

# Can YKL-40 be used as a biomarker for interstitial lung disease?

## A systematic review and meta-analysis

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### Abstract

**Background:** Interstitial lung disease (ILD) has a poor prognosis and lacks specific biomarkers for early diagnosis, assessment of disease severity, and prognosis. YKL-40 levels were found to be elevated in patients with ILD, but these results are inconsistent. Therefore, we conducted a systematic review and meta-analysis to accurately study the relation between YKL-40 and ILD.

**Methods:** We performed a systematic literature search in many databases (PubMed, Embase, the China National Knowledge Infrastructure, and Wanfang databases) and commercial Internet search engines to identify studies involving the role of YKL-40 in patients with ILD. The weighted mean difference with its 95% confidence interval were used to investigate the effect sizes. If obvious heterogeneity was found in the meta-analysis, the level of YKL-40 was directly compared by the Mann-Whitney test.

**Results:** Sixteen eligible articles were finally identified. The results showed that the serum YKL-40 levels of patients with idiopathic pulmonary fibrosis, connective tissue-related ILD, sarcoidosis, cryptogenic tissue pneumonia, asbestosis-ILD, and idiopathic nonspecific interstitial pneumonia were higher than those in controls, but there was no increase in patients with pulmonary alveolar proteinosis. We also found that there are certain differences in the serum YKL-40 levels in patients with different types of ILD. The results showed that the bronchoalveolar lavage fluid YKL-40 levels of patients with idiopathic pulmonary fibrosis were significantly higher than that in controls. A systematic review indicated that there were correlations between the serum YKL-40 levels and lung function in patients with different ILD. In addition, YKL-40 may be used as a valuable biomarker for survival, with risk ratios ranging from 1.006 to 10.9.

**Conclusions:** This study suggests that YKL-40 may be a useful biomarker for the diagnosis and prognosis of ILD.

**Abbreviations:** BALF = bronchoalveolar lavage fluid, CI = confidence interval, CNKI = China National Knowledge Infrastructure, COP = cryptogenic tissue pneumonia, CTD = connective tissue disease, CTD-ILD = connective tissue disease-related interstitial lung disease, ILD = interstitial lung disease, IPF = idiopathic pulmonary fibrosis, NSIP = idiopathic nonspecific interstitial pneumonia, PAP = pulmonary alveolar proteinosis, WMD = weighted mean difference.

**Keywords:** biomarker, interstitial lung disease, meta-analysis, YKL-40

### 1. Introduction

Interstitial lung disease (ILD) is regarded as a heterogeneous disease that shows marked differences in the clinical process, radiological patterns, treatment, and prognosis.<sup>[1]</sup> There are many diseases or etiologies that can lead to ILD, such as

connective tissue disease (CTD), occupational exposure, drugs, radiotherapy, or allergens (allergic pneumonia). Some ILD have no identified cause, such as idiopathic interstitial pneumonia.<sup>[2]</sup> The major ILD include idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), hypersensitivity

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pneumonitis, sarcoidosis, cryptogenic tissue pneumonia (COP), pneumoconiosis, and connective tissue disease-related ILD (CTD-ILD).<sup>[3–5]</sup> The overall prognosis of ILD is poor, including low life quality, high mortality and disability rates, and high medical cost burden.<sup>[6,7]</sup> Although recent advances have contributed to a better understanding of the etiology of ILD, there has not been a breakthrough in the treatment of ILD, and there is a lack of drugs that can slow the progress of the disease, as well as a lack of specific biomarkers to evaluate its prognosis.<sup>[8,9]</sup>

