

Organizing pneumonia with elevated surfactant protein-D needs attention to the possibility of relapse

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Abstract

Background and Objectives Organizing pneumonia (OP) usually responds spectacularly well to initial treatment, but relapses can occur and some cases run a fatal course. Still the issue of relapse has been addressed in relatively few studies and predictors have not been clarified. The purpose of this study was to examine the pattern of relapses in OP, to determine whether relapse affects morbidity and mortality and to identify possible predictors of relapse. **Methods** Blood sampling, pulmonary function testing, computed tomography (CT) of the chest and bronchofiberscopy were performed for all patients and were retrospectively reviewed along with clinical information. To determine relapse of OP, additional chest CT was performed regularly or when relapse of OP was clinically suspected. All patients were followed regarding treatment response, treatment duration and presence of relapse. Results were compared between two groups based on serum concentrations of surfactant protein (SP)-D: normal SP-D; and high SP-D. **Results** Twenty-two patients were analyzed in this study. SP-D showed a negative correlation with percutaneous oxygen saturation, and positive correlations with serum lactate dehydrogenase (LDH), Krebs von den Lungen (KL)-6 and percentage lymphocytes in bronchoalveolar lavage (BAL). Prognosis was good for all patients, but relapse was significantly more frequent in the high SP-D group (6 cases) than in the normal SP-D group (0 cases; $p=0.049$). Serum KL-6 and percentage monocytes in BAL were significantly higher and pulmonary vital capacity and forced expiratory volume in 1 s were significantly lower in the high SP-D group than in the low SP-D group. **Conclusions** When treating cases of OP with high serum concentrations of SP-D, attention should be paid to the possibility of relapse.

Introduction

Organizing pneumonia (OP) is a type of diffuse interstitial lung disease (ILD) in which the pathological pattern was defined by the characteristic presence of buds of granulation tissue within the lumen of distal pulmonary airspaces, comprising fibroblasts and myofibroblasts intermixed with loose connective matrix. The process of intraalveolar organization results from a sequence of alveolar injury, alveolar deposition of fibrin, and colonization of fibrin with proliferating fibroblasts⁽¹⁾.

OP can be classified into cryptogenic OP (COP), as the idiopathic form of OP mentioned in the American Thoracic Society (ATS) and European Respiratory Society (ERS) statements regarding the classification of idiopathic interstitial pneumonias⁽²⁾, and secondary OP (SOP), on the basis of underlying factors such as infection, pharmacotherapy, connective tissue disease, radiation, organ transplantation and others⁽³⁾. The clinical and radiographic findings, treatment response and prognosis in patients with both COP and SOP are reported to be similar and nonspecific⁽⁴⁾.

OP usually responds spectacularly well to initial treatment and typically runs a benign course. However, relapses can occur and some cases do not completely resolve, with the potential for severe or fulminant respiratory failure requiring mechanical ventilation, occasionally leading to death. Onishi et al. reported that a high percentage of neutrophils in bronchoalveolar lavage (BAL) and the level of fibrin deposition in lung biopsy specimens were considered as predictors of OP relapse during tapering or after cessation of

steroid therapy⁽⁵⁾. Lazor et al. retrospectively studied 48 cases of COP and reported delayed treatment increased the risk of relapse⁽⁶⁾. The issue of relapse has been addressed in relatively few studies, and predictors have yet to be clarified.

Among the blood biomarkers, Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D have been widely used in clinical practice⁽⁷⁾. KL-6 is a high-molecular-weight, circulating glycoprotein recently classified in humans as MUC1 mucin⁽⁸⁾. In a previous study, KL-6 was suggested as a useful marker in differentiating between ILD, evaluation of disease activity, and prediction of disease outcome⁽⁹⁾. SP-D belongs to the collectin subgroup of the C-type lectin superfamily⁽¹⁰⁾ and is also reportedly useful as a biomarker of ILD⁽¹¹⁾. Although both biomarkers are derived from regenerating alveolar epithelial type II cells (AECII), discrepancies between them have been reported⁽¹²⁾. The discrepancies between serum KL-6 and SP-D may be due to the different sources of KL-6 and SP-D. SP-D is expressed in mature ACEII, whereas KL-6 is expressed in the initial phase, before SP-D is expressed⁽¹³⁾.

