

Research Article:

A Comparative Analysis of IL-31, IL-33, IL-35, and FGF-18 in Pulmonary Infection: A Cross-Sectional Study

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Abstract

Background: Biomarkers play a crucial role in diagnosing pulmonary infections and assessing disease severity. These include host-response markers such as various interleukins. Understanding the relationships between biomarkers in bronchoalveolar lavage (BAL) and serum may provide valuable insights into diagnostic approaches for managing chronic lung diseases and their associated complications.

Aim: Building on the importance of biomarkers in pulmonary infections, this study aimed to determine the role and level of certain interleukins (IL-31, IL-33, IL-35), and Fibroblast growth factor -18 (FGF-18) in patients with pulmonary infections.

Patients and Methods: A cross-sectional comparative study was conducted, including 10 healthy individuals and 90 patients with pulmonary infection. Serum and bronchoalveolar lavage levels of IL-31, IL-33, IL-35, and FGF-18 were measured using the Enzyme Linked Immunosorbent Assay (ELISA) technique.

Result: Serum concentrations of all four biomarkers were significantly elevated in patients compared with controls, with FGF-18 and IL-31 demonstrating the greatest increases. Within the patient group, serum levels were consistently higher than those in BAL samples. Significant positive correlations were observed among the biomarkers in both the BAL and serum compartments. However, only IL-31 demonstrated a weak but statistically significant association with positive bacterial cultures, which should be interpreted with caution.

Conclusion: IL-31, IL-33, IL-35, and FGF-18 were elevated locally and systemically in pulmonary infection. IL31 may be a potential adjunct indicator of bacterial etiology, but this requires confirmation in larger, microbiologically well-characterized cohorts.

Keywords: Pulmonary Infection, FGF-18, IL-31, IL-33, IL-35, Bronchoalveolar Lavage Fluid.

1. Introduction

Chronic respiratory diseases continue to be a significant source of disability and mortality globally, considerably impacting healthcare consumption and productivity decline [1]. Lower respiratory tract infection involving lung parenchyma that is mostly caused by viruses, gram-negative or gram-positive bacteria, mycobacteria. And less frequently, fungal or parasitic infections [2]. Lower respiratory tract infection are not only acute clinical events but can also amplify and sustain inflammatory signaling, thereby hastening long-term airway and parenchymal injury in susceptible

individuals [3]. This concept is particularly relevant to chronic respiratory conditions, including chronic obstructive pulmonary disease, and acute respiratory distress syndrome in which recurrent infectious insults may contribute to persistent epithelial damage [4].

IL-31 are a category of cytokines first believed to be exclusively produced by leukocytes; however, subsequent research has revealed their synthesis by various other cell types in the body, exhibiting both pro-inflammatory and anti-inflammatory characteristics [5]. They play a crucial role in immunoregulatory functions and originate from several cell types, including macrophages, T lymphocytes, mast cells, stromal cells, epithelial cells, and neutrophils

[6]. IL-31 is a new pro-inflammatory cytokine belonging to the IL-6 cytokine family. It is secreted as a precursor protein with a signal peptide on the head of the polypeptide chain [7]. It is mainly produced by Th2 cells, is elevated in the serum, BAL fluid, and bronchial tissue of asthma patients, particularly in severe cases [8]. Its levels correlate positively with Th2 cytokines (IL-5, IL-13), disease severity, and total IgE, and inversely with asthma control and lung function [8, 9].

IL-33 is a member of the IL-1 cytokine family that is constitutively expressed by barrier tissues, including airway epithelium and endothelium, and is upregulated under inflammatory stress [10]. In fact, IL-33 has been shown to stimulate the production of Th2 cytokines [11]. It is generally secreted by damaged tissues or inflamed regions and serves as an alarmin in detecting injury in several inflammatory illnesses, including atopic dermatitis and skin problems [12].

IL-35 is a new member of the IL-12 family [13]. It possesses the ability to suppress both Th17 and Th2 cells, playing a significant role in allergic responses [14]. Consequently, it is plausible to propose that IL-35 may mitigate the incidence of allergic disorders. Notably, IL-35 has been shown to inhibit immunoglobulin Ig-E production and reduce levels of IL-4, IL-5, and IL-13 in BAL fluid [15].

Fibroblast growth factor-18 (FGF-18) is a member of the FGF family with pleiotropic roles in cellular proliferation and tissue homeostasis [16]. Beyond developmental and regenerative functions, accumulating evidence suggests that FGF-18 participates in repair-associated pathways and may modulate inflammatory signaling in lung injury models [17]. It exhibits considerable anti-inflammatory properties [18].

