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Title: KL-6, SP-D and MMP-7 as serum biomarkers for early detection of interstitial lung diseases

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**Body:** Background: Since therapy with corticosteroids and/or immunosuppressants is largely ineffective for advanced stages of interstitial lung diseases (ILDs), early diagnosis of ILDs is of utmost importance. Recent clinical studies have suggested that Krebs von den lungen-6 (KL-6), surfactant proteins (SP), matrix metalloproteinase (MMP), and C-C motif chemokine ligand-18 (CCL-18) are potential serum biomarkers for ILDs. However, each of these biomarkers has been studied separately and the clinical significance of these biomarkers for early detection of ILDs has not been adequately evaluated. Aims: We aimed to determine whether serum levels of these biomarkers are of any diagnostic value in patients with early-stage ILDs. Methods: We collected the data of 55 patients with early-stage ILD who underwent surgical lung biopsy and 102 healthy controls. Serum levels of KL-6, SP-A, SP-D, MMP-1, MMP-7 and CCL-18 were measured in 55 patients with ILDs and 102 healthy controls. Results: The receiver operating characteristic curve analysis revealed that KL-6, SP-D and MMP-7 showed greater clinical significance than other biomarkers. The cut-off levels for these biomarkers that resulted in the highest diagnostic accuracy were determined. The sensitivity, specificity and diagnostic accuracy were 94.5%, 100% and 98.1% for KL-6; 69.1%, 86.3% and 80.3% for SP-A; 83.6%, 97.1% and 92.4 for SP-D; 58.2%, 37.3% and 44.6% for MMP-1; 87.3%, 97.1 and 93.6% for MMP-7; and 81.8%, 88.2% and 86.0% for CCL-18. Conclusion: KL-6, SP-D and MMP-7 may be the most useful biomarkers for ILDs even in the early stages of the disease and may greatly improve the currently employed diagnostic methods for ILD.