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Elevated serum D-dimer level is associated with an increased risk of acute exacerbation in interstitial lung disease

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ABSTRACT

Background: Early recognition of patients with interstitial lung disease (ILD) who have an increased risk of developing acute exacerbation (AE) or preclinical AE may be clinically useful, since AE is associated with poor outcome and preventive measures would be of interest to ILD researchers. This study evaluated the relationship between elevated serum D-dimer level (≥0.4 mcg/mL) and subsequent AE or preclinical AE in patients with ILD.

Methods: This single-center, retrospective study was performed from October 2009 through September 2015 in patients with ILD who were ≥18 years old and had idiopathic pulmonary fibrosis, other idiopathic interstitial pneumonias, chronic hypersensitivity pneumonitis, ILD related to collagen tissue disease, or combined pulmonary fibrosis/emphysema. The primary outcome measure was AE development within three months from each D-dimer measurement. The secondary outcome measures were respiratory-related hospitalization, all-cause hospitalization, venous thromboembolism (VTE), and all-cause mortality within three months.

Results: A total of 263 patients (mean age, 64.1 years) with 374 D-dimer measurements (median, 0.44 mcg/mL) were included. The risk of developing AE was significantly higher in patients with elevated serum D-dimer level (adjusted odds ratio: 10.46; 95% CI: 1.24–88.11; $p = 0.03$). Patients with elevated serum D-dimer level had increased risk for respiratory-related hospitalization, all-cause hospitalization, VTE, and all-cause mortality. The other factors predictive for AE were home oxygen therapy, increased serum lactate dehydrogenase, decreased FVC, and decreased $FEV_{1.0}$.

Conclusions: Elevated serum D-dimer is associated with the risk of developing AE. Serum D-dimer may be used as a prognostic marker to predict AE or recognize preclinical AE.

1. Introduction

Interstitial lung disease (ILD) is defined as any lung disease occurring in the parenchymal interstitium (i.e., alveolar wall or alveolar septa) or loose-binding connective tissue (i.e., the peribronchovascular sheath, interlobular septa, or pleura) [1]. Patients with idiopathic pulmonary fibrosis (IPF) are at risk of developing an acute exacerbation (AE). AEs from other types of ILD, such as other idiopathic interstitial pneumonia (IIP), ILD associated with collagen tissue disease (CTD-ILD), chronic hypersensitivity pneumonitis (CHP), and combined pulmonary emphysema and fibrosis (CPFE), have been reported sporadically [2–4]. AE, which is estimated to affect 5–20% of IPF cases [5,6], is defined as (1) rapid deterioration of the disease state in the absence of infection, heart failure, pulmonary embolism, or other identifiable cause [5,7]; and (2) a combination of clinical (i.e., worsening of dyspnea within days to few weeks), physiological (i.e., severe decrease of PaO_2 in arterial blood), or radiological findings (i.e., bilateral ground-glass opacities and consolidation [see Fig. 1]) [8]. In our study, patients with IIP-not IPF, CTD-ILD, CHP, and CPFE were defined as having an AE if they had a pre-existing diagnosis of interstitial lung disease and had an acute deterioration of their respiratory status unexplained by an identifiable cause. AE is associated with poor outcome: mortality

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Abbreviations list

AE	acute exacerbation
CI	confidence interval
CTD-ILD	connective tissue disease-associated interstitial lung disease
CPFE	combined pulmonary fibrosis and emphysema
DVT	deep venous thromboembolism
IIP	idiopathic interstitial pneumonia
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
LDH	lactate dehydrogenase
NYHA	New York Heart Association
OR	odds ratio
PE	pulmonary embolus
VTE	venous thromboembolism

exceeds 60% during hospital admission and exceeds 90% within six months after discharge among survivors [1,8]. Although the pathophysiology of AE is poorly understood, activated intravascular coagulation disturbance has been suggested to occur in AE in IPF due to significantly elevated levels of plasma FDP, D-dimer, and thrombin-antithrombin III complex [9]. The pathology of AE in ILD is similar to that of acute lung injury. Small vessels often exhibit small luminal fibrin thrombi; this is thought to be secondary to the activation of coagulation cascades due to tissue damage [10]. Further, a number of different coagulation system proteases including Tissue Factor-Factor VIIa/Factor Xa complex, thrombin, and activated protein C, can activate protease activated receptor-1 and protease activated receptor-2 which induce pro-inflammatory responses. D-dimer is the end-product of cross-linked fibrin degradation and is considered a useful marker of abnormal coagulation balance.

