ORIGINAL RESEARCH

Utility of Bronchoalveolar Lavage Fluid Cellular Composition in the Differential Diagnosis of Idiopathic Pulmonary Fibrosis: a preliminary study

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Abstract

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease with poor prognosis. Its early diagnosis is challenging due to nonspecific clinical features and overlap with infectious pulmonary diseases. Bronchoalveolar lavage fluid (BALF) provides direct access to lower respiratory tract cellular components, offering potential adjunctive diagnostic value. This study aimed to evaluate the cytological characteristics of BALF in IPF and assess their utility in differentiating IPF from non-fibrotic pneumonia.

Methods

We retrospectively analyzed 64 IPF patients and 64 age-, sex-, and intensive care unit (ICU) admission–matched patients with community-acquired pneumonia (CAP) who underwent BAL at the First Affiliated Hospital of Xi'an Jiaotong University (January 2021–November 2025). BALF total cell counts and differential cell proportions were measured. Multivariable logistic regression identified independent discriminators, and receiver operating characteristic (ROC) curve analysis evaluated the diagnostic performance of individual and combined BALF parameters.

Results

IPF patients showed significantly higher proportions of macrophages (median 29.55% vs. 11.70%, P<0.001), lymphocytes (7.20% vs. 3.60%, P=0.031), and eosinophils (1.00% vs. 0.40%, P=0.008), and a significantly lower neutrophil proportion (58.50% vs. 80.90%, P<0.001) compared with pneumonia patients. Multivariable analysis confirmed eosinophil percentage (OR=1.871, 95%CI:1.123–2.836) and macrophage percentage (OR=1.139, 95%CI:1.082–1.199) as independent discriminators of IPF. The combined logistic regression model incorporating these two parameters yielded an area under the curve (AUC) of 0.832 (95%CI:0.761–0.903), with a sensitivity of 93.8% and a specificity of 65.6%, outperforming either parameter alone.

Conclusions

BALF cellular profiles differ significantly between IPF and non-fibrotic pneumonia. Macrophage and eosinophil percentages are independent discriminators of IPF, and their combination provides good discriminative performance. Although BALF cytology alone is insufficient for a definitive diagnosis, it serves as a valuable adjunctive tool, particularly when high-resolution computed tomography findings are atypical or when infection is suspected. These findings support the potential utility of BALF cellular analysis in the diagnostic workup of IPF and warrant further prospective validation, including integration with molecular biomarkers.

Keywords: Bronchoalveolar lavage fluid, Idiopathic pulmonary fibrosis, Differential diagnosis, ROC curve

Introduction

Interstitial lung disease (ILD) is a heterogeneous group of diffuse parenchymal lung disorders that primarily involve the pulmonary interstitium and alveolar spaces, and are pathologically characterized by varying degrees of alveolitis and fibrosis[1]. Epidemiological studies report an annual incidence of ILD of 20–30 per 100,000 population, with a prevalence of 60–80 per 100,000[2]. The most common forms include sarcoidosis, idiopathic pulmonary fibrosis (IPF), and connective tissue disease–associated ILD (CTD-ILD), with occurrence and progression influenced by age, sex, and geographic factors[3].

Among idiopathic interstitial pneumonias (IIPs), IPF is the most frequent and carries the poorest prognosis. It is a chronic, progressive interstitial pneumonia of unknown etiology, characterized by irreversible pulmonary fibrosis, predominantly affecting older adults and confined to the lungs[4]. Although antifibrotic therapies can slow disease progression, overall survival remains limited, and early diagnosis is often challenging.

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Clinical features of IPF are nonspecific, particularly in early stages or during acute exacerbations, making differentiation from infectious pulmonary diseases, such as community-acquired pneumonia and bronchopneumonia, difficult and prone to misdiagnosis. High-resolution computed tomography (HRCT) is essential for diagnosis, but imaging findings may be atypical, and definitive diagnosis cannot always be established[5,6]. Surgical lung biopsy remains the histopathological gold standard, yet its utility is limited by sampling bias, interobserver variability, and procedural risks, including acute exacerbation[7].

