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# Interleukin-1 and Interleukin-8 are Prominent Inflammatory Markers in Patients with Cystic Fibrosis and Non-Cystic Fibrosis

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**Background:** Bronchiectasis is characterized by pathological inflammation and infection that cause thickening and dilation of the airways. It is categorized into cystic fibrosis (CF) and non-cystic fibrosis bronchiectasis (NCFB). Given the disease's inflammatory nature, this study aimed to assess the levels of interleukin-1 (IL-1), IL-8, and tumor necrosis factor-alpha (TNF-α) in CF and NCFB patients compared to a healthy control (HC) group.

**Materials and Methods:** A total of 35 bronchiectasis patients (18 with CF and 16 with NCFB) and 18 individuals in the HC group were selected based on specific inclusion and exclusion criteria. After receiving informed consent, the levels of IL-1, IL-8, and TNF-α in serum and broncho-alveolar lavage (BAL) fluid were measured using ELISA. Additionally, spirometry results for the study participants were recorded before and after bronchoscopy.

**Results:** Significant differences were observed in serum IL-8 ($p = 0.018$) and in BAL IL-1 and IL-8 levels ($p = 0.018$ and $p < 0.0001$, respectively). A notable positive correlation was found between serum IL-1 and both serum and BAL IL-8 ($p < 0.0001$). Similarly, serum IL-8 showed a significant positive correlation with its BAL levels ($p = 0.007$).

**Conclusion:** Findings from this study suggest that elevated IL-1 in the lungs is a key factor in bronchiectasis-related inflammation, and the increase in IL-8 may occur via an IL-1-dependent pathway. The heightened levels of IL-8 in BAL and serum among bronchiectasis patients align with known neutrophilia in these cases. Spirometry results showed no significant association with these cytokine increases, indicating that relying solely on spirometry may be insufficient for monitoring inflammation in bronchiectasis patients.

**Keywords:** Bronchiectasis; Cystic fibrosis; Interleukin-1; Interleukin-8; Tumor necrosis factor-alpha

## INTRODUCTION

Bronchiectasis is a pathological condition characterized by the thickening and dilation of airways due to persistent inflammation, infection, and structural deformities in the bronchi. Numerous factors contribute to the disease's pathogenesis, which is generally viewed as irreversible; however, studies suggest that early intervention may potentially reverse this condition (1). Common clinical symptoms include a chronic cough lasting four weeks or more with purulent sputum, disease flare-ups, repeated lung infections, shortness of breath, wheezing, hemoptysis, clubbing, nasal discharge, frequent middle ear infections,

and stunted growth. Pulmonary function tests in affected individuals often reveal airway obstruction.

Bronchiectasis is divided into two main types: cystic fibrosis (CF) and non-cystic fibrosis (NCFB) (1-8). Since neutrophil-centered inflammatory processes significantly contribute to disease progression, assessing inflammatory and pro-inflammatory markers can aid in diagnosing and managing bronchiectasis. Among these markers, interleukins 1 and 8 (IL-1 and IL-8), as well as tumor necrosis factor-alpha (TNF-α), play key roles in neutrophil trafficking and activation. In CF bronchiectasis, elevated levels of bronchial IL-8 have been observed, while in NCFB patients, IL-8 and TNF-α in sputum correlate strongly with symptom severity (9-11). Furthermore, in bronchiectatic inflammation, IL-1-stimulated pulmonary endothelial cells produce granulocyte colony-stimulating factor (G-CSF), which enhances granulopoiesis in the bone marrow and supports neutrophil survival, function, and recruitment to the lungs (12-18).

Despite the significance of these inflammatory markers, comparative studies between CF and NCFB bronchiectasis are limited. The present study seeks to compare serum and bronchoalveolar lavage (BAL) levels of IL-1, IL-8, and TNF-α as major pro-inflammatory markers, in relation to spirometry results, by distinguishing between CF and NCFB types. This approach aims to provide a clearer understanding of the differences and similarities between these forms of bronchiectasis.