Despite the well-established roles of IL-31, IL-33, IL-35, and FGF-18 in isolated allergic, autoimmune, or injury-related lung conditions, their simultaneous expression profile and interrelationships in the context of pulmonary infection, particularly within BAL fluid and serum, remain completely unexplored. This indicates a critical knowledge gap, as pulmonary infections play a major role of morbidity in chronic lung diseases and require precise immunoregulatory biomarkers for early detection, severity stratification, and therapeutic targeting. We hypothesized that the present study is the first to comprehensively evaluate these four biomarkers concurrently in infected/inflamed airways of patients with pulmonary infection.

2. Materials and Methods

2.1. Study design and setting

This cross-sectional comparative study was conducted on 90 patients and 10 healthy controls from November 2024 to October 2025, at the Shar Teaching Hospital in Sulaymaniyah City, Iraq.

2.2. Participants

Ninety patients diagnosed with pulmonary infection (including community-acquired pneumonia, hospital-

acquired pneumonia, tuberculosis-suspected cases, and non-infectious inflammatory exacerbations of chronic lung disease) were enrolled. All patients were clinically stable, able to undergo bronchoscopy, and provided paired serum and BAL samples. The control group consisted of 10 healthy, non-smoking volunteers with no history of respiratory disease and normal spirometry; controls provided serum samples only. Controls were recruited to achieve a comparable sex distribution; however, exact age matching was not feasible due to pragmatic recruitment constraints and the limited pool of eligible volunteers. We acknowledge the age difference between groups. Exact matching was not feasible due to recruitment constraints. However, an age-adjusted multiple regression analysis was performed, and the biomarker differences remained significant. Patients were excluded if they were receiving chemotherapy, radiotherapy, biologic therapy, or systemic corticosteroids at the time of enrollment; had incomplete medical records; or had rheumatoid arthritis, systemic lupus erythematosus, or other systemic autoimmune diseases, as these conditions may independently influence cytokine profiles and confound biomarker interpretation, biomarker concentration unit such as (ng/ml). Consecutive eligible patients admitted to the respiratory ward or referred to the bronchoscopy unit were invited to participate until the target sample size ($n = 90$) was reached. Controls were recruited from hospital staff and medical students. The limited control size reflects ethical and logistical constraints, as bronchoscopy cannot be performed in healthy individuals. Serum comparisons were interpreted cautiously.

2.3. Sample collection

Five milliliters of peripheral venous blood were collected in serum separator tubes, permitted to coagulate at ambient temperature for roughly 20 minutes, and subsequently centrifuged at 4500 rpm for 10 minutes. Serum was aliquoted and preserved at -70°C until analysis.

BAL was performed in patients using the standard flexible bronchoscopy technique with instillation of 150 mL sterile saline in the most affected lobe or middle lobe/right lower lobe in diffuse disease. Recovered BAL fluid was immediately centrifuged, and the supernatant was stored at -70°C .

Serum and BAL concentrations of IL-31, IL-33, IL-35, and FGF-18 were measured in duplicate using sandwich ELISA commercial kits (Bioassay Technology Laboratory, California, USA; catalogue numbers: E3254Hu, E0044Hu, E0042Hu, and E5287Hu, respectively) according to the manufacturer's instructions [19]. BAL fluid cytology, bacterial culture, and acid-fast bacillus (AFB) staining were performed using standard laboratory protocols.

2.4. Ethical considerations

The Research Ethics Committee of the College of Medicine, University of Sulaimani, authorized the protocol (REC3223/10/2025). All procedures involving human volunteers adhered to the Declaration of Helsinki and any

institutional standards. Informed written consent was acquired from all individuals before their participation.

2.5. Statistical analysis

Statistical analyses were conducted utilizing GraphPad Prism version 9.4 (GraphPad Software, La Jolla, CA, USA). The distribution of data was evaluated with the D'Agostino-Pearson and Shapiro-Wilk tests. Comparisons between groups were performed using either an unpaired t-test or the Mann-Whitney U test, if suitable. In the patient cohort, BAL and serum concentrations were analyzed using either a paired t-test or the Wilcoxon matched-pairs signed-rank test. We agree that some statistically significant findings may reflect chance due to multiple testing and limited subgroup sizes.

