

Diagnostic and prognostic predictive values of circulating KL-6 for interstitial lung disease

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Past investigations showed inconsistent results for diagnostic and prognostic predictive values of Krebs von den Lungen-6 (KL-6) for interstitial lung disease (ILD).

Methods: Web of Science and PubMed were systematically searched on for articles exploring the association of KL-6 and ILDs published between September 1993 and March 2019. For comparisons between-groups, the standard mean difference and 95% confidence intervals (CIs) were computed as the effect sizes. For diagnostic studies, a summary of sensitivity, specificity, positive likelihood ratios, negative likelihood ratios, and diagnostic odds ratio, which indicated the accuracy of KL-6 in the differentiation of ILDs and no ILDs, were calculated from the true positive, true negative, false positive, and false negative of each study. In addition, the summary receive-operating characteristics curve was constructed to summarize the TP and FP rates. For follow-up study, we computed hazard ratios (HRs) and 95% CIs for mortality. ILD patients showed elevated concentrations of KL-6, compared to healthy controls and patients without ILD.

Results: The meta-analysis showed a sensitivity (0.85 [95% CI: 0.77–0.91]) and specificity (0.97 [95% CI: 0.90–0.99]) of KL-6 for ILDs. In addition, it showed elevated baseline circulating levels of KL-6 in subsequent active ILD, compared to subsequent inactive ILD. Moreover, there was a significant association between baseline levels of circulating KL-6 and mortality of ILD (HR 2.95, 95% CI 2.45–3.55, $I^2 = 65.9\%$, $P = .032$).

Conclusion: In conclusion, the study suggested that circulating KL-6 showed diagnostic and prognostic predictive values for ILDs.

Abbreviations: AE, acute exacerbation, AECs, alveolar epithelial cells, ALDH, aldehyde dehydrogenase, AUC, area under curve, CIs, confidence intervals, CTD-ILDs, connective tissue disease-associated ILDs, DOR, diagnostic odds ratio, FEV1, forced expiratory volume in the first second, FN, false negative, FP, false positive, FVC, forced vital capacity, HP, hypersensitive pneumonia, HRs, hazard ratios, ILD, interstitial lung disease, IPF, idiopathic pulmonary fibrosis, KL-6, Krebs von den Lungen-6, NLR, negative likelihood ratios, PLR, positive likelihood ratios, PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SMD, standard mean difference, SROC, summary receive-operating characteristics, TN, true negative, TP, true positive.

Keywords: interstitial lung disease, krebs von den Lungen-6, meta-analysis, systematic review

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1. Introduction

Interstitial lung disease (ILD) is a group of diffuse parenchymal lung diseases affecting the alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues.^[1] ILDs concern idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILDs (CTD-ILDs), and hypersensitive pneumonia (HP). The global incidence of ILDs is between 10.7 and 27.14 per 100,000 people.^[2] In 2013, ILDs affected 595,000 people worldwide and resulted in 471,000 deaths.^[3]

Krebs von den Lungen-6 (KL-6), a high-molecular-weight glycoprotein encoded by the *MUC1* gene and distributed mainly on the cell surface of type II alveolar epithelial cells (AECs), was firstly identified by Kohno in 1994.^[4] KL-6 splits off at the S-S bond near the membrane surface of damaged typeIIAECs. After that, soluble KL-6 is released into pulmonary epithelial lining fluid and blood flow.^[5] Therefore, serum KL-6 is usually identified as a biomarker for pulmonary damage.^[5] Previous studies supported that serum KL-6 levels might be a diagnostic biomarker of ILDs and could evaluate disease activity of ILDs. However, different studies showed incompatible results regard-

ing the associations between circulating KL-6 levels and ILDs. Hamai et al^[6] reported that circulating KL-6 levels showed high sensitivity and high specificity in the diagnosis of ILDs, whereas Hu et al^[7] found that circulating KL-6 levels showed low sensitivity and high specificity in the diagnosis of ILDs. To enhance the strength of evidence, meta-analysis was conducted to summarize results of studies evaluating diagnostic and prognostic predictive values of circulating KL-6 levels for ILDs.

