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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Association between YKL-40 and asthma: a systematic meta-analysis

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Abstract

Purpose Many studies have shown that chitinase-3-like protein 1 (CHI3L1), also known as YKL-40, is associated with asthma. The purpose of this meta-analysis was to evaluate the role of serum YKL-40 in the diagnosis and differential diagnosis of asthma, severity grading, and determination of disease state.

Methods The PubMed, Ovid, and Cochrane databases were searched. A total of 17 articles involving 5696 subjects were included in this meta-analysis.

Results The results showed that the level of YKL-40 was significantly higher in asthmatic patients than in the normal group regardless of age and residential location, and increased with severity and acute exacerbation ($p < 0.05$). YKL-40 levels were significantly different between chronic obstructive pulmonary disease (COPD) and asthma, and also between asthma-COPD overlap syndrome (ACO) and asthma ($p < 0.05$).

Conclusion YKL-40 may act as a potential serological marker for the diagnosis of asthma, assessment of severity, indicator of the disease state, and differential diagnosis of COPD, ACO, and asthma.

Keywords YKL-40 · Asthma · Clinical trials · Meta-analysis · Systematic review

Introduction

Asthma is a common chronic respiratory disease, accompanied by airway inflammation. The clinical manifestations of asthma include wheezing, shortness of breath, chest tightness, and intermittent cough caused by reversible airway restriction. Although the clinical symptoms are similar, there are differences in serum markers and therapeutic sensitivities among different types of asthma. Th2 immune response-related markers such as IgE do not fully reflect the severity and prognosis of neutrophilic asthma and obesity asthma.

In recent years, chitinase and chitinase-like proteins (CLPs) have become a research hotspot in respiratory diseases such as chronic bronchitis, chronic obstructive pulmonary disease (COPD), and asthma. Chitinase exists in lower organisms, such as arthropods and fungi, and has the function of degrading chitin, which is one of the important components of the shell or cell wall [1, 2]. Chitinases can also be found in hosts that are infected with organisms containing chitin. CLPs are similar to chitinase, which can bind to chitin, but have no enzymatic activity. Human cartilage glycoprotein (hcgp)/YKL-40 is a CLP. It was originally discovered as an effector secreted by macrophages to combat parasitic and fungal infections. Subsequently, YKL-40 was found to be related to various infectious diseases, autoimmune diseases, and cancers [3–5]. The immune mechanism of the human body against parasitic or fungal infections is similar to allergic reactions, which is one of the pathogeneses of asthma. Allergen stimulation results in the increase of YKL-40 and allergen deposition sites are higher [6]. Furthermore, airway neutrophil inflammation, fat accumulation, and other causes are related to YKL-40. Some clinical studies have shown that the serum YKL-40 level is higher in patients with asthma than in healthy controls. The purpose of this study was to explore the utility of serum YKL-40 as a serological marker in the diagnosis and differential

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diagnosis, severity grading, and determination of disease state of asthma.

Materials and methods

Search strategy

The PubMed, OVID, and Cochrane databases were searched using the following search terms: ("Asthmas" OR "Bronchial Asthma" OR "Asthma, Bronchial" OR "asthma") AND ("human cartilage gp39" OR "human cartilage glycoprotein-39" OR "38-kDa heparin-binding glycoprotein, human" OR "YKL40 protein, human" OR "YKL-40 protein, human" OR "chitinase 3-like 1, human" OR "HCGP39 protein, human" OR "HC-gp39 protein, human" OR "chitinase 3-like 1 (cartilage glycoprotein-39) protein, human" OR "GP39 protein, human" OR "cartilage gp-39, human" OR "Chondrex"). Two reviewers independently selected the articles by reading the title and abstract, and subsequently read the full text and extracted the data after inclusion of the study. Any disagreements were resolved by a third reviewer after reading the article. If the data were incomplete, we attempted to contact the author to request the data. The flow chart for literature search is shown in Fig. 1.

Data extraction

The following data were extracted from the included articles: type of study, age, gender, residential location, BMI and methods of measuring YKL-40 levels, mean or median value, SD, SEM, 95% CI, and interquartile range of asthmatic patients and healthy subjects.

Outcome measures

The primary outcome measure was the relationship between YKL-40 serum level and the diagnosis, severity, determination of disease state of asthma, and its role in the differential diagnosis of asthma with COPD and asthma-COPD overlap syndrome (ACO).

Statistical analysis

Statistical analysis was conducted using Comprehensive Meta-Analysis, V.2.0 (Biostat, Englewood, NJ, USA) software. The heterogeneity was analyzed by Cochran-2 statistical method. Heterogeneity was judged by I^2 statistic: no heterogeneity ($I^2 = 0$–25%), moderate heterogeneity ($I^2 = 25$–50%), large heterogeneity ($I^2 = 50$–75%), and extreme heterogeneity ($I^2 = 75$–100%). When the heterogeneity was large ($I^2 > 50\%$), the combined estimates of the