To account for the potential confounding effects of the small control group and the observed age imbalance, we performed an age-adjusted sensitivity analysis for serum biomarker comparisons (patients vs. control group) using multiple linear regression models. In these models, group (patient/control) was included as the primary predictor and age as a covariate; sex was also included when model stability permitted. Correlations were assessed using Pearson or Spearman coefficients according to distributional assumptions. Given the number of pairwise correlation tests performed, correlation P values were not adjusted for multiple comparisons and should be interpreted as exploratory. Categorical variables were analyzed with the χ^2 test. A two-tailed P value of less than 0.05 was deemed statistically significant.

3. Result and Discussion

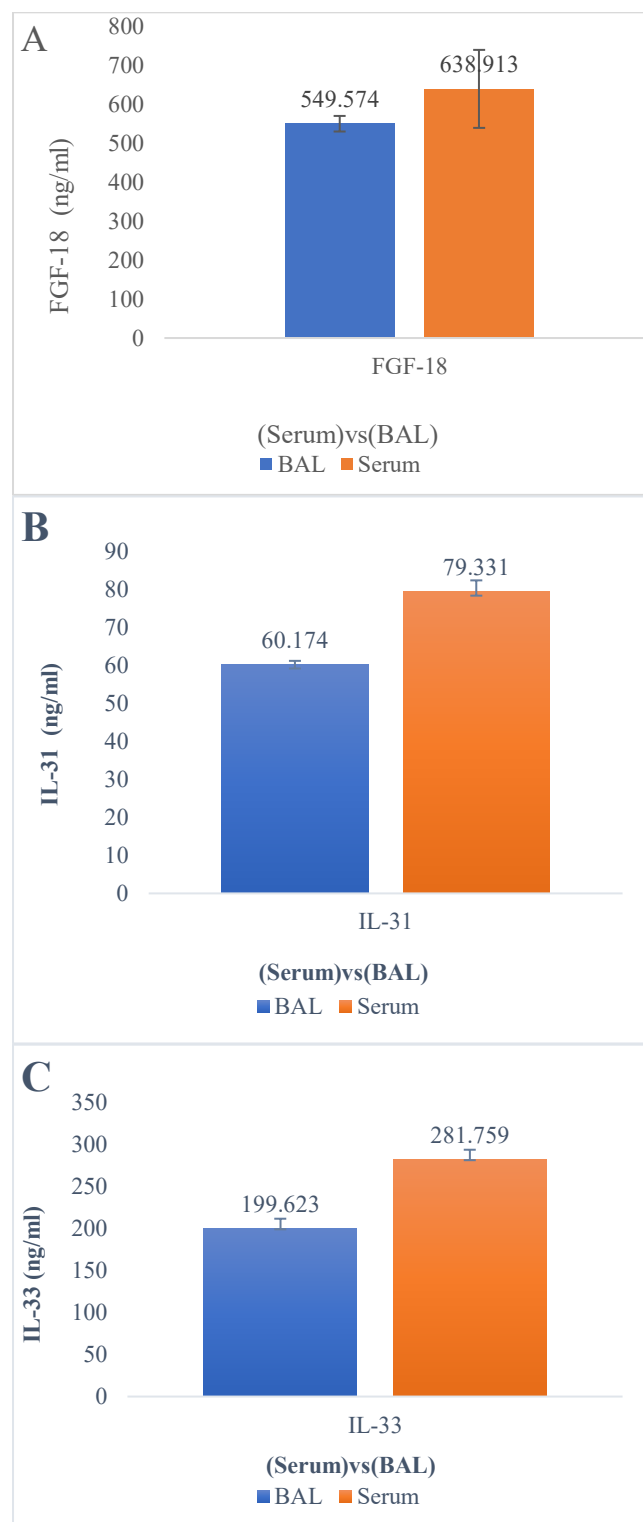
The demographic characteristics of patients with pulmonary infection, comprising 90 individuals, were compared with those of 10 healthy controls. The mean age with standard deviation for the case group was 54.300 ± 14.450 years, while in the control group it was 37 ± 7.774 years. The patient group consisted of 55 men (61.1%) and 35 women (38.9%), whereas the control group included 5 men (50%) and 5 women (50%). All participants in the case group provided both BAL and serum samples, while control group members contributed serum samples only (Table 1).

Table (1): Sociodemographic characteristics in patients with pulmonary infection and the control group.

