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ORIGINAL RESEARCH

IL-6 and TIMP-1 Correlated to Airway Pathogen Colonization and Predict Disease Severity in Patients with Non-Cystic Fibrosis Bronchiectasis

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Background: Non-cystic fibrosis bronchiectasis is associated with airway pathogen colonization. We planned to investigate the inflammatory markers in patients with different airway pathogens and their correlation with disease severity.

Methods: We enrolled patients aged between 20 and 75 from October 2021 to August 2022. All patients had sputum evaluation for bacterial and fungal cultures before enrollment, and were classified into four groups according to the culture results.

Results: Forty-four patients with non-CF bronchiectasis and six controls were enrolled and categorized as follows: Group 1, no pathogens identified in sputum cultures (n = 14); Group 2, positive fungal culture results (n = 18); Group 3, positive *P. aeruginosa* culture results (n = 7); and Group 4, positive culture results for both fungi and *P. aeruginosa* (n = 5). Group 4 had significantly higher serum defensin α1, IL-6 and tissue inhibitors of MMP (TIMP)-1 levels than group 1 patients. The serum levels of IL-6 and TIMP-1 were positively correlated with the FACED score and negatively correlated with distance-saturation product.

Conclusion: Significantly higher levels of serum IL-6 and TIMP-1 were found in the patients who had concomitant fungal and *P. aeruginosa* colonization, and were closely related to clinical severity and may have important roles in disease monitoring.

Keywords: TIMP-1, non-cystic fibrosis bronchiectasis, clinical severity

Introduction

Non-cystic fibrosis (non-CF) bronchiectasis is a progressively inflammatory lung disease, which is characterized by recurrent bacterial colonization, infection and airway structural destruction.[1,2] Inflammation in bronchiectasis is mainly neutrophil induced, leading to impaired lung function.[3] Degranulation of neutrophil granules releases proteases, and neutrophil elastase (NE), which are responsible for increased lung damage. Active NE is associated with *P. aeruginosa* infection and low microbiome diversity, along with a decline in lung function, increased exacerbations and death.[4,5] Antibiotic treatment reduces inflammatory markers, including NE, interleukin (IL)-8 and tumor necrosis factor (TNF)-α.[6,7] NE seems to be a useful biomarker for categorizing disease severity, as well as predicting exacerbations and outcomes in bronchiectasis.

Matrix metalloproteinases (MMPs) are activated by NE and play important roles in extracellular matrix modelling. A higher MMP-9/tissue inhibitor of MMP (TIMP)-1 ratio has been associated with NE activity, and active MMP-9 and MMP-9/TIMP-1 have been closely correlated with the disease severity of bronchiectasis.[8] Moreover, Taylor et al found

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that MMPs vary with airway microbiota composition.[9] Not only bacteria (mainly *P. aeruginosa*) but also *Aspergillus spp*. elicit MMP expression and activation. Garratt et al identified associations between airways with *Aspergillus spp*. present and both higher total MMP-9 and MMP-9/TIMP-1.[8] These findings suggest an important role of the lung mycobiome in airway inflammation and remodeling.

Moreover, to limit colonization and pathogen invasion, epithelial cells utilize many antimicrobial peptides (AMPs) including defensin.[10] Parducho et al reported that epithelial β-defensin exhibited a novel antibacterial, in that it reduced the formation of biofilm but did not reduce the activity of *A. baumannii* or *P. aeruginosa*.[11] However, there is limited data concerning the association between antimicrobial peptides and airway microbiota in bronchiectasis.

