Int J Clin Exp Med 2015;8(9):14935-14943
www.ijcem.com /ISSN:1940-5901/IJCEM0011152

Original Article

Interleukin-33 and receptor ST2 as indicators in patients with asthma: a meta-analysis

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Received June 7, 2015; Accepted September 9, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: IL33/ST2 axis activates airway eosinophils that exacerbate airway inflammation. The data was obtained from PubMed, EMBASE, Clinical trial, Cochrane Library, Web of science, CNKI and Wanfang database with time restrictions of 1 Jan, 2000 to 15 Feb, 2016. The meta-analysis was performed using Review Manager 5.2 software. After searching, total 15 documents were included into this meta-analysis, involving in 633 asthma patients and 379 healthy people. The meta-analysis results revealed that the serum IL33 or ST2 level was higher in asthma patients compared to that in healthy people. (P=0.02, 95% CI (7.57, 72.74); P<0.0001, 95% CI (31.27, 91.32)). Compared to healthy people, severe, moderate or mild asthma patients had much higher serum IL33 level. (P<0.00001, 95% CI (87.86, 188.09); P<0.00001, 95% CI (31.93, 72.29); P<0.00001, 95% CI (100.51, 153.08), respectively). The serum ST2 level in different asthma progress included severe or moderate was higher, (P<0.00001, 95% CI (50.76, 76.93); P<0.00001, 95% CI (1.02, 1.79), respectively) but nor mild. (P=0.30, 95% CI (-22.37, 72.61)). The meta-analysis result shown the sputum IL33 was not higher in moderate asthma patients than that in healthy people. (P=0.20, 95% CI (-1.99, 9.52)) The meta-analysis results shown that there were significantly difference between and among two asthma progress, (P<0.00001, 95% CI (14.02, 19.09), severe vs moderate; P<0.00001, 95% CI (0.52, 1.24), moderate vs mild) However, there was no significant differences between severe group and mild group. (P=0.08, 95% CI (-20.95, 336.50)). Serum IL33 and ST2 level is relevant to asthma disease. With asthma disease progress, IL33 and ST2 are increased significantly.

Keywords: Interleukin-33, ST2, asthma, meta-analysis

Introduction

Asthma is a complex inflammatory disease, characterized by airway hyperresponsiveness (AHR), airway inflammation, and reversible airway obstruction, affecting up to 300 million people worldwide [1]. The development of asthma is a multifactorial process which is associated with a variety of risk factors, including environmental factors and genetic factors [2]. Allergens, viral infections, environmental tobacco smokes and pollutants represent the most important exogenous risk factors [3]. As we known, the bronchial asthma is a disease that T helper 2 (Th2) cell plays important role. Th2 cells can produce a lot of cytokines, including interleukin (IL)-33 [4].

Interleukin-33 (IL-33) is a novel cytokine belonging to the IL-1 family which was found in 2005 [5]. It can bind to receptors ST2, which highly expressed on some cells, included mast cells and Th2 cells [6]. It is found in various cells included fibroblasts, bronchial and epithelial cells, endothelial cells, and some immune cells, including macrophages and dendritic cells [7]. IL-33 participates in many diseases with dual, proinflammatory or protective roles depending on the cellular and cytokine context, including asthma [8, 9]. Moreover, the previous study also shown that ST2 is expressed in the adults and children patients with acute asthma [10]. However, the correlation between IL33 and its receptor ST2 and asthma is unknown. It is unknown whether IL33 or ST2 expression can be an indicator for asthma progress.

In this meta-analysis, we searched and analyzed the role of IL33 and ST2 in patients with asthma, which may be provide a foundation for clinical diagnosis and therapy.

