbidity, ILD type, PLT, T-Bil, or Scr ($P>0.05$) (see Table 1). Multicollinearity testing of included variables showed all VIF values were less than 5, indicating no significant collinearity.

2.2 ROC Curves of Clinical Indicators for Predicting 28-Day Prognosis in AE-ILD Patients

ROC curves were plotted for LYM levels at different time points, disease severity scores, and other major clinical indicators to predict 28-day prognosis in AE-ILD patients. Results showed that the AUC of day 3 LYM for predicting 28-day death was 0.723 (95%CI=0.626~0.820), with an optimal cut-off value of 0.55; the AUC of day 5 LYM was 0.764 (95%CI=0.672~0.856), with an optimal cut-off value of 0.7. Delong test results showed that the AUC of day 5 LYM was higher than that of day 3 LYM, with a statistically significant difference ($Z=1.86$, $P=0.04$). The AUCs of PCT, CRP, Lac, P/F, Hb, Alb, and LDH were all below 0.7, suggesting their limited predictive value for 28-day prognosis as single indicators.

2.3 Univariate and Multivariate COX Regression Analysis of 28-Day Prognosis in AE-ILD Patients

Based on intergroup comparison results, clinical predictive indicators potentially closely related to AE-ILD patient prognosis were selected. With 28-day prognosis as the dependent variable (assignment: death=1, survival=0) and clinical predictive indicators (including SOFA score, APACHE II score, Lac, P/F, PCT, LDH, Alb, CRP, Hb, day 3 LYM, day 5 LYM, all assigned as actual measured values) as independent variables, univariate Cox proportional hazards regression analysis was performed. Results showed that SOFA score (HR=2.20, 95%CI=1.27~3.81), APACHE II score (HR=3.15, 95%CI=1.78~5.58), Lac (HR=2.06, 95%CI=1.14~3.73), P/F (HR=2.57, 95%CI=1.47~4.47), PCT (HR=4.23, 95%CI=2.16~8.27), LDH (HR=4.12, 95%CI=1.28~13.2), Alb (HR=2.16, 95%CI=1.22~3.82), CRP (HR=2.20, 95%CI=1.26~3.84), Hb (HR=3.52, 95%CI=1.98~6.28), day 3 LYM (HR=3.56, 95%CI=2.02~6.27), and day 5 LYM (HR=3.93, 95%CI=1.96~7.88) were influencing factors for 28-day death in AE-ILD patients (see Table 3). Factors with P<0.01 in univariate Cox regression were included as independent variables, with 28-day prognosis as the dependent variable for multivariate Cox proportional hazards regression analysis. Results showed that P/F (HR=2.01, 95%CI=1.08~3.75), PCT (HR=2.14, 95%CI=1.02~4.49), Hb (HR=2.34, 95%CI=1.22~4.48), and day 5 LYM (HR=2.40, 95%CI=1.01~5.70) were independent risk factors for 28-day death in infection-related AE-ILD patients (see Table 4).

2.4 Construction and Performance Validation of Multi-parameter Model for Predicting 28-Day Prognosis in AE-ILD Patients

Using R software, a nomogram prediction model was constructed based on influencing factors from multivariate Cox regression analysis. First, scores were assigned to each influencing factor: day 5 LYM, P/F, PCT, and Hb. Variable scores in the nomogram were non-integer values; for clinical convenience, scores were assigned as follows: day 5 LYM (>0.7$\times 10^{\{9\}/L = 0 points, < 0.7\times 10}\{9\}$/L=1 point), P/F (>132 mmHg=0 points, <132 mmHg=1 point), PCT (<0.12 g/L=0 points, >0.12 g/L=2 points), Hb (>100 g/L=0 points, <100 g/L=1 point) (see Figure 2 [Figure 2: see original paper]). After calculating the total score, optimal risk stratification was performed using X-tile software, with 0-2 points as the low-risk group and 3-6 points as the high-risk group.

The ROC curve of the nomogram model for predicting 28-day prognosis was plotted. Results showed that the AUC value of the nomogram model for predicting 28-day death was 0.853 (95%CI=0.781~0.925), with an optimal cut-off value of 2, sensitivity of 88.24%, and specificity of 82.35% (see Figure 3 [Figure 3: see original paper]).