Here, we plan to investigate the systemic inflammatory markers in different airway colonizing pathogens and their correlation with clinical severity, including the distance-saturation product (DSP) as derived from a 6 minute-walk test (6MWT), FACED score, and Bronchiectasis Severity Index (BSI).[12]

Methods

Patient Population

We enrolled patients from the outpatient department of thoracic medicine at our hospital with non-CF bronchiectasis from the Department of Thoracic Medicine from October 2021 to August 2022. Healthy patients had no evidence of any long-term lung condition and no chest infection in the preceding 4 weeks. The age of the enrolled patients ranged from 20 to 75 years. The inclusion criteria were as follows: bronchiectasis documented in chest high-resolution computed tomography (HRCT), chronic sputum production, and steady state defined by the absence of change in symptoms noted by the patient over the past 3 weeks. The exclusion criteria were as follows: bronchiectasis with defined etiology (i.e, pulmonary tuberculosis, asthma, chronic obstructive pulmonary disease, pneumoconiosis), common variable immunodeficiency, and use of antibiotics within the last 3 weeks, without sputum evaluations to isolate pathogens. Patients with hepatic failure, malignancy, or pregnancy, and those without complete medical record and follow-up data were also excluded. Data for calculating the BSI and FACED scores were taken from the patients' medical records. We defined acute exacerbation (AE) as an event that was clinically diagnosed by the physician and required antibiotic prescription for acute onset of cough, dyspnea, and changes in sputum characteristics.[12]

Before enrollment, all of the patients underwent regular sputum analysis for nontuberculous mycobacteria, bacterial and fungal cultures. They were then classified into four groups based on culture results. This study was approved by the Ethics Committee of Chang Gung Memorial Hospital (IRB 202002288B0), and all participants gave written informed consent before they were enrolled into the study.

Six-Minute Walk Test

All of the patients underwent the 6MWT following standard protocols, according to the 2002 ATS statement by experienced technicians during clinic visits. Oxygen saturation in room air was measured before and after the test, and the Borg scale, walking distance, and standard spirometry before the test were recorded. The tests were conducted in room air. The DSP was calculated as final 6MWT distance in meters × lowest oxygen saturation value during the 6MWT.

Enzyme-Linked Immunosorbent Assay

Blood samples were centrifuged at 3000 rpm at 4°C for 15 minutes and then stored at −70°C. Enzyme-linked immunosorbent assays were performed to measure levels of serum defensin α1, elastase 2 (MyBiosource, San Diego, CA), TNF-α, MMP-9, TIMP-1, IL-17A, IL-8, IL-1β and IL-6 (R&D Systems, Inc., Minneapolis, MN) according to the manufacturers' instructions. All assays were performed in duplicate. For each test, absorbance was first read at 450 nm, and then the concentration was calculated based on standard curves.

Statistical Analysis

Parametric data are shown as median (range) or mean (± SD), and categorical data are shown as number (%). Comparisons of continuous variables were performed with the nonparametric exact two-tailed Mann–Whitney *U*-test.

Comparisons of categorical variables were performed with Fisher's exact test. Correlations between parameters were evaluated using Spearman's rank correlation. These statistical analyses were performed using Prism version 9.0 (GraphPad Prism Software Inc, CA), and a p value ≤ 0.05 was considered to be statistically significant.

Results

We enrolled 6 control subjects (mean age 43.5 years old) and 44 patients with non-CF bronchiectasis (mean age 64.3 years old). Compared with the control subjects, the patients with non-CF bronchiectasis demonstrated higher serum defensin α1 (8137 ± 1623 vs 12281 ± 6742, respectively, p = 0.0275; Table 1, Figure 1A), higher serum IL-6 (0.16 ± 0.39 vs 4.12 ± 6.33, respectively, p < 0.0001; Table 1, Figure 1B) and higher serum TIMP-1 (155.8 ± 18.5 vs 187.3 ± 34.9, respectively, p = 0.0089; Table 1, Figure 1D). The serum MMP-9 were comparable between groups (431.7 ± 125.9 vs 610.9 ± 276.8, respectively, p = 0.1790, Table 1, Figure 1C).

The patients with non-CF bronchiectasis were further classified into four groups based on sputum fungal and bacterial culture results: Group 1, patients who had no pathogens identified from their sputum (n = 14); Group 2, positive fungal isolates (n = 18); Group 3, positive *P. aeruginosa* isolates (n = 7); and Group 4, with both *P. aeruginosa* and fungal isolates (n = 5).