YKL-40 is a member of the mammalian chitinase-like protein family, which is coded by a gene located on chromosome 1q32.1.<sup>[10]</sup> It is produced by a variety of cell types, including airway epithelial cells, macrophages, neutrophils, monocytes, vascular smooth muscle cells, and chondrocytes.<sup>[11]</sup> The detailed function of YKL-40 is not fully clear, but as an inflammatory glycoprotein, YKL-40 has been found to be involved in many normal and pathological conditions, including cell proliferation and survival, migration, recombination, and tissue remodeling.<sup>[12,13]</sup> Previous studies have found that serum YKL-40 levels were increased in patients with ILD.<sup>[14,15]</sup> The results also showed that the serum YKL-40 levels were closely related to the deterioration of lung function and prognosis of patients with ILD.<sup>[16]</sup> However, sample sizes in most studies are small, and a single study may not be powerful enough to investigate the potentially small effect of the YKL-40 levels on ILD. In addition, it is unclear whether the serum YKL-40 levels in patients with different types of ILD are similar or different, and whether they can be used as a biomarker (the measurable change associated with a physiological or pathophysiological process) for differential diagnosis of ILD. In order to solve those limitations and to better explore the possible role of YKL-40 in ILD, we performed a meta-analysis and systematic review to study the relationship between YKL-40 and ILD patients.

## 2. Methods

### 2.1. Literature search

Our retrieval strategy is similar to previously published study.<sup>[17]</sup> We performed a systematic literature search in PubMed, Embase, the China National Knowledge Infrastructure (CNKI) ([www.cnki.net](http://www.cnki.net)), and Wanfang databases ([www.wanfangdata.com.cn](http://www.wanfangdata.com.cn)) to identify studies involving the role of YKL-40 in patients with ILD, with the most recent search having been conducted on July 1, 2020. The key search terms were as follows: (*YKL-40 OR chitinase-3-like-1 protein OR CHI3L1*) AND (*interstitial lung diseases OR ILD OR pulmonary fibrosis OR interstitial pneumonitis OR collagen vascular disease OR organizing pneumonia OR sarcoidosis OR asbestosis OR pneumosilicosis OR connective tissue disease*). The language was restricted to English or Chinese. Moreover, we used the same keywords to search literatures in multiple academic Internet search engines (such as Google and Baidu scholars). All analyses in the current meta-analysis were based on previously published studies; therefore, ethical approval is not required.

### 2.2. Study selection

The inclusion criteria were defined as follows:

- (1) a study involving the role of YKL-40 in ILD designed as a case-control study;
- (2) a primary study provided available data (e.g., mean, median, standard deviation [SD], standard error) for counting weighted mean difference (WMD) with a 95% CI; and

- (3) if there was duplication of data, only the most complete and recent study was included.

The exclusion criteria were similar to the previously published study,<sup>[17]</sup> as follows:

- (1) study was not designed as a case-control study;
- (2) study did not provide useful data for pooling the effects;
- (3) study was missing other essential information; and
- (4) review, abstract, or overlapping study.

### 2.3. Data extraction

Like the previous study,<sup>[17]</sup> two independent authors (XT and YM) extracted the detailed information and data from each primary study using a predesigned data extraction Excel form. If there was any disagreement or doubt, the third author (TL) further reviewed these articles. The extractions included the following: first author, year of publication, age of the participant, sample sizes of patients and controls, YKL-40 levels in serum and bronchoalveolar lavage fluid (BALF), and correlation coefficient (*r*). According to validated methods provided in the literature,<sup>[18]</sup> if a study provided medians and ranges (or interquartile ranges, IQR), we can convert the data into approximate means and SD for meta-analysis.

### 2.4. Statistical methods

The statistical methods used in this study were similar to those of the previous study.<sup>[17]</sup> After appropriate conversion, the WMD with a 95% confidence interval (CI) was used to compare the YKL-40 levels of serum or BALF in the patients with ILD with the levels in controls. In addition, the study also compared the differences in serum YKL-40 levels between patients with different types of ILD. The existing exact data<sup>[19]</sup> shows that the random effect model will be more conservative when it is used to merge data, and it leads to a lower type I error rate and a wider CI of effects, when compared with the fixed-effect model. The between-study heterogeneity was investigated by the chi-square ( $\chi^2$ )-based Q-test and *I*-square ( $I^2$ ) statistics test. The  $I^2$  value of > 50% or *P* value of < .10 suggested statistically significant heterogeneity. If a notable heterogeneity was found, we used a Mann-Whitney test to directly compare the levels of YKL-40 in patients with ILD with the levels in controls and reported the *P* value of this analysis. In the current study, all data analyses were performed using STATA 12.0 (Stata Corp., College Station, TX, USA) and (IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1. Study characteristics

