

Post-Infectious Bronchiolitis Obliterans in Children: Long-Term Outcome, Prognostic Factors, and Relation with Serum KL-6 Levels

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Background: Post-infectious bronchiolitis obliterans (PIBO) is a rare form of chronic obstructive lung disease in children, with insufficient data on the factors that predict the prognosis of PIBO.

Objectives: The aims of this study were to assess the long-term outcome of PIBO patients, evaluate prognostic factors, and investigate the relation between serum Krebs von den Lungen 6 (KL-6) level and disease severity.

Methods: Thirty-eight children with a clinical and radiological diagnosis of PIBO were enrolled on this study. Information was obtained from medical records regarding the clinical characteristics related to the first severe lung infection, the patient's clinical presentation at PIBO diagnosis, treatment, and overall outcome. The clinical conditions of the patients at the time of their PIBO diagnosis and at their last follow-up admission were evaluated using the clinical severity score (CSS). Samples for serum KL-6 level were obtained in 36 PIBO and 42 control group patients. The association of KL-6 level and PIBO severity was analyzed. KL-6 was also compared with the control group.

Results: The median age of the 38 PIBO patients was 8.3 years (range 1.4–17.1 years), and the patients were monitored for a median of 52.5 months (range 1–180 months). The last CSSs of patients who were mechanically ventilated at first severe lung infection were greater than others ($p=0.033$). First and last CSSs were significantly correlated ($r=0.355$, $p=0.029$). Serum KL-6 levels of PIBO patients were between 2 and 321.73 IU/mL (median 4.87 IU/mL). Serum KL-6 levels of PIBO patients were significantly lower than in the control group ($p\leq 0.01$). Patients hospitalized for a longer time at the first severe pulmonary infection had significantly lower KL-6 levels at their last control ($r=-0.498$, $p=0.004$).

Conclusions: PIBO patients who were mechanically ventilated during the first severe lung infection had worse clinical outcomes after long-term follow-up. Serum KL-6 concentrations in PIBO patients were lower than in the control group. PIBO patients who were hospitalized and mechanically ventilated at first severe pulmonary infection were prone to having lower KL-6 concentrations.

Introduction

BRONCHIOLITIS OBLITERANS (BO) is a rare fibrosing form of chronic obstructive lung disease secondary to severe injury to the lower respiratory tract that results in narrowing and/or complete obliteration of the small airways.¹ BO in children is most often seen following a severe lower respiratory tract infection and is accepted as long-term sequelae of viral infections.² The initial clinical and radiological presentation of BO does not differ from that of acute bronchiolitis or viral pneumonia. However, the clinical and radiographic features of the disease characteristically wax and wane for several weeks or months, and include recurrent episodes of atelectasis, pneumonia, and wheezing.³ In gen-

eral, a more severe initial insult to the lower respiratory tract leads to a more severe long-term disability.² However, satisfactory data about the factors that affect the prognosis of BO have not yet been collected.

Krebs von den Lungen 6 (KL-6) is a high molecular weight glycoprotein that is expressed on the surface of type II pneumocytes and respiratory bronchiolar epithelial cells.⁴ Moreover, the presence of KL-6 can also be detected in serum, much like other proteins secreted by airway and alveolar cells.^{4,5} According to previous research, serum KL-6 levels are elevated in various interstitial lung diseases, and increasing levels have been positively correlated with disease activity.^{6,7} Elevation in serum KL-6 levels is thought to be associated with increased type II pneumocyte activity

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following lung injury and increased permeability of the lung–blood interface.^{6,7} Walter et al. suggested that increased serum KL-6 levels after lung transplantation are a predictor of post-transplantation BO. Furthermore, they found that patients with higher serum KL-6 levels demonstrate a greater decrease in forced expiratory volume in 1 second (FEV1) values compared with that of other post-transplantation patients.⁸ Similarly, Haberman et al. reported that an increase in serum KL-6 levels is more significantly related to BO development in lung transplant patients.⁹ To the authors' knowledge, the relationship of serum KL-6 levels with the development, severity, and clinical outcome of BO in children has not been published.