2. Materials and methods

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.^[8] Ethical approval was not applicable in the study.

2.1. Search strategy and selection criteria

Articles published between September 1993 and March 2019 were searched in Web of Science and PubMed databases. Search terms showed as follows: (“Interstitial lung disease” OR “ILD”) AND (“Krebs von den Lungen-6” OR “KL-6”). After removing duplicates, 381 articles detecting association of circulating KL-6 and ILD were screened in this study. In addition, only literatures with English language were included. Moreover, we excluded reviews, meta-analysis, and case studies.

2.2. Data collection and meta-analysis

Titles and abstracts of articles were looked through by 2 individuals. Full texts of 23 articles were read after excluding some articles. Following data were extracted from these articles: author and publication years, country, sample size, specimen, detection methods, time of circulating sampling follow-up periods, and clinical outcomes. For cross-sectional studies, we extracted mean and standard deviation (SD) of concentrations of circulating KL-6 in ILD patients, patients without ILD and healthy controls (HC). For diagnostic studies, true positive (TP), true negative (TN), false positive (FP), and false negative (FN) were collected or calculated from selected studies. For follow-up

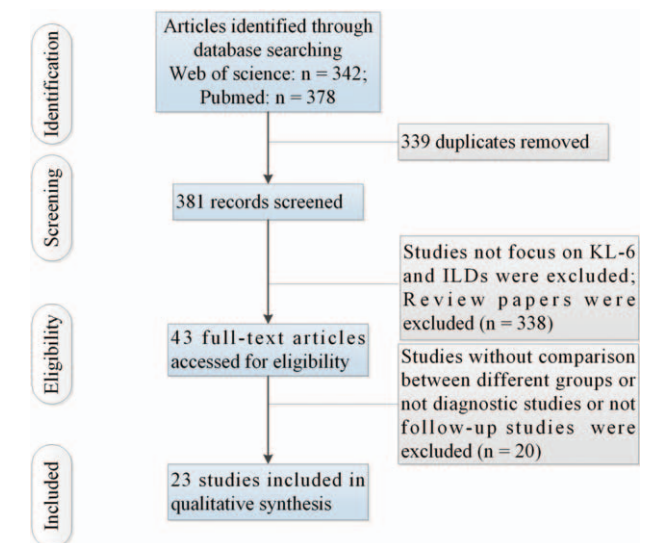


Figure 1. Flow of information through the different phases of a systematic review.

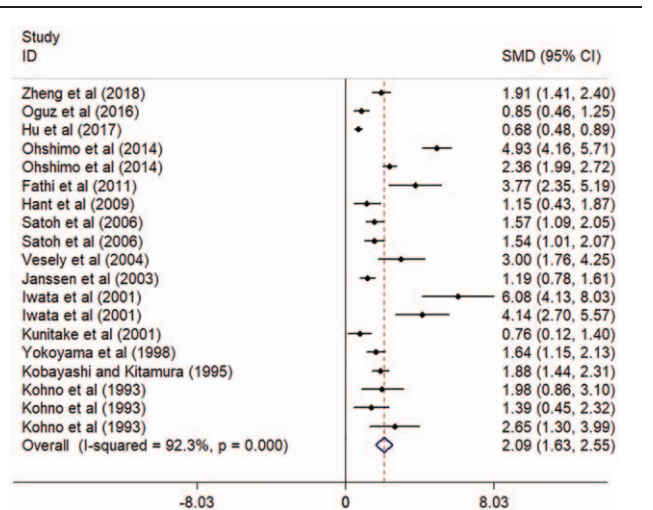


Figure 2. Forest plot of the circulating KL-6 levels in ILD patients and HC. CI= confidence interval, HC=healthy controls, ILD=interstitial lung disease, KL-6=Krebs von den Lungen-6, SMD=standard mean difference.

studies, the hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical outcomes were extracted from included studies.

