

# Association of positive and negative autologous serum skin test responses with clinical features of chronic spontaneous urticaria in Asian patients: A systematic review and meta-analysis

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**Abstract.** Previous studies on the correlation between positive autologous serum skin test (ASST) responses and the clinical features of patients with chronic spontaneous urticaria (CSU) have provided conflicting results. To evaluate the significance of ASST responses in CSU, a variety of databases were searched from inception to March 2018 to identify relevant studies on CSU. Data were analyzed with use of the Cochrane Collaboration's Review Manager 5.2. Multiple relevant factors of CSU were evaluated by calculating the weighted mean difference, odds ratio and 95% confidence interval. The results indicated that CSU cases with positive ASST responses had higher urticaria activity scores and higher levels of total serum immunoglobulin E than CSU cases with negative responses in the ASST. In addition, a positive ASST response was more likely to be accompanied with the presence of thyroid autoantibodies and angioedema. An increased prevalence of CSU was identified in females, who were more likely to have a positive response in the ASST. It was also indicated that a greater incidence of positive ASST responses was present in CSU patients as compared with that in healthy controls. No statistically significant differences were obtained between positive and negative ASST responses with regard to age and duration of disease. Based on these results, it was concluded

that the ASST provides an effective means of predicting urticaria activity and recurrence in CSU patients.

## Introduction

Chronic urticaria (CU), more commonly referred to as hives, is a frequently occurring condition that may persist for >6 weeks. CU is subdivided into chronic autoimmune urticaria (CAU), chronic spontaneous urticaria (CSU) and physical urticaria (PU), and CSU accounts for 35% of CU patients (1). The mechanisms of CSU are complex and may be triggered by drugs, physical stimuli, as part of inflammatory or inherited diseases, or may be idiopathic in nature. Over half of all CSU cases are thought to involve autoimmune mechanisms (2). The autologous serum skin test (ASST) provides an *in vivo* assay for diagnosing autoimmune urticaria. The ASST procedure consists of collecting an autologous serum sample from the CU patient, followed by injection of this sample into an area of normal skin. A positive response is indicated by the appearance of an erythematous papule within 30 min following injection (3).

The ASST serves as an effective clinical screening tool and has become the established method for the detection of functional circulating auto-antibodies in patients with CU. The negative predictive value (NPV) of the ASST has been reported to be 82.5±14% (4). This means that in CU patients with a negative response to the ASST, no functional circulating auto-antibodies were present in their serum. However, a positive ASST response may occur in patients with allergic diseases and even in healthy controls. Therefore, to confirm the presence of an autoimmune disorders, a quantitative analysis is required (5). It has been reported that in cases with positive ASST responses, a higher urticaria activity score (UAS), longer disease durations, lower scores on quality of life questionnaires and increased potentials for accompanying angioedema were present (6,7).

CU is a benign disease, has an autoimmune basis in 40% of cases (8) and is more prevalent in females. Immunoglobulin (IgE) has an indispensable role in the occurrence of CSU (9,10), with autoantibodies targeting high-affinity IgE receptors (FcεRI) or IgE in patients with CSU (11). Thyroid disease is

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the most commonly reported autoimmune condition in patients with CSU. CSU patients with coexisting thyroid autoimmunity tend to have a more severe and prolonged course of their urticaria than those without thyroid autoimmunity. A recent study has indicated that 9.8% of CU patients had hypothyroidism, compared with 0.6% in the control group (12). CU and thyroid disease may be interlinked, and the latter may promote the occurrence of CU (13). Previous studies have produced controversial results about the associations between positive ASST responses and the clinical features of CSU. Therefore, the current meta-analysis was undertaken to clarify the association between ASST and CSU.