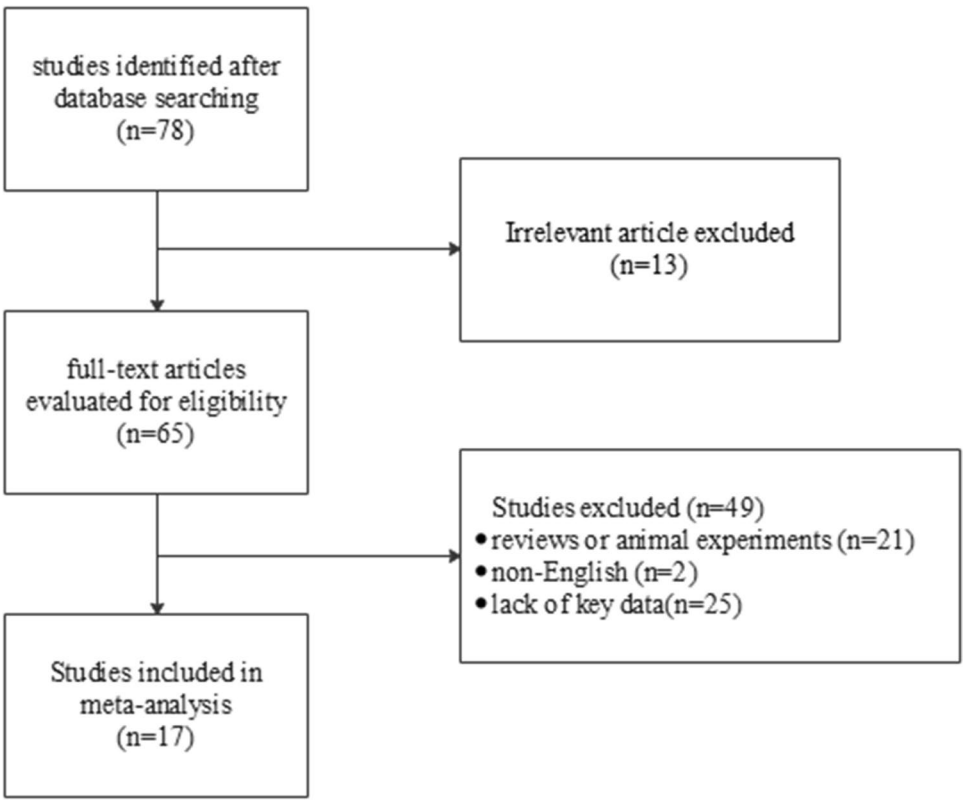

Fig. 1 Flow chart for literature search

standard deviation of the mean were calculated using the random effects model; otherwise, the fixed effects model was applied. Simultaneously, subgroup analysis was conducted according to the age and residential location of participants. One-study removed approach was used in sensitivity analysis. Egger's test and funnel plot were used to evaluate the publication bias. If the single tailed $p < 0.1$, the funnel diagram was asymmetric and there was publication bias. Quality in Prognosis Studies (QUIPS) tool was used for quality assessment.

Results

Literature search

A total of 78 articles were initially retrieved. After reading the summary or the full text carefully, 13 were not related to asthma or YKL-40, 21 were reviews or animal experiments, two were non-English, and 25 lacked key data. Finally, the remaining 17 trials met the inclusion criteria.

Basic characteristics

Of the 17 included articles, 13 [7–19] were case-controlled studies, three [20–22] were cross-sectional studies, and one [23] was a cohort study. A total of 5696 subjects were included, of which subjects in three studies were children or adolescents, while subjects in 14 studies [7–13, 15–19, 21, 23] were adults. The age range was 7–89 years, and sample size ranged from 52 to 1256 cases.

Association between the diagnosis of asthma and YKL-40

A total of 13 articles [7–17, 19, 20] examined the association between the diagnosis of asthma and YKL-40, three of which were multi-centric and independent of each other. A total of 4394 subjects were included (Table 1). The pooled results showed that the level of YKL-40 in asthmatic patients was significantly higher than that in healthy subjects (pooled standardized difference in means = 0.544, 95% CI 0.303 to 0.784, $p < 0.0001$) (Fig. 2A), but heterogeneity was extremely high ($Q = 149.146$, $p < 0.0001$, $I^2 = 89.943\%$). Subgroup analysis was based on age (subgroups: age < 18 years, age ≥ 18 years) and heterogeneity decreased (age < 18 years: $Q = 4.907$, $p = 0.027$, $I^2 = 79.620\%$; age ≥ 18 years: $Q = 112.163$, $p < 0.0001$, $I^2 = 89.30\%$); the results showed that YKL-40 was higher in both adults and children (age < 18 years: pooled standardized difference in means = 0.977, 95% CI 0.355 to 1.599, $p = 0.002$; age ≥ 18 years: pooled standardized difference in means = 0.510, 95% CI 0.265 to 0.756, $p < 0.0001$). Subgroup analysis according to the residence of subjects (subgroup: Africa, Asia, Europe, North America) also showed a correlation between asthma and serum YKL-40 (Asia: pooled standardized difference in means = 0.576, 95% CI 0.138 to 1.014, $p = 0.010$; Europe: pooled standardized difference in means = 0.518, 95% CI 0.294 to 0.742, $p < 0.0001$; North America: pooled standardized difference in means = 0.294, 95% CI 0.036 to 0.551, $p = 0.025$). There was only one study from Africa, and the studies from Europe and North America were homogeneous, while the heterogeneity in Asia was higher than that in the whole population (Asia: $Q = 97.091$, $p < 0.0001$, $I^2 = 93.820\%$; Europe: $Q = 4.285$, $p = 0.232$, $I^2 = 29.982\%$; North America: $Q = 5.920$, $p = 0.116$, $I^2 = 49.328\%$) (Fig. 2B, Fig. 2C). Figure 2D shows the sensitivity analysis using one-study removed approach. Removing any of the studies did not change the results, indicating that the results were robust. The funnel plot (Fig. 2E) showed that the analysis had publication bias. Egger's test suggested that funnel plot was asymmetric ($t = 3.00$, $df = 14$, one-tailed $p = 0.00478$).

Association between the severity of asthma and YKL-40

Five articles [9–11, 22, 23] examined the association between the severity of asthma and YKL-40, one of which was multi-centric and independent of others. Asthma was graded as severe and non-severe based on the degree of asthma severity according to ATS criteria. Any one of the following four criteria qualifies a patient as having uncontrolled asthma: (1) poor symptom control, Asthma Control Questionnaire (ACQ) consistently ≥ 1.5, or Asthma Control Test (ACT) < 20 (or "not well controlled" by National Asthma Education and Prevention Program or Global Initiative for Asthma guidelines over the 3 months of evaluation); (2) frequent severe exacerbations, defined as two or more bursts of systemic corticosteroids (≥ 3 days each) in the previous year; (3) serious exacerbations, defined as at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year; (4) airflow limitation, i.e. forced expiratory volume in 1 s (FEV1) < 80% predicted (in the presence of reduced FEV1/forced vital capacity (FVC) defined as less than the lower limit of normal) following a withhold of both short- and long-acting bronchodilators. A total of 1864 subjects were included (Table 2). The pooled results indicated that the YKL-40 level increased with the severity of asthma (pooled standardized difference in means = −0.423, 95% CI −0.534 to −0.316, $p < 0.0001$) (Fig. 3A). These studies were homogeneous ($Q = 13.532$, $p = 0.06$, $I^2 = 48.272\%$). Sensitivity analysis indicated that the results were robust (Fig. 3B). The funnel plot (Fig. 3C) showed no publication bias. Egger's test suggested that the