These data were conducted with STATA 12.0 software and Meta-Disc Version 1.4. For cross-sectional studies, the standard mean difference (SMD) and 95% CI were computed as the effect size of following comparisons (comparison between patients with and without ILD, comparison between ILD patients and HC, comparison between patients with active ILD and inactive ILD). For diagnostic studies, after a summary of sensitivity, specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), and diagnostic odds ratio (DOR), the receive-operating characteristics (SROC) curve was performed to summarize TP and FP rates. For follow-up studies, HRs and 95% CIs were computed for individual clinical outcomes. Heterogeneity between studies and the amount of variation derived from heterogeneity were evaluated with Q test and computed I^2 , respectively. With high heterogeneity (P value for Q test ≤ 0.05 , $I^2 \geq 50\%$), random effects models were performed as pooling methods. Otherwise, fixed-effects models were conducted as pooling methods.

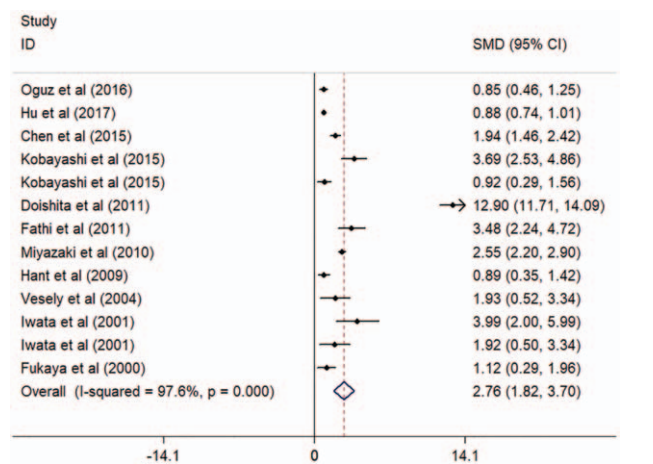


Figure 3. Forest plot of the circulating KL-6 levels in patients with and without ILDs. CI= confidence interval, ILD=interstitial lung disease, KL-6=Krebs von den Lungen-6, SMD=standard mean difference.

3. Results

3.1. Search results

Figure 1 showed the processing flow. Supplementary Table 1, <http://links.lww.com/MD/E59> showed some important elements

of the included 23 articles. Mean and standard deviation (SD) of concentrations of circulating KL-6 in ILD and HC were extracted from 14 studies^[7,9-21] (ILD patients: n=1120, HC: n=625). Mean and SD of concentrations of circulating KL-6 for patients with and without ILD were collected from 11 stud-