In OP, Yamaguchi et al. reported that chest X-ray scores correlated with serum KL-6 levels, and patients needing treatment with prednisolone were included in the high KL-6 group⁽¹⁴⁾. Hara et al. suggested that OP with elevated serum KL-6 may be more severe and unstable than that with normal serum KL-6⁽¹⁵⁾, and Okada et al. reported the frequency of relapse as higher in patients with an elevated KL-6 level than in those with a normal KL-6 level⁽¹⁶⁾.

SP-D is a good predictor of prognosis in patients with idiopathic pulmonary fibrosis (IPF)⁽¹⁷⁾⁻⁽¹⁹⁾, but few reports have clarified associations with SP-D or OP. The objectives of this study were to examine patterns of relapse in OP; to determine whether relapses affect morbidity and mortality rates and to identify possible predictors of relapse.

Methods

Subjects

This study received ethical approval from the special committee of Toho University Ohashi Medical Center (project registration number H17081) to proceed between 2011 and 2017. Prior to enrolment, each patient provided written informed consent to participate. Eligible subjects were adults with OP pathologically confirmed from transbronchial lung biopsy (TBLB) under bronchofiberscopy (BF) or surgical lung biopsy. OP was classified into COP and SOP on the basis of the identification of underlying diseases.

Study design

Blood sampling (white blood cell count (WBC), lactate dehydrogenase (LDH), C-reactive protein (CRP), KL-6, and SP-D), pulmonary function testing (vital capacity (VC), percentage predicted VC (%VC), forced expiratory volume in 1 s (FEV1.0), FEV1.0/ forced vital capacity ratio (FEV1.0%), carbon monoxide diffusing capacity (DLCO)), computed tomography (CT) of the chest and BF were performed for all patients and were retrospectively reviewed along with clinical information. To identify relapse of OP, additional chest CT was performed regularly or when relapse of OP was clinically suspected. Two experienced respiratory physicians and two radiologists evaluated cases to diagnose relapsed OP. Relapsed OP was defined as the presence of abnormal shadows in the absence of other causes based on clinical examinations. Imaging findings were classified using high-resolution CT criteria for usual interstitial pneumonia (UIP) pattern according to the guidelines of ATS/ERS/JRS/ALAT (subpleural basal predominance, reticular abnormality, honeycombing, upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping, consolidation in bronchopulmonary segments). BF (BF-1T30; Olympus, Tokyo, Japan) was performed under standard premedication and local anesthesia. BAL was performed at a selected site at the presence of abnormal shadow. Total cell counts, cellular components and concentrations of the ratio of CD4/CD8 T-lymphocytes in BAL fluid were determined. Simultaneously, blood tests including serum KL-6 and SP-D levels were determined and pulmonary function testing (FUDAC-77®; Fukuda Denshi; Tokyo, Japan) was performed. Total cell count was determined using a Bürker chamber and the differential cell count was evaluated under light microscopy on May Grunwald Giemsa-stained slides. The ratio of CD4/CD8 T-lymphocytes was determined using flow cytometric analysis with monoclonal anti-CD4 and anti-CD8 antibodies (Becton Dickinson & Co., Franklin Lakes, New Jersey). SP-D and KL-6 were measured by EIA (Eidea, Tokyo, Japan). Detection limits were 17.3 pg/mL and 0 ng/ml, respectively. Results were compared between groups based on serum SP-D levels (normal, 0~109.9 ng/mL) into normal SP-D and high SP-D groups.

All patients were followed regarding treatment response, treatment duration and presence of relapse.

Analysis

Results are expressed as mean \pm standard deviation. Correlations between SP-D and each parameter were examined by Spearman's rank-order correlation. To clarify differences between normal and high SP-D groups, discrete variables were examined using Pearson's chi-square test and continuous variables were examined using the Wilcoxon rank-sum test. All statistical analyses were performed using SPSS Statistics (Japan IBM; Tokyo, Japan). Values of $P < 0.05$ were considered statistically significant.

Results

Twenty-two patients were analyzed in this study. Mean age was 71 ± 8 years, and the underlying pathology was COP in 10 patients and SOP in 12 patients. Causes of SOP were rheumatoid arthritis in 4 patients, adverse effects of pharmacotherapy in 2 patients, radiation exposure in 2 patients and severe

pneumonia in 2 patients. SP-D showed a negative correlation with percutaneous oxygen saturation, and positive correlations with serum LDH, KL-6 and percentage lymphocytes in BAL (Figs. 1, 2). Comparisons between COP and SOP showed no significant differences in any variables (data not shown).