Table 1 Summary of basic characteristics of selected studies

Study	Study design	Type of asthma	Number of patients	Age (years)	Age < 18 years	Male (%)	Mean BMI
Basha 2018 [20]	Cross-sectional	Asthma	120	7.67 ± 2.40	Y	76 (43%)	NR
		Control	60	7.68 ± 2.48		34 (57%)	
Wang 2018 [7]	Case–control	Asthma	124	48.4912.25	N	55 (44%)	24.43 ± 1.67
		Control	50	49.60 ± 18.14		28 (56%)	23.50 ± 1.11
Han 2016 [19]	Case–control	Asthma	20	50.00 ± 11.25	N	1 (5%)	NR
		Control	20	50.00 ± 4.25		20 (100%) (female)	
Gomez 2015 [9]	Case–control	Asthma (YCAAD EA)	174	48.76 ± 21.30	N	53 (30%)	26.94 ± 6.13
		Control (YCAAD EA)	39	45.00 ± 19.26		12 (31%)	25.50 ± 3.19
	Case–control	Asthma (SARP EA)	562	36.83 ± 15.31	N	204 (36%)	27.20 ± 6.66
		Control (SARP EA)	122	27.00 ± 12.59		54 (44%)	24.40 ± 4.96
	Case–control	Asthma (Y&S AA)	259	32.43 ± 15.63	N	89 (34%)	30.62 ± 9.73
		Control (Y&S AA)	22	35.00 ± 8.15		6 (27%)	28.70 ± 6.59
Kim 2015 [10]	Case–control	Asthma	546	42.50 ± 13.57	N	213 (39%)	NR
		Control	99	28.64 ± 7.89		51 (52%)	
Specjalski 2015 [8]	Case–control	Asthma	167	50.10 ± 15.30	N	51 (31%)	25.70 ± 3.10
		Control	81	48.60 ± 15.30		31 (38%)	25.10 ± 3.20
Tsai 2014 [17]	Cross-sectional	Asthma	628	51.44 ± 14.13	N	289 (46%)	25.27 ± 4.07
		Control	628	50.42 ± 11.84		289 (46%)	23.95 ± 3.40
Duru 2013 [16]	Case–control	Asthma	60	38.80 ± 11.21	N	32 (53%)	24.69 ± 4.37
		Control	30	38.10 ± 10.98		15 (50%)	25.34 ± 3.70
Konradsen 2013 [14]	Case–control	Asthma	34	13.30 ± 3.10	Y	NR	20.40 ± 3.50
		Control	39	13.80 ± 2.90			20.00 ± 3.10
Kim 2012 [15]	Case–control	Asthma	36	45.00 ± 19.00	N	22 (61%)	NR
		Control	73	48.00 ± 13.00		41 (56%)	
Specjalski 2011 [13]	Case–control	Asthma	59	45.00 ± 12.30	N	20 (34%)	NR
		Control	29	41.00 ± 15.60		11 (38%)	
Tang 2010 [12]	Case–control	Asthma	62	40.10 ± 18.60	N	29 (46%)	NR
		Control	64	42.20 ± 11.90		31 (48%)	
Chupp 2007 [11]	Case–control	Asthma (Yale)	97	44.00 ± 13.00	N	24 (25%)	31.40 ± 8.30
		Control (Yale)	38	42.00 ± 11.00		11 (29%)	27.10 ± 4.10
	Case–control	Asthma (Paris)	40	47.88 ± 14.41	N	17 (43%)	NR
		Control (Paris)	12	51.70 ± 9.60		6 (50%)	

BMI, body mass index; *N*, no; *Y*, yes; *NR*, not reported

funnel plot was symmetrical ($t = 0.76670$, $df = 6$, one-tailed $p = 0.23617$).

Association between the exacerbation of asthma and YKL-40

Three studies [12, 16, 20] examined the association between asthma exacerbation and YKL-40, and included 242 subjects (Table 3). YKL-40 was weakly correlated with asthma exacerbation (pooled standardized differentiation in means = − 2.588, 95% CI − 5.059 to − 0.117, $p = 0.04$) (Fig. 4A), but there was extreme heterogeneity ($Q = 88.686$, $p < 0.0001$, $I^2 = 97.745\%$). After excluding the Basha et al. [20] trial, which included children, the heterogeneity decreased and the correlation increased ($Q = 8.289$, $p = 0.004$, $I^2 = 87.935\%$; pooled standardized differentiation in means = − 1.295; 95% CI − 2.509 to − 0.080, $p = 0.037$) (Fig. 4B). Egger's test showed that the funnel plot was asymmetric ($t = 8.8588$, $df = 1$, one-tailed $p = 0.03578$), indicating publication bias (Fig. 4C).

Association between serum YKL-40 level in COPD and asthma

Five studies [7, 15, 18, 19, 21, 23] examined the association between serum YKL-40 in COPD and asthma,

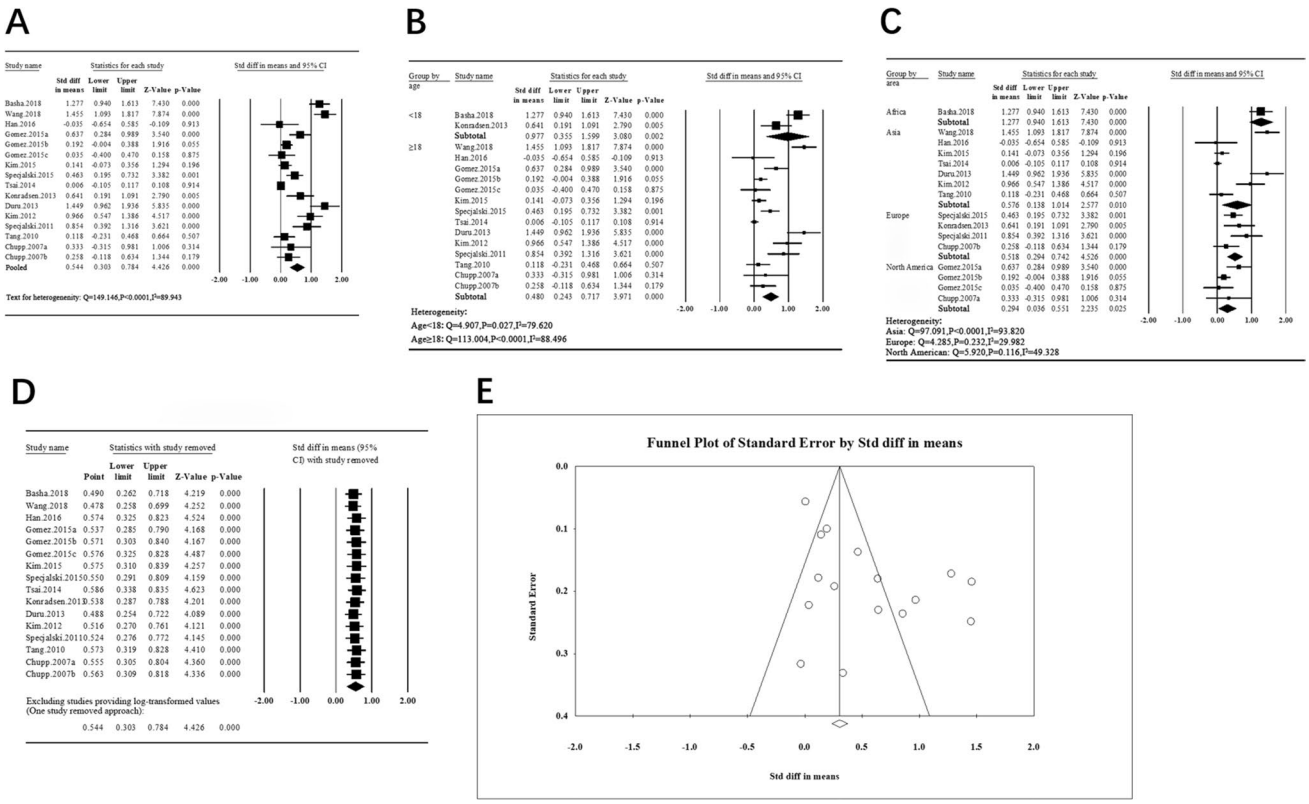

Fig. 2 Forest plot for association between asthma and YKL-40 (**A**), sensitivity analysis for association between asthma and YKL-40 (**B**), subgroup analysis for association between asthma and YKL-40 according to age of patients (**C**), subgroup analysis for association between asthma and YKL-40 according to residence of patients (**D**), funnel plot for association between asthma and YKL-40 (**E**)