All 101 articles were found in our initial search of Embase, PubMed, CNKI, and Wanfang databases, and academic internet search engines. As shown in the flowchart (Fig. 1), 64 studies were deleted because they were duplicated across databases. When we carefully read the title and abstract, 11 articles were excluded because their content was not relevant to YKL-40 in relation to ILD. The remaining 26 articles were full-text browsed. Two articles were excluded because they investigated the association between cystic fibrosis and YKL-40. Two studies were eliminated since they did not have control individuals. One article was deleted because it only studied the relationship

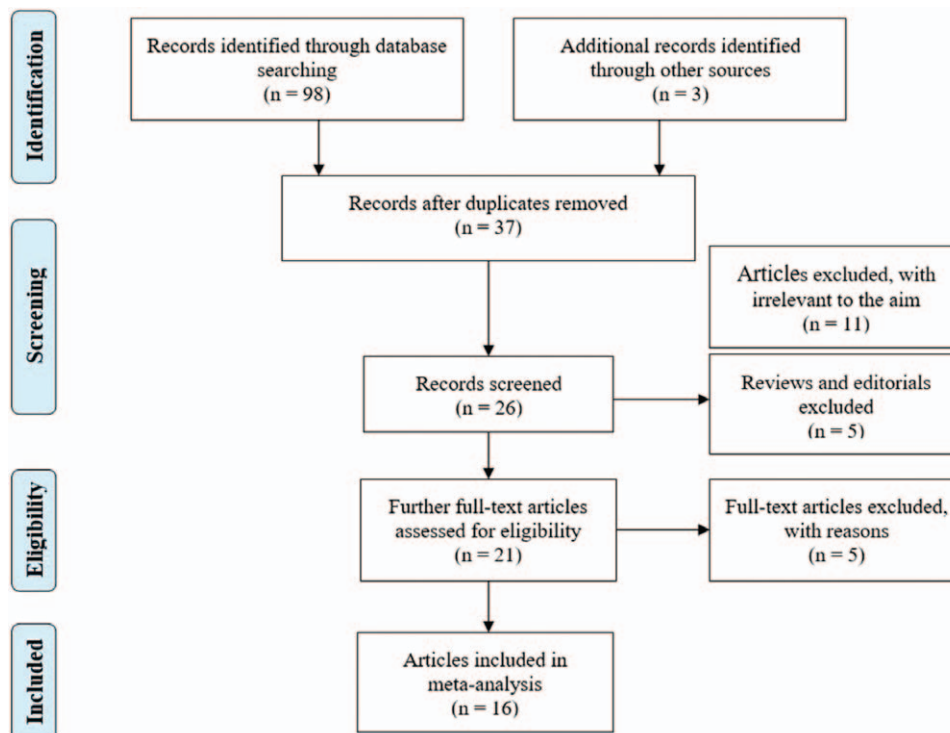


Figure 1. The flow diagram of included and excluded studies.

between the level of YKL-40 in sputum and patients with ILD. Another five articles were excluded because they were reviews. Finally, 16 eligible articles were included in this study.<sup>[14–16,20–32]</sup>

Of these articles, 6 studied the relationship between YKL-40 and CTD-ILD,<sup>[20,21,23,25,27,28]</sup> four reported the relationship between YKL-40 and IPF,<sup>[14,16,20,22]</sup> and 8 explored the association between COP, sarcoidosis, asbestosis-ILD, pulmonary alveolar proteinosis (PAP), and NSIP and YKL-40.<sup>[15,20,22,24,26,29,30,32]</sup> Among them, 15 studies reported the relationship between serum YKL-40 levels and ILD, and 3 articles reported the relationship between BALF YKL-40 levels and IPF. In addition, some studies have sporadically reported the correlations between serum YKL-40 and lung function, and the diagnostic value of YKL-40 as a biomarker. Nine studies were from Europe and six were from Asia (Table 1).