This study intended to determine the prognostic factors for PIBO in pediatric patients by retrospectively examining the clinical course and investigating the relationship between serum KL-6 levels and the clinical characteristics of these PIBO pediatric patients. It was hypothesized that in PIBO patients, serum KL-6 levels would be elevated and would be associated with disease severity similar to post-transplantation BO patients. Delineating the prognostic factors of PIBO may provide the information needed to prevent poor outcomes by allowing clinicians to give more attention to patients in groups with the most severe prognoses.

Methods

This study was performed at the Hacettepe University Ihsan Dogramaci Children's Hospital. For the sample population, 38 children with a clinical and radiological diagnosis of PIBO who had last been seen between September of 2010 and February of 2012 were enrolled. Their medical records were reviewed retrospectively. The criteria used for the diagnosis of PIBO were as follows: (1) history of bronchiolitis or acute viral pneumonia in a previously healthy child; (2) evidence of persistent obstruction of the airway for 60 days after an acute event, as identified either by physical examination and/or by lung function tests (i.e., airway obstruction unresponsive to a ≥ 2 week course of systemic corticosteroids and bronchodilator therapy); (3) the mosaic pattern of air trapping on a chest computed tomography (CT) scan; and (4) exclusion of other chronic lung diseases that progress with permanent respiratory symptoms (e.g., tuberculosis, cystic fibrosis, bronchopulmonary dysplasia, severe asthma, and α -1-antitrypsin deficiency).² In PIBO patients, specific information was extracted from medical records regarding the clinical characteristics related to the first severe lung infection, the patient's clinical presentation at the PIBO diagnosis, the treatment, and the overall outcome. The first CT images were obtained for 21 of the PIBO patients. These images were evaluated by a pediatric radiologist utilizing the modified Bhalla scoring system, which is based on the extent and severity of the lung findings. Scores range from 0 to 31, with a score of zero indicating normal findings.¹⁰

The clinical conditions of patients at the time of their PIBO diagnosis and at their last follow-up admission were evaluated using the clinical severity score (CSS) with some modifications (Table 1).¹¹ More specifically, the scoring depends on continuing symptoms for at least 1 month, SaO₂ of <93%, and pulmonary artery hypertension. Pulmonary artery hypertension was assessed via echocardiography. Scoring is based on four points: 1, asymptomatic; 2, symptomatic with normal oxygen saturation while breathing room air; 3

TABLE 1. CLINICAL SEVERITY SCORE

Point	Symptoms	O ₂ saturation <93%	Pulmonary artery hypertension
1	No	No	No
2	Yes	No	No
3	Yes	Yes	No
4	Yes	Yes	Yes

symptomatic with SaO₂ of <93%; and 4, symptomatic with pulmonary hypertension. The original form of scoring is based on five points; point 3 denotes abnormal SaO₂ with exercise, and point 4 denotes abnormal SaO₂ at resting. Point 3 from the original form was omitted, and patients were evaluated according to scoring based on four points.

At the last clinical discharge visit, the FEV1 was recorded given that the patient could perform the test.

Serum KL-6 levels were obtained from all 36 patients with BO at discharge from the outpatient clinic. Levels were not collected at the time of diagnosis. KL-6 levels were obtained from a control group of 42 children seen in the authors' emergency department for asthma, acute bronchiolitis, pneumonia, or upper airway infection. The control group patients were without any other underlying lung diseases. Patients with these diseases were included in the study because elevated KL-6 levels were expected in patients with PIBO, and the study planned to determine whether these increases were more significant in PIBO patients than in patients with other acute lung diseases. This study was approved by the Hacettepe University Ethics Committee, and the investigations were performed only after informed consent was obtained from the subjects' parents.

The collected serum samples were stored at -80°C until they were used. The serum KL-6 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (KL-6; Cusabio Biotech Co., Ltd., China). This test kit measures KL-6 levels via a quantitative sandwich enzyme immunoassay technique.

All statistical analyses were performed using SPSS v15 (SPSS, Inc., Chicago, IL). The Mann–Whitney *U*-test was used to compare two groups, the Kruskal–Wallis test was used to compare three or more groups, and the Conover–Dunn test was used to detect differences between these groups. The correlation of numeric variables was tested via Spearman's rank correlation test. Statistical significance was defined as $p < 0.05$, and r revealed the degree of significance.