Table 2 Summary of basic characteristics of selected studies

Study	Study design	Type of asthma	Number of patients	Age (years)	Age < 18 years	Male (%)	Mean BMI
James 2016 [23]	Cohort	NA	76	43.40 ± 1.60	N	31 (40%)	25.20 ± 0.50
		SA	93	50.20 ± 1.40		40 (43%)	28.30 ± 0.60
Gomez 2015 [9]	Case–control	NA	137	46.00 ± 22.22	N	39 (28%)	26.30 ± 6.30
		SA	37	59.00 ± 13.33		14 (38%)	29.30 ± 4.81
	Case–control	NA	234	31.00 ± 14.07	N	66 (28%)	25.10 ± 5.33
		SA	328	41.00 ± 14.81		138 (42%)	28.70 ± 7.11
	Case–control	NA	132	29.00 ± 13.33	N	44 (33%)	29.00 ± 8.81
		SA	127	36.00 ± 17.04		45 (35%)	32.30 ± 10.37
Kim 2015 [10]	Case–control	NA	370	41.72 ± 13.48	N	148 (40%)	NR
		SA	75	46.36 ± 12.78		31 (41%)	
Santos 2014 [22]	Cross-sectional	NA	42	11.69 ± 0.87	Y	28 (67%)	21.68 ± 2.48
		SA	19	12.20 ± 2.10		10 (53%)	24.50 ± 2.10
Chupp 2007 [11]	Case–control	NA (Yale)	53	43.92 ± 13.77	N	14 (26%)	29.38 ± 6.95
		SA (Yale)	44	44.00 ± 12.00		10 (23%)	33.80 ± 8.80
	Case–control	NA (Paris)	25	46.18 ± 14.44	N	10 (40%)	NR
		SA (Paris)	15	50.70 ± 14.40		7 (47%)	
	Case–control	NA (Wisconsin)	30	26.00 ± 7.39	N	16 (53%)	NR
		SA (Wisconsin)	27	39.00 ± 12.00		12 (44%)	

NA, non-severe asthma; *SA*, severe asthma; *BMI*, body mass index; *N*, no; *Y*, yes; *NR*, not reported

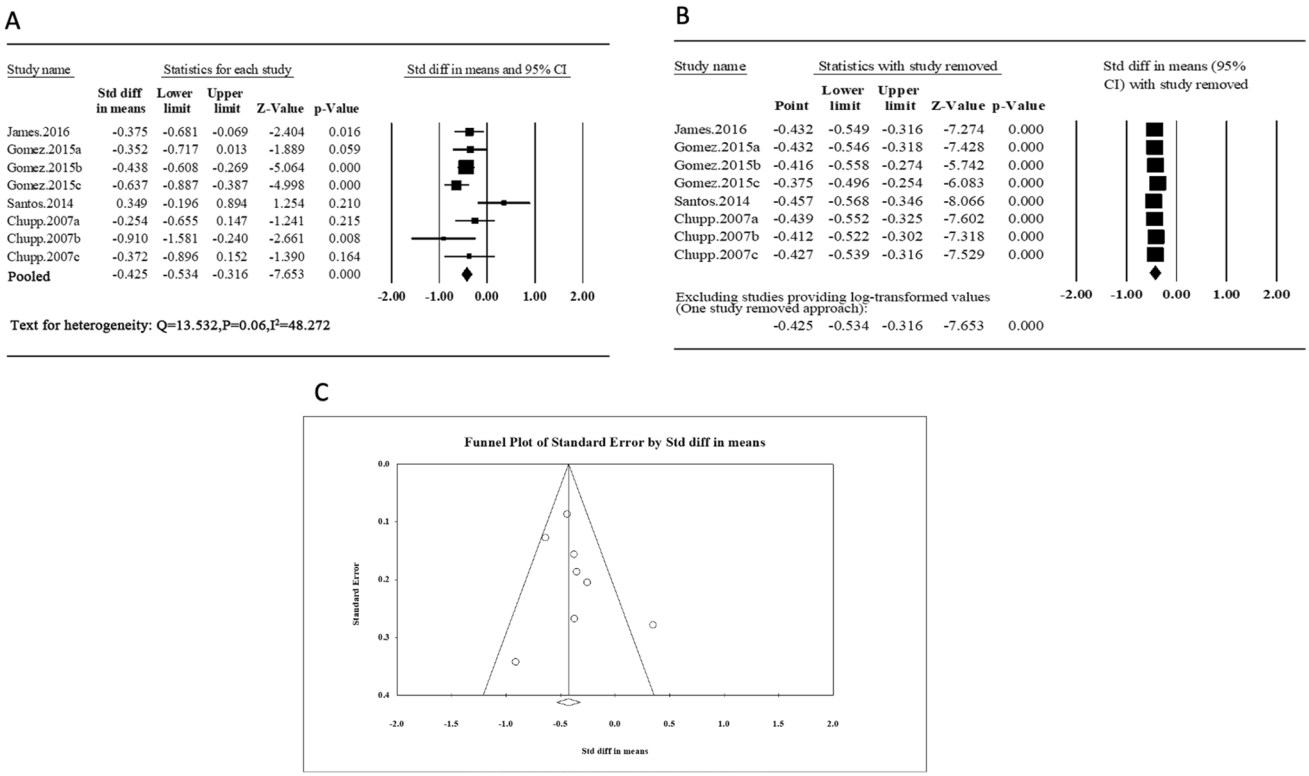

Fig. 3 Forest plot for association between the severity of asthma and YKL-40 (**A**), sensitivity analysis for association between the severity of asthma and YKL-40 (**B**), funnel plot for association between the severity of asthma and YKL-40 (**C**)