### 3.2. The association between serum YKL-40 levels and patients with IPF and CTD-ILD

The meta-analysis results indicated that the levels of serum YKL-40 of IPF and CTD-ILD patients were significantly higher than those of healthy subjects (WMD=130.55, 95% CI=60.77–200.34,  $P < .001$ ; WMD=50.53, 95% CI=40.59–60.47,  $P < .001$ ; respectively) (Fig. 2). A significant heterogeneity between studies was observed ( $I^2=98.4%$ ,  $I^2=60.8%$ , respectively). Therefore, we compared the levels of serum YKL-40 in patients with IPF and CTD-ILD with the levels in controls using the Mann-Whitney test. The results showed that the serum YKL-40 levels of CTD-ILD patients were significantly different from that of the control group ( $P=.037$ ), and the serum YKL-40 levels of patients with IPF were slightly statistically different from that of the control group ( $P=.05$ ) (Table 2).

### 3.3. The association between serum YKL-40 levels and patients with other ILD

The meta-analysis results showed that the serum YKL-40 levels in patients with sarcoidosis, COP, asbestosis-ILD, and NSIP were significantly higher than those in the control group (WMD=245.22, 95% CI=20.24–470.19,  $P=.033$ ; WMD=163.10, 95% CI=130.43–195.78,  $P < .001$ ; WMD=39.18, 95% CI=5.89–72.47,  $P=.021$ ; WMD=144.57, 95% CI=137.52–151.63,  $P < .001$ , respectively) (Table 2). However, there was no significant difference in serum YKL-40 levels between patients with PAP and the control group (WMD=139.64, 95% CI=–70.96 to 350.24,  $P=.194$ ) (Table 2).

### 3.4. The differences of serum YKL-40 levels between patients with different types of ILD

By comparing the levels of serum YKL-40 in patients with different types of ILD, it was found that patients with sarcoidosis had the highest levels of serum YKL-40 ( $262.09 \pm 303.76$  ng/mL), and those with CTD-ILD and asbestosis-ILD had the lowest levels of serum YKL-40 ( $98.76 \pm 81.02$  ng/mL;  $98.31 \pm 108.17$  ng/mL, respectively). There was no differences in serum levels of YKL-40 among patients with other ILDs (IPF,  $170.39 \pm 123.0$  ng/mL; PAP,  $182.84 \pm 112.78$  ng/mL; COP,  $197.53 \pm 96.42$  ng/mL; NSIP,  $179.08 \pm 81.65$  ng/mL, respectively).

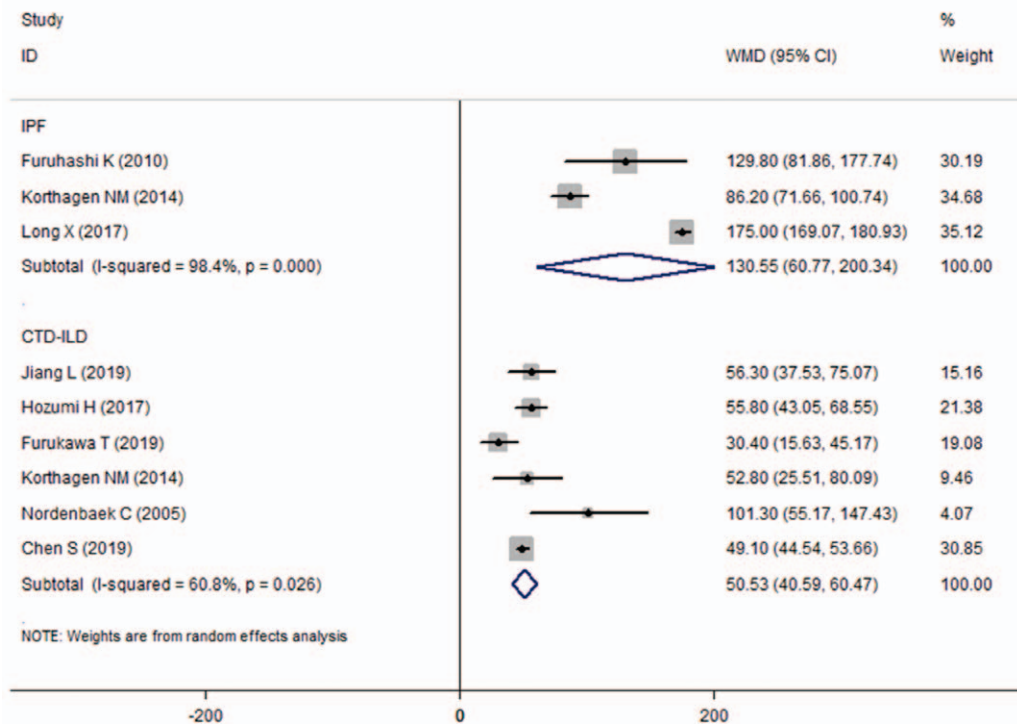
### 3.5. The association between BALF YKL-40 levels and patients with IPF