## MATERIALS AND METHODS

### Study population & ethical considerations

This non-interventional case-control study involved 35 bronchiectasis patients (18 with CF and 16 with NCFB) who had experienced symptom exacerbations within the past six weeks and were admitted to the pediatric ward. Ethical protocols were strictly followed, with written consent obtained from the patients or their guardians after receiving approval from the Masih Daneshvari Hospital ethics committee (IR.SBMU.NRITLD.REC.1400.060). All results were kept confidential, and participants incurred no costs. Inclusion criteria required a diagnosis of bronchiectasis localized to the lungs. For the 18 CF cases, confirmed CF was mandatory, verified by at least two positive sweat tests, with patients hospitalized due to pulmonary exacerbation and requiring fibroptic bronchoscopy. Sixteen NCFB patients with bronchiectasis confirmed via high-resolution CT (HRCT) scans and admitted for pulmonary exacerbation with fibroptic bronchoscopy were also eligible. Additionally, recent lung involvement and signs of collapse or atelectasis on CT scan served as inclusion criteria for both CF and NCFB groups, indicating the need for diagnostic and therapeutic bronchoscopy.

Exclusion criteria included severely impaired pulmonary function tests (PFT) during bronchoscopy (with forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) below 30% in baseline PFT), hypoxia (room-air pulse oximetry below 92%) during bronchoscopy, general malaise, or any other condition preventing bronchoscopy. Finally, 18 healthy, age- and gender-matched volunteers were included as a control group.

### Collection of samples

Blood samples (5 cc) were drawn from each study participant's veins, and after centrifugation, the resulting serum was stored at -80°C for later analysis. Bronchoalveolar lavage (BAL) fluid was collected during bronchoscopy from the affected lung lobe identified through each patient's recent HRCT scan. In brief, sterile saline was infused into the abnormal lobe and then immediately suctioned out. Approximately 10 cc of the collected sample was centrifuged at 1000 g for 10 minutes, and the cell-free supernatant was also frozen at -80°C until further analysis.

### ELISA Test

Serum and BAL samples from all participants in the study were analyzed using ELISA to measure the levels of IL-1, IL-8, and TNF-α (all sourced from R&D Systems, USA), following the manufacturer's guidelines.

### Statistical analysis

Statistical analysis of the data in this study was conducted using IBM SPSS Statistics version 23. For populations with a normal distribution, results were presented as means, and Student's t-test was employed to assess significance. In cases where the data did not follow a normal distribution, results were reported as medians, and the Mann–Whitney U test was used to evaluate significance. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

Among the 52 participants, the mean (±SD) age was 14.8 (±5.4) years, consisting of 16 males and 36 females. The study included 18 subjects with cystic fibrosis (CF) (5 males and 13 females, aged 15.5±6.1 years) and 16 subjects with non-cystic fibrosis bronchiectasis (NCFB) (6 males and 10 females, aged 14.0±4.0 years). Additionally, 18 healthy age- and sex-matched individuals (5 males and 13 females, aged 14.9±6.0 years) served as the healthy control group (HC). Spirometry results did not reveal a statistically significant difference between the CF and NCFB groups (Table 1).

Statistical analysis indicated significant differences in serum IL-8, as well as BAL IL-1 and BAL IL-8 (Tables 2, 3, and Figure 1).

**Table 1.** Spirometric factors of participants in the study before and after bronchoscopy

| | Diagnosis | N | Mean (±SD) | *p*.value |
|---|---|---|---|---|
| **FVC before bronchoscopy** | CF | 18 | 56.78 (±6.06) | 0.890 |
| | NCFB | 16 | 55.63 (±4.67) | |
| **FEV1 before bronchoscopy** | CF | 18 | 47.28 (±4.62) | 0.097 |
| | NCFB | 16 | 61.06 (±6.53) | |
| **FVC after bronchoscopy** | CF | 18 | 57.28 (±5.78) | 0.448 |
| | NCFB | 16 | 63.81 (±5.73) | |
| **FEV1 after bronchoscopy** | CF | 18 | 54.50 (±4.78) | 0.195 |
| | NCFB | 16 | 64.38 (±6.49) | |

BAL, Broncho-alveolar lavage fluid; HC, Healthy Control; CF, Cystic Fibrosis; NCFB, non-cystic fibrosis bronchiectasis; FVC, Forced vital capacity; FEV1, Forced expiratory volume 1.