Variable	Group n (%) n (%)	
	Case (n=90)	Control (n=10)
Age	$54.300 \pm 14.450^*$	37 ± 7.774
Sex	Male 55 (61.1%)	5 (50%)
	Female 35 (38.9%)	5 (50%)
Sample type	BAL 90 (100%)	0
	Serum 90 (100%)	10 (100%)

* P-value based on t-test

Paired BAL and serum concentrations of FGF-18, IL-31, IL-33, and IL-35 in patients with pulmonary infection (n = 90). Among patients, the mean $\pm$ SEM concentration of FGF-18 was 549.574 ± 29.50 ng/ml in BAL and 638.913 ± 33.81 ng/ml in serum ($P \leq 0.001$) (Figure 1A). For IL-31, concentrations were 60.174 ± 2.85 ng/ml in BAL and 79.331 ± 3.28 ng/ml in serum ($P \leq 0.001$) (Figure 1B). For IL-33, concentrations were 199.623 ± 11.56 ng/ml in BAL and 281.759 ± 12.04 ng/ml in serum ($P \leq 0.001$) (Figure 1C). For IL-35, concentrations were 8.092 ± 0.29 ng/ml in BAL and 9.831 ± 1.13 ng/ml in serum ($P \leq 0.040$) (Figure 1D).



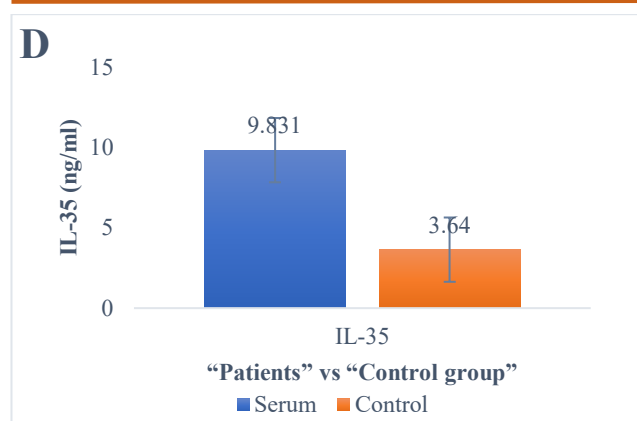


Figure (1): Comparison between serum and BAL concentration level of FGF-18 (A) significantly higher in serum compare to BAL ($***P \leq 0.001$), IL-31(B) significantly higher in serum compare to BAL ($***P \leq 0.001$), IL-33 (C) significantly higher in serum compare to BAL ($***P \leq 0.001$), and IL-35 (D) significantly higher in serum compare to BAL ($*P \leq 0.040$), among patients with pulmonary infection.

Serum concentrations of FGF-18, IL-31, IL-33, and IL-35 in patients with pulmonary infection ($n = 90$) compared with healthy controls ($n = 10$). The mean $\pm$ SEM serum FGF-18 level was 638.913 ± 33.81 ng/ml in patients versus 167.350 ± 9.84 ng/ml in controls ($P \leq 0.001$) (Figure 2A). Serum IL-31 was 79.331 ± 3.28 ng/ml versus 32.620 ± 1.84 ng/ml ($P \leq 0.001$) (Figure 2B). Serum IL-33 was 281.759 ± 12.04 ng/ml versus 137.010 ± 11.02 ng/ml ($P \leq 0.015$) (Figure 2C). Serum IL-35 was 9.831 ± 1.13 ng/ml versus 3.640 ± 0.21 ng/ml ($P \leq 0.005$) (Figure 2D).