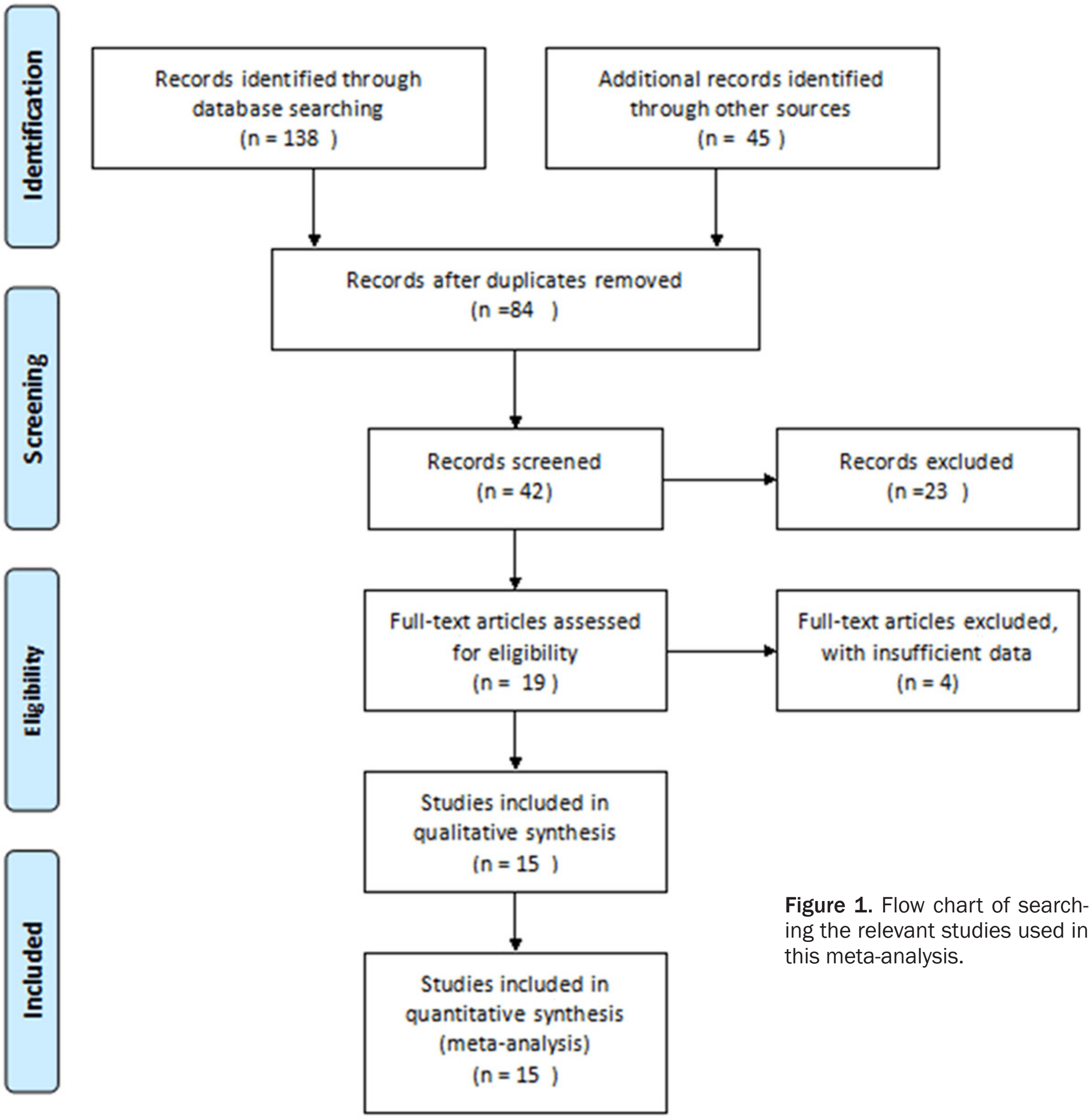

Figure 1. Flow chart of searching the relevant studies used in this meta-analysis.