No significant differences were found in sex, body mass index, clinical severity or age between the four groups (Table 2). The patients in group 4 who presented with both *P. aeruginosa* and fungal isolates from their sputa had significantly higher serum levels of defensin α1, TIMP-1 and IL-6 compared to those in group 1 (Table 2, Figure 2). In addition, serum levels of defensin α1 and TIMP-1 in group 4 were significantly higher than those in group 1 and group 2 (Figure 2, Table 2). Serum MMP-9/TIMP-1 and MMP-9 were similar between the control subjects and non-CF bronchiectasis patients (Table 1) and between all groups (Table 2). The isolated fungal species were listed in Table 3.

We also analyzed the correlation between serum inflammatory markers, antimicrobial peptides, anti-protease makers, the 6MWT, and clinical severity scores. Significant negative correlations were found between the serum levels of TIMP-1 and IL-6 with DSP, whereas positive correlations were found between the serum levels of TIMP-1 and IL-6 with FACED score (Figure 3).

Discussion

This prospective study may be the first to focus on levels of serum inflammatory markers, antimicrobial peptides and proteases from different airways colonizing pathogens in patients with non-CF bronchiectasis, and investigate their

Table 1 Baseline Characteristics and Immunochemistry Results of Normal Subjects and Patients with Bronchiectasis

	Normal Subjects n = 6	**Bronchiectasis n = 44**	**P value**
Age (years), mean ± SD	43.5±6.7	64.3±10.0	<0.0001
Male, n (%)	3 (50)	18 (41)	0.6861
BMI (kg/m^2), mean ± SD	21.6±2.7	22.9±3.7	0.4105
Serum biomarker			
IL-1 β, pg/ml, mean ± SD	0.00	0.09±0.28	0.3271
Defensin α1, pg/ml, mean ± SD	8137±1623	12,281±6742	0.0275
Elastase 2, ng/ml, mean ± SD	56.56±28.57	44.94±34.36	0.2959
IL-6, pg/ml, mean ± SD	0.16±0.39	4.12±6.33	<0.0001
IL-8, pg/ml, mean ± SD	10.54±2.70	16.43±14.41	0.6675
IL-17A, pg/ml, mean ± SD	2.57±6.10	0.89±1.53	0.8337
TNF-α, pg/ml, mean ± SD	6.35±1.94	6.11±6.73	0.3147
MMP-9, ng/ml, mean ± SD	431.7±125.9	610.9±276.8	0.1790
TIMP-1, ng/ml, mean ± SD	155.8±18.5	187.3±34.9	0.0089
MMP-9/TIMP-1, mean ± SD	2.9±1.1	3.3±1.6	0.6942

Abbreviations: SD, standard deviation; BMI, body mass index.