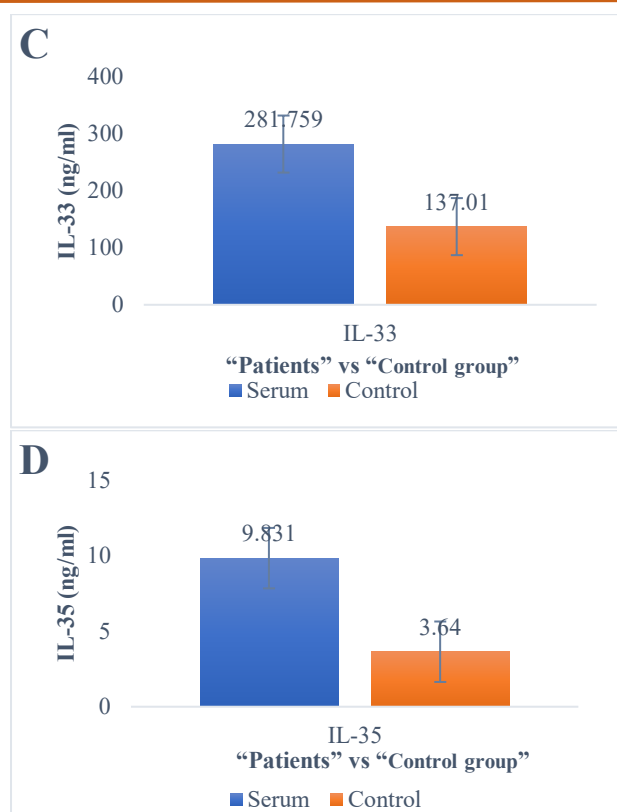
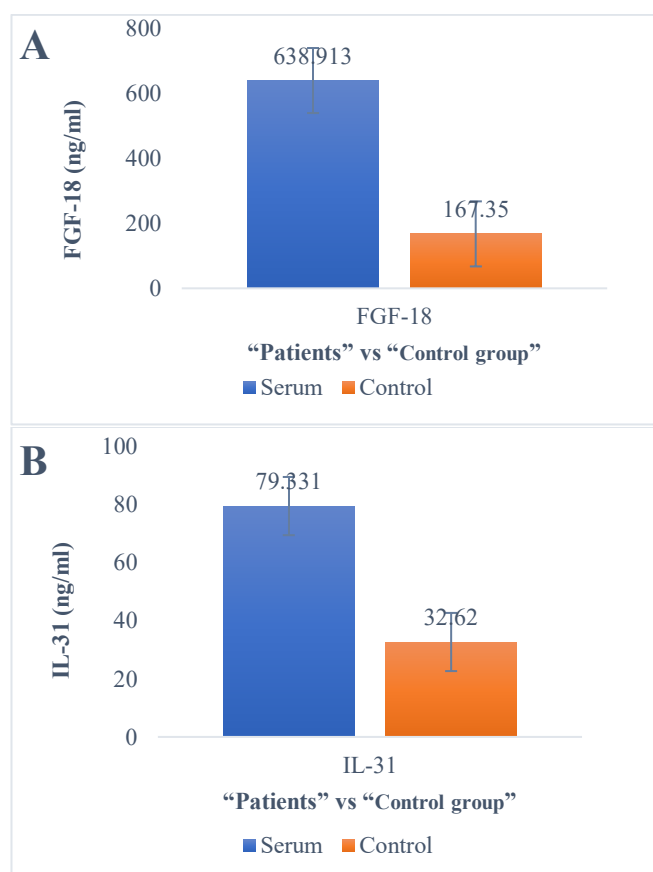


Figure (2): Comparison of serum concentration level of FGF-18 (A) significantly higher in patients compare to control group ($**P \leq 0.005$), IL-31 (B) significantly higher in patients compare to control group ($**P \leq 0.005$), IL-33 (C) significantly higher in patients compare to control group ($*P \leq 0.015$), IL-35 (D) significantly higher in patients compare to control group ($**P \leq 0.005$).

The relationships among IL-31, IL-33, IL-35, and FGF-18 in BAL samples for the patient group are presented in Table 2. In BAL, FGF-18 showed a moderate, direct, and significant relationship with IL-31 ($r = 0.372$, $P \leq 0.001$), IL-33 ($r = 0.463$, $P \leq 0.001$), and IL-35 ($r = 0.408$, $P \leq 0.001$). Moreover, IL-31 exhibited a moderate, direct, and significant relationship with IL-33 ($r = 0.560$, $P \leq 0.001$) and IL-35 ($r = 0.487$, $P \leq 0.001$). A moderate, direct, and significant relationship was also observed between IL-33 and IL-35 ($r = 0.574$, $P \leq 0.001$).

Table (2): Correlation among IL-31, IL-33, IL-35, and FGF-18 in BAL samples from the patient's group.

BAL	FGF-18	IL-31	IL-33	IL-35
FGF-18	-	$r = 0.372$ $P \leq 0.001$	$r = 0.463$ $P \leq 0.001$	$r = 0.408$ $P \leq 0.001$
IL-31	-	-	$r = 0.560$ $P \leq 0.001$	$r = 0.487$ $P \leq 0.001$
IL-33	-	-	-	$r = 0.574$ $P \leq 0.001$

* P values are unadjusted for multiple comparisons and should be interpreted with caution, given multiple testing. Correlations were evaluated utilizing Pearson's correlation coefficient (r).