Advances in laboratory diagnostics have enabled the use of noninvasive or minimally invasive techniques in ILD evaluation. Bronchoalveolar lavage (BAL) has emerged as a useful adjunct. Bronchoalveolar lavage fluid (BALF) provides direct access to cellular and noncellular components of the lower respiratory tract, allowing a more accurate reflection of local pulmonary inflammation and fibrosis-related pathological changes than peripheral blood biomarkers, with greater anatomical and pathological specificity[8].

Although BALF cytology holds considerable potential, its clinical utility is limited by the relative difficulty of sample collection compared with serum, as well as variability in recovery rates and lavage sites, which can lead to substantial differences in sample quality. Consequently, the value of BALF in the assessment of patients with IPF has likely been underestimated. The present study aimed to retrospectively characterize BALF cytological profiles in patients with IPF and systematically evaluate the distribution and diagnostic utility of various BALF cellular components, with particular emphasis on their potential to differentiate IPF from other infectious pulmonary diseases.

Methods

Study Population

This retrospective study included patients with IPF who underwent BAL at the First Affiliated Hospital of Xi'an Jiaotong University between January 2021 and November 2025. A total of 64 patients with IPF were enrolled, all of whom met the diagnostic criteria for interstitial lung disease established by the American Thoracic Society/European Respiratory Society (ATS/ERS)[1].

During the same period, 64 patients with community-acquired pneumonia (CAP) who underwent BAL at the same institution were retrospectively collected as a control group, matched 1:1 by sex, age, and intensive care unit (ICU) admission status. All patients in the pneumonia group fulfilled the diagnostic criteria outlined in the Guidelines for the Primary Diagnosis and Treatment of Adult Community-Acquired Pneumonia (2018)[9].

Exclusion Criteria

Patients meeting any of the following criteria were excluded: (1) presence of malignant tumors; (2) history of hematopoietic stem cell transplantation or other organ transplantation; (3) active pulmonary tuberculosis; (4) severe hepatic or renal dysfunction; (5) documented cardiovascular diseases; (6) coexistence of other pulmonary diseases or active infections; (7) long-term use of systemic corticosteroids or immunosuppressive agents; (8) psychiatric disorders; and (9) age younger than 18 years.

BALF Collection and Cytological Analysis

BAL was performed according to standardized guidelines. All patients underwent bronchoscopy after routine preprocedural nebulized local anesthesia. BAL was performed in the right middle lobe or the left lingular segment. Sterile normal saline was instilled in aliquots of 25–50 mL, with a total lavage volume ranging from 100 to 250 mL. The lavage fluid was recovered using a negative pressure of 50–100 mmHg (1 mmHg = 0.133 kPa), and a recovery rate of at least 30% was required. Collected specimens were transported to the laboratory immediately and processed within 30 minutes.

Recovered BALF samples were transferred into sterile plastic centrifuge tubes. Total cell counts were determined using a modified Neubauer hemocytometer. The samples were then centrifuged at 400 × g for 10 minutes at 4 °C (Thermo Fisher Scientific, USA). After removal of the supernatant, the cell pellet was used to prepare cytospin slides, which were stained with Wright–Giemsa stain (Baso Diagnostics Inc., Zhuhai, China). Differential cell counts were performed under a light microscope at ×1,000 magnification in a blinded manner by two experienced technicians, with at least 200 cells counted per slide. The relative proportions of neutrophils, lymphocytes, macrophages, eosinophils, and ciliated epithelial cells were calculated.

Data Collection

Clinical and laboratory data were retrospectively retrieved from the hospital laboratory information system (LIS). Collected variables included age, gender, admitting department, primary diagnosis, and laboratory results of BALF analysis.

Ethical Approval

All procedures performed in our studies involving human participants followed all the ethical standards of the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (approval number: XJTU1AF2025LSYY-945). Due to the retrospective nature of the study, the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University waived the need of obtaining informed consent.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA), and graphical visualizations were generated using GraphPad Prism (version 9.5). Continuous variables with a normal distribution are presented as mean ± standard deviation (Mean ± SD) and were compared between groups using the independent samples t-test. Non-normally distributed continuous variables are presented as median (interquartile range) [M (Q_1, Q_3)] and were compared using the Mann–Whitney U test. Categorical variables are expressed as counts and percentages [n (%)] and were compared using the χ^2 test or Fisher's exact test, as appropriate.