Table 3 Summary of basic characteristics of selected studies

Study	Study design	Type of asthma	Number of patients	Age (years)	Age < 18 years	Male (%)	Mean BMI
Basha 2018 [20]	Cross-sectional	SBA	60	NR	Y	NR	NR
		AE	60				
Duru 2013 [16]	Case–control	SBA	30	38.80 ± 11.31	N	18 (60%)	24.19 ± 4.64
		AE	30	38.80 ± 11.31		14 (47%)	25.19 ± 4.09
Tang 2010 [12]	Case–control	SBA	16	30.90 ± 21.80	N	6 (37%)	NR
		AE	46	43.30 ± 16.60		23 (50%)	

SBA, stable asthma; *AE*, asthma exacerbation; *BMI*, body mass index; *N*, no; *Y*, yes; *NR*, not reported

and included 925 subjects (Table 4). The serum YKL-40 in COPD patients was significantly higher than that in patients with asthma (pooled standardized difference in means = − 2.436, 95% CI − 3.562 to − 1.309, $p < 0.0001$) (Fig. 5A), and there was a large heterogeneity between studies ($Q = 224.445$, $p < 0.0001$, $I^2 = 97.772\%$). After removing the study by Gon et al. [21], the heterogeneity was reduced and the analysis results remained unchanged ($Q = 4.856$, $p = 0.302$, $I^2 = 17.635\%$; pooled standardized differentiation in means = − 0.874; 95% CI − 1.029 to − 0.718, $p < 0.0001$) (Fig. 5B, Fig. 5C). Egger's test showed that the funnel plot was asymmetric ($t = 2.16895$, $df = 4$, one-tailed $p = 0.04796$), indicating a publication bias (Fig. 5D).

Association between serum YKL-40 level in ACO and asthma

Only three studies [7, 18, 21] examined the relationship between ACO and serum YKL-40 level in asthmatic patients, and included 649 subjects (Table 5). YKL-40 could not differentiate ACO from asthma (pooled standardized difference in means = − 2.804, 95% CI − 4.748 to − 0.860, $p = 0.005$) (Fig. 6A), and there was extreme

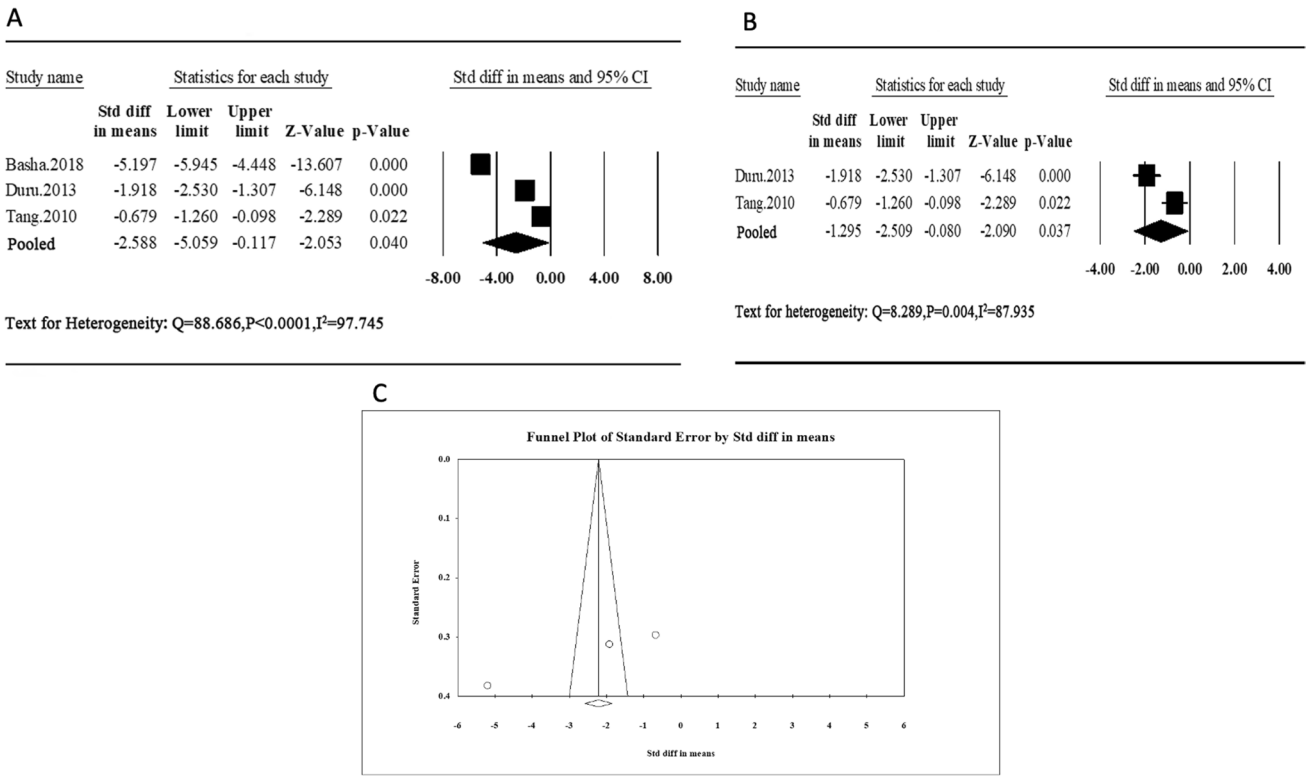

Fig. 4 Forest plot for association between the exacerbation of asthma and YKL-40 (**A**); forest plot for association between the exacerbation of asthma and YKL-40, after removal of the study by Basha et al. [20] (**B**); funnel plot for association between the exacerbation of asthma and YKL-40 (**C**)

Table 4 Summary of basic characteristics of selected studies

Study	Study design	Type of asthma	Number of patients	Age (years)	Age < 18 years	Male (%)	Mean BMI
Shirai 2018 [18]	Case–control	Asthma	177	59.00 ± 20.74	Y	52 (29%)	23.00 ± 3.70
		COPD	61	74.00 ± 6.67		49 (80%)	21.00 ± 2.96
Wang 2018 [7]	Case–control	Asthma	124	48.49 ± 12.25	N	55 (44%)	24.43 ± 1.67
		COPD	147	67.56 ± 9.18		99 (67%)	22.43 ± 1.56
Gon 2017 [21]	Cross-sectional	Asthma	91	53.20 ± 1.62	N	21 (23%)	23.20 ± 0.45
		COPD	45	72.60 ± 1.12		35 (78%)	21.30 ± 0.49
Han 2016 [19]	Case–control	Asthma	20	50.00 ± 11.25		1 (5%)	NR
		COPD	16	73.00 ± 10.00		16 (100%)	
James 2016 [23]	Cohort	Asthma	169	47.14 ± 4.03	N	71 (42%)	NR
		COPD	45	64.30 ± 1.10		50 (78%)	27.30 ± 0.70
Kim 2012 [15]	Case–control	Asthma	36	45.00 ± 19.00	N	22 (61%)	NR
		COPD	30	70.00 ± 13.00		20 (67%)	

BMI, body mass index; *N*, no; *NR*, not reported

heterogeneity between the three studies ($Q = 208.646$, $p < 0.0001$, $I^2 = 99.041\%$). After removing the study by Gon et al., the heterogeneity was reduced and the analysis results remained unchanged ($Q = 0.535$, $p = 0.464$, $I^2 = 0.0001\%$); pooled standardized differentiation in means = − 0.313; 95% CI − 0.481 to − 0.144, $p < 0.0001$ (Fig. 6B).