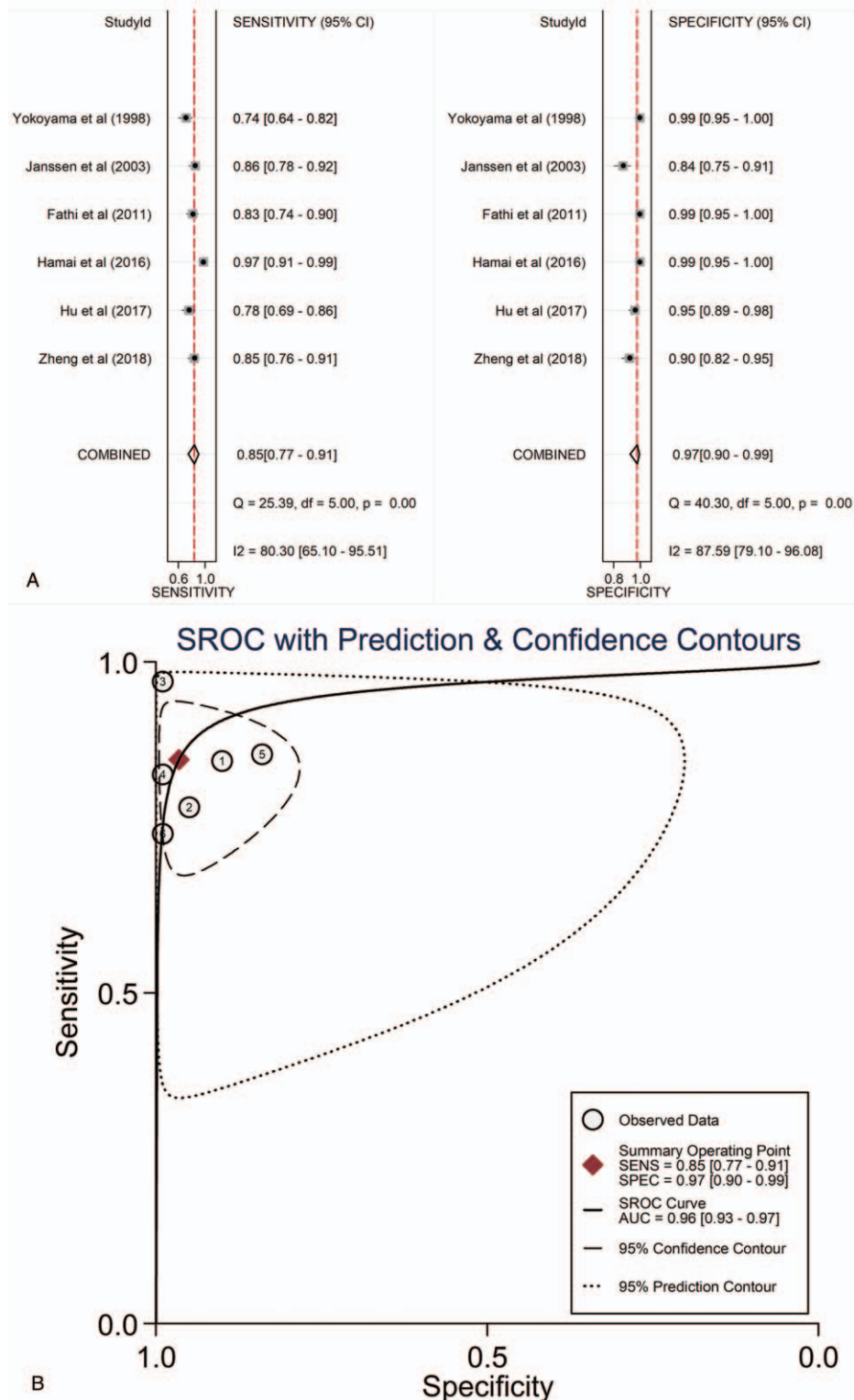


Figure 4. The sensitivity, specificity, DOR, SROC curve with AUC of circulating KL-6 in the diagnosis of ILDs. (A) Sensitivity and specificity. (B) SROC curve with AUC. AUC = area under the curve, DOR = diagnostic odds ratio, ILDs = interstitial lung diseases, KL-6 = Krebs von den Lungen-6, SROC = summary receiver operator characteristic.

ies^[7,9,16,18,19,21–26] (ILD patients: n = 767, patients without ILD: n = 1132). Data were collected from 6 studies^[6,7,11,12,16,20] for the diagnostic studies with circulating KL-6 for ILD (ILD patients: n = 634, HC: n = 365). Baseline circulating levels of KL-6 between patients with active ILD and inactive ILD were collected from 3 studies^[10,17,25] to explore the predictive effect of KL-6 for acute exacerbation (AE) of ILD. Moreover, data were collected from 4 studies^[6,11,13,27] for follow-up studies with clinical outcome of mortality.