The SP-D group comprised 7 patients and the high SP-D group comprised 15 patients. No significant differences were seen between groups in terms of patient background, necessity for and duration of treatment. Prognosis was good for all patients, but relapse was significantly more frequent in the high SP-D group (6 cases) than in the normal SP-D group (0 cases; $p = 0.049$) (Table 1).

The high SP-D group showed significantly higher serum concentrations of KL-6 and percentage monocytes in BAL, and significantly decreased pulmonary VC and FEV1.0 (Figs. 3, 4). No significant differences were seen in imaging findings (data not shown). In addition, no significant differences between the normal and high KL-6 groups were seen in any variables (data not shown).

Discussion

In our study, the high SP-D group showed a significantly higher relapse rate, and significantly decreased pulmonary VC and FEV1.0. Although VC is already known to be decreased in ILD⁽²⁰⁾ and a rapid decrease in %VC has been reported as a risk factor for acute exacerbation of IPF⁽²¹⁾, relatively few studies have investigated the relationship between ILD and FEV1.0. Milne et al. reported that frailty index was associated with FEV1.0 in a patient with fibrotic ILD⁽²²⁾. Parra et al. used histochemistry, immunohistochemistry and morphometric analysis to evaluate collagen/elastic fibers and immune cells in the bronchiolar interstitium on open lung biopsies in patients with COP. Multivariate analysis showed a decreasing risk of death from COP with high FEV1.0⁽²³⁾. We therefore considered that the relationship between collagen/elastic fibers, immune cells and FEV1.0 might have contributed to the relapse of OP.

Although Onishi et al. reported a high percentage of neutrophils in BAL as a predictor of OP relapse⁽⁵⁾, our study found that the percentage of monocytes in BAL was significantly higher in the high SP-D group, which showed a significantly higher relapse rate. Several reports have suggested that the development of fibrosis is associated with activation of monocytes^{(24)–26}. Monocytes comprise a variety of subsets with diverse functions. Satoh et al. showed that Ceacam1+Msr1+Ly6C-F4/80-Mac1+ monocytes, which they termed “segregated-nucleus-containing atypical monocytes” (SatM), are regulated by CCAAT/enhancer-binding protein β (Cebpb), and are critical for fibrosis. Cebpb deficiency results in a complete lack of SatM and the development of bleomycin-induced fibrosis (but not inflammation) was prevented in chimeric mice with Cebpb-/- hematopoietic cells. Adoptive transfer of SatM into Cebpb-/- mice resulted in fibrosis and showed that SatM is critical for fibrosis⁽²⁴⁾. Several reports have noted that fibrocytes, which are spindle-shaped fibroblast-like cells that differentiate from a subpopulation of CD14+ monocytes, are associated with induction of fibrosis. Phillips et al. showed that CD45+Col I+CXCR4+ fibrocytes contribute to the pathogenesis of pulmonary fibrosis. In the murine model of bleomycin-induced pulmonary fibrosis, marked collagen deposition was observed after bleomycin exposure, and represented the peak period of CD45+Col I+CXCR4+ fibrocyte infiltration⁽²⁵⁾. Moeller et al. reported that a threefold

increase in circulating fibrocytes (CD45/Col-11 cells) was observed in patients with stable IPF compared with healthy control individuals. During episodes of acute disease exacerbation, fibrocyte counts further increased to an average of 15% of peripheral blood leukocytes and returned to pre-exacerbation levels in patients who recovered⁽²⁶⁾.

Although the relationship between SP-D and monocytes remains unclear, Jiang et al. reported that depletion of circulating monocytes by intravenous injection of CL 2 days before intratracheal lipopolysaccharide (LPS) treatment significantly reduced SP-D in the lungs of mice treated with intratracheal LPS for 2 days⁽²⁷⁾ and Hirano et al. reported that SP-D deficiency reduced blood monocytes in atherosclerosis-prone apolipoprotein E-knockout mice⁽²⁸⁾. We therefore considered that elevation of SP-D was involved in the elevation of monocytes, and that the development of fibrosis associated with monocyte activation played a role in the relapse of OP.