The BALF was collected from 168 patients with IPF and 144 healthy controls to investigate the association between the YKL-40 levels and IPF. The results of this meta-analysis indicated that

**Table 1**  
**Characteristics of studies reporting the association between serum/BALF YKL-40 levels and ILD.**

Authors	Year	Cases/Controls	Type	Age Case/control	Case (ng/mL)			Control (ng/mL)		
					Mean	SD	N	Mean	SD	N
Bonella F	2017	34/50	PAP	49 ± 2/42 ± 2	286	27	34	39	4	50
Chen S	2019	23/87	CTD-ILD	NA <sup>6</sup> /59.6 ± 8.6	76.5	10.8	23	27.4	5.5	87
Corradi M	2013	16/66	Asbestosis-ILD	72.2 ± 8.7/61.6 ± 10	121	131.7	16	86.3	60.6	66
Furuhashi K	2010	63/41	IPF	70.2 ± 7.8/67.5 ± 8.5	245.8	180.2	63	116	58.3	41
Furukawa T	2019	18/17	CTD-ILD	63.3 ± 13.8/59.6 ± 13.9	54.3	26.7	18	23.9	17.1	17
Hozumi H	2017	69/34	CTD-ILD	53.8 ± 9.5/51.0 ± 10.5	86.9	49.0	69	31.1	16.0	34
Jiang L	2019	41/44	CTD-ILD	52.6 ± 10.5/45.6 ± 12.1	72.2	60.7	41	15.9	9.0	44
Johansen J	2005	27/173	Sarcoidosis	42.5 ± 10.0/39.0 ± 7.4	486.5	223.8	27	124.7	115.1	173
Korthagen NM	2014	185/124	IPF	63.8 ± 10.7/51.6 ± 7.7	134.1	96.1	185	47.9	25.1	124
		38/124	CTD-ILD	57.8 ± 12.5/51.6 ± 7.7	100.7	84.7	38	47.9	25.1	124
		27/124	COP	60.8 ± 12.2/51.6 ± 7.7	185.5	125	27	47.9	25.1	124
		25/124	NSIP	66.3 ± 9.5/51.6 ± 7.7	172.4	124.2	25	47.9	25.1	124
Kruit A	2007	75/333	Sarcoidosis	39.0 ± 11.2/40.1 ± 11.5	181.3	288.7	75	49.1	16.9	333
Li Y	2014	31/25	PAP	47 ± 8/45 ± 7	69.7	32.3	31	37.6	25.5	25
Long X	2017	45/60	IPF	71 ± 1/40 ± 2	214.0	20	45	39	4	60
		21/60	COP	61 ± 3/40 ± 2	213	33	21	39	4	60
		34/60	NSIP	68 ± 2/40 ± 2	184	21	34	39	4	60
Nordenbaek C	2005	27/70	CTD-ILD	NA/54.0 ± 12.4	215.3	119.0	27	114	45.4	70
Vaananen T	2017	19/28	Asbestosis-ILD	68.5 ± 6.0/62.2 ± 6.6	79.2	82.5	19	38.5	28.0	28
BALF										
Korthagen NM	2011	60/43	IPF	65 ± 10/32 ± 16	12.53	7.43	60	5.43	4.68	43
Furuhashi K	2010	63/41	IPF	70.2 ± 7.8/67.5 ± 8.5	17.8	19.1	18	0.3	0.9	16
Long X	2017	45/60	IPF	71 ± 1/40 ± 2	9	2	42	3	1	10