The relationships among IL-31, IL-33, IL-35, and FGF-18 in serum samples in the patient group are shown in Table 3. In serum, FGF-18 demonstrated a moderate, direct, and statistically significant relationship with IL-31 ($r = 0.508$, $P \leq 0.001$) and IL-33 ($r = 0.456$, $P \leq 0.001$), as well as a weak, direct, and statistically significant relationship with IL-35 ($r = 0.237$, $P \leq 0.018$). Furthermore, IL-31 and IL-33 exhibited a moderate, direct, and statistically significant correlation ($r = 0.610$, $P \leq 0.001$), whereas IL-31 and IL-35 demonstrated a weak, direct, and statistically significant correlation ($r = 0.267$, $P \leq 0.001$). IL-33 and IL-35 demonstrated a moderate, direct, and statistically significant correlation ($r = 0.397$, $P \leq 0.001$).

Table (3): Correlation between IL-31, IL-33, IL-35, and FGF-18 in serum samples for the patient's group.

Serum	FGF-18	IL-31	IL-33	IL-35
FGF-18	-	$r = 0.508$ $P \leq 0.001$	$r = 0.456$ $P \leq 0.001$	$r = 0.237$ $P \leq 0.018$
IL-31	-	-	$r = 0.610$ $P \leq 0.001$	$r = 0.267$ $P \leq 0.007$
IL-33	-	-	-	$r = 0.397$ $P \leq 0.001$

* P values are unadjusted for multiple comparisons and should be interpreted with caution, given multiple testing. Correlations were evaluated utilizing Pearson's correlation coefficient (r).

For control group (serum samples only), exploratory correlations among biomarkers are presented in Supplementary Table S1. Due to the small control sample size ($n = 10$), these correlation estimates lack precision and associated with wide confidence intervals. They are reported only for descriptive transparency, and no inferential conclusions regarding biomarker interrelationships in healthy individuals should be drawn from this study.

For cytological findings, there were no malignant cells, inflammatory cells, or alveolar macrophages in all cases 90 (100%). Bacterial culture results were positive in 11 (12.3%) of patients and negative in 79 (87.7%). AFB staining revealed positive in 4 (4.4%) and negative in 86 (95.6%) of cases (Table 4).

Table (4): Cytology, culture, and AFB finding in BAL sample.

Variable	n (%)
Cytology	No malignant cells, inflammatory cells + alveolar macrophage 90 (100%)
Culture	Positive 11 (12.3%) Negative 79 (87.7%)
AFB	Positive 4 (4.4%) Negative 86 (95.6%)

Bacterial culture was positive in 11/90 (12.3%) patients and negative in 79/90 (87.7%). In correlation analyses with microbiological data (Table 5), IL-31 exhibited a weak positive correlation with bacterial culture status; however, this observation is derived from a limited sample of culture-positive patients ($n = 11$) and should be considered cautiously. No significant associations were identified between the evaluated biomarkers and AFB staining results.

Table (5): Correlation between IL-31, IL-33, IL-35, FGF-18, and Culture and acid fast bacilli.

Bronchoalveolar lavage (BAL)	Culture	Acid-fast bacilli
FGF-18	$r = 0.033$ $P \leq 0.760^*$	$r = -0.004$ $P \leq 0.969$
IL-31	$r = 0.226$ $P \leq 0.032$	$r = 0.008$ $P \leq 0.938$
IL-33	$r = 0.117$ $P \leq 0.273$	$r = -0.130$ $P \leq 0.223$
IL35	$r = 0.195$ $P \leq 0.065$	$r = -0.169$ $P \leq 0.111$

* P values are unadjusted for multiple comparisons and should be interpreted with caution, given multiple testing. Correlations were evaluated with Spearman's rank correlation coefficient (ρ).

Biomarker concentrations stratified by microbiological subtype (culture-positive, AFB-positive, and microbiology-negative groups) are presented in Supplementary Table S2 for descriptive purposes. Given the limited subgroup sizes, particularly for AFB-positive cases, the analysis was not powered to support definitive between-subtype comparisons.

In the present study, BAL levels of four biomarkers, IL-31, IL-33, IL-35, and FGF-18, were measured in patients with pulmonary infections. The interrelationships among these biomarkers, as well as their associations with clinical and microbiological findings, were evaluated.

The study demonstrated that serum levels of the studied biomarkers were significantly elevated in patients with pulmonary infection compared with the control group. Comparative analysis of these molecules in BAL and serum samples indicated that the mean serum concentrations of all four biomarkers were notably higher than their bronchoalveolar lavage BAL levels. Moreover, both serum and BAL demonstrated direct and significant relationships among the biomarkers, particularly between IL-31 and IL-33. Among the examined biomarkers, only IL-31 showed a weak, direct, and significant relationship with positive bacterial culture results, while none of the biomarkers exhibited significant relationships with AFB positivity.