For variables that showed statistically significant differences between groups in univariate analysis, multivariable logistic regression was performed. Receiver operating characteristic (ROC) curves were constructed to evaluate diagnostic performance. The optimal cutoff value was determined as the value corresponding to the maximum Youden index. An area under the curve (AUC) between 0.5 and 1 was considered to indicate diagnostic value. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

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Table 1. Baseline characteristics and BALF cellular profiles of patients with IPF and pneumonia

Variables	Total (n = 128)	Pneumonia (n = 64)	IPF (n = 64)	Statistic	P value
Age, Mean ± SD	57.81 ± 10.96	56.91 ± 11.78	58.72 ± 10.08	t=-0.94	0.351
Male, n (%)	66 (51.56)	34 (53.12)	32 (50.00)	χ^2=0.13	0.724
ICU admission, n (%)				χ^2=0.50	0.478
No	70 (54.69)	33 (51.56)	37 (57.81)		
Yes	58 (45.31)	31 (48.44)	27 (42.19)		
BALF appearance, n (%)				χ^2=10.16	**0.006**
Clear	29 (22.66)	7 (10.94)	22 (34.38)		
Slightly turbid	38 (29.69)	21 (32.81)	17 (26.56)		
Turbid	61 (47.66)	36 (56.25)	25 (39.06)		
BALF color, n (%)				χ^2=15.00	**0.002**
Colorless	39 (30.47)	15 (23.44)	24 (37.50)		
Bloody	38 (29.69)	21 (32.81)	17 (26.56)		
Yellowish	24 (18.75)	7 (10.94)	17 (26.56)		
Whitish	27 (21.09)	21 (32.81)	6 (9.38)		
Iron stain positive, n (%)	28 (21.88)	15 (23.44)	13 (20.31)	χ^2=0.18	0.669
Total cell count (×10⁶/mL) [M (Q1, Q3)]	868.50 (137.50, 3099.25)	1721.50 (552.75, 3207.00)	271.00 (74.50, 2769.50)	Z=-3.09	**0.002**
Macrophages, % [M (Q1, Q3)]	17.95 (9.17, 29.42)	11.70 (6.00, 19.60)	29.55 (13.55, 39.25)	Z=-5.85	**<0.001**
Neutrophils, % [M (Q1, Q3)]	72.10 (52.98, 85.12)	80.90 (70.42, 89.67)	58.50 (45.25, 79.78)	Z=-4.67	**<0.001**
Lymphocytes, % [M (Q1, Q3)]	5.20 (2.35, 12.12)	3.60 (1.95, 10.70)	7.20 (3.27, 13.00)	Z=-2.15	**0.031**
Eosinophils, % [M (Q1, Q3)]	0.70 (0.20, 1.30)	0.40 (0.10, 1.00)	1.00 (0.47, 1.80)	Z=-2.66	**0.008**

Table 2. Independent discriminators of IPF identified by multivariable logistic regression analysis

Variables	β	S.E	Z	*P*	OR (95%CI)
Intercept	-2.118	0.740	-2.860	**0.004**	0.120 (0.028 ~ 0.513)
Macrophages（%）	0.130	0.026	4.990	**<0.001**	1.139 (1.082 ~ 1.199)
Eosinophils（%）	0.626	0.212	2.953	**0.003**	1.871 (1.234 ~ 2.836)

Table 3. ROC analysis of individual and combined parameters for the diagnosis of IPF

Parameter	AUC (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Cut off
Macrophages (%)	0.80 (0.723-0.876)	0.984 (0.954 – 1.000)	0.547 (0.425 - 0.669)	0.685 (0.590 - 0.780)	0.972 (0.919 – 1.000)	27.6
Eosinophils (%)	0.636(0.538-0.734)	0.578 (0.457 - 0.699)	0.719 (0.609 - 0.829)	0.673 (0.549 - 0.797)	0.630 (0.519 - 0.741)	0.6
Combined diagnostic model	0.832 (0.761-0.903)	0.938(0.878 - 0.997)	0.656(0.540 - 0.773)	0.732 (0.636 - 0.828)	0.913 (0.832 - 0.994)	0.6