Methods

A computerized literature search was conducted using Pubmed, MEDLINE, EMBASE and Chinese databases (including CNKI and WanFang database) from 1 Jan 2000 through 15 Feb 2016. The search strategy used medical subject heading (MeSH) terms and keywords "interleukin-33" or "IL-33", "ST2", "asthma", "endotrachial", "sputum", "lung" and "randomized controlled trials". The patient had no other severe disease, including immune deficiencies. We also manually reviewed the reference lists to identify additional relevant studies. No language restrictions were imposed.

Inclusion and exclusion criteria

All studies should be fulfilled the following criteria: (1) the exposure of interest was interleukin-33 or the ST2; (2) the outcome of interest was asthma; (3) all included studies should be case-control study, cohort study, randomized controlled trials or cross-sectional study; (4) all included studies had no language limitation. The study that it was comment, duplicate data, abstract, review, and editorial or insufficient data should be excluded.

Data extraction

Two investigators independently performed the data extraction. When discrepancies were

Table 1. The general data of included documents

First Author	Publishing year	Methodological quality				Intervention	
		Study design	Randomized method	Allocation concalment	Double-blind	Baseline	Outcomes
Azazi [11]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S; SA; MA
Liu [12]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; S; ST; SA; MDA
Zhang [13]	2011	RCT	Unclear	Unclear	No	Similar	IL33; S; SA; MDA
Yang [14]	2011	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA
Prefontaine [15]	2009	RCT	Unclear	Unclear	No	Similar	IL33; S; SA; MDA
Prefontaine [16]	2010	RCT	Unclear	Unclear	No	Similar	IL33; S; SA; MDA; MA
Hamzaoui [17]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S; ST; MDA; MA
Liao [18]	2014	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA
Li [19]	2013(a)	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA; MA
Ma [20]	2011	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA; MA
Gong [21]	2002	RCT	Unclear	Unclear	Yes	Similar	ST2; S
Zhang [22]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; S
Li [23]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; S
MiAeChu [24]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S
Gluck [25]	2012	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S

S: serum; ST: sputum; SA: severe asthma; MDA: moderate asthma; MA: mild asthma.

Table 2. The general data of included documents

First Author	Publishing year	Methohodological quality				Intervention	
		Study design	Randomized method	Allocation concalment	Double-blind	Baseline	Outcomes
Azazi [11]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S; SA; MA
Liu [12]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; S; ST; SA; MDA
Zhang [13]	2011	RCT	Unclear	Unclear	No	Similar	IL33; S; SA; MDA
Yang [14]	2011	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA
Prefontaine [15]	2009	RCT	Unclear	Unclear	No	Similar	IL33; S; SA; MDA
Prefontaine [16]	2010	RCT	Unclear	Unclear	No	Similar	IL33; S; SA; MDA; MA
Hamzaoui [17]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S; ST; MDA; MA
Liao [18]	2014	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA
Li [19]	2013(a)	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA; MA
Ma [20]	2011	RCT	Unclear	Unclear	Yes	Similar	IL33; S; SA; MDA; MA
Gong [21]	2002	RCT	Unclear	Unclear	Yes	Similar	ST2; S
Zhang [22]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; S
Li [23]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; S
MiAeChu [24]	2013	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S
Gluck [25]	2012	RCT	Unclear	Unclear	Yes	Similar	IL33; ST2; S

S: serum; ST: sputum; SA: severe asthma; MDA: moderate asthma; MA: mild asthma.

found, a third investigator would make the definitive decision for data extraction. The extracted information included: the first author's last name, publication year, participant characteristics (age and sex), sample size, variables adjusted in the analysis.

Statistical analysis

Statistical analyses were performed with Review manager version 5.2 software (The Cochrane Collaboration). The heterogeneity of trail outcome among RCTs was assessed by χ^2 test (P<0.1 was defined as a significant heterogeneity) or I^2 test. The publication bias was assessed by examining the funnel plot. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for all primary and secondary outcomes were calculated by Mantel-Haenszel fixed-effect model (FEM) if there was no statistical heterogeneity; otherwise, the DerSimonian-Laird random effects model (REM) was used.