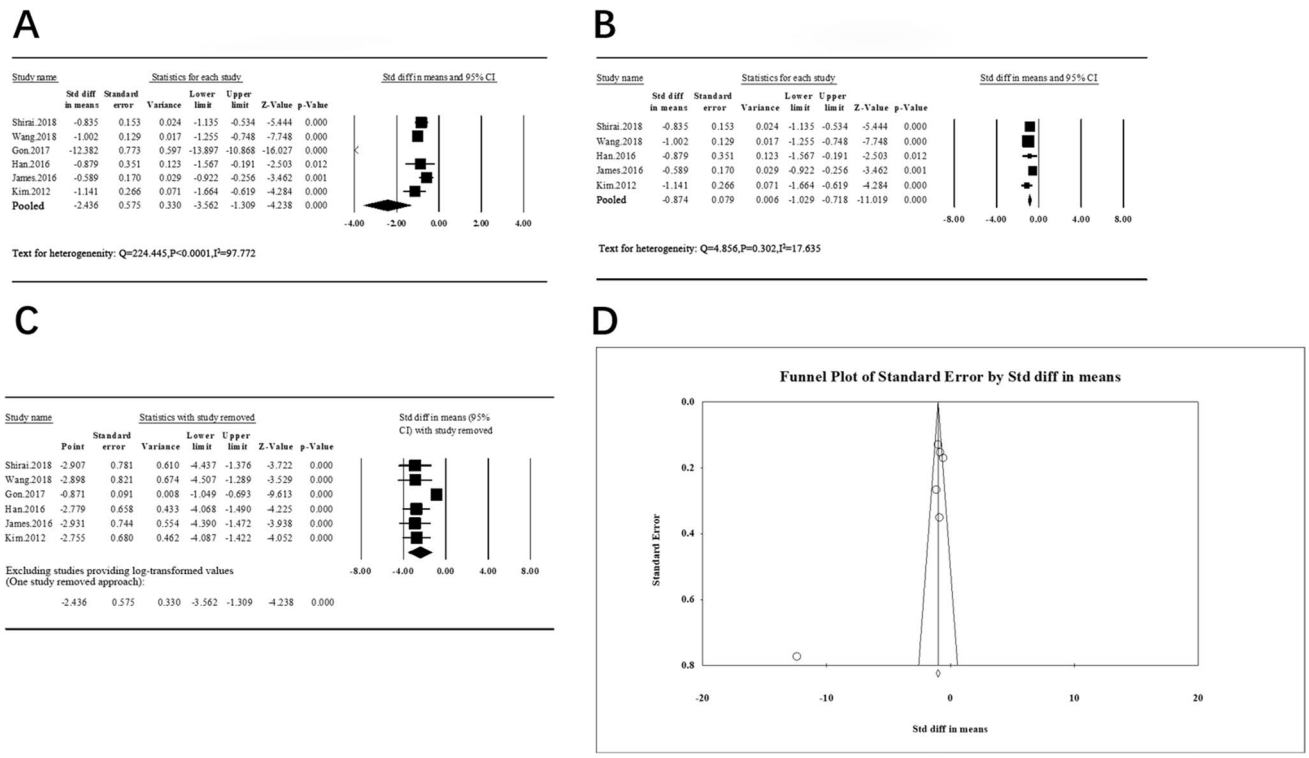

Fig. 5 Forest plot for association between serum YKL-40 level in COPD and asthma (**A**); sensitivity analysis for association between asthma and YKL-40 (**B**); forest plot for association between serum YKL-40 level in COPD and asthma, after removal of the study by Gon et al. [21] (**C**); funnel plot for association between serum YKL-40 level in COPD and asthma (**D**)

Table 5 Summary of basic characteristics of selected studies

Study	Study design	Type of asthma	Number of patients	Age (years)	Age < 18 years	Male (%)	Mean BMI
Shirai 2018 [18]	Case–control	Asthma	177	59.00 ± 20.74	Y	52 (29%)	23.00 ± 3.70
		ACO	115	70.00 ± 8.89		91 (79%)	23.00 ± 2.96
Wang 2018 [7]	Case–control	Asthma	124	48.49 ± 12.25	N	55 (44%)	24.43 ± 1.67
		ACO	102	62.54 ± 9.07		40 (39%)	25.55 ± 1.21
Gon 2017 [21]	Cross-sectional	Asthma	91	53.20 ± 1.62	N	21 (23%)	23.20 ± 0.45
		ACO	40	66.20 ± 1.51		29 (73%)	23.40 ± 0.60

BMI, body mass index; *N*, no; *NR*, not reported

Quality assessment

The included articles were evaluated based on the following four aspects: (a) study specialization, (b) study authority, (c) diagnostic practice assurance, (d) meeting measurement, and account (e) analysis. However, four studies [8, 12, 13, 20] had confounding factors. One study [15] had a small number of subjects. The recruitment time of a study was unclear and the baseline characteristics were unstable [21]. Another study did not illustrate the analytical method (Fig. 7A, Fig. 7B).

Discussion

YKL-40 is a chitinase-like protein encoded by chitinase-3-like 1 gene (CHI3L1). YKL-40 can bind to chitin but has no enzymatic activity [24]. The serum YKL-40 level is increased in various immune diseases, cancers, and infectious diseases. The results of this meta-analysis showed that the serum YKL-40 level of asthmatic patients was significantly higher than that of healthy subjects. According to the age group, the conclusion in both adult asthma and childhood asthma was consistent with the general analysis.