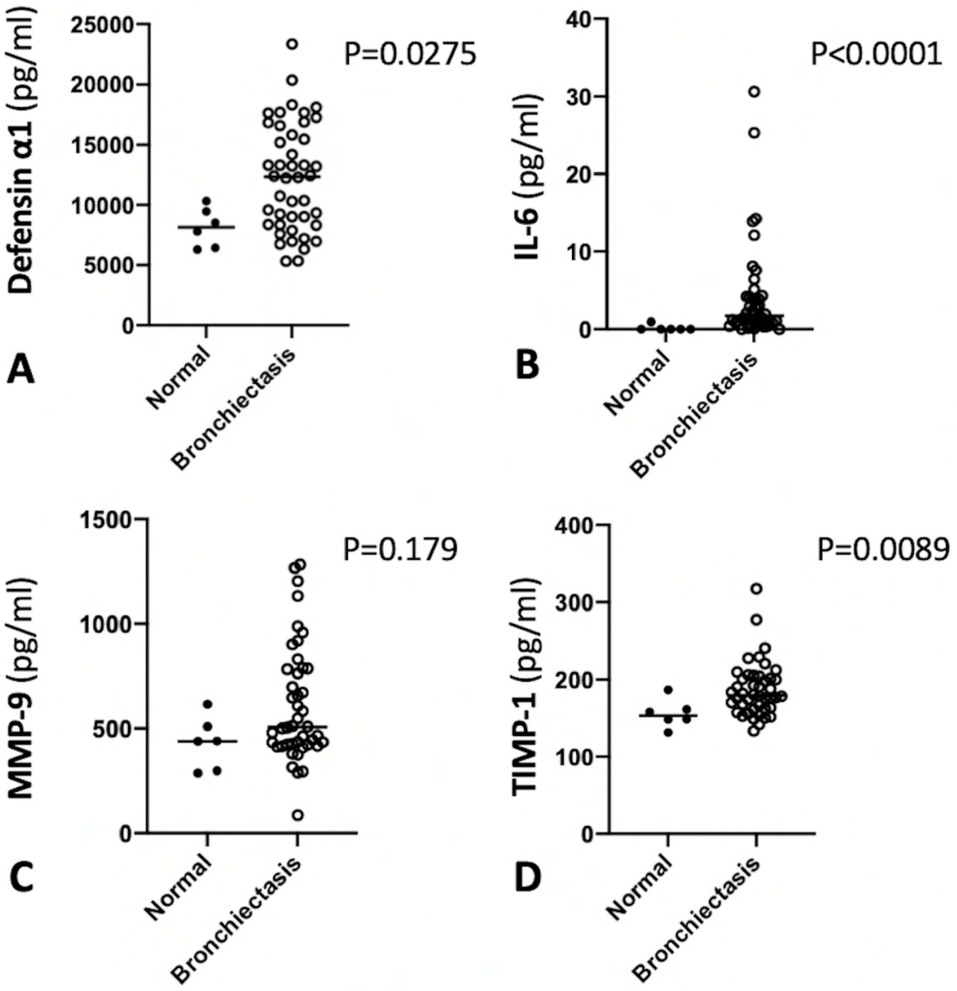

Figure 1 Comparison of inflammatory markers in sera collected from normal subjects (n = 6) and non-CF bronchiectasis patients (n = 44) examined by ELISA.
Notes: Serum levels of (**A**) defensin α1; (**B**) IL-6; (**C**) MMP-9; (**D**) TIMP-1. Horizontal lines represent the median values for each group.

correlation with clinical severity. Our results demonstrated higher levels of antimicrobial peptides, α defensin, and serum IL-6 in the patients with non-CF bronchiectasis compared to the control subjects, and also significantly higher levels of TIMP-1. However, no significant differences were found between the two groups in MMP-9 and MMP-9/TIMP-1. With regard to airway pathogens, the highest serum levels of α defensin and TIMP-1 were found in patients with concomitant fungus and *P. aeruginosa* colonization. In addition, positive correlations were noted between serum IL-6 and TIMP-1 with the FACED score, and negative correlations were noted between serum IL-6 and TIMP-1 with the DSP.

Repeated bacterial colonization, inflammation and bronchial wall destruction are features of non-CF bronchiectasis.[1] AMPs play key roles in host microbial defense, however they have also been shown to be inflammatory markers in bronchiectasis.[13] Increasing studies have focused on AMPs including defensins and LL-37, which may exhibit activity against *P. aeruginosa* and inhibit biofilm production of *P. aeruginosa*.[11,14] Sibila et al found that elevated sputum LL-37 levels were associated with *P. aeruginosa* infection and correlated to exacerbations in bronchiectasis.[13] In this study, we found significantly higher serum levels of defensin α1 in the non-CF bronchiectasis patients than in the control group. Moreover, the levels of serum defensin α1 in the patients with both *P. aeruginosa* and fungus colonization were higher than in those with only fungus colonization and those with neither fungus nor *P. aeruginosa* colonization. However, serum defensin α1 had no significant correlation with clinical severity, including BSI, FACED score and DSP.