2.5 Comparison of 28-Day Survival Curves Between High-Risk and Low-Risk AE-ILD Patients

Based on the established nomogram model, survival curves for 28-day death in high-risk and low-risk AE-ILD patients were plotted. Results showed that the difference in 28-day survival rates between high-risk and low-risk patients was statistically significant (^{2}=51, P<0.001) (see Figure 4 [Figure 4: see original paper]).

Discussion

Acute exacerbation is a common event in the natural course of ILD patients, with high mortality rates [2]. Studies have confirmed that infection is an important external cause of AE-ILD [19-20], with approximately 30% of AE-ILD patients complicated with infection [21]. The mechanism by which infection leads to ILD exacerbation may be related to pathogens triggering immune responses. For example, CHO et al. [22] found that *Streptococcus pneumoniae* infection could accelerate pulmonary fibrosis progression through AIM2 inflammasome activation. AE-ILD patients complicated with infection often exhibit decreased LYM [23-24]. Considering that LYM is closely related to both infection and ILD progression, this study focused on the predictive value of dynamic LYM monitoring for prognosis in AE-ILD patients with infection, aiming to construct a practical model to guide clinical decision-making.

Baseline data analysis in this study showed that the death group of AE-ILD patients had significantly higher rates of comorbid cardiovascular disease and renal insufficiency, as well as higher APACHE II scores, SOFA scores, PCT, CRP, and LDH than the survival group. This suggests that systemic inflammatory response, organ dysfunction, and immune suppression may be closely related to short-term prognosis in AE-ILD patients. Over time, LYM in the death group showed a downward trend, while LYM in the survival group gradually increased, with both day 3 and day 5 LYM associated with patient prognosis. The mechanism of LYM reduction in AE-ILD patients may be related to pulmonary inflammation releasing chemokines such as CXCL9/CXCL10, which drive peripheral blood T lymphocyte migration to lung tissue, ultimately resulting in decreased peripheral blood LYM [25]. This phenomenon is closely related to disease deterioration and poor prognosis.

ROC curve results showed that day 3 LYM, day 5 LYM, APACHE II score, and SOFA score all had certain predictive value for 28-day prognosis, with day 5 LYM having the highest predictive value (AUC=0.764). This suggests that dynamic monitoring of LYM levels (especially on day 5) may be more beneficial for early identification of high-risk patients, while single inflammatory markers (such as PCT, CRP) have limited predictive ability. Similar to our findings, in septic shock patients, day 4 lymphocyte count can predict 28-day mortality [26]. Cox regression analysis ultimately identified day 5 LYM, P/F,

PCT, and Hb as independent risk factors for 28-day death, suggesting that oxygenation impairment, inflammatory response, anemia, and immune suppression are core drivers of short-term death in infection-related AE-ILD patients. The nomogram model constructed based on these indicators (AUC=0.853, sensitivity 88.24%, specificity 82.35%) achieved efficient risk stratification after survival analysis validation using a cut-off value of 2 points (low risk 0-2 points, high risk 3-6 points), suggesting that this model can provide quantitative basis for clinical intervention.

To enable rapid prognosis assessment and timely intervention for infection-related AE-ILD patients, this study established a nomogram model using four relatively simple and easily obtainable clinical indicators (day 5 LYM, P/F, PCT, Hb). Currently commonly used clinical severity scoring systems (such as APACHE II, SOFA), while able to assess patient condition severity, focus on systemic organ status and are complex to operate, potentially underestimating respiratory system-specific risks. This model focuses on infection-related AE-ILD patients, with high sensitivity and specificity. Its advantages lie in convenient operation, low cost, and strong applicability, making it suitable for medical institutions at all levels and providing a practical tool for rapid prognosis assessment and stratified management of infection-related AE-ILD patients.

This study has several limitations: (1) It is a single-center study lacking patient data from other centers; (2) The number of enrolled patients is relatively small, requiring further expansion of sample size to reduce bias; (3) This study only tracked 28-day survival status without longer-term follow-up.

In summary, this study found that dynamic decrease in LYM is associated with increased 28-day mortality in infection-related AE-ILD patients, and established a nomogram model for predicting prognosis in infection-related AE-ILD patients based on indicators including day 5 LYM. This model can help clinicians early identify severe AE-ILD patients, enable timely intervention, and improve prognosis. Future research will conduct multi-center large-sample studies to explore the prognostic value of other clinical indicators and perform long-term follow-up studies.