Results

Baseline Characteristics of the Study Population

A total of 128 patients were included in this study, comprising 64 patients with IPF and 64 patients with pneumonia. Baseline characteristics of the cohort are presented in Table 1. No significant differences were observed between the two groups in age (58.72 ± 10.08 years vs. 56.91 ± 11.78 years, P = 0.351), male proportion (50.00% vs. 53.13%, P = 0.724), or ICU admission rate (42.19% vs. 48.44%, P = 0.478).

BALF Cellular Profiles

Significant differences in BALF cellular profiles were observed between the IPF and pneumonia groups. The IPF group showed significantly higher proportions of macrophages (median: 29.55% vs. 11.70%, P < 0.001), lymphocytes (7.20% vs. 3.60%, P = 0.031), and eosinophils (1.00% vs. 0.40%, P = 0.008), and a significantly lower proportion of neutrophils (58.50% vs. 80.90%, P < 0.001) compared with the pneumonia group. In addition, the total cell count was significantly lower in the IPF group than in the pneumonia group (271.00 × 10^6/mL vs. 1721.50 × 10^6/mL, P = 0.002). No significant difference was found in iron stain positivity between the two groups (P = 0.669), whereas significant differences were observed in BALF appearance and color (P < 0.001) (Table 1).

Multivariable Logistic Regression Analysis

Variables that showed statistically significant differences between groups in Table 1 were simultaneously entered into

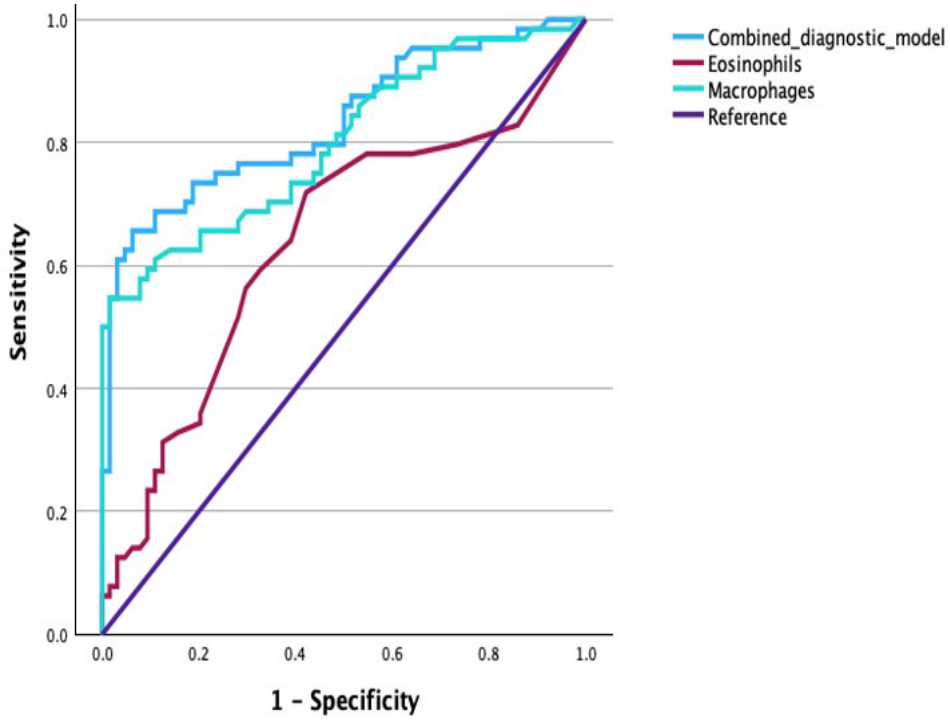

Figure 1. ROC curves of individual and combined BALF parameters for differentiating IPF from pneumonia

a multivariable logistic regression analysis to control for potential confounders. Ultimately, eosinophil percentage (OR 1.871, 95% CI 1.123–2.836) and macrophage percentage (OR 1.139, 95% CI 1.082–1.199) were confirmed as independent discriminators of IPF (Table 2). The diagnostic equation constructed based on the multivariable logistic regression analysis is as follows:

Logit(P) = –2.118 + 0.130 × (Macrophages %) + 0.626 × (Eosinophils %).