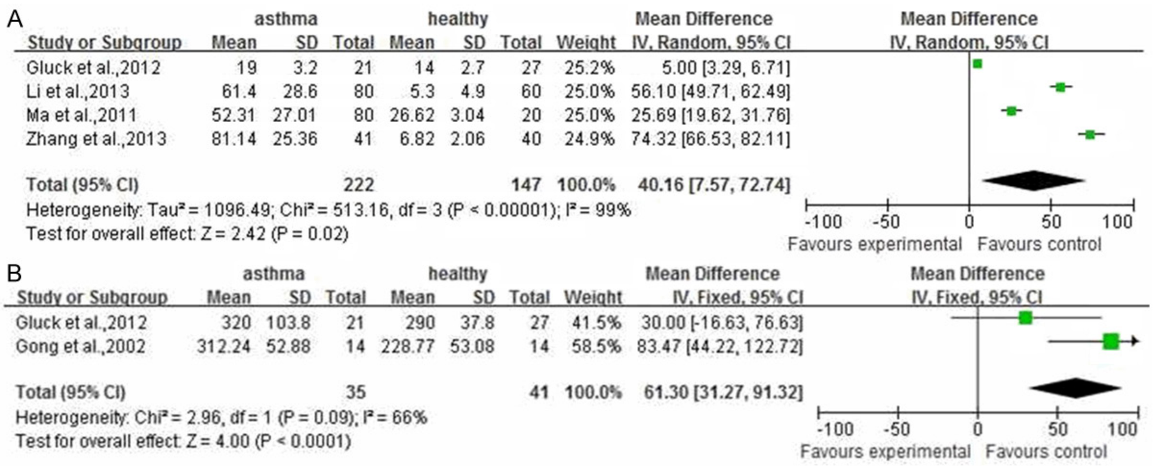

Figure 2. The meta-analysis of correlation between IL33 or ST2 and patients with asthma.

Results

The general data

After searching, total 15 documents [11-25] were included into this meta-analysis (**Figure 1**), involving in 633 asthma patients and 379 healthy people. The characteristics of the included studies were shown in **Table 1**. No studies described randomized methods and allocation concealment. Three studies adopted double-blind, and the baseline of all researches was similar (**Table 2**).

Correlation between IL33 or ST2 and patients with asthma

Four documents [20, 22, 23, 25] representing 222 asthma patients and two papers [21, 25] involving in 335 cases evaluated the correlation with serum IL33 and ST2 level, respectively. As shown in **Figure 2A** and **2B**, the meta-analysis results revealed that the serum IL33 or ST2 level was higher in asthma patients compared to that in healthy people (P=0.02, 95% CI (7.57, 72.74); P<0.0001, 95% CI (31.27, 91.32)).

Subgroup analysis for IL33 or ST2 in patients with asthma

As described above result, there were significant difference between serum IL33 or ST2 level in asthma patients and healthy people. However, the correlation IL33 or ST2 level between different asthma progress and healthy people is unknown. As shown in **Figure 3**, compared to healthy people, the severe (involving in 10 documents [11, 12-16, 18-20, 24]), moderate (involving in 10 documents [12-20, 24]) or mild (involving in 5 documents [11, 15, 17, 19, 20]) asthma patients had more higher serum IL33 level. (P<0.00001, 95% CI (87.86, 188.09); P<0.00001, 95% CI (31.93, 72.29); P<0.00001, 95% CI (100.51, 153.08), respectively). Similarly to IL33 in asthma patients, the serum ST2 level in different asthma progress included severe (involving in 2 documents [11, 24]), or moderate (involving in 2 documents [17, 24]) was higher (**Figure 4A** and **4B**) (P<0.00001, 95% CI (50.40, 76.57); P=0.03, 95% CI (3.41, 55.73)), but not mild involving in 2 documents [11, 17]. (**Figure 4C**) (P=0.30, 95% CI (-22.37, 72.61) For sputum tissues from asthma patients or healthy people, only two documents [12, 17] were included into here to reveal the correlation between IL33 level and moderate asthma progress. The meta-analysis result shown the sputum IL33 was not higher in moderate asthma patients than that in healthy people (**Figure 5**, P=0.20, 95% CI (-1.99, 9.52).