* *p-value* less than 0.05 is considered statistically significant

**Table 2.** Inflammatory cytokines in serum and BAL of study participants

| | | N | Mean (±SD) | p.value |
|---|---|---|---|---|
| **Serum IL-1** | CF | 18 | 46.65 (±86.41) | 0.169 |
| | NCFB | 16 | 15.57 (±37.31) | |
| | HC | 18 | 15.70 (±11.92) | |
| **Serum IL-8** | CF | 18 | 333.21 (±586.89) | 0.018* |
| | NCFB | 16 | 37.64 (±77.03) | |
| | HC | 18 | 30.00 (±31.16) | |
| **Serum TNF-α1** | CF | 18 | 162.00 (±313.39) | 0.157 |
| | NCFB | 16 | 46.00 (±54.02) | |
| | HC | 18 | 63.17 (±44.89) | |
| **BAL IL-1** | CF | 18 | 90.19 (±73.90) | 0.018* |
| | NCFB | 16 | 112.63 (±165.89) | |
| | HC | 18 | 15.26 (±14.94) | |
| **BAL IL-8** | CF | 18 | 1873.88 (±227.09) | 0.0001* |
| | NCFB | 16 | 694.04 (±671.21) | |
| | HC | 18 | 24.37 (±19.24) | |
| **BAL TNF-α1** | CF | 18 | 63.01 (±233.88) | 0.439 |
| | NCFB | 16 | 9.77 (±13.38) | |
| | HC | 18 | 65.92 (±48.30) | |

SD, Standard Deviation; BAL, Broncho-alveolar lavage fluid; IL-1, Interleukin-1; IL-8, Interleukin-8; TNF-α, Tumor Necrosis Factor-Alpha; HC, Healthy Control; CF, Cystic Fibrosis; NCFB, non-cystic fibrosis bronchiectasis.

* p-value less than 0.05 considered statistically significant

**Table 3.** Inflammatory cytokines in serum and BAL of the studied groups

| Cytokine | Diagnosis | Diagnosis | *p*.value |
|---|---|---|---|
| **Serum IL-1** | CF | NCFB | 0.109 |
| | | HC | 0.100 |
| | NCFB | CF | 0.109 |
| | | HC | 0.995 |
| **Serum IL-8** | CF | NCFB | **0.017*** |
| | | HC | **0.012*** |
| | NCFB | CF | **0.017*** |
| | | HC | 0.949 |
| **Serum TNF-α1** | CF | NCFB | 0.080 |
| | | HC | 0.123 |
| | NCFB | CF | 0.080 |
| | | HC | 0.792 |
| **BAL IL-1** | CF | NCFB | 0.525 |
| | | HC | **0.032*** |
| | NCFB | CF | 0.525 |
| | | HC | **0.008*** |
| **BAL IL-8** | CF | NCFB | **0.0001*** |
| | | HC | **0.0001*** |
| | NCFB | CF | **0.0001*** |
| | | HC | **0.0001*** |
| **BAL TNF-α1** | CF | NCFB | 0.277 |
| | | HC | 0.951 |
| | NCFB | CF | 0.277 |
| | | HC | 0.252 |

BAL, Broncho-alveolar lavage fluid; IL-1, Interleukin-1; IL-8, Interleukin-8; TNF-α, Tumor Necrosis Factor-Alpha; HC, Healthy Control; CF, Cystic Fibrosis; NCFB, non-cystic fibrosis bronchiectasis.

* *p-value* less than 0.05 is considered statistically significant

A significant positive correlation was found between serum IL-1 and both serum and BAL IL-8 (Table 4). Furthermore, serum IL-8 showed a significant positive correlation with its BAL levels (Table 4), and serum TNF-α also positively correlated with its BAL levels (Table 4).

In the CF group, serum IL-1 and TNF-α positively correlated with BAL IL-1 and TNF-α, respectively (Table 5). Among NCFB patients, serum IL-8 had a positive correlation with its BAL levels (Table 5). In HC subjects, serum IL-1 positively correlated with serum IL-8 and TNF-α, as well as BAL IL-8 (Table 5).