BALF = bronchoalveolar lavage fluid, COP = cryptogenic tissue pneumonia, CTD-ILD = connective tissue disease-interstitial lung diseases, IPF = idiopathic pulmonary fibrosis, NA = not available, NSIP = idiopathic nonspecific interstitial pneumonia, PAP = pulmonary alveolar proteinosis, SD = standard deviation.



**Figure 2.** The results of associations between the serum YKL-40 levels and IPF and CTD-ILD. CTD-ILD = connective tissue disease-interstitial lung diseases, IPF = idiopathic pulmonary fibrosis.



**Table 2****The pooled results of the serum/BALF YKL-40 levels in patients with ILD compared with those in healthy controls.**

Diseases	WMD	95%CI	P value	Mann-Whitney test (P value)
Serum				
IPF	130.55	60.77–200.34	<.001	0.05
CTD-ILD	50.53	40.59–60.47	<.001	0.037
Sarcoidosis	245.22	20.24–470.19	.033	NA <sup>9</sup>
COP	163.1	130.43–195.78	<.001	NA
Asbestosis-ILD	39.18	5.89–72.47	.021	NA
NSIP	144.57	137.52–151.63	<.001	NA
PAP	139.64	–421.2	.194	NA
BALF				
IPF	7.43	4.60–10.26	<.001	0.05

BALF=bronchoalveolar lavage fluid, CI=confidence interval, COP=cryptogenic tissue pneumonia, CTD-ILD=connective tissue disease-interstitial lung diseases, NSIP=idiopathic nonspecific interstitial pneumonia, IPF=idiopathic pulmonary fibrosis, NA=not available, PAP=pulmonary alveolar proteinosis, WMD=weighted mean difference.

YKL-40 level in the BALF of patients with IPF was significantly higher than that of the control group (WMD=7.43, 95%CI=4.60–10.26,  $P<.001$ ) (Table 2). We also used the Mann-Whitney test to compare the two groups, and the results showed that YKL-40 in the BALF of patients with IPF was slightly statistically different from the control group ( $P=.05$ ) (Table 2).

### 3.6. A systematic review of the correlation between YKL-40 and lung function and prognosis

A total of 6 studies reported the correlation between serum YKL-40 levels and lung function in patients with different ILD. Among them, serum YKL-40 levels were negatively correlated with DL<sub>CO</sub> in sarcoidosis (two studies;  $r=-0.40$ ,  $P=.04$ ;  $r=0.27$ ,  $P=.03$ ; respectively),<sup>[15,32]</sup> PAP (2 studies;  $r=-0.53$ ,  $P=.002$ ;  $r=-.29$ ,  $P=.116$ ), IPF (1 study;  $r=-0.41$ ,  $P=.003$ ), and CTD-ILD (one study;  $r=-0.41$ ,  $P=.01$ ).<sup>[14,23,26,29]</sup> There was no correlation with FEV<sub>1</sub>/Predict in CTD-ILD (one study;  $r=-0.18$ ,  $P=.16$ ).<sup>[23]</sup> The studies did not find a correlation between BALF YKL-40 levels and other clinical parameters in the patients with ILD. Although cut-off values were different among the studies, the results suggested that YKL-40 could be used as a valuable biomarker for survival analysis, with hazard ratios ranging from 1.006 to 10.9. In addition, although there are few studies on the sensitivity and specificity of YKL-40 in ILD, the results showed that the serum YKL-40 may have high sensitivity and specificity in predicting prognosis.