The study had several limitations. As the data came from a relatively small number of patients with a variety of underlying diseases, the results could have been influenced by confounders such as types of concurrent medication. The statistical power of this study was 0.5. As OP is a relatively rare disease, sample sizes were small in previous studies despite the subjects collected for more than 10 years or in several hospitals⁽⁶⁾⁽²⁹⁾⁽³⁰⁾. The number of registered patients in this study was small because this was conducted in one hospital in a short period. Despite this limitation, we believe this study has valuable implications for clinical practice. Another limitation was the lack of surgical lung biopsy. To obtain sufficient tissue for the pathologist to exclude other processes, such as nonspecific interstitial pneumonia or usual interstitial pneumonia, lung biopsy should be preferably performed via video-assisted thoracoscopic surgery or open thoracotomy rather than transbronchial biopsy⁽³¹⁾. On the other hand, some reports have suggested that diagnosis can be made on the basis of transbronchial biopsy in a patient with typical clinical and radiologic features⁽³²⁾⁽³³⁾.

Conclusion

In conclusion, patients with elevated serum levels of SP-D in OP showed significant increases in serum KL-6 and monocytes in BAL and showed significant decreases in pulmonary VC and FEV1.0. The high SP-D group showed a significantly higher relapse rate than the normal SP-D group. These findings suggest that attention should be paid to the risk of relapse when treating OP in patients with a high serum concentration of SP-D.

Abbreviations

AECIIs, alveolar epithelial type II cells; BAL, bronchoalveolar lavage; BF, bronchofiberscopy; Cebpb, CCAAT/enhancer-binding protein β ; COP, cryptogenic organizing pneumonia; CRP, C-reactive protein; CT, computed tomography; DLCO, carbon monoxide diffusing capacity; FEV1.0, forced expiratory volume in 1 s; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; OP, organizing pneumonia; SatM, segregated-nucleus-

containing atypical monocytes; SOP, secondary organizing pneumonia; SP-D, surfactant protein D; TBLB, transbronchial lung biopsy; UIP, usual interstitial pneumonia; VC, vital capacity; WBC, white blood cell count.

Declarations

Acknowledgement

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Availability of data and materials

The anonymised datasets analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

T. Y. collected data, analysed data, created the tables and figures, designed the study, wrote and revised the manuscript. N. K., C. N., T. O., K. W., K. N., C. I., and H. M. collected data. H. M. critically revised the manuscript. All authors read and approved the final manuscript. None of the authors received any funding from the public, commercial, or not-for-profit sectors.

Competing interests

All authors declare no conflicts of interest in relation to this article.

Consent for publication

Not required.

Ethics approval and consent to participate

This research was conducted using information previously collected in the course of normal care (without an intention to use it for research at the time of collection). This study received ethical approval from the special committee of Toho University Ohashi Medical Center (project registration number H17081)

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Tables

Due to technical limitations, Table 1 is only available as a download in the supplemental files section.