Additionally, serum IL-8 levels in healthy subjects positively correlated with their BAL levels (Table 5). Moreover, serum TNF-α in the HC group positively correlated with BAL IL-1, IL-8, and TNF-α (Table 5). However, no significant relationships were found between spirometric parameters and serum cytokine or BAL levels (Table 6).

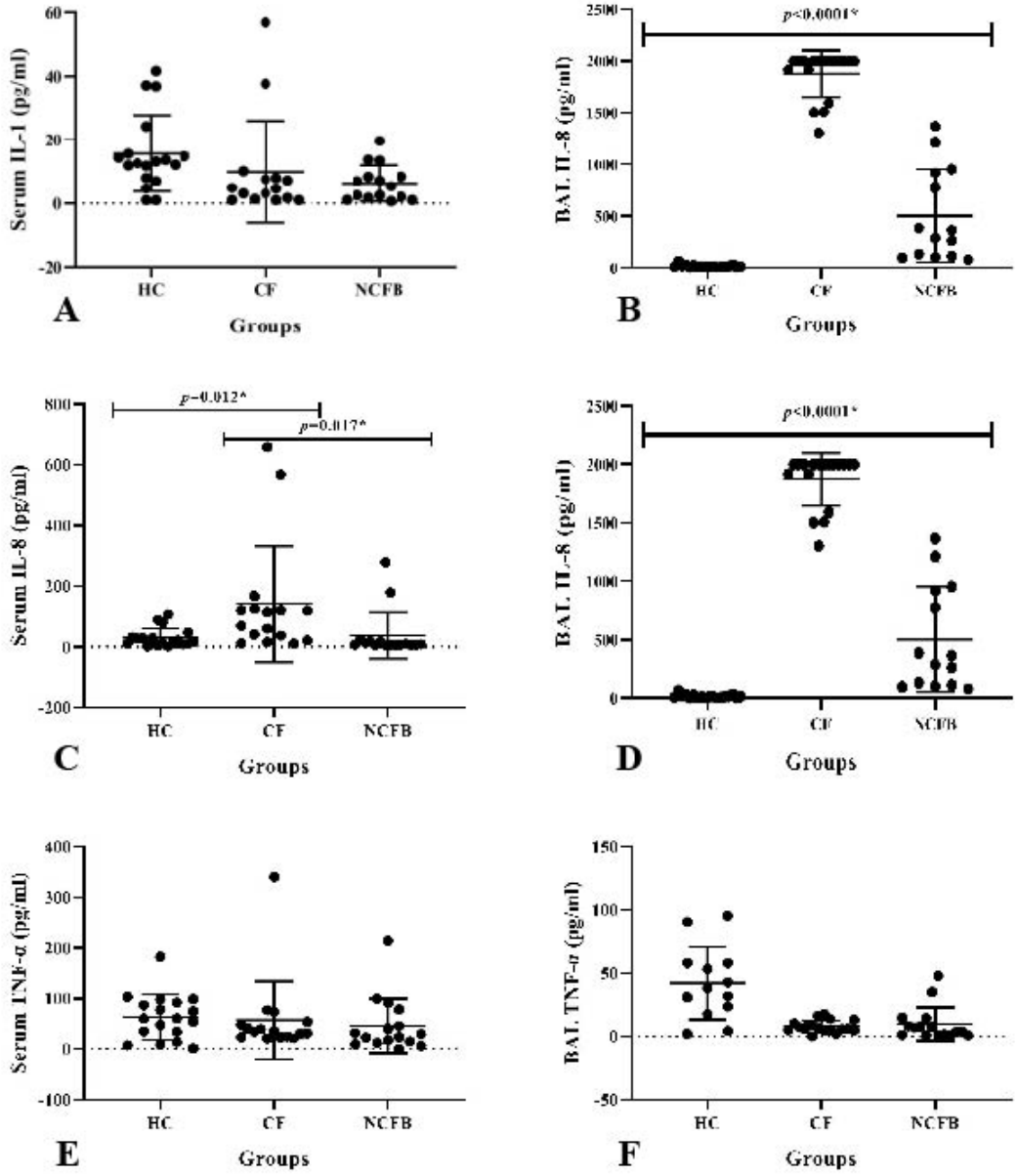


**Figure 1. Serum and BAL inflammatory cytokines.** BAL, Broncho-alveolar lavage; IL-1, Interleukin-1; IL-8, Interleukin-8; TNF-α, Tumor Necrosis Factor-Alpha; pg/ml, picogram/milliliter; HC, Healthy Control; CF, Cystic Fibrosis; NCFB, non-cystic fibrosis bronchiectasis.