Results

A total of 38 PIBO pediatric patients (20 girls) were identified for the study. The median age of the participants was 8.3 years (range 1.4–17.1 years), and the patients were monitored for a median of 52.5 months (range 1–180 months). The general characteristics of the patients at the time of the first severe infection are summarized in Table 2. The median age of patients at PIBO diagnosis was 38 months (range 7–162 months). At the time of the PIBO diagnosis, CSSs were 3 for 19 (50%) of the patients, 2 for 16 (42.1%) of the patients, 4 for two (5.3%) of the patients, and 1 for four (10.5%) of the patients (Table 3). At last control, the mean CSS of patients who required mechanical ventilation during first severe infection was 2.28 ($SD = 0.75$), while the mean CSS for patients

TABLE 2. GENERAL CHARACTERISTICS OF PATIENTS AT THE TIME OF THE FIRST SEVERE PULMONARY INFECTION

	N (%)
Sex	
Female	20 (52.6)
Male	18 (47.4)
Age at first infection	Median 11.5 months (1–152)
First diagnosis	
Pneumonia	31 (81.6)
Bronchiolitis	7 (18.4)
Causative pathogens	
Not identified	33 (86.8)
Adenovirus	2 (5.3)
Influenza	1 (2.6)
RSV	1 (2.6)
Measles	1 (2.6)
Hospitalization	34 (89.5)
Hospitalization duration	Median 30 days (3–120)
Mechanically ventilated	7 (18.4)

who did not require mechanical ventilation was 1.54 ($SD=0.75$). Indeed, this difference was significant ($p=0.033$). There was a weak, positive correlation between the CSS at diagnosis and at the clinic discharge visit ($r=0.355$, $p=0.029$).

Thorax CT images at the time of the PIBO diagnosis revealed the following findings: mosaic patterns, atelectasis, and bronchiectasis for 18 (47.4%) patients; mosaic patterns and atelectasis for 11 (28.9%) patients; only mosaic patterns for six (15.8%) patients; and mosaic patterns and bronchiectasis for three (7.9%) patients. The modified Bhalla score was computed for 21 PIBO patients, was between 7 and 19 (median 14).

Medical treatment was initiated at an average of 30.5 months (range 1.5–148 months) after the first severe pulmonary infection. Eighteen patients were treated with oral systemic steroids for a mean treatment duration of 8.7 months (range 1–21 months). Systemic steroid treatment was decided based on clinicians' clinical approach. When the initial CSS of patients treated with systemic steroids was compared with patients who did not receive any systemic steroid, the CSS of the systemic steroid-treated group was statistically worse than others ($p=0.04$). All of the patients used inhaled steroids for an average of 21 months (range 1–180 months). At the clinic discharge visit, 33 (86.8%) patients were still using inhaled steroids, and one patient was still being treated with both systemic and inhaled steroids.

At the clinic discharge visit, 21 patients could achieve respiratory function tests. The mean results for the respira-

tory function tests were: FEV1 = 53.2% ($SD=19.35$), forced expiratory vital capacity (FVC) = 70.7% ($SD=5.44$), and forced expiratory flow from 25% to 75% of vital capacity (FEF_{25–75%}) = 38.8% ($SD=21.73$).

The modified Bhalla score for thorax CT scans at the PIBO diagnosis and the CSS at the clinic discharge visit were not significantly correlated ($r=0.106$, $p=0.648$). No correlation was detected between the modified Bhalla score and the last FEV1 values ($r=-0.501$, $p=0.116$). A moderate, negative relationship was observed between the last CSS and FEV1 value at the clinic discharge visit ($r=-0.524$, $p=0.012$).

The mean CSS at the clinic discharge visit was 0.89 points lower than the mean CSS at the time of diagnosis. The 18 patients who were treated with systemic steroids had a mean CSS decrease of 0.83 ($SD=0.87$), while the other 20 patients had a mean CSS decrease of 0.95 ($SD=0.68$). No significant difference was found between these two groups ($p=0.718$). When the effect of steroid treatment duration on CSS change was examined, no significant association of both systemic and inhaled steroid with CSS change was found ($p=0.77$ and $p=0.89$, respectively).