Chronic inflammation in non-CF bronchiectasis also plays a major role in bronchial injury, and can induce pro-inflammatory cytokine released, including TNF- α, IL-8 and IL-6.[15] Gao et al found that serum TNF-α and IL-6 were

Table 2 Clinical Characteristics and Immunochemistry Results of the Four Groups of Bronchiectasis According to the Pathogen Isolated from Sputum Samples

	Group 1 n =14	Group 2 n =18	Group 3 n =7	Group 4 n =5	P value
Age (years), mean ± SD	63.4±8.4	63.8±10.7	66.6±3.5	63.6±16.5	0.8763
Male, n (%)	6 (43)	9 (50)	2 (29)	1 (20)	0.5526
BMI (kg/m^2), mean ± SD	22.9±3.7	23.9±3.3	21.1±4.0	21.6±4.3	0.3211
Allergic rhinitis, n (%)	7, 50%	13, 72%	2, 29%	4, 80%	0.1470
FEV1, %, mean ± SD	66.6±19.7	72.2±23.5	56.3±22.9	62.6±12.7	0.3967
Lobe involvement					0.4944
≥ 3 lobes, n (%)	6, 43%	12, 67%	5, 71%	3, 60%	
BSI, mean ± SD	5.9±2.4	5.5±2.4	10.3±3.8	6.8±4.3	0.0385
FACED, mean ± SD	2.4±1.5	2.7±1.4	3.4±1.1	3.4±1.5	0.3317
DSP, mean ± SD	457±78	375±172	367±65	442±133	0.2640
Serum biomarker					
IL-1β, pg/ml, mean ± SD	0.033±0.06	0.056±0.24	0.152±0.29	0.300±0.62	0.4267
Defensin α1, pg/ml, mean ± SD	12154±5141	10,686±3168	13,284±5037	16,975±2754	0.0417
Elastase 2,ng/ml, mean ± SD	50.0±33.6	41.4±35.9	32.3±27.5	61.2±40.5	0.4449
IL-6, pg/ml, mean ± SD	1.79±2.0	4.33±7.2	3.92±4.6	10.2±9.9	0.075
IL-8, pg/ml, mean ± SD	21.2±18.3	9.9±5.2	21.4±17.3	19.6±16.0	0.1209
IL-17A, pg/ml, mean ± SD	0.56±1.1	1.17±1.9	0.21±.56	1.80±2.0	0.2024
TNF-α, pg/ml, mean ± SD	5.79±4.9	4.80±7.1	8.20±10.6	8.81±1.8	0.1147
MMP-9, ng/ml, mean ± SD	651.4±228.0	555.3±275.9	625.3±349.5	677.5±349.8	0.6270
TIMP-1, ng/ml, mean ± SD	175.5±26.0	180.7±24.8	189.0±22.5	241.1±56.1	0.0353
MMP-9/TIMP-1, mean ± SD	3.8±1.5	3.1±1.6	3.4±2.1	2.7±0.9	0.3176

Abbreviations: SD, standard deviation; BMI, body mass index; BSI, bronchiectasis severity index; DSP, distance-saturation product.

markers for viral infection in patients with bronchiectasis exacerbation.[16] Recently, Camargo et al reported significantly higher levels of IL-6 in adults with bronchiectasis and were negatively correlated with aerobic capacity.[15] We demonstrated a similar finding, as our patients had significantly higher serum IL-6 levels compared to the controls. We also found that patients with both *P. aeruginosa* and fungus colonization had the highest serum IL-6 levels. Furthermore, the levels of serum IL-6 were positively associated with the FACED score and negatively associated with DSP, which we have previously shown to have comparable predictive ability for mortality.[12] These findings elucidated a potential