For further understanding the IL33 and ST2 changes in asthma progress, we evaluated the relations between and among severe, moderate and mild asthma patients for IL33 or ST2 level. As shown in **Figure 6**, the meta-analysis results shown that there were significantly difference between and among two asthma progress (**Figure 6A**, P<0.00001, 95% CI (24.02, 62.00), severe vs moderate; **Figure 6C**, P=0.0006, 95% CI (31.85, 116.92), moderate vs mild). However, there was no significant differ-

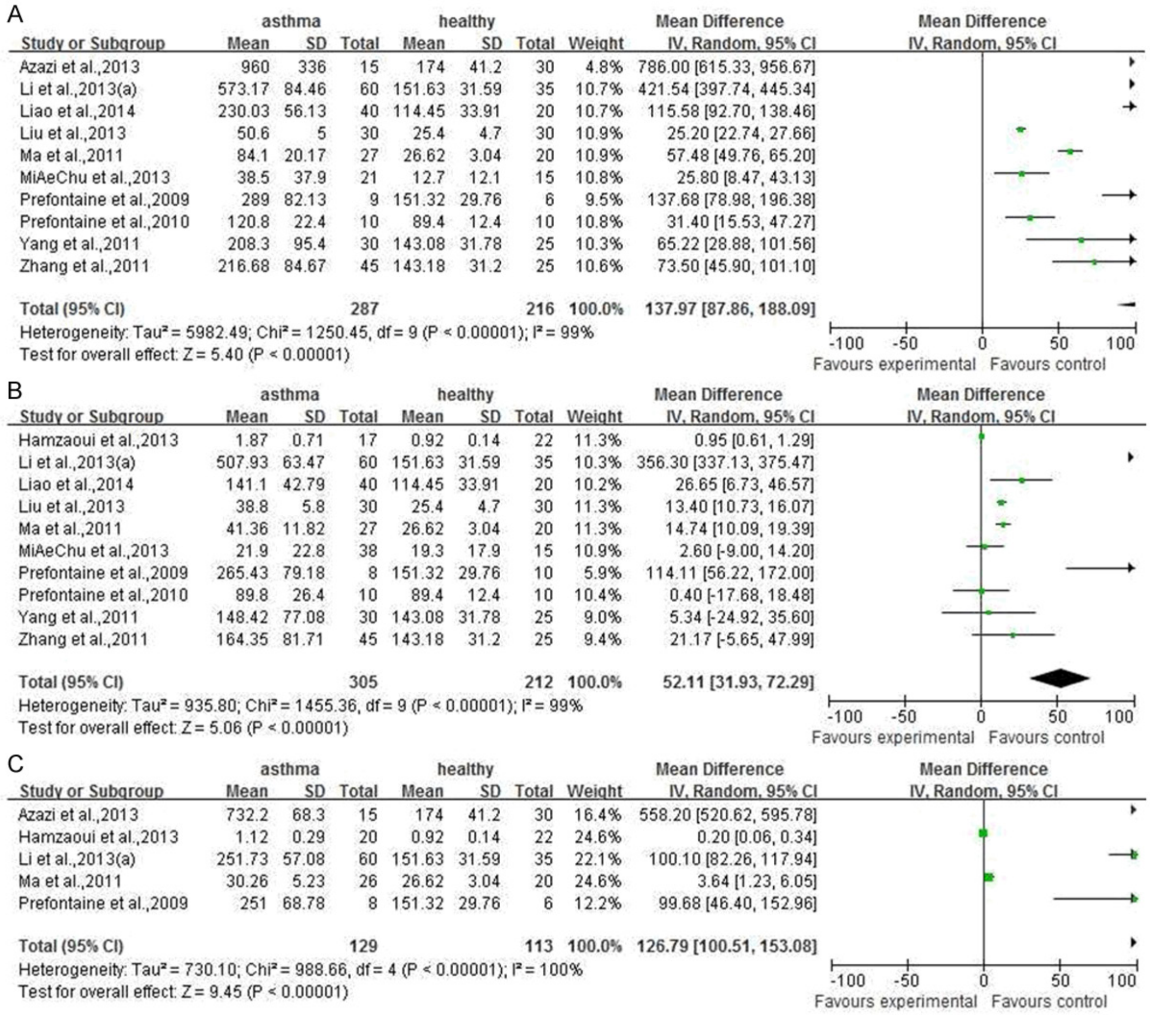

Figure 3. The meta-analysis of comparion between serum IL33 level in asthmatic with different disease progress and that in healthy people.

ences between severe group and mild group (**Figure 6B**, P=0.08, 95% CI (-20.95, 336.50)).

Discussion

In this meta-analysis, we reported that there was a stronger relation between IL33 and/or ST2 level of serum and/or sputum in asthma progress. Moreover, the IL33 and/or ST2 level in serum and/or sputum of asthma patients were higher than that in healthy people.

Interleukin-33 (IL-33) is a recently finding cytokine with lots of functions. IL-33 has been reported as a potent inducer of Th2 immune responses as well as "alarmin" cytokine released from necrotic cells [26-28]. IL33 binds to its receptor ST2 play role, including regulation of g inflammation and immunity [29]. IL33/ST2 axis interaction is thought to be involved in allergic inflammation promotion and maintenance by Th2 cells, basophils, mast cells and airway epithelium etc [30]. Therefore, IL33/ST2 axis aggravates air way inflammation by activates air way eosinophils [31]. The previous researches [17, 32] revealed the IL33 and/or ST2 have previously been demonstrated to be elevated in young and adult asthmatic patients. However, as there were a series of factors influencing the IL33 and ST2 expression level in asthma patients, including year, sex, races, disease progress, which revealed difference research results, therefore, it is need to evaluate the relation between IL33 and ST2 and asthma patients by a systematic reviews.

As we known, IL33 is increased in airway epithelial cells and smooth muscle from asthmat-