Serum KL-6 levels were assessed for 36 PIBO patients when they were free of any acute infection. This assessment took place on average 87 months (range 4–202) months after the first severe lung infection. The median KL-6 level was 4.87 IU/mL (range 2–321.73 IU/mL; Table 4). The control group consisted of 42 patients (i.e., 18 girls) with a mean age of 3.7 years (range 2 months–15.5 years). The diagnoses for this group included 19 (45.2%) cases of pneumonia, 8 (19%) cases of acute bronchiolitis, 5 (11.9%) cases of asthma attacks, and 10 (23.8%) cases of upper airway infections. For the 42 control cases, the serum KL-6 levels ranged between 2 and 1,500 IU/mL with a median level of 40.93 IU/mL. According to the diagnoses, the median (minimum–maximum) values of the serum KL-6 levels were: pneumonia 45.92 IU/mL (range 2–1,500 IU/mL), acute bronchiolitis 83.12 IU/mL (range 4.65–1,500 IU/mL), asthma attack 14.54 IU/mL (2–42.2 IU/mL), and upper airway infection 38.65 IU/mL (range 4.66–122.61 IU/mL; Table 4).

The Kruskal–Wallis test revealed that the serum KL-6 levels of PIBO patients were significantly lower than those of the control group ($p<0.01$). The Conover–Dunn test was used to detect differences between groups, and this test indicated that the serum KL-6 levels for the PIBO patients were significantly lower than those of the pneumonia, acute bronchiolitis, and upper airway infection groups ($p<0.05$). No difference was observed between the PIBO and asthma attack groups (Table 4).

Serum KL-6 levels were compared based on the type of initial infection, the need for hospitalization, and the need for mechanical ventilation during initial infection, and there was no significant difference between groups (Table 5). There was a moderate, negative correlation between the hospitalization duration and the serum KL-6 levels ($r=-0.498$, $p=0.004$). The CSS at the time of PIBO diagnosis and the CSS and FEV1 values at the time of the last visit were not significantly correlated with the serum KL-6 levels.

Discussion

PIBO is an uncommon, chronic, obstructive lung disease that follows a severe pulmonary infection caused by many

TABLE 3. CLINICAL SEVERITY SCORE AT THE TIME OF THE PIBO DIAGNOSIS AND THE CLINIC DISCHARGE VISIT

	At PIBO diagnosis N (%)	At clinic discharge visit N (%)
Clinical severity score		
1	1 (2.6)	21 (55.3)
2	16 (42.1)	10 (26.3)
3	19 (50)	5 (13.2)
4	2 (5.3)	2 (5.3)

PIBO, post-infectious bronchiolitis obliterans.

TABLE 4. SERUM KL-6 LEVELS FOR PIBO PATIENTS AND CONTROL GROUPS

		Number of patients	Median	Min-max	p*
PIBO patients		36	4.87	2-321	
Control groups	Pneumonia	19	45.92	2-1,500	<0.05
	Acute bronchiolitis	8	83.12	4.65-1,500	<0.05
	Asthma attack	5	14.54	2-42.2	>0.05
	Upper airway infection	10	38.65	4.66-122.61	<0.05
	Total	42	40.93	2-1,500	<0.01

Significant values are shown in bold.

*Comparison with PIBO patients.

microorganisms with the capacity to insult the airway epithelium. Generally, more severe initial lung damage results in greater long-term morbidity.² A few studies have focused on the prognosis of PIBO, but specific prognostic factors have not yet been denoted.^{10,12-14}

Potential prognostic factors of PIBO were evaluated via CSS at the clinic discharge visit. When the effects of the clinical characteristics at the time of the first lung infection on the last CSS were examined, only the need for mechanical ventilation was significantly related to an increased CSS at the clinic discharge visit. This indicates that patients who required mechanical ventilation at the first infection were in worse clinical condition than those who did not require mechanical ventilation, despite the passage of an average of 88.7 months (range 4-202 months) after the first infection. Previous studies revealed that patients who required mechanical ventilation are at increased risk of BO development after severe pulmonary infection.¹⁵⁻¹⁷ However, no data have been collected to date about the impact of mechanical ventilation on the clinical severity of BO patients after long-term follow-up. The requirement for mechanical ventilation may be a sign of severe pulmonary infection, and mechanical ventilation may also exacerbate the initial injury to the lungs. Hospitalization can be considered another reflection of pulmonary infection severity. In the present study, hospitalized patients had an average CSS of 1.76 points, whereas outpatients had a mean CSS of 1 point. Although the hospitalized patients' outcomes seemed slightly worse, the difference was not statistically significant. Additionally, the duration of hospitalization was not correlated with the last CSS. Mechanical ventilation may be a unique prognostic factor that is unrelated to infection severity.