## 4. Discussion

The main findings of the current study are as follows:

- (1) the serum YKL-40 levels in patients with CTD-ILD were significantly higher than that in the healthy control group by meta-analysis and Mann-Whitney test.
- (2) The serum YKL-40 levels in patients with IPF may be higher than that in the healthy control group by meta-analysis and Mann-Whitney test, and the results showed that YKL-40 levels in the BALF of patients with IPF were higher than that of the control group.
- (3) The serum YKL-40 levels in patients with sarcoidosis, COP, asbestosis-ILD, and NSIP may be higher than those in the control group, but the levels of YKL-40 in patients with PAP is not significantly higher than that in the control group. However, it is worth noting that only a few studies have explored the relationship between serum YKL-40 levels and

these diseases, so the sample size is insufficient, and we need to be cautious in citing these results.

- (4) Sarcoidosis patients had the highest serum YKL-40 levels, while CTD-ILD and asbestosis-ILD patients had the lowest serum YKL-40 levels.

In addition, a systematic review showed that the serum YKL-40 levels were negatively correlated with pulmonary function, especially DL<sub>CO</sub> in patients with different ILD. Interestingly, YKL-40 may be able to predict the prognosis of ILD with high sensitivity and specificity. Unfortunately, the studies did not find a correlation between BALF YKL-40 levels and other clinical parameters in patients with ILD. The small sample sizes of the included studies may explain the negative results. It is necessary to further verify the accurate correlation between serum and BALF YKL-40 levels of patients with ILD and other clinical parameters through large samples in the future.

It is well known that although ILD is a heterogeneous disease, inflammation, tissue remodeling, and fibrosis are common and important pathophysiological features of ILD. A large number of studies in the literature have suggested that YKL-40 may play an important role in inflammatory response.<sup>[12,33–35]</sup> In addition, YKL-40 increases Th2 inflammatory responses and decreases inflammatory cell apoptosis.<sup>[36]</sup> Moreover, YKL-40 can regulate a series of signaling pathways,<sup>[37–39]</sup> which are closely related to the pathogenesis of ILD. Previous studies suggest that YKL-40 is involved in tissue remodeling and fibrosis. Importantly, tissue remodeling and fibrosis are often closely related to lung function and clinical prognosis, which may explain the negative correlation between YKL-40 levels and lung function in patients with ILD found in previous studies. We also found that there may be differences in serum YKL-40 levels in patients with different types of ILD, which may provide a possible reference for differential diagnosis of ILD. Therefore, the current study also suggests that YKL-40 may be a potential biomarker for the diagnosis and prognosis of ILD.

There are some limitations of this study. First of all, language was limited to English and Chinese, so some valuable articles published in other languages may not be included, which may contribute to a bias for overall results. Secondly, we only included published studies in a few databases, and most of them were small in sample sizes, so this may lead to publication bias or overestimation of the effect size. Third, we failed to conduct further subgroup analyses based on risk factors (such as occupation, smoking status, and environmental factors), which may have some affected on the meta-analysis results. However, in

spite of these shortcomings, we used a detailed protocol for research screening, data extraction, and statistical analysis to minimize bias and reduce possible errors.

In summary, the present meta-analysis and systematic review suggest that YKL-40 may be a useful biomarker for the diagnosis and prognosis prediction of ILD. Further rigorous and consistent studies are needed to better explore the association between and ILD and to examine whether monitoring the levels of YKL-40 contributes to successful clinical decision-making.

## Author contributions

**Conceptualization:** Xiang Tong, Guihui Wu, Hong Fan.

**Data curation:** Xiang Tong, Tao Liu, Zhenzhen Li, Sitong Liu.

**Formal analysis:** Yao Ma.

**Methodology:** Xiang Tong, Yao Ma, Hong Fan.

**Supervision:** Guihui Wu, Hong Fan.

**Writing – original draft:** Xiang Tong, Yao Ma, Tao Liu, Zhenzhen Li.

**Writing – review & editing:** Xiang Tong, Guihui Wu, Hong Fan.

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