**Table 4.** Pearson correlation test for serum and BAL fluid cytokines

| | | Serum IL-1 | Serum IL-8 | Serum TNF-α1 | BAL IL-1 | BAL IL-8 | BAL TNF-α1 |
|---|---|---|---|---|---|---|---|
| **Serum IL-1** | Correlation | 1.000 | **0.735**** | -0.102 | -0.013 | **0.288*** | -0.083 |
| | Sig. (2-tailed) | | **<0.0001*** | 0.473 | 0.930 | **0.039*** | 0.557 |
| **Serum IL-8** | Correlation | **0.735**** | 1.000 | -0.093 | 0.019 | **0.367**** | -0.072 |
| | Sig. (2-tailed) | **<0.0001*** | | 0.512 | 0.894 | **0.007*** | 0.610 |
| **Serum TNF-α1** | Correlation | -0.102 | -0.093 | 1.000 | 0.100 | 0.157 | **0.642**** |
| | Sig. (2-tailed) | 0.473 | 0.512 | | 0.478 | 0.268 | **<0.0001*** |
| **BAL IL-1** | Correlation | -0.013 | 0.019 | 0.100 | 1.000 | 0.155 | 0.105 |
| | Sig. (2-tailed) | 0.930 | 0.894 | 0.478 | | 0.272 | 0.457 |
| **BAL IL-8** | Correlation | **0.288*** | **0.367**** | 0.157 | 0.155 | 1.000 | 0.047 |
| | Sig. (2-tailed) | **0.039*** | **0.007*** | 0.268 | 0.272 | | 0.743 |
| **BAL TNF-α1** | Correlation | -0.083 | -0.072 | **0.642**** | 0.105 | 0.047 | 1.000 |
| | Sig. (2-tailed) | 0.557 | 0.610 | **<0.0001*** | 0.457 | 0.743 | |

BAL, Broncho-alveolar lavage fluid; IL-1, Interleukin-1; IL-8, Interleukin-8; TNF-α, Tumor Necrosis Factor-Alpha; HC, Healthy Control; CF, Cystic Fibrosis; NCFB, non-cystic fibrosis bronchiectasis.

* Correlation is significant at the 0.05 level (2-tailed). A *p-value* less than 0.05 is considered statistically significant.