Generally, a relative improvement in the complaints of PIBO pediatric patients is observed in subsequent years. Proposed explanations include the fact that the general growth and development of children includes an ongoing alveolarization of the lung areas that were unaffected by the

initial infection, as well as continued overall airway growth, resulting in an increased lumen area.¹⁴ Nevertheless, this improvement is usually partial for most patients, and they still demonstrate abnormal clinical findings and report mild symptoms, particularly during physical exercise.¹⁸ In the present study, a mean decrease in the CSS of 0.89 was observed during the follow-up period (i.e., approximately 52 months). An increase in the CSS was detected in only two patients who developed pulmonary artery hypertension after their diagnosis of PIBO. Additionally, the CSS remained constant for 10 patients. No evidence was found to support a significant relationship between CSS change and systemic steroid usage. Although corticosteroids are frequently used for BO patients, their effectiveness in improving the outcome of patients with BO is unknown.¹⁹ If a decision is made to treat a BO patient with these drugs, the corticosteroids should be given early while the disease process is still in the developing phase (i.e., before the airway fibrosis is complete).² In conjunction with the delay in PIBO diagnosis, a delay in the initiation of treatment in patients was observed ($M=30.5$ months). Because of this long interval, permanent airway fibrosis might have been developed, which may explain why treatment seems unrelated to CSS change. The systemic care of patients and the anatomic changes with age may contribute to the improvement observed in all patients, which may hide the effects of medical treatment.

A positive, weak correlation was observed between the first and last CSSs ($r=0.355$, $p=0.029$). The mean period that passed between these two examinations was 58.26 months ($SD=40.91$). These data suggest that despite any improvements observed over the course of treatment, patients who had worse clinical parameters at their diagnosis continued to have lower pulmonary evaluations (i.e., according to the CSS) than the other patients did approximately 5 years later.

Thorax CT scans were obtained for 21 patients and were graded via the modified Bhalla scoring system. Bhalla

TABLE 5. COMPARISON OF SERUM KL-6 LEVEL BASED ON CLINICAL CHARACTERISTICS

		n	Median KL-6 level (min-max)	p
First severe lung infection	Pneumonia	29	4.92 (2-56.96)	0.815
	Bronchiolitis	7	2 (2-321.73)	
Hospitalization	Yes	32	4.76 (2-321.73)	0.269
	No	4	20.43 (2-45.62)	
Mechanically ventilation	Yes	6	3.77 (2-56.96)	0.634
	No	30	4.86 (2-321.73)	

scores were not correlated with last CSSs and FEV1 values (for 11 patients). These outcomes conflict with the findings from a study by Mattiello et al.¹⁰ where it was claimed that the modified Bhalla score could be used to predict respiratory function 10 years later in 21 PIBO patients. For the assessment using FEV1, the present sample size may be insufficient. However, the CSS is a good indicator of the clinical situation and is correlated with FEV1. If a meaningful relationship had been discovered between the CSS and the Bhalla score, this would be a good confirmation of the prognostic worth of the Bhalla score. However, suggestions about this score's prognostic value for PIBO patients should be made only after more studies with greater numbers of patients are conducted.

To date, the serum KL-6 levels in BO patients have been investigated in three studies, but all of them focused on lung transplant patients.^{8,9,20} Serum KL-6 levels in PIBO patients have been studied for first time in this investigation. In the present study, 36 PIBO patients were assessed for serum KL-6 levels. The median KL-6 level was 4.87 IU/mL, and the mean KL-6 level was 20.84 IU/mL ($SD=53.38$). Walter et al.⁸ found that the mean serum KL-6 level was 688.7 IU/mL ($SD=225.8$) in eight post-transplant BO patients. Similarly, Haberman et al.⁹ found a mean serum KL-6 level of 559.25 IU/mL ($SD=283.84$) in seven post-transplant BO patients. Although the sample sizes were small and the standard deviations were excessive in these studies, the observed serum KL-6 levels were much greater than in the present study. Imai et al.²¹ claimed that serum KL-6 concentrations of ≥ 250 IU/mL in a child might reflect alveolar damage and/or the regeneration of type II pneumocytes. In the present study, only one patient's serum KL-6 level exceeded this cutoff value (321.73 IU/mL), and the second-highest observed concentration was only 56.96 IU/mL. The serum KL-6 concentration in PIBO patients was lower than that of the control group. Both patients with acute pulmonary inflammation (i.e., the bronchiolitis and pneumonia groups) and patients without lung infections (i.e., the upper airway infection group) had greater average serum KL-6 values than the PIBO group. The average serum KL-6 level of the asthma attack group was slightly higher than that of the PIBO group, but it was not statistically significant. The small sample size of this group (only five patients) can be responsible for this result.