3.2. Meta-analysis results

Circulating KL-6 showed a diagnostic value for ILD. ILD patients showed elevated concentrations of KL-6, compared to HC and patients without ILD (comparison between ILD patients and HC: $I^2 = 92.3\%$, $P < .001$; mean value of KL-6 level [ILD patients vs HC]: 1096 vs 224 U/mL; comparison between patients with and

without ILD: $I^2 = 97.6\%$, $P < .001$; mean value of KL-6 level [ILD patients vs patients without ILD]: 1284 vs 329 U/mL; see Figs. 2 and 3). Additionally, the pooled parameters calculated were as follows: sensitivity, 0.85 (95% CI: 0.77–0.91); specificity, 0.97 (95% CI: 0.90–0.99); PLR, 24.4 (95% CI: 8.6–69.3); NLR, 0.15 (95% CI: 0.10–0.24); and DOR, 159 (95% CI: 46–551). The analysis showed a significant heterogeneity (sensitivity, $I^2 = 80.30\%$, $P < .01$; specificity, $I^2 = 87.59\%$, $P < .01$, see Fig. 4A). Figure 4B showed the SROC curve, with an area under curve (AUC) of 0.96 (95% CI: 0.93–0.97).

Circulating KL-6 showed a predictive value of AE and mortality for ILD. The study showed elevated baseline circulating levels of KL-6 in subsequent active ILD, compared to subsequent inactive ILD (mean value of KL-6 level [active ILD vs inactive ILD]: 1977 vs 917 U/mL; Figure 5A). In addition, there was a significant association between baseline levels of circulating KL-6