** Correlation is significant at the 0.01 level (2-tailed).

**Table 5.** Pearson correlation test for serum and BAL fluid cytokines of the studied groups

| Diagnosis | | | Serum IL-1 | Serum IL-8 | Serum TNF-α | BAL IL-1 | BAL IL-8 | BAL TNF-α |
|---|---|---|---|---|---|---|---|---|
| **CF** | Serum IL-1 | Correlation | 1.000 | **0.735**** | -0.220 | -0.005 | 0.289 | -.128 |
| | | Sig. | | **0.001*** | 0.381 | 0.985 | 0.245 | 0.613 |
| | Serum IL-8 | Correlation | **0.735**** | 1.000 | -0.230 | -0.075 | 0.254 | -0.118 |
| | | Sig. | **0.001*** | | 0.359 | 0.769 | 0.309 | 0.640 |
| | Serum TNF-α1 | Correlation | -0.220 | -0.230 | 1.000 | 0.182 | -0.274 | **0.665**** |
| | | Sig. | 0.381 | 0.359 | | 0.469 | 0.270 | **0.003*** |
| | BAL IL-1 | Correlation | -0.005 | -0.075 | 0.182 | 1.000 | 0.100 | 0.375 |
| | | Sig. | 0.985 | 0.769 | 0.469 | | 0.694 | 0.125 |
| | BAL IL-8 | Correlation | 0.289 | 0.254 | -0.274 | 0.100 | 1.000 | 0.148 |
| | | Sig. | 0.245 | 0.309 | 0.270 | 0.694 | | 0.558 |
| | BAL TNF-α1 | Correlation | -0.128 | -0.118 | **0.665**** | 0.375 | 0.148 | 1.000 |
| | | Sig. | 0.613 | 0.640 | **0.003*** | 0.125 | 0.558 | |
| **NCFB** | Serum IL-1 | Correlation | 1.000 | **0.835**** | 0.030 | -0.171 | 0.176 | 0.122 |
| | | Sig. | | **<0.0001*** | 0.911 | 0.527 | 0.515 | 0.654 |
| | Serum IL-8 | Correlation | **0.835**** | 1.000 | -0.096 | -0.103 | 0.062 | -0.031 |
| | | Sig. | **<0.0001*** | | 0.723 | 0.705 | 0.820 | 0.909 |
| | Serum TNF-α1 | Correlation | 0.030 | -0.096 | 1.000 | 0.033 | -0.303 | -0.070 |
| | | Sig. | 0.911 | 0.723 | | 0.904 | 0.255 | 0.795 |
| | BAL IL-1 | Correlation | -0.171 | -0.103 | 0.033 | 1.000 | -0.214 | 0.153 |
| | | Sig. | 0.527 | 0.705 | 0.904 | | 0.427 | 0.572 |
| | BAL IL-8 | Correlation | 0.176 | 0.062 | -0.303 | -0.214 | 1.000 | 0.320 |
| | | Sig. | 0.515 | 0.820 | 0.255 | 0.427 | | 0.227 |
| | BAL TNF-α1 | Correlation | 0.122 | -0.031 | -0.070 | 0.153 | 0.320 | 1.000 |
| | | Sig. | 0.654 | 0.909 | 0.795 | 0.572 | 0.227 | |
| **HC** | Serum IL-1 | Correlation | 1.000 | **0.519*** | **0.563*** | **0.647**** | 0.415 | 0.087 |
| | | Sig. | | **0.027*** | **0.015*** | **0.004*** | 0.087 | 0.731 |
| | Serum IL-8 | Correlation | **0.519*** | 1.000 | 0.420 | **0.608**** | 0.439 | 0.204 |
| | | Sig. | **0.027*** | | 0.083 | **0.007*** | 0.068 | 0.417 |
| | Serum TNF-α1 | Correlation | **0.563*** | 0.420 | 1.000 | **0.721**** | **0.539*** | **0.520*** |
| | | Sig. | **0.015*** | 0.083 | | **0.001*** | **0.021*** | **0.027*** |
| | BAL IL-1 | Correlation | **0.647**** | **0.608**** | **0.721**** | 1.000 | **0.568*** | 0.393 |
| | | Sig. | **0.004*** | **0.007*** | **0.001*** | | **0.014*** | 0.107 |
| | BAL IL-8 | Correlation | 0.415 | 0.439 | **0.539*** | **0.568*** | 1.000 | **0.582*** |
| | | Sig. | 0.087 | 0.068 | **0.021*** | **0.014*** | | **0.011*** |
| | BAL TNF-α1 | Correlation | 0.087 | 0.204 | **0.520*** | 0.393 | **0.582*** | 1.000 |
| | | Sig. | 0.731 | 0.417 | **0.027*** | 0.107 | **0.011*** | |

BAL, Broncho-alveolar lavage fluid; IL-1, Interleukin-1; IL-8, Interleukin-8; TNF-α, Tumor Necrosis Factor-Alpha; HC, Healthy Control; CF, Cystic Fibrosis; NCFB, non-cystic fibrosis bronchiectasis.

* Correlation is significant at the 0.05 level (2-tailed). A *p-value* less than 0.05 is considered statistically significant.