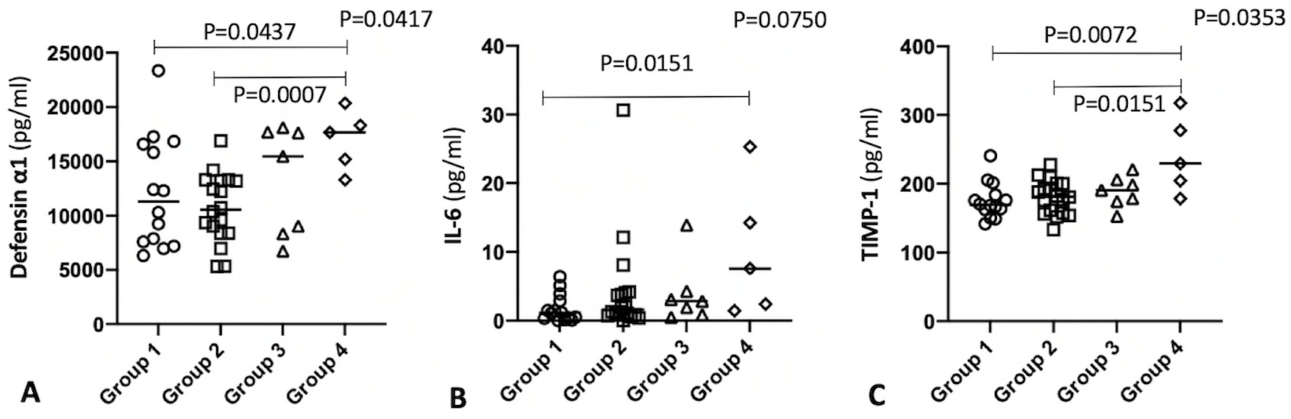

Figure 2 Comparison of inflammatory markers in sera collected from non-CF bronchiectasis patients, dividing into 4 groups.
Notes: Group 1, patients who had no any pathogen identified from sputum (n = 14); Group 2, positive fungal isolates (n = 18); Group 3, positive P. aeruginosa isolates (n = 7); and Group 4, concomitant P. aeruginosa and fungus isolates (n = 5). Serum levels of (**A**) defensin α1; (**B**) IL-6; (**C**) TIMP-1. Horizontal lines represent the median values for each group.

Table 3 Fungal Species Isolated from Sputum Samples in Non-CF Bronchiectasis Patients

Fungal Species	Group 2 n=18, (n, %)	Group 4 n=5 (n, %)
Aspergillus Flavus	4, 22%	1, 20%
Aspergillus Niger	1, 6%	0
Aspergillus versicolor	2, 11%	0
Aspergillus spp	1, 6%	0
Penicillium	9, 50%	3, 60%
Cladosporium	6, 33%	1, 20%
Mold	6, 33%	4, 80%

association between serum levels of IL-6 and pathogen infection, and that serum levels of IL-6 may play a key role in the clinical severity of non-CF bronchiectasis.

MMPs are extracellular matrix remodeling peptidases, which can degrade extracellular matrix components and participate in inflammatory processes of several chronic lung diseases.[17] An inverse correlation between serum MMP-9 with forced expiratory volume of 1 second has been demonstrated in patients with chronic obstructive pulmonary disease.[18] MMPs are inhibited by TIMPs, which are endogenous protein regulators. Elevated serum MMP-9 concentrations and MMP-9/TIMP-1 ratio have also been associated with an increased risk of mortality[19] and to be predictors of emphysema.[20,21] Lin et al found significantly increased expressions of lung connective tissue growth factor in OVA-challenged mice, and that this was positively associated with smooth muscle proliferation, MMP-9, and TIMP-1.[22] Matsumoto et al stated that TIMP-1 may play an important role in thickening of airway smooth muscle in patients with asthma, resulting in airflow obstruction.[23] Recently, Garratt et al reported associations between both active MMP-9 and MMP-9/TIMP-1 in sputum with increased expressions of free NE and the progression of cystic fibrosis. The elevated MMP-9/TIMP-1 ratio in sputum suggests that proteinase-anti-proteinase imbalance may be involved in airway