Figures

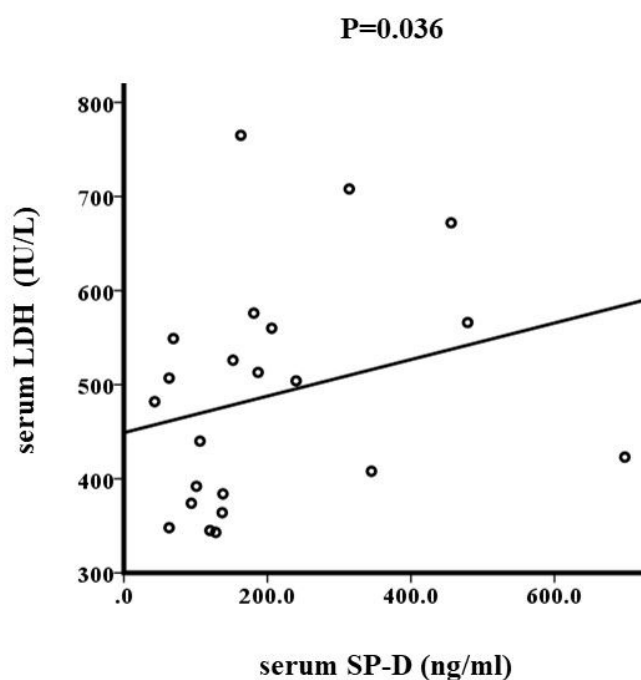
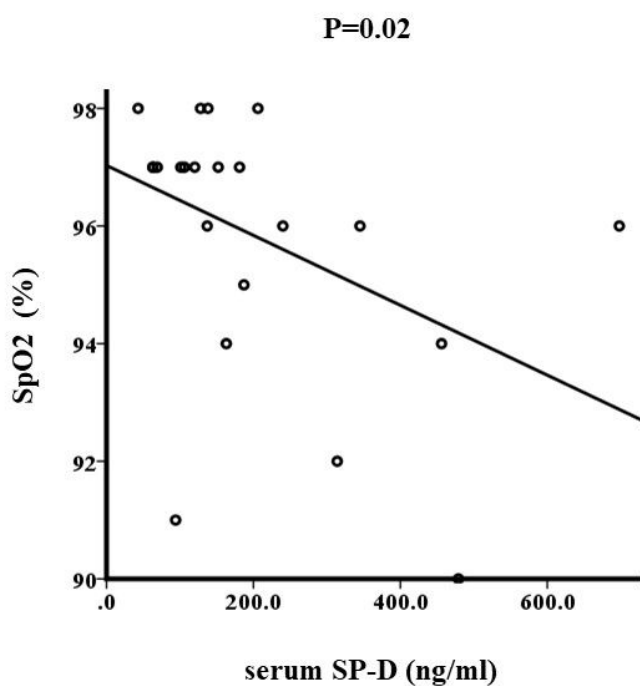


Figure 1

Correlations of SpO₂ and LDH with the levels of serum SP-D. Serum SP-D showed a negative correlation with SpO₂ and showed positive correlation with serum LDH. LDH: lactate dehydrogenase; SP-D: surfactant protein-D; SpO₂: percutaneous oxygen saturation.