** Correlation is significant at the 0.01 level (2-tailed).

**Table 6.** Correlation of spirometric factors with levels of inflammatory cytokines in serum and BAL fluid of individuals in the study

| | | FVC Before | FEV1 Before | FVC After | FEV1 After |
|---|---|---|---|---|---|
| **Serum IL-1** | Spearman Correlation | 0.195 | 0.144 | 0.141 | 0.124 |
| | Sig. (2-tailed) | 0.268 | 0.415 | 0.425 | 0.483 |
| **Serum IL-8** | Spearman Correlation | 0.011 | -0.156 | -0.058 | -0.104 |
| | Sig. (2-tailed) | 0.952 | 0.379 | 0.743 | 0.559 |
| **Serum TNF-α** | Spearman Correlation | 0.225 | 0.031 | 0.068 | 0.010 |
| | Sig. (2-tailed) | 0.200 | 0.863 | 0.704 | 0.956 |
| **BAL IL-1** | Spearman Correlation | 0.013 | -0.009 | -0.020 | -0.057 |
| | Sig. (2-tailed) | 0.942 | 0.962 | 0.912 | 0.750 |
| **BAL IL-8** | Spearman Correlation | 0.047 | -0.101 | -0.088 | -0.077 |
| | Sig. (2-tailed) | 0.792 | 0.571 | 0.623 | 0.666 |
| **BAL TNF-α** | Spearman Correlation | 0.169 | 0.110 | 0.072 | 0.143 |
| | Sig. (2-tailed) | 0.338 | 0.537 | 0.686 | 0.419 |

BAL, Broncho-alveolar lavage fluid; IL-1, Interleukin-1; IL-8, Interleukin-8; TNF-α, Tumor Necrosis Factor-Alpha; HC, Healthy Control; CF, Cystic Fibrosis; NCFB, non-cystic fibrosis bronchiectasis.

* Correlation is significant at the 0.05 level (2-tailed). A *p-value* less than 0.05 is considered statistically significant.

** Correlation is significant at the 0.01 level (2-tailed).

## DISCUSSION

Bronchiectasis is a pathological condition involving thickened and dilated airways due to chronic inflammation and infection, leading to anatomical deformities and bronchial expansion. Bronchiectasis is categorized into two types: cystic fibrosis (CF) and non-cystic fibrosis bronchiectasis (NCFB) (1). Given the critical role of inflammation in the disease's progression, assessing levels of inflammatory and pro-inflammatory markers is essential for diagnosing and treating bronchiectasis. Due to its inflammatory nature, this study focused on examining IL-1, IL-8, and TNF-α levels in CF patients compared to NCFB patients. Findings revealed that serum and bronchoalveolar lavage (BAL) IL-8, as well as BAL IL-1, were significantly elevated in both CF and NCFB patients. A positive and significant correlation was also observed between serum IL-1 and both serum and BAL IL-8 levels.

Neutrophils, CD4+ T lymphocytes, and macrophages are critical players in the development and progression of bronchiectasis, as shown by their presence in bronchial biopsies from patients with bronchiectasis (9). However, the factors causing airway neutrophilia in CF patients beyond infections remain largely unknown. Recent studies using β-Epithelial Na+ Channel (βENaC) overexpressing mice as a CF pulmonary disease model have demonstrated that mucosal obstruction is linked to airway inflammation, even in germ-free mice (10, 11). In early life, mucosal stiffness is associated with systemic and cellular hypoxia in epithelial cells, leading to respiratory tract epithelial necrosis, which precedes airway neutrophilia (12-14). These preclinical studies indicate that the severity of mucosal obstruction is related to the number of necrotic airway epithelial cells (AECs) (15, 16). Furthermore, AEC necrosis in obstructed airways has been associated with elevated IL-1α levels. Evidence for this includes decreased airway neutrophilia and lung structural damage in βENaC transgenic mice with IL-1R gene deletion (17). The current study found that BAL IL-1 levels in NCFB patients were significantly higher than those in the healthy control group (p=0.018). Additionally, in healthy control individuals, serum IL-1 levels correlated positively with BAL IL-1 levels (p=0.004), but this relationship was absent in patient groups, suggesting that local inflammation impacts this cytokine's levels only at the site of inflammation. This is likely due to enhanced NLRP3 activation and IL-1 release in the CF airway, triggered by *Pseudomonas aeruginosa* flagella, hypoxia-induced reactive oxygen species, and mitochondria released from necrotic AECs (11-13,18-20).