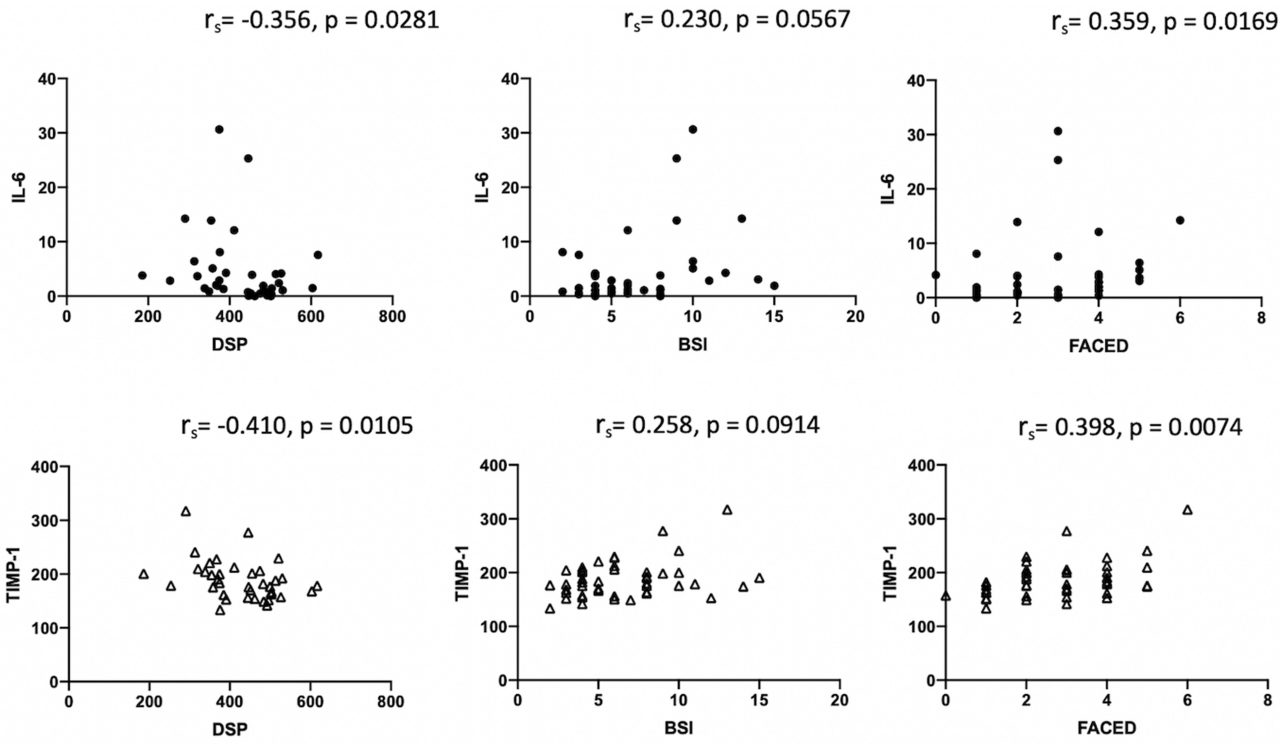

Figure 3 The correlation between serum IL-6, TIMP-1 and DSP, the clinical severity score (BSI, FACED).

damage.[8] Moreover, the levels of MMP-8 and MMP-9 have been associated with clinical severity, including high-resolution computed tomography scores, pulmonary function and BSI.[24] Taylor et al also reported that patients with bronchiectasis with *H. influenzae*–dominant infections of the airway had elevated MMP-8 activity than those with *P. aeruginosa*– dominant infections of the airway. In addition, they found that forced expiratory volume in 1 second was significantly inversely correlated with MMP-9/TIMP-1, MMP-8, and MMP-8/TIMP-1, and also positive correlations among MMP-1, MMP-8, MMP-9, and TIMP-2 with multiple inflammatory markers (serum CRP level, and sputum neutrophil, IL-8, IL-1β levels).[9] In this study, we did not find significantly elevated levels of serum MMP-9 or MMP-9/TIMP-1 in the patients with non-CF bronchiectasis compared with the controls. In subgroup analysis of the different airway-colonizing pathogens, we also no significant differences among the groups. Levels of MMP can be affected by inflammation and infections of the airway, and MMP-9/TIMP-1 may differ according to the stage of non-CF bronchiectasis.