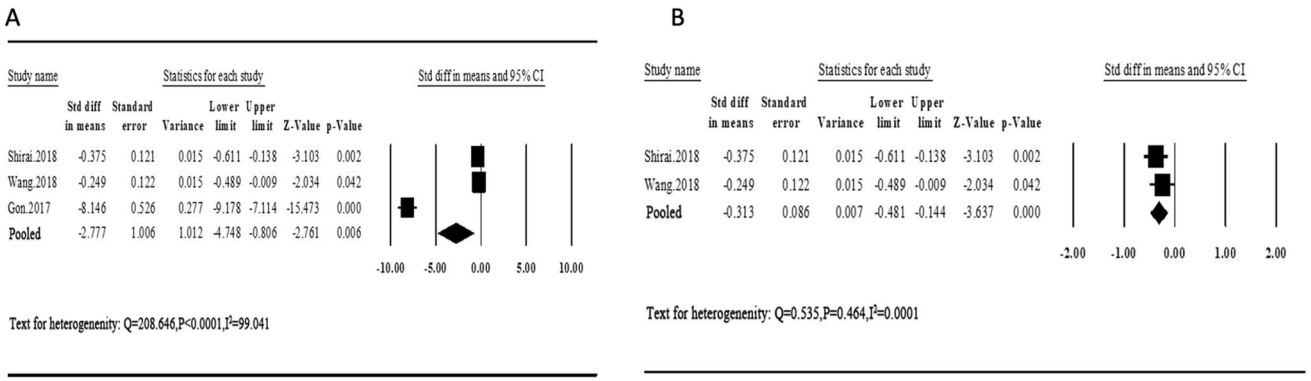

Fig. 6 Forest plot for association between serum YKL-40 level in ACO and asthma (**A**). Forest plot for association between serum YKL-40 level in ACO and asthma, after removal of the study by Gon et al. [21] (**B**)

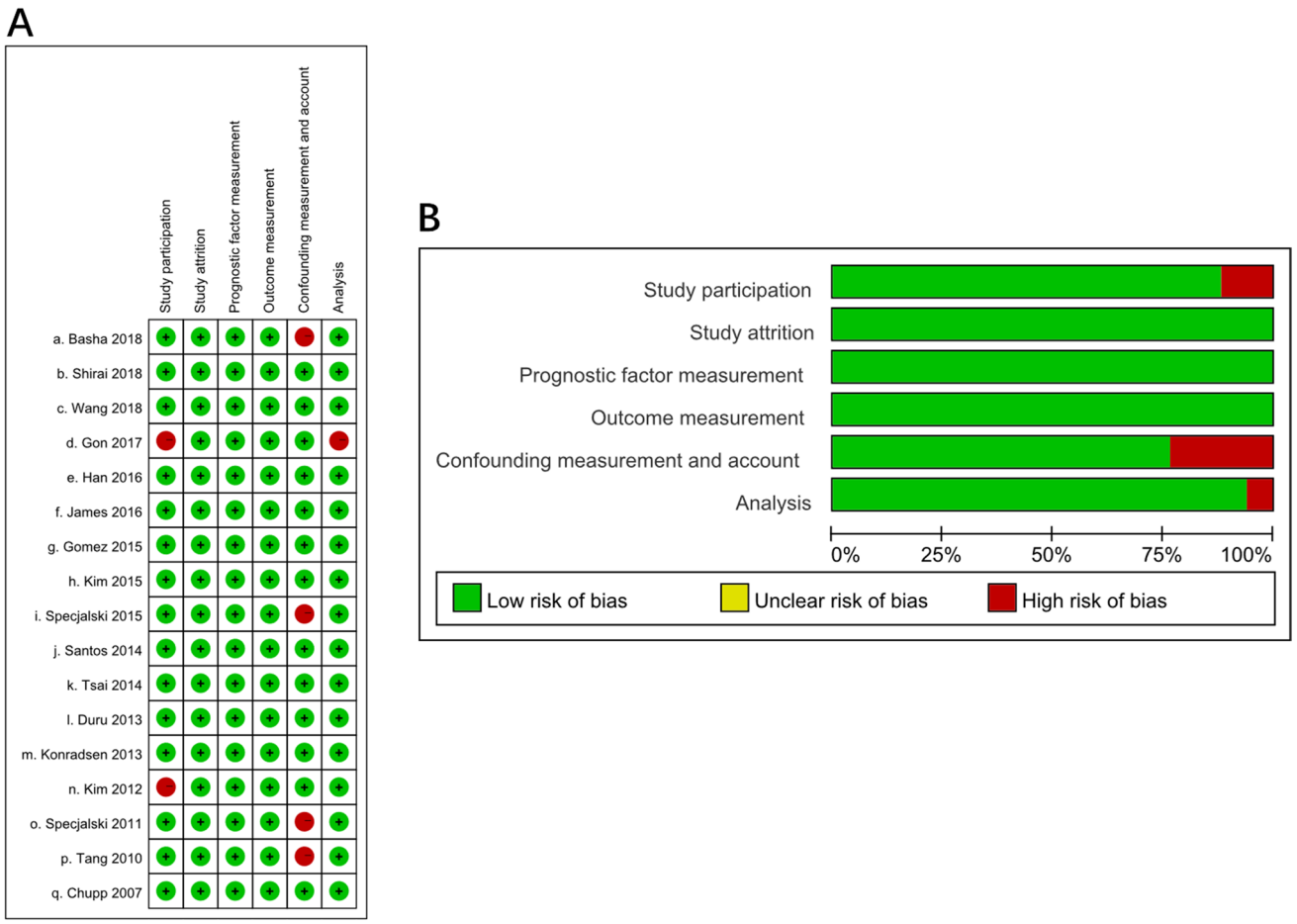

Fig. 7 Risk of bias summary (**A**), risk of bias graph in Quality in Prognosis Studies (QUIPS) tool among the pooled studies (**B**)

The results of subjects grouped by residence locations were the same. These results suggested a close and stable relationship between asthma and YKL-40, which was not affected by age and location. Sensitivity analysis indicated that the results were robust, but there was publication bias. In addition, YKL-40 could also reflect the severity of asthma. Sensitivity analysis indicated that the results were reliable, and there was no publication bias.

Airway remodeling and inflammation are the pathogeneses of asthma. Airway remodeling leads to airflow limitation and lung function impairment; airway inflammation causes airway damage and stimulates airway

hyper-responsiveness, which further worsens the disease. YKL-40 plays a key role in both processes. Clinical studies have shown that the serum level of YKL-40 in bronchial smooth muscle cells is positively correlated with the thickness of bronchial epithelial basement membrane in asthmatic patients, and experimental studies have confirmed that YKL-40 can accelerate the proliferation and migration of bronchial smooth muscle cells [25, 26]. In addition, YKL-40 can inhibit the degradation of type I collagen, forming collagenous fiber, stimulating the release of pro-fibrogenic factors and inflammatory cytokines, and participate in tissue remodeling [27, 28].