Moreover, in healthy control subjects, serum IL-1 also positively correlated with BAL IL-1 and serum levels of IL-8 and TNF-α (p=0.004, 0.027, and 0.015, respectively), indicating that serum IL-1 levels may reflect lung health status. Additionally, BAL IL-1 in control subjects showed significant positive correlations with serum IL-8, BAL IL-8,

and serum TNF-α (p=0.007, 0.014, and 0.001, respectively), suggesting that these inflammatory cytokines may enhance each other's effects.

In all study groups (CF, NCFB, and healthy controls), serum IL-1 showed significant positive correlations with both serum and BAL IL-8 levels ($p < 0.0001$ and $p = 0.039$, respectively), emphasizing the role of IL-1 and MyD88 signaling in neutrophil attraction to the lungs, especially in bronchiectasis patients. This points to an increased influx of neutrophils in the airways through the activation of IL-1R-MyD88 signaling, NF-κB activation, and consequent IL-8 upregulation, underscoring the therapeutic potential of IL-1R (17-21). Correspondingly, serum IL-8 levels were significantly higher in CF patients compared to NCFB and healthy controls (p=0.018), and there was a significant positive correlation between serum IL-8 and BAL IL-8 levels. Studies suggest that the overproduction of IL-8 in CF bronchiectasis can exacerbate the disease by promoting neutrophil influx and inflammation (22,23). These findings imply that IL-1R-MyD88 pathway activation through elevated IL-1 could lead to IL-8 release, subsequently activating neutrophils and enhancing neutrophil elastase activity in CF lungs. BAL neutrophil elastase activity is a crucial predictor of persistent bronchiectasis in CF patients, and structural lung changes detectable through CT scans in CF children can occur even in the absence of respiratory infection (24, 25).

Montgomery et al.'s study on BAL IL-1α, IL-1β, and IL-8 levels in 102 CF patients, along with neutrophil elastase activity and lung structural changes (assessed via CT), revealed similar results, indicating detectable IL-1α and IL-1β levels in the absence of infection, which increased in the presence of bacterial infection and were associated with IL-8 levels, neutrophil counts, and neutrophil elastase activity (26). Additionally, IL-1 and neutrophil elastase are significant contributors to lung inflammation in CF (27). Chen et al. also noted elevated levels of Th17 cytokines, including IL-17A, IL-6, IL-8, IL-23, TNF-α, and IL-1 (all $p<0.001$) in NCFB patients (28). Their findings highlighted a significant rise in IL-1 and IL-8 gene expression in NCFB biopsies compared to controls (p=0.02 and 0.04, respectively). Their study also indicated that non-CF bronchiectasis might be more closely linked to Th17 pathway activation, whereas innate immunity activation through neutrophils is more pertinent in CF bronchiectasis.

In a comparative study, Olveira et al. analyzed bronchiectasis in 93 patients (43 with CF, 31 with NCFB, and 19 with CFTR-associated bronchiectasis) and 100 healthy controls. They found that serum IL-6 levels were significantly elevated in patients compared to controls; however, no significant correlation was observed between TNF-α and FEV1 levels (29). In this study, CF patients showed a non-significant increase in serum TNF-α compared to NCFB patients. Similarly, Ayhan et al.'s comparison of bronchiectasis in 40 patients with 20 controls showed no significant differences in serum and BAL TNF-α levels (p=0.120 and 0.186, respectively) (30). Generally, increased TNF-α activity and production are known to exacerbate bronchiectasis. Additional studies also underscore that IL-8 levels may be modulated by genetic variants in CF patients, impacting their lung disease severity (31, 32).

## CONCLUSION

These findings suggest that high BAL IL-1 levels are crucial in bronchiectasis and that IL-8 elevation may also be associated with IL-1 activity. Elevated levels of serum and BAL IL-8 are linked to increased neutrophil recruitment in the lungs in bronchiectasis patients. Spirometry results showed no correlation with these cytokines, indicating that spirometry alone is inadequate for monitoring bronchiectasis-related inflammation. Further studies are recommended to assess both inflammatory and anti-inflammatory cytokine levels, particularly during exacerbations, to determine the clinical relevance of cytokine profiles for these patients.

### Conflict of interest

The authors declare that they have no conflicts of interest.

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