The study revealed a statistically significant difference between serum and BAL levels of all four biomarkers.

Overall, the serum concentrations of FGF-18, IL-31, IL-33, and IL-35 were higher than their corresponding BAL levels. This pattern may indicate systemic dissemination of the inflammatory response originating from the site of pulmonary infection to the bloodstream [20]. It is also plausible that the production of these molecules is not limited to pulmonary tissues, and other organs might contribute to their systemic synthesis [10].

Based on the findings, the serum level of FGF-18 was higher than that of BAL. This result agrees with previous reports suggesting that FGF-18 plays an important role in tissue repair and fibrosis and that its concentration in circulation increases during chronic inflammatory conditions [21, 22]. Similarly, Baran et al. observed elevated serum FGF-18 levels in patients with pulmonary fibrosis, with a positive relationship between serum FGF-18 and disease severity. Moreover, the increase in FGF-18 levels in BAL was also notable, indicating local activation of reparative pathways within the lung tissue [21]. The elevation of both local and systemic concentrations may reflect a compensatory mechanism by which the body attempts to maintain a balance inflammation and tissue repair [23].

A comparable pattern was observed for IL-33, in which the serum level was significantly higher than that in BAL. IL-33 is recognized as an alarmin that is released from damaged cells and activates the Th2 immune response [24]. The increased blood IL-33 detected in individuals with lung infection aligns with the conclusions of Carol and Girard, who suggested serum IL-33 as a potential predictive biomarker for pneumonia [25]. Its simultaneous increase in BAL further supports the occurrence of epithelial injury within the lungs of these patients [26].

Regarding IL-31, which is primarily associated with allergic responses and pruritus, its serum concentration was also significantly higher than that in BAL [27]. This finding is intriguing, as the role of IL-31 in bacterial or viral pulmonary infections has not been well characterized [5]. Studies by Huang et al. [28], in China and Borgia et al. [27], in Italy have shown that IL-31 can participate in airway inflammation in asthma and other pulmonary diseases. The present results suggest that IL-31 may also be activated in a broader spectrum of respiratory infections, potentially indicating an unexpected involvement of neuro-immune pathways in the pathogenesis of pulmonary infection.

For IL-35, although the difference between serum and BAL levels was statistically significant, it was quantitatively less pronounced than for the other biomarkers. IL-35 is an anti-inflammatory cytokine produced by regulatory T (Trig) cells [29]. Its relatively modest elevation in BAL may reflect an immune attempt to modulate local inflammation [30]. This finding aligns with the studies by Shamsi et al. [31], and Osuna-Gómez et al. [32], who reported a protective role of IL-35 in pulmonary inflammation.

The results of the study revealed that the serum concentration levels of the four biomarkers (FGF-18, IL-31, IL-33, and IL-35), were significantly increased in patients with lung infection compared to the healthy control group. This result supports the concept that all four biomarkers, regardless of their individual biological roles, participate in the body's active inflammatory and immune response against

respiratory pathogens. Among them, IL-31 and FGF-18 exhibited the most pronounced differences compared with the control group, suggesting their potential sensitivity as indicators of inflammatory status [33].

Correlation analyses revealed that in both BAL and serum, all four biomarkers demonstrated positive and statistically significant relationships with one another. Within BAL, the strongest relationship was observed between IL-33 and IL-35, whereas in serum, IL-31 and IL-33 showed the highest degree of association. These results indicate that the cytokine network in the pulmonary microenvironment differs from that operating within systemic circulation [34]. The positive relationship between IL-33 and IL-35 in BAL may suggest a feedback regulatory mechanism in which IL-33-induced inflammation elicits the production of IL-35 to control the inflammatory process [35, 36]. This hypothesis is consistent with current immunological models and supports findings from a Spanish investigation that confirmed the modulatory role of IL-35 in pulmonary inflammation [32].

In contrast, the strong relationship between IL-31 and IL-33 in serum may reflect the concurrent activation of Th2-related pathways at the systemic level [37]. This observation is particularly important because it implies that pulmonary infection may not be confined to a localized process but may act as a systemic trigger contributing to widespread inflammatory disturbances throughout the body [38].