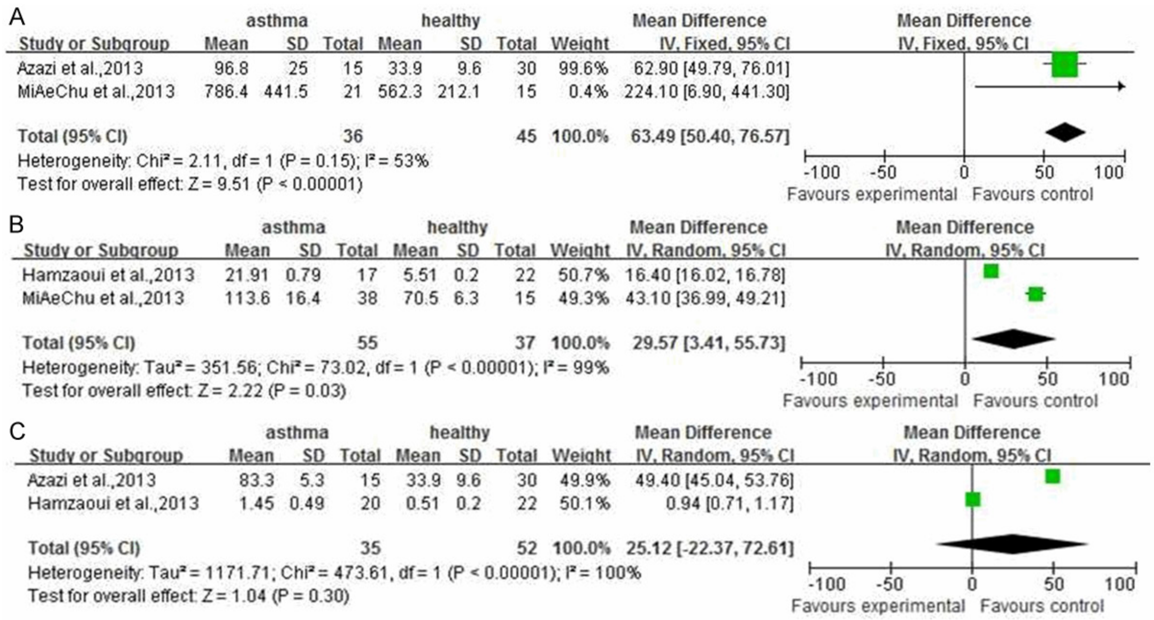

Figure 4. The meta-analysis of comparison between serum ST2 level in asthmatic with different disease progress and that in healthy people.

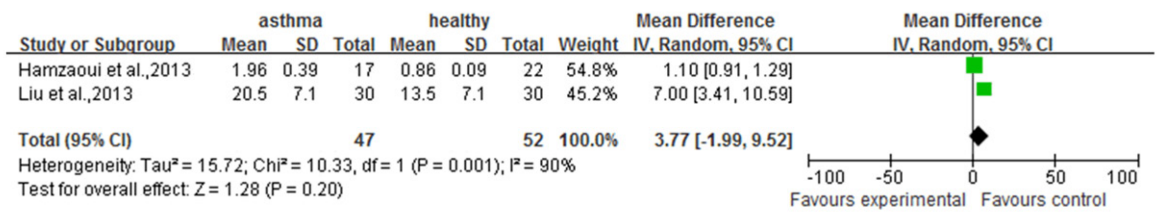

Figure 5. The meta-analysis of comparion between sputum IL33 level in moderate asthmatic and that in healthy people.

ics, and increasing IL33 maybe correlates with asthma disease severit [33]. And likewise, soluble ST2 (sST2) is elevated in the serum and sputum of asthma patients [17, 33]. A study have reported that serum ST2 expression level is increased in patients with acute exacerbation of atopic asthma.15 Accumulated data suggesting that IL-33 is involved in lung inflammation, and support the concept that ST2 maybe a therapeutic target in patients with asthma. Endobronchial biopsies from adults with severe asthma mild and moderate were obtained. IL-33 was predominantly expressed by airway smooth muscle cells (ASMC) and endothelial and epithelial cells in patients with asthmatic lungs but was absent in control samples.

In this meta-analysis, the results shown there were significant differences between serum IL33 and ST2 level in asthma patients and healthy people (**Figure 1**). However, there is only a document involving in ST2 in sputum sample, so, the meta-analysis for sputum IL33 or ST2 level in patients with asthma was not shown in here. Two papers reported IL33 was also higher in the sputum sample from asthma patients, however, one of them only described the IL33 level in the sputum samples of severe and moderate asthma patients. Therefore, the meta-analysis results for IL33 and ST2 in sputum were not included into this paper. Even so, Liu et al. [12] and Hamzaoui et al. [17] reported IL33 and ST2 in sputum of patients with different asthma progress were higher than that in healthy.