When a relationship between the serum KL-6 levels and the clinical characteristics of the patients was examined, only one hospitalization duration and serum KL-6 levels had a moderate, negative correlation ($r=-0.498$, $p=0.004$). In other words, the patients who were hospitalized longer with the first severe pulmonary infection had moderately lower KL-6 concentrations, even after much time had passed (mean 87 months). Other results were not statistically significant, but patients with more severe first lung infections had lower KL-6 concentrations (Table 5). These results are contrary to those of previously published studies about KL-6 concentrations in post-transplant BO patients. In the present study, the KL-6 levels of PIBO patients were lower than those of the control group and the previously advised cutoff values.^{9,21}

Additionally, patients who suffered from serious pulmonary infections at the first insult had lower KL-6 concentrations. At the first severe pulmonary infection, the type II pneumocyte cells of the intensively affected patients may have been excessively lost, which may result in decreased KL-6 production. Impaired and decreased type II pneumo-

cyte activity is also a cause of chronic obstructive lung disease.²² The pulmonary alveoli are lined with two types of cells: type I and type II pneumocytes. When type I cells are damaged, type II cells proliferate, migrate, and spread along the denuded basement membrane surface to reform the epithelium and then differentiate into type I cells. Thus, type II pneumocytes are believed to play an important role in the repair process of the alveolar epithelial barrier.²² Loss of alveolar type II cells compromises this reparative mechanism and is thought to play a significant role in the development and progression of pulmonary fibrosis.²³ The elevation of KL-6 concentrations in post-transplant BO patients have been explained by an increase in KL-6 expression in the bronchiolar epithelium and an increase in the permeability of the lung-blood interface due to the chronic inflammation associated with BO.⁸ A reasonable conclusion suggests that PIBO is a different disease from post-transplant BO. The mechanisms of PIBO development may lead to the permanent loss of type II pneumocyte cells after the first infection instead of a chronic inflammation. Cazzato et al.¹² suggested that PIBO involves continuing inflammation due to the observation of worsening respiratory function tests during the 10 years of follow-up, but decreased type II pneumocyte activity can diminish the regeneration capacity of the lung, thereby allowing repetitive insults to the lung to result in reduced respiratory functions. Serrano-Mollar et al.²³ demonstrated the reversible treatment of rats with bleomycin induced pulmonary fibrosis via the intratracheal transplantation of alveolar type II cells. Pneumocyte type II cell transplantation could perhaps be a new and definitive treatment for PIBO patients in the future.

No correlation could be demonstrated between the serum KL-6 levels and the clinical severity of PIBO patients. The KL-6 concentrations were generally near to or at the lower limit of the ELISA test. Therefore, more specific tests may be helpful to distinguish smaller values and achieve more accurate results.

This study has some limitations. As a limitation, a control group was chosen for serum KL-6 evaluation from patients with acute infections because elevated KL-6 levels were expected in patients with PIBO, and the study tried to detect if these increases were more significant in PIBO patients than in patients with active infections. However, the control group also included patients without pulmonary disease (patients with upper airway infection), and this group also had significantly higher level of KL-6 than patients with PIBO. Another limitation was that the serum KL-6 level was only measured once. Repeated evaluation of KL-6 may be more valuable for determination of KL-6 level and disease severity association. The long time period that passed between the first infection and the serum KL-6 investigation (i.e., $M=87$ months; range 4–202 months) was also a limitation of this study. However, a correlation was not found between the serum KL-6 levels and the time that passed after infection (data not shown). Furthermore, the KL-6 level could not be measured at the time of PIBO diagnosis. Nevertheless, prospective studies should be arranged studying newly diagnosed PIBO patients.

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Author Disclosure Statement

Authors have no conflicts of interest to disclose.

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