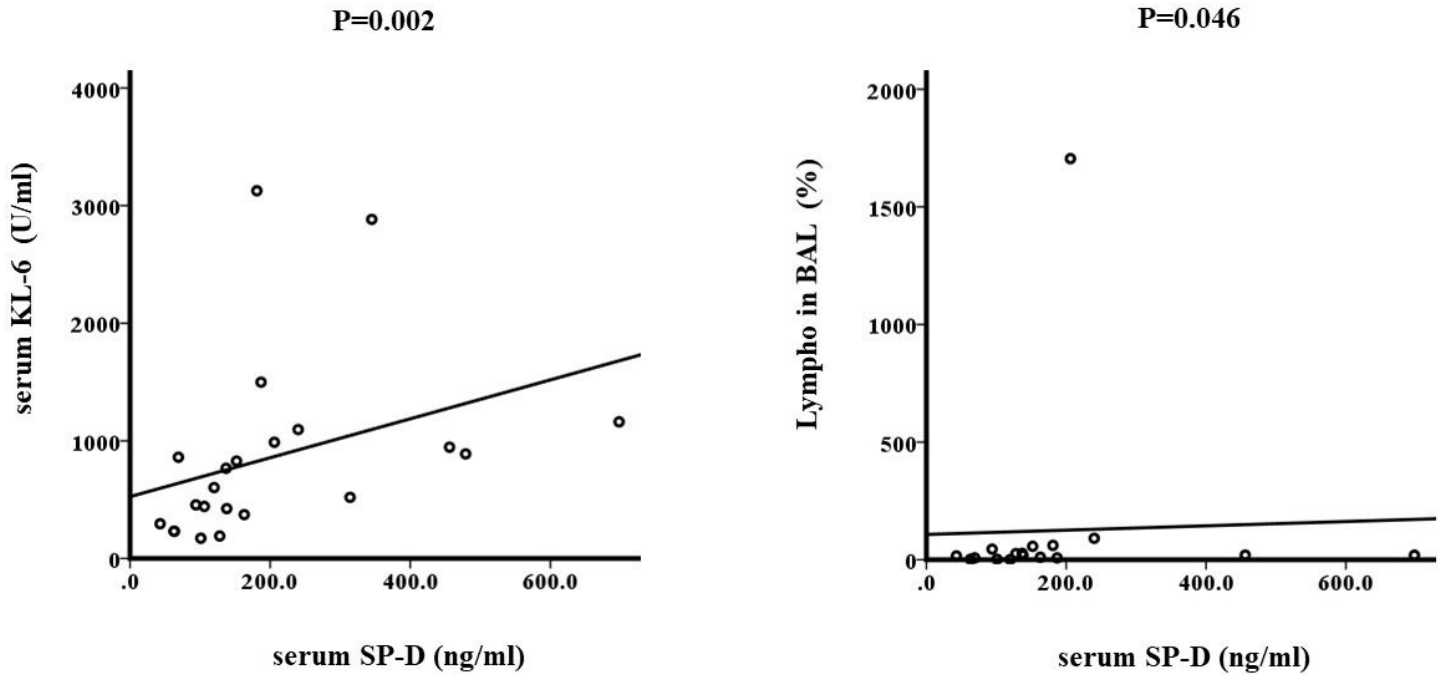


Figure 2

Correlations of serum KL-6 and Lymphocytes in BAL with the levels of serum SP-D. Serum SP-D showed positive correlation with serum KL-6 and lymphocytes in BAL. BAL: bronchoalveolar lavage; KL-6:Krebs von den Lungen-6;lympho:lymphocytes; SP-D: surfactant protein-D.

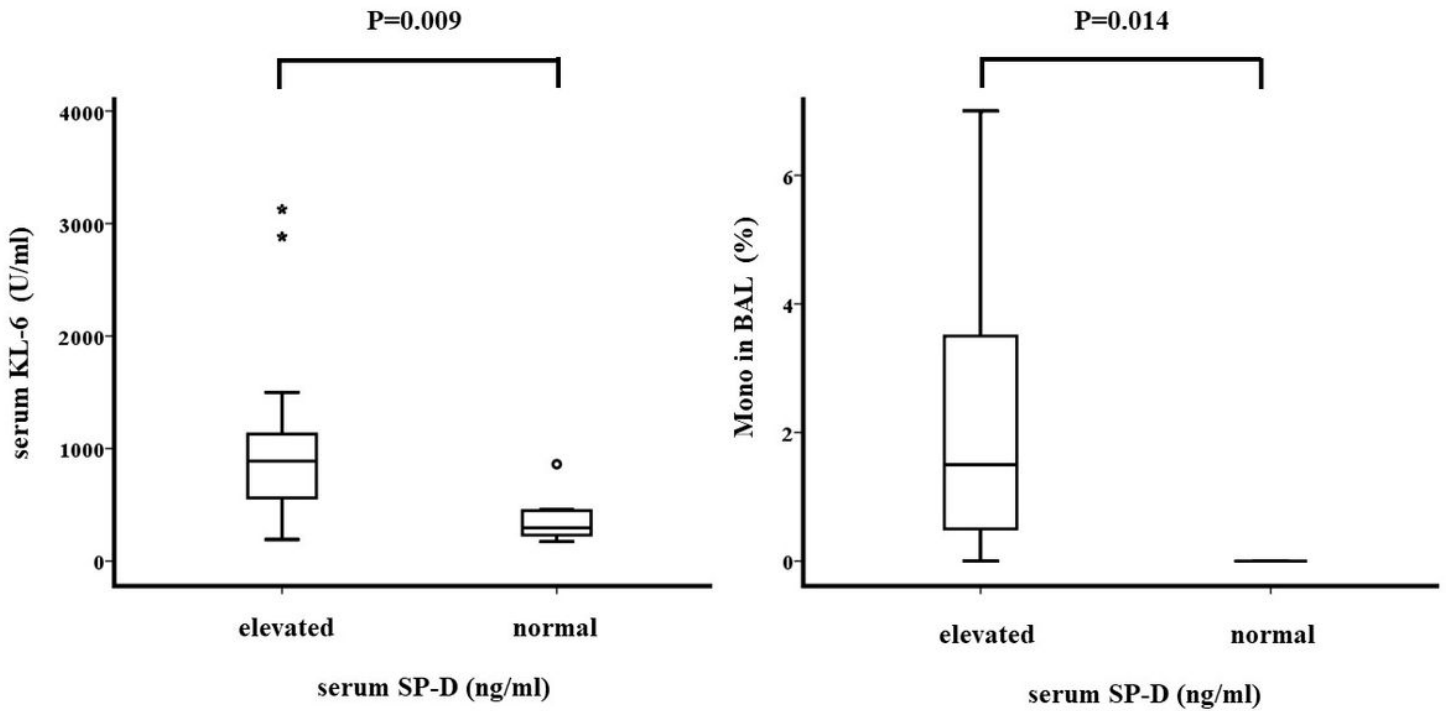


Figure 3

Comparison between the levels of serum SP-D in serum KL-6 and Monocytes in BAL. In high SP-D group, serum KL-6 and monocytes in BAL were significantly higher. BAL: bronchoalveolar lavage; mono: monocytes; KL-6: Krebs von den Lungen-6; SP-D: surfactant protein-D.