References

[1] JIANG H D, CHEN B. Re-recognition of interstitial lung disease [J]. National Medical Journal of China, 2021, 101(20): 1453-1457. DOI:10.3760/cma.j.cn112137-

[2] CHAROKOPOS A, TENG M A, RYU J H, et al. Acute exacerbation of interstitial lung disease in the intensive care unit [J]. World J Crit Care Med, 2022, 11(1): 22-32. DOI:10.5492/wjccm.v11.i1.22.

[3] SALONEN J, PUROKIVI M, BLOIGU R, et al. Prognosis and causes of death of patients with acute exacerbation of fibrosing interstitial lung diseases [J]. BMJ Open Respir Res, 2020, 7(1): e000563. DOI:10.1136/bmjresp-2020-

000563.
[4] HOYER N, BENDSTRUP E, DAVIDSEN J R, et al. Acute exacerbation of fibrotic interstitial lung diseases [J]. Ugeskr Laeger, 2023, 185(33): V04230261.
[5] HOZUMI H, KONO M, HASEGAWA H, et al. Acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: mortality and its prediction model [J]. Respir Res, 2022, 23(1): 57. DOI:10.1186/s12931-022-01978-y.
[6] PARK I N, KIM D S, SHIM T S, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis [J]. Chest, 2007, 132(1): 214-220. DOI:10.1378/chest.07-0323.
[7] KOLB M, BONDUE B, PESCI A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases [J]. Eur Respir Rev, 2018, 27(150): 180071. DOI:10.1183/16000617.0071-2018.
[8] SUZUKI A, KONDOH Y, BROWN K K, et al. Acute exacerbations of fibrotic interstitial lung diseases [J]. Respirology, 2020, 25(5): 525-534. DOI:10.1111/resp.13682.
[9] GAN W H, SONG W W, GAO Y J, et al. Exosomal circRNAs in the plasma serve as novel biomarkers for IPF diagnosis and progression prediction [J]. J Transl Med, 2024, 22(1): 264. DOI:10.1186/s12967-024-05034-9.
[10] CILLONIZ C, PERONI H J, GABARRÚS A, et al. Lymphopenia is associated with poor outcomes of patients with community-acquired pneumonia and sepsis [J]. Open Forum Infect Dis, 2021, 8(6): ofab169. DOI:10.1093/ofid/ofab169.
[11] PODD B S, BANKS R K, REEDER R, et al. Early, persistent lymphopenia is associated with prolonged multiple organ failure and mortality in septic children [J]. Crit Care Med, 2023, 51(12): 1766-1776. DOI:10.1097/CCM.0000000000005993.
[12] XU Y H, LAN P X, WANG T. The role of immune cells in the pathogenesis of idiopathic pulmonary fibrosis [J]. Medicina, 2023, 59(11): 1984. DOI:10.3390/medicina59111984.
[13] RAO M, WANG X L, GUO G R, et al. Resolving the intertwining of inflammation and fibrosis in human heart failure at single-cell level [J]. Basic Res Cardiol, 2021, 116(1): 55. DOI:10.1007/s00395-021-00897-1.
[14] ZHANG M J, ZHANG S. T cells in fibrosis and fibrotic diseases [J]. Front Immunol, 2020, 11: 1142. DOI:10.3389/fimmu.2020.01142.
[15] MENG X, XI B, CHEN B, et al. Predictive value of lymphocyte count for short-term prognosis of patients with acute exacerbation of interstitial lung disease [J]. International Journal of Respiration, 2024, 44(05): 576-584. DOI:10.3760/cma.j.cn131368-20231117-00337.
[16] CHEN Y, GUO D Z, ZHU C L, et al. The implication of targeting PD-1:PD-L1 pathway in treating sepsis through immunostimulatory and anti-inflammatory pathways [J]. Front Immunol, 2023, 14: 1323797. DOI:10.3389/fimmu.2023.1323797.
[17] Interstitial Lung Disease Group of Chinese Thoracic Society, Interstitial Lung Disease Working Committee of Chinese Association of Chest Physicians. Chinese expert consensus on diagnosis and treatment of acute exacerbation