TIMPs are well recognized for the ability of controlling the activity of MMPs.[25] Dong et al reported significant elevations of secreted TIMP-1 in the serum and bronchoalveolar lavage fluid in a mouse model of multi-walled carbon nanotube exposure. Increased TIMP-1 levels have also been reported in other lung diseases, including idiopathic pulmonary fibrosis and bleomycin-induced lung fibrosis.[26] Thus, it is possible that TIMP-1 elevation represents a shared molecular response and that it plays a crucial role in the development of fibrosis, particularly in the initial phase of inflammation and tissue remodeling.[27] Although the serum levels of MMP-9 in the non-CF bronchiectasis patients were not significantly different from those in the controls in the present study, we found that serum levels TIMP-1 were significantly higher than in normal subjects. In addition, the group with concomitant fungus and *P. aeruginosa* demonstrated the highest serum TIMP-1 levels. Furthermore, serum levels of TIMP-1 were significantly positively correlated with the FACED score, significantly negatively correlated with DSP, and showed a trend of a positive correlation with BSI, all of which represent clinical severity and are predictors of mortality.[12] These findings suggest that serum levels of IL-6 and TIMP-1 may be primarily triggered by airway pathogens, and that they are closely associated with clinical severity.

There are several limitations to this study. First, biomarker analysis was only performed at the serum level. We found no differences in MMP-9 or MMP-9/TIMP-1, however this may be because serum levels of these markers could not properly reflect activity in the airway. However, we still found significant associations between the serum levels of TIMP-1 and IL-6 with airway pathogens and disease severity, indicating the key role that systemic inflammation plays in non-CF bronchiectasis. Second, the prognosis was assessed in terms of mortality from any cause, and associations with the biomarkers would be of interest. We enrolled patients from outpatient clinics, and all patients are still currently alive, so we were unable to determine an association between these biomarkers and mortality. Third, patients with positive fungal culture may be higher in our study, this may attribute to the warm and humid weather in Taiwan. Forth, we only identified pathogens from the sputum through fungal and bacterial culture. 16S rRNA gene sequencing of sputum samples would be a better method. Furthermore, the age was significantly different between healthy control and patients with bronchiectasis in our study, which may have an impact on systemic inflammatory marker. Nevertheless, the levels of serum IL-6 and TIMP-1 were still higher in group 4 patients with concomitant *P. aeruginosa* and fungal isolates, suggested more significant inflammation. The number of included patients was also limited, and larger prospective studies are warranted to validate our findings.

In conclusion, our results demonstrated significantly higher serum levels of TIMP-1, α defensin and IL-6 in the patients with bronchiectasis and concomitant fungus and *P. aeruginosa* colonization. In addition, the levels of serum of TIMP-1 and IL-6 were closely related to clinical severity and may have important roles in disease monitoring.

Abbreviations

AMP: antimicrobial peptide; BSI: Bronchiectasis Severity Index; CF: cystic fibrosis; DSP: distance-saturation product; MMP: matrix metalloproteinase; NE: neutrophil elastase; TIMP-1: tissue inhibitor of MMP.

Data Sharing Statement

The data sets analyzed in the current study are available from the corresponding author, Chun-Yu Lin, upon reasonable request.

Ethics Approval and Consent to Participate

This study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Review Committee of Chang Gung Medical Foundation (approval no. IRB 202002288B0). All participants provided written informed consent. All procedures followed were in accordance with the ethical standards of the IRB of Chang Gung Medical Foundation and with the Helsinki Declaration.

Consent for Publication

Informed consent was obtained from all individual participants included in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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