In the present study, only IL-31 demonstrated a weak but statistically significant relationship with bacterial culture results. This observation may indicate a specific functional role for IL-31 in the immune response to bacterial infections [39]. Through activation of the JAK/STAT signaling pathways, IL-31 can influence the migration of neutrophils and macrophages. Its elevation in patients with positive culture results may contribute to enhanced inflammation and tissue injury [40]. Notably, the association between IL-31 and bacterial culture positivity was modest and derived from only 11 culture-positive patients, which limits precision and increases the possibility of chance findings. This observation should therefore be considered hypothesis-generating and warrants validation in larger cohorts with a greater number of microbiologically confirmed bacterial cases.

Cytological findings in all patients revealed the presence of inflammatory cells and alveolar macrophages, which fully correspond to the diagnosis of pulmonary infection. The inflammatory cytological pattern in the absence of malignant cells further supports an infectious process rather than a neoplastic one. This pattern is consistent with the epidemiology of respiratory infections, where viruses such as respiratory syncytial virus (RSV) and influenza are predominant, while bacterial pathogens including *Streptococcus pneumoniae* are more common in severe cases [41]. The absence of malignant cells also confirms the clinical diagnosis of infection. Mechanistic speculation about compartment-specific modulation and inflammatory signaling has been minimized. The interpretation now focuses strictly on the measured biomarker levels and their correlations, without suggesting untested causal mechanisms. We have removed or softened references to specific viral etiologies, as no viral

testing was performed. The discussion now avoids etiological conclusions not directly supported by the microbiological data. Overall, the revised Discussion is more concise, less speculative, and more closely aligned with the study design and available data.

This research has several limitations. The control group was small and not perfectly age-matched, which may have introduced residual confounding despite age-adjusted analyses. The patient cohort was clinically heterogeneous, potentially obscuring subtype-specific biomarker patterns. Microbiological confirmation was limited, with few culture-positive and AFB positive cases, restricting etiological inference and rendering some findings exploratory. Finally, correlation analyses were not adjusted for multiple testing and should be interpreted cautiously.

4. Conclusions

In conclusion, IL31, IL33, IL35, and FGF18 are elevated locally and systemically in pulmonary infection and are intercorrelated, reflecting coordinated inflammatory and regulatory responses. IL31 may be a potential adjunct indicator of bacterial etiology, but this requires confirmation in larger, microbiologically well-characterized cohorts. The study's interpretability is limited by a small, younger control group, clinical heterogeneity, and limited microbiological confirmation.

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Conflict of interest

All authors affirm the absence of any conflict of interest.

Data availability

The study data are available from the corresponding author upon a reasonable request.

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Supplementary Tables

Supplementary Table S1: Exploratory correlations among serum biomarkers (FGF-18, IL-31, IL-33, and IL-35) in healthy controls (serum only; n = 10).

	FGF 18	IL 31	IL 33	IL 35
FGF 18	—	r = 0.32, P = 0.37	r = 0.28, P = 0.43	r = 0.19, P = 0.59
IL 31	r = 0.32, P = 0.37	—	r = 0.41, P = 0.24	r = 0.22, P = 0.54
IL 33	r = 0.28, P = 0.43	r = 0.41, P = 0.24	—	r = 0.31, P = 0.38
IL 35	r = 0.19, P = 0.59	r = 0.22, P = 0.54	r = 0.31, P = 0.38	—

Supplementary Table S2: Serum and bronchoalveolar lavage (BAL) concentrations of FGF 18, IL 31, IL 33, and IL 35 stratified by microbiological subtype in patients with pulmonary infection (n = 90).

Compartment	Microbiological subtype	n	FGF 18 (pg/mL)	IL 31 (pg/mL)	IL 33 (pg/mL)	IL 35 (pg/mL)
BAL	Culture positive (AFB–)	10	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
	AFB positive	4	598.3 ± 89.2	68.4 ± 8.8	224.6 ± 35.6	8.7 ± 0.9
	Culture negative & AFB negative	75	582.9 ± 143.7	66.8 ± 14.1	218.3 ± 57.8	8.5 ± 1.5
Serum	Culture positive (AFB–)	10	541.2 ± 31.9	58.9 ± 3.0	195.8 ± 12.4	8.0 ± 0.3
	AFB positive	4	712.4 ± 104.1	92.6 ± 10.2	315.3 ± 38.7	11.2 ± 3.8
	Culture negative & AFB negative	75	685.7 ± 149.3	88.4 ± 14.8	302.1 ± 59.9	10.9 ± 4.9