BALF Cellular Profiles as a Differential Diagnostic Tool

The discriminative ability of individual BALF parameters, as well as a combined diagnostic model, was assessed using receiver operating ROC curve analysis. The results are summarized in Table 3 and Figure 1. The AUC for macrophage percentage was 0.800 (95% CI: 0.723–0.876), with a sensitivity of 98.4% (95% CI: 0.954–1.000) and a specificity of 54.7% (95% CI: 0.425–0.669). For eosinophil percentage, the AUC was 0.636 (95% CI: 0.538–0.734), with a sensitivity of 57.8% (95% CI: 0.457–0.699) and a specificity of 71.9% (95% CI: 0.609–0.829). The combined diagnostic model, constructed using logistic regression incorporating macrophage and eosinophil percentages, demonstrated the highest discriminative performance, with an AUC of 0.832 (95% CI: 0.761–0.903), a sensitivity of 93.8% (95% CI: 0.878–0.997), and a specificity of 65.6% (95% CI: 0.540–0.773). The optimal cutoff values derived from the Youden index were 27.6 for macrophage percentage, 0.6 for eosinophil percentage, and 0.6 for the combined diagnostic model.

Discussion

In the diagnosis of IPF, in addition to HRCT, the 2011 ATS/ERS international multidisciplinary consensus statement and subsequent guidelines[1] have emphasized the adjunctive role of BALF cellular analysis. The guidelines recommend that, in centers equipped to perform BAL and analyze BALF cell differentials, BALF cytology can be conducted when HRCT shows atypical patterns of usual interstitial pneumonia (UIP) to aid in distinguishing specific subtypes of interstitial lung disease, malignancies, or other pulmonary conditions.

In this study, we retrospectively analyzed BALF cellular profiles in patients with IPF and compared them with those of patients with non-fibrotic pneumonia. Significant differences were observed between the two groups, particularly in the proportions of macrophages, lymphocytes, eosinophils, and neutrophils. Multivariable logistic regression analysis identified eosinophil percentage (OR =1.871, 95% CI: 1.123–2.836) and macrophage percentage (OR=1.139, 95%CI:1.082–1.199) as independent discriminators of IPF. ROC curve analysis demonstrated that a combined model integrating multiple cellular parameters exhibited superior discriminative performance in differentiating IPF from pneumonia (AUC = 0.832, 95% CI: 0.761–0.903).

Pulmonary macrophages are activated in IPF, secreting profibrotic mediators that stimulate fibroblasts and promote fibrosis[10]. Lung macrophages comprise alveolar macrophages (AMs) in the airways and interstitial macrophages (IMs) in the parenchyma. AMs exhibit dual effects on fibrosis: they secrete cytokines and chemokines such as TGF-β1 and platelet-derived growth factor to promote fibrosis, but they can also phagocytose collagen or degrade extracellular matrix to limit matrix deposition. IMs typically express CD206, IL-10, and arginase-1, contributing to fibrosis development[11]. Clinical studies have shown that increased BALF eosinophils in IPF may relate to eosinophil-mediated inflammatory injury[12], with eosinophils secreting monocyte chemoattractant protein-1, TGF-β, and other proinflammatory/profibrotic factors. Peptidyl-prolyl cis-trans isomerases in eosinophils may enhance TGF-β mRNA stability, further promoting fibrosis[13]. In this study, IPF patients had significantly higher percentages of eosinophils and macrophages in BALF compared with pneumonia patients. However, these findings should be interpreted cautiously, as their mechanistic and clinical significance require further prospective validation.