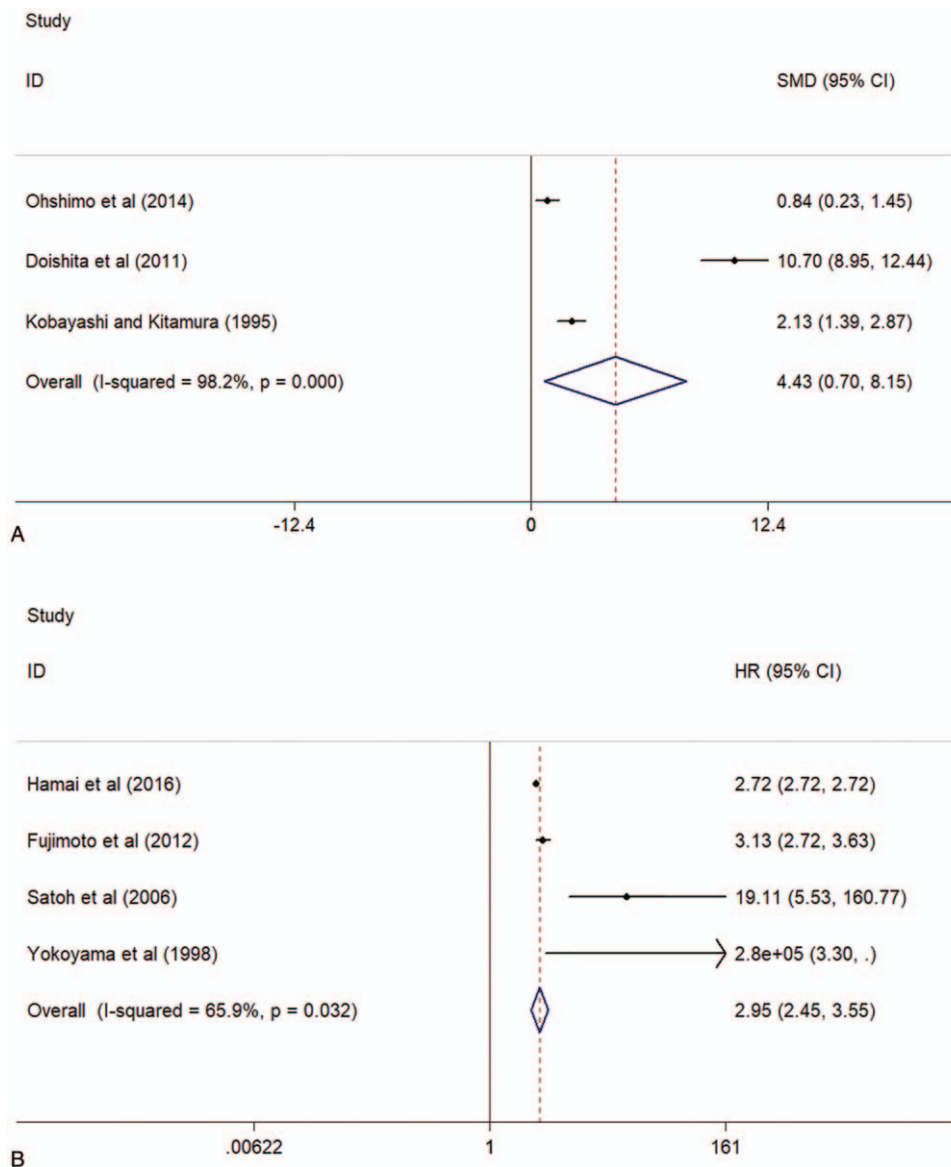


Figure 5. Forest plot of the baseline circulating KL-6 levels in patients with active ILDs and inactive ILDs (A) and the associations between baseline circulating KL-6 and mortality after ILDs (B). ILDs=interstitial lung diseases, KL-6=Krebs von den Lungen-6.

and mortality of ILD (HR 2.95, 95% CI 2.45–3.55, $I^2=65.9\%$, $P=.032$, Fig. 5B).

4. Discussion

The study showed that circulating KL-6 showed a diagnostic value and a predictive value of AE and mortality for ILD.

Recently, a lot of studies have supported that elevated levels of circulating KL-6 were detected in different kinds of ILDs patients (including IPF, CTD-ILD, and HP), compared to HC.^[9,28,29] The present study showed increased levels of circulating KL-6 in ILD patient, compared to HC and patients with following diseases (CTD, pulmonary diseases and lung cancer) and without ILDs.^[9,25,26] These changes might be caused by increased KL-6 production by regenerating typeII AECs and/or increased permeability caused by destroyed air-blood barrier in ILDs.^[28] Additionally, the study showed a high sensitivity (0.85 [95% CI: 0.77–0.91]) and high specificity (0.97 [95% CI: 0.90–0.99]) of circulating KL-6 levels for ILDs. In Chinese participants, Zheng et al^[12] reported that at a cutoff value of 500 U/mL, the sensitivity and specificity of serum KL-6 levels as a diagnostic biomarker of ILDs was 77.75% and 94.51%, respectively. In Sweden, Fathi et al^[16] indicated that at a cutoff value of 549 U/mL, the sensitivity and specificity of KL-6 for diagnosis of ILD were 83% and 100%, respectively. Moreover, previous studies indicated that serum KL-6 levels were associated with disease severity of ILDs. A study showed that serum KL-6 levels were significantly negatively correlated with the percentage values of forced expiratory volume in the first second (FEV₁) and forced vital capacity.^[16] The present study supported that circulating KL-6 levels were highly valuable for the diagnosis of ILDs. The study was the first meta-analysis to summarize results of studies evaluating diagnostic and prognostic predictive values of circulating KL-6 levels for ILDs.

The study indicated that baseline circulating levels of KL-6 were higher in subsequent active ILD, compared to subsequent inactive ILD. In addition, a significant association was indicated between baseline levels of circulating KL-6 and mortality of ILD. AE of ILDs is a condition characterized by an acute worsening of dyspnea resulting in hypoxemic respiratory failure. The process of AE-ILDs usually was accompanied by new infiltrates on radiologic images. In addition, AE is the major cause of ILDs-related mortality.^[30] These studies supported that circulating KL-6 levels were highly valuable for the prognostic prediction of ILDs.

Most of these meta-analyses showed significant heterogeneities between studies. Previous studies demonstrated ethnic difference in development and progression of ILDs.^[31] Additionally, serum KL-6 levels were significantly affected by MUC1 genetic polymorphism. Moreover, the study included studies for different kinds of ILDs (IPF, CTD-ILD, and HP).

The present study had some limitations. Most importantly, the number of included studies was limited to explore the sources of heterogeneities.

In conclusion, the present study suggested that circulating KL-6 showed diagnostic and prognostic predictive values for ILDs.

Author contributions

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