of idiopathic pulmonary fibrosis [J]. National Medical Journal of China, 2019, 99(26): 2014-2023. DOI:10.3760/cma.j.issn.0376-2491.2019.26.005.
[18] BA C R, JIANG C G, WANG H J, et al. Prognostic value of serum oncomarkers for patients hospitalized with acute exacerbation of interstitial lung disease [J]. Ther Adv Respir Dis, 2024, 18: 17534666241250332. DOI:10.1177/17534666241250332.
[19] ZHONG B Y, ZHOU J Q, LYU X, et al. Anti-heat shock protein 70 autoantibodies from patients with idiopathic pulmonary fibrosis epigenetically enhance lung fibroblast apoptosis resistance and bcl-2 expression [J]. J Immunol, 2024, 213(8): 1150-1156. DOI:10.4049/jimmunol.2400106.
[20] ZANUSSI J T, ZHAO J, WEI W Q, et al. Clinical diagnoses associated with a positive antinuclear antibody test in patients with and without autoimmune disease [J]. BMC Rheumatol, 2023, 7(1): 24. DOI:10.1186/s41927-023-00349-4.
[21] TENG M A, WESTERLY B D, DULOHERY M M, et al. Patients with fibrotic interstitial lung disease hospitalized for acute respiratory worsening a large cohort analysis [J]. Chest, 2016, 149(5): 1205-1214. DOI:10.1016/j.chest.2015.12.026.
[22] CHO S J, MOON J S, NIKAHIRA K, et al. GLUT1-dependent glycolysis regulates exacerbation of fibrosis via AIM2 inflammasome activation [J]. Thorax, 2020, 75(3): 227-236. DOI:10.1136/thoraxjnl-2019-213571.
[23] WENG D, CHEN X Q, QIU H, et al. The role of infection in acute exacerbation of idiopathic pulmonary fibrosis [J]. Mediators Inflamm, 2019, 2019: 5160694. DOI:10.1155/2019/5160694.
[24] LIANG J Y, CAO H, KE Y N, et al. Acute exacerbation of interstitial lung disease in adult patients with idiopathic inflammatory myopathies: a retrospective case-control study [J]. Front Med (Lausanne), 2020, 7: 12. DOI:10.3389/fmed.2020.00012.
[25] WANG M M, SONG L Q, CHEN J, et al. Analysis of peripheral blood lymphocyte subsets in patients with acute exacerbation of interstitial lung disease [J]. Journal of Clinical Pulmonary Medicine, 2024, 29(5): 660-664. DOI:10.3969/j.issn.1009-6663.2024.05.003.
[26] JING J J, WEI Y S, DONG X, et al. Characteristics and clinical prognosis of septic patients with persistent lymphopenia [J]. J Intensive Care Med, 2024, 39(8): 733-741. DOI:10.1177/08850666241226877.

Figure Captions

Figure 1 [Figure 1: see original paper] ROC curves of various clinical indicators for predicting the 28-day prognosis of AE-ILD patients. Note: A shows ROC curves of P/F and Alb indicators for predicting 28-day prognosis in AE-ILD patients; B shows ROC curves of Hb, PLT, day 3 LYM, and day 5 LYM indicators for predicting 28-day prognosis in AE-ILD patients; C shows ROC curves of PCT, Lac, CRP, LDH, APACHE II, and SOFA scores for predicting 28-day prognosis in AE-ILD patients. APACHE II=Acute Physiology and Chronic Health Evaluation II, SOFA=Sequential Organ Failure

Assessment, LYM=Lymphocyte count, Hb=Hemoglobin, PLT=Platelet count, PCT=Procalcitonin, CRP=C-reactive protein, LDH=Lactate dehydrogenase, P/F=Oxygenation index, Lac=Lactate, d1=Day 1, d3=Day 3, d5=Day 5.

Figure 2 [**Figure 2: see original paper**] Nomogram for predicting the 28-day mortality risk in patients with AE-ILD.

Figure 3 [**Figure 3: see original paper**] ROC curve for predicting the 28-day mortality risk of AE-ILD patients using nomogram model.

Figure 4 [**Figure 4: see original paper**] Survival curves of 28-day mortality for AE-ILD patients in the high-risk group and the low-risk group.

Note: Figure translations are in progress. See original paper for figures.