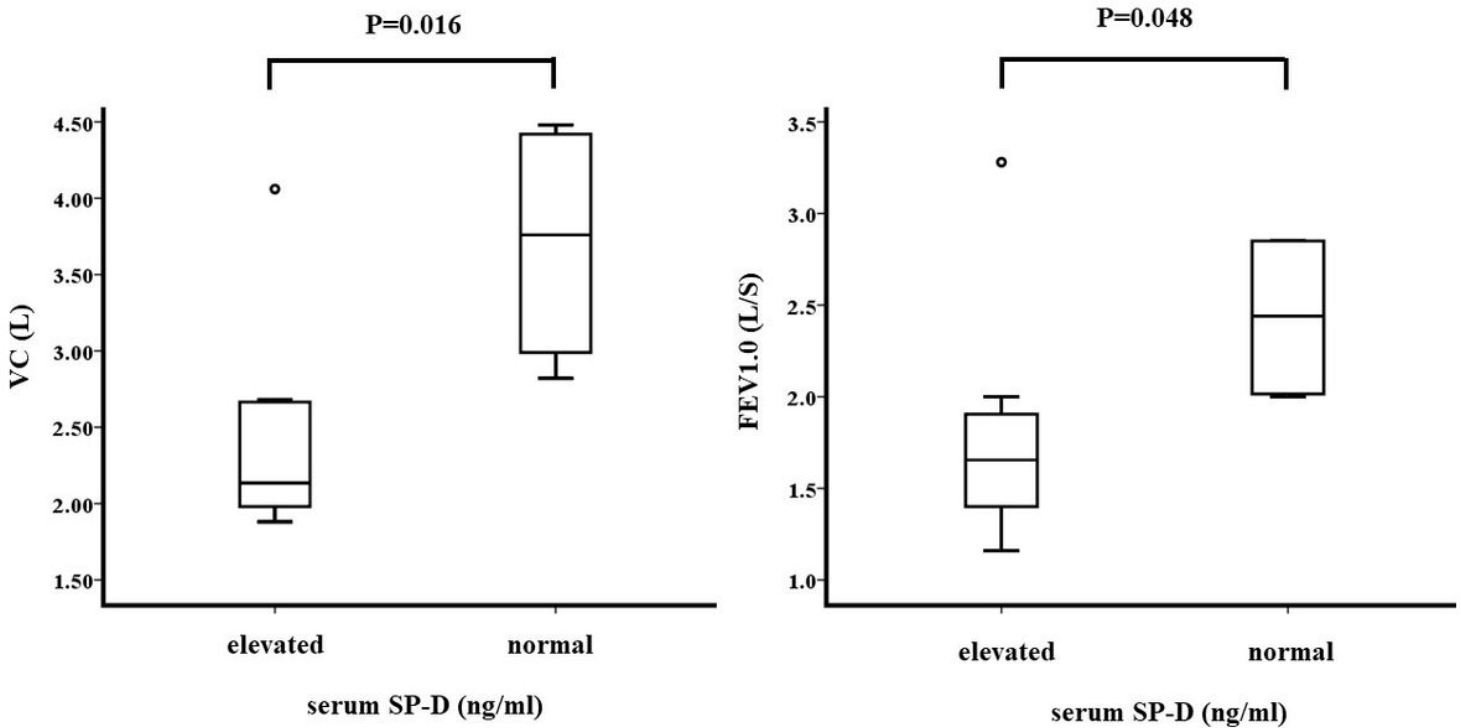


Figure 4

Comparison between the levels of serum SP-D in pulmonary function test. High SP-D group showed significant decreases in pulmonary VC and FEV1.0. FEV1.0: forced expiratory volume in one second ;SP-D: surfactant protein-D ; VC: vital capacity.

Supplementary Files

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- [Table1.pdf](#)