Airway inflammation is another pathological feature of asthma. Th1/Th2 immune imbalance is involved in the pathogenesis of asthma airway inflammation, and YKL-40, as a key factor in Th2 response, has potential value. Experimental studies by Zhu et al. [29] and Lee et al. [30] confirmed that YKL-40 may enhance the effector responses of the key cytokine IL-13 in Th2 responses. Besides, YKL-40 is involved in the regulation of oxidant injury and has a protective role in smoke-induced inflammation through an IL-18-dependent pathway [31]. It is reported that YKL-40 plays an essential role in IL-13-mediated Th2 inflammation, connecting to antigen sensitization and IgE production [30]. However, the correlation between YKL-40 and Th2-related inflammation is still controversial in asthma. Santos et al. [22] found that FeNO, IgE, and other highly related markers of Th2 responses were significantly increased in children with severe persistent asthma, while YKL-40 had no correlation with Th2 response-related markers and severity of asthma. There are a few similar studies on adults. Interestingly, in some articles that classified asthma patients into different phenotypes according to certain characteristics, the majority of patients with high serum YKL-40 level had non-eosinophilic asthma (NEA) and obese asthma [32]. YKL-40 can be produced by neutrophils. Some studies have shown that YKL-40 is not only involved in Th2 inflammation but also positively correlated with IL-1β, IL-6, and other neutrophil-related cytokines. Liu et al. [33] found that the serum YKL-40 level was extremely higher in patients with NEA than in patients with eosinophilic asthma (EA). NSA, including neutrophil asthma, is characterized by high risk of deterioration, poor efficacy of hormone therapy, and severe airflow obstruction. Meanwhile, visceral fat is closely related to the secretion of YKL-40. Ahangari et al. [34] found that visceral obesity and asthma share an important CHI3L1/YKL-40-dependent pathway. CHI3L1 gene may regulate SIRT1 to increase visceral fat content and mediate obesity-related asthma. Correlation between CHI3L1 single nucleotide polymorphism (SNP) and asthma is evident. CHI3L1 polymorphism was associated with asthma characteristics and serum YKL-40 levels [35–38]. Thus, YKL-40 is closely related to the pathogenesis of asthma. It is involved in airway inflammation and remodeling from many aspects such as gene and immune pathways, and participates in the pathogenesis of various types of asthma.

In this study, the results showed the heterogeneity of data was higher in Asia comparing with Europe and North America, the possible reason might be the number of studies from Asia was limited, or there is a huge gap in the economic development level in different Asian countries, and they both can contribute to the high heterogeneity and publication bias. Besides, Kun Li et al. [39] identified that elevated serum YKL-40 level associates with hypertension in obstructive sleep apnea (OSA) patients, which can be considered as a potential biomarker for OSA and hypertension. Another study [40] also indicated the overexpression of serum YKL-40 levels is related to the severity of OSA. Interestingly, OSA and asthma share several common risk factors, such as obesity, rhinitis, and gastroesophageal reflux. And it is reported that there is a bidirectional correlation between severe asthma and OSA; OSA not only acts as an independent risk factor of asthma exacerbations, but its coexistence can also worsen asthma symptoms [41].

This study also found that serum YKL-40 levels were higher in COPD than in asthma. Neutrophils and macrophages can secrete YKL-40, which are higher in sputum of patients with COPD. Smoking is one of the important pathogenic factors of COPD. James et al. [23] found that smoking history is positively associated with chitinase activity through regression analysis. However, Han et al. [19] demonstrated that there is no difference in serum YKL-40 between asthma and COPD patients after adjusting for age and FEV1, but there are negative correlations between CCL18 and age in asthma and a positive correlation between IL-18 and CCL18 in COPD. Junnan Peng et al. [42] demonstrated that the high YKL-40 level could be served as a predictive biomarker for COPD-related readmission rate. Furthermore, abnormal YKL-40 expression level has been reported in multiple lung diseases, such as interstitial lung disease, asthma exacerbation, and lung cancer. Elevated serum level of YKL-40 is a promising biomarker for evaluating the activity/severity and predicting disease prognosis of interstitial lung disease [43], lung cancer, and pneumonia [44]. However, no particular cut-off values of YKL-40 to differentiate different lung diseases have been demonstrated. Therefore, further studies are required to analyze the specific values of YKL-40 for different lung diseases, which has a great significance for the diagnosis, treatment, and evaluation of lung diseases.

ACO was formally defined in 2014. In terms of clinical practice, ACO is more likely to deteriorate than COPD and asthma, and has a higher risk of persistent airway obstruction. However, once diagnosed and intervened early, the prognosis of ACO is better than that of COPD and asthma. Consequently, the diagnosis of ACO is very important, but doctors do not have complete knowledge of this disease. The GINA recommends to differentiate ACO from COPD and asthma based on clinical symptoms and Th2 inflammatory markers, but this differentiation is error-prone. Finding reliable serum markers

is critical. Meanwhile, there was a significant difference in YKL-40 level between ACO and asthma. Only three studies examining ACO and asthma were included. The results of Gon et al. [21] and Shirai et al. [18] were contrary to those of Wang et al. [7]. Gon et al. [21] found that the degree of lung function damage in ACO was higher than that in simple asthma, and BMI was the same. YKL-40 was positively correlated with the degree of lung function injury, and was closely related to BMI. Under the dual effects, YKL-40 was very likely to be used as a marker for the differential diagnosis of ACO and asthma. The results of Gon et al. [21] also supported the notion. In addition, the elevation of plasma YKL-40 also occurs in different cancer types with variant possibilities [45]. Further studies are required in this field in the future.

Conclusion

There are some limitations in this study. Due to the limited number of included articles, some results were not robust, with high heterogeneity and publication bias. Due to incomplete data, it was not possible to assess the correlation between YKL-40 and other factors. Altogether, this study found that YKL-40, as a serum marker, has potential importance in the diagnosis of asthma, evaluation of severity, determination of disease state, and differential diagnosis with COPD. However, due to the limited number of included articles, some results were not robust, with high heterogeneity and publication bias. Further research is needed to explore the role of YKL-40 in asthma.

Data availability All the data can be requested from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication None.

Conflict of interest The authors declare no competing interests.

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Comment

The quest for a reliable biomarker for asthma, which can clearly confirm the diagnosis, indicate when exacerbations occur and differentiate from other common diseases with similar symptoms, has been so far unanswered.

The meta-analysis done by Yihan Jin et al. explores the role of YKL-40 as a biomarker for asthma. Analysis of 5696 subjects from 17 studies demonstrates the utility of YKL-40 in diagnosis of asthma, in assessing the severity of asthma and asthma exacerbation. YKL-40 demonstrates statistically significant difference between controls and asthmatics. However, its role has still not clearly emerged for differentiating asthma from COPD, where YKL-40 levels are higher, or from asthma COPD overlap (ACO).

This meta-analysis shines light on the important fact that more studies need to be conducted before we can draw conclusions on the relevance of YKL-40 levels in asthma.

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