ROC analysis of individual and combined BALF parameters showed that macrophage percentage had an AUC of 0.800 (95% CI: 0.723–0.876), with a sensitivity of 98.4% (95% CI: 0.954–1.000) and a specificity of 54.7% (95% CI: 0.425–

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0.669). Eosinophil percentage had an AUC of 0.636 (95% CI: 0.538–0.734), with a sensitivity of 57.8% (95% CI: 0.457–0.699) and a specificity of 71.9% (95% CI: 0.609–0.829). The logistic regression–based combined model incorporating both macrophage and eosinophil percentages demonstrated the highest discriminative performance, with an AUC of 0.832 (95% CI: 0.761–0.903), sensitivity of 93.8% (95% CI: 0.878–0.997), and specificity of 65.6% (95% CI: 0.540–0.773).

Recent studies have also reported the utility of other BALF biomarkers in differentiating IPF from other interstitial lung diseases. For instance, the neutrophil-to-lymphocyte (NL) ratio achieved an AUC of 0.73, with a threshold of 0.48 yielding 73% sensitivity and 63% specificity[14]. Hara[15] et al. demonstrated that BALF S100A9 levels discriminated IPF from idiopathic nonspecific interstitial pneumonia (I-NSIP) and interstitial pneumonia associated with collagen vascular disease (CVD-IP) with an AUC of 0.972, 96.4% sensitivity, and 87.8% specificity. Similarly, d'Alessandro16 et al. found that Apo A1, adipsin, Apo C3, and adiponectin concentrations in BALF could differentiate IPF from hypersensitivity pneumonitis, with AUC of 93%, 79%, 68%, and 66%, respectively.

Despite these findings, the pathogenesis of IPF remains incompletely understood, and immune dysregulation plays a key role in fibrosis progression. Interactions among immune cells, cytokines, and immunoglobulins form a complex regulatory network that warrants further investigation. Although combined diagnostic models show promising performance, they should be considered adjunctive rather than standalone diagnostic tools. BALF cytology alone is insufficient for a definitive diagnosis of IPF and should be used primarily as a complementary approach, particularly when HRCT findings are atypical or infection is suspected.

Limitations

This study has several limitations. First, the retrospective single-center design may introduce selection bias, limiting the generalizability of the findings to other populations or healthcare settings. Second, the sample size was relatively small; although the statistical estimates were precise, the clinical applicability and robustness of the results require validation in larger cohorts. Third, healthy controls were not included due to ethical and practical constraints, which limits the ability to compare BALF cellular patterns with normal baseline values. Fourth, variability in BAL sampling sites, operator technique, and fluid recovery may affect cell composition despite adherence to standardized protocols. Fifth, pneumonia cases were not stratified by etiology (bacterial, viral, or mixed), which could potentially influence BALF cellular profiles and limit interpretation of the differential patterns. Finally, despite the high performance of combined diagnostic models, these tools remain adjunctive and should not be considered as definitive diagnostic methods for IPF.

Conclusion

This study demonstrates that BALF cellular profiles differ significantly between patients with IPF and those with non-fibrotic pneumonia. Macrophages and eosinophils were identified as independent discriminators of IPF, and a logistic regression–based combined diagnostic model integrating these cell populations exhibited robust discriminative performance. Although BALF cytology alone is insufficient for a definitive diagnosis, it provides valuable adjunctive information. When HRCT findings are atypical or differentiation from infectious pulmonary diseases is required, BALF cellular analysis may facilitate early suspicion of IPF, guiding further evaluation with fibrosis biomarkers or multidisciplinary consultation. These findings underscore the potential utility of BALF cellular analysis as a complementary diagnostic tool for IPF and support further prospective studies to validate its effectiveness and integrate it with molecular biomarker analyses.

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Authors contributions

Research idea and study design: QW and YFM; data acquisition: QZ and XXH; statistical analysis: QW and SWL; data interpretation: QW and YL; writing: QW, T.S.M. and D.M.N.; manuscript revision: XQW; supervision/mentorship: XQW. All authors read and approved the final manuscript.

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Availability of data and materials

The data are contained within the article.

Declarations

Ethics approval and consent to participate This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Protocol No: XJTU1AF2025LSYY-945). The need for informed consent was waived by the same ethics committee due to the retrospective nature of this study. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests

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