AE is characterized by in situ thrombosis and D-dimer as a marker of fibrinolysis may help understand the pathophysiology of this disease. This supports the rationale for monitoring D-dimer levels. Routine measurements of D-dimer in patients with ILD have been obtained in the Advanced Lung/Interstitial Lung Disease Program at the Mount Sinai Hospital in New York, as part of Mount Sinai Hospital Research Registry for Interstitial Lung Disease (HS#: 14-00584, GCO#1: 14-1444[0001] at Icahn School of Medicine at Mount Sinai). This study evaluated of the correlation between D-dimer and subsequent evolution of AE in ILD. We hypothesized that patients with elevated serum D-dimer level ($\geq$0.4 mcg/mL) have an increased risk of developing AE within three months from D-dimer measurement.

2. Materials and methods

2.1. Patients

This was a single-center, retrospective, observational study at the Advanced Lung/Interstitial Lung Disease Program at Mount Sinai Medical Center, New York. The medical records of 939 consecutive patients with ILD were reviewed retrospectively. The inclusion criteria were as follows: patients who visited the Advanced Lung/Interstitial Lung Disease Program from October 2009 to September 2015, had at least one routine D-dimer measurement, age $\geq$18 years old, and diagnosed with IPF, other IIPs (i.e., desquamative interstitial pneumonia, respiratory bronchiolitis interstitial lung disease, acute interstitial lung disease, non-specific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, or idiopathic pleuroparenchymal fibroelastosis), CHP, CTD-ILD, or CPFE. Interstitial pneumonia with autoimmune features (IPAF), used to identify individuals with IIP and features suggestive of, but not definitive for collagen vascular disease, was categorized into CTD-ILD group in this study, since a hypercoagulable state is often related to chronic inflammation induced by collagen vascular disease and we hypothesized that IPAF may share a similar pathogenesis which includes an abnormal coagulable state [11]. If more than one measurement of D-dimer had been obtained in the three months prior to AE, only the earliest measurement was included in order to avoid duplicate measurements (i.e., exposures) on one outcome. Patients receiving current anticoagulation treatment as well as those with a history of VTE, malignancy, sickle-cell disease, pregnancy, cirrhosis, or chronic infections (e.g., *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, and fungal species) were excluded. Serum D-dimer measurements made during acute coronary syndrome, cerebrovascular attack, or hospitalization were excluded. The primary outcome measure was the development of AE within three months from the date of serum D-dimer measurement. The secondary outcome measures were respiratory-related hospitalization, all-cause hospitalization, VTE, and all-cause mortality within three months. We developed a receiver operating characteristic curve to predict the primary outcome measure by D-dimer (See Fig. 2). The area under the curve was 0.7352 with optimal probability cutoff of

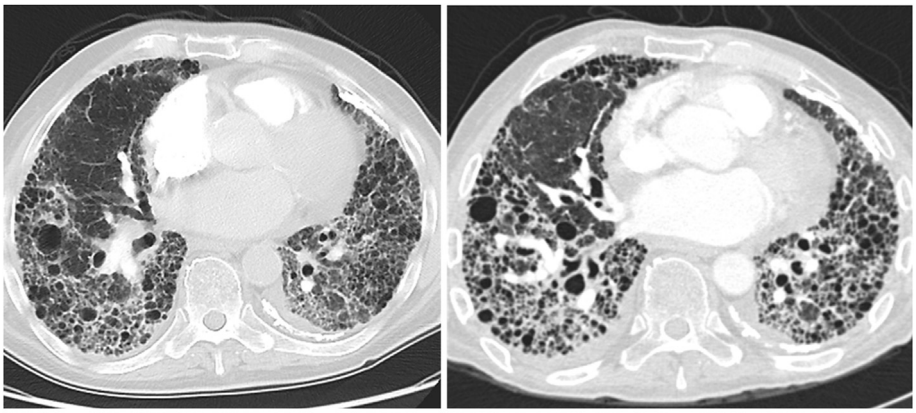

Fig. 1. Acute Exacerbation. Before (left) After Exacerbation (right) with worsening consolidation on underlying honeycomb fibrosis.