As described in **Figures 2** and **3**, we known that different asthma progress included severe, moderate and mild asthma have higher IL33

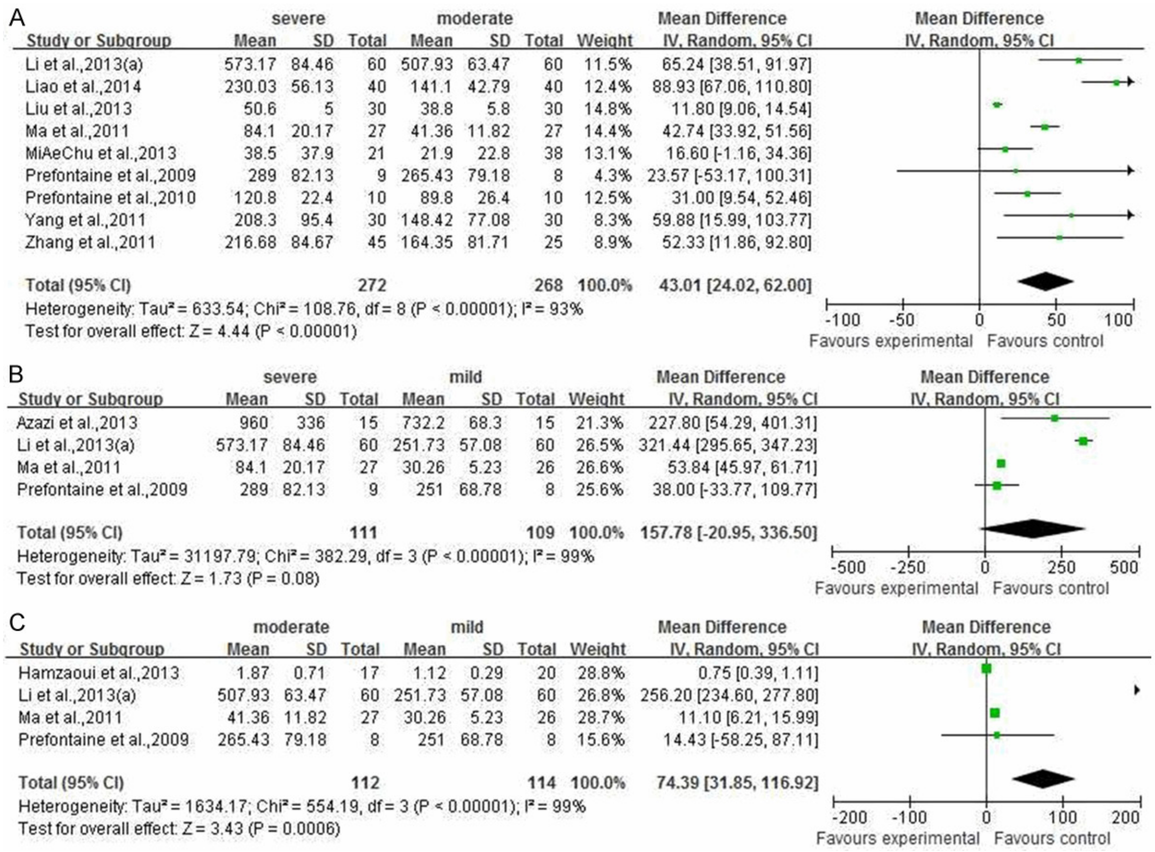

Figure 6. The meta-analysis of comparison among and between severe, moderate and mild asthmatic.

and ST2 expression level than healthy people. For sputum sample, Hamzaoui et al. [17] reported IL33 and ST2 in sputum of patients with moderate and mild asthma progresses were higher than that in healthy. Similarly, with progress of asthma disease, the serum IL33 and ST2 expression level were increased significantly (**Figure 5**). However, there is also a paucity of evidence in the published literature to help interpret relation between the sputum IL33 and/or ST2 and patients with severe, moderate and mild. The evidence base was also limited by non-standardized and non-systematic reporting of outcomes.

In conclusion, although limited literatures have reported the relation between sputum IL33 and ST2 protein expression levels and asthma patients, our meta-analysis results shown serum IL33 and ST2 level in asthma patients are higher than that in healthy people. Moreover, with development of asthma disease, the serum IL33 and ST2 level is increased significantly. These findings may be useful for targeted therapy and prognosis for asthma patients.

Disclosure of conflict of interest

None.

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