## Materials and methods

**Literature search.** The PubMed, Embase, Medline, Ovid, Cochrane Library, China National Knowledge Infrastructure, China Biology Medicine and Wangfang databases, as well as the VIP Database for Chinese Technical Periodicals were searched to identify relevant studies involving ASST and clinical features of CSU. This search included the period from inception of the database until March 2018. The search strategy combined the following terms: 'Autologous serum skin test' and 'chronic spontaneous urticaria'. There was no restriction regarding language or the type of article. An additional manual search was performed by screening the references listed in key publications retrieved in this search.

**Inclusion and exclusion criteria.** An overall literature search was performed and relevant studies were screened independently by two reviewers. Eligible studies were selected based on the following criteria: i) Study design: Prospective observational study. ii) Patients with clinically defined CU. iii) Information on responses to the ASST. iv) Information on at least one of the following parameters: Average age, duration of disease, UAS, angioedema, anti-thyroid antibodies, total serum IgE, erythrocyte sedimentation rate and allergic rhinitis. The exclusion criteria were as follows: i) Experiments on animal models; ii) cases lacking a definitive diagnosis of CU; iii) intervention trials; iv) reports lacking relevant/sufficient data; v) duplicate publications.

**Data extraction.** Relevant data were extracted by two reviewers independently. Information included in the forms prepared by these reviewers comprised the following: First author's name, publication year, number of patients, mean age, duration of disease, results of ASST, UAS, angioedema, anti-thyroid antibodies, total serum IgE and allergic rhinitis.

**Assessment of study quality.** Quality assessment of included studies was independently performed and crosschecked by two reviewers using the Newcastle-Ottawa scale (NOS), which assesses bias on a scale of up to nine stars; >6 stars on the NOS were regarded as indicative of a high quality.

**Statistical analysis.** The meta-analysis was performed using Review Manager 5.2 (the Cochrane Institute, London, UK). The inverse-variance test was applied for continuous variables and the Mantel-Haenszel test for examination of dichotomous variables. The weighted mean difference (WMD) was used

for continuous variables across studies that were measured on the same scale. Dichotomous variables were assessed by calculating the odds ratio (OR). All data were expressed as the WMD or OR along with their associated 95% confidence intervals (CI). Heterogeneity between studies was tested by using  $I^2$  tests.  $P < 0.1$  or  $I^2 > 50\%$  was considered to indicate a high degree of heterogeneity between studies. If a significant heterogeneity was present ( $P < 0.1$ ), the random effects model was selected for heterogeneous outcomes ( $P < 0.05$  or  $I^2 \geq 50\%$ ), otherwise, the fixed effects model was performed for homogeneous outcomes ( $P \geq 0.05$  and  $I^2 < 50\%$ ).  $P < 0.05$  was considered to represent statistically significant differences.

A sensitivity analysis was performed by removing studies one at a time to confirm the robustness of the results. Finally, publication bias in the analysis was determined using a funnel plot and Egger's regression test.

## Results

**Study characteristics.** A total of 1,629 relevant studies were retrieved. After removal of duplicates by title, 851 articles were further screened. Following a careful review of these studies, the full text of 39 studies were assessed. Finally, 16 articles met the inclusion criteria and were included in the systematic review (6,7,14-27). The selection process for these studies is summarized in Fig. 1. A total of 2,554 patients, including 1,284 with positive and 1,270 with negative ASST results were assessed. The characteristics of these patients are presented in Table I. The publication year ranged from 2005 to 2017. Of note, the search of all databases for eligible articles revealed that the region of all studies retrieved was Asia, including China, Thailand, Korea, India, Taiwan and Japan.

**Quality assessment of included studies.** Detailed results regarding the quality assessment are summarized in Table I. All included studies were prospective observational studies. The present meta-analysis was restricted to studies with a low risk of bias (NOS  $\geq 7$ ), and the entire analysis was replicated following removal of the most influential study on the basis of its weight.

**Comparison of the influence of ASST responses on CSU cases and healthy controls.** Of all studies reviewed, 6 provided data on ASST responses in healthy controls (15,19,21,23,25). Statistical analysis revealed a high degree of homogeneity across studies ( $P = 0.18$ ,  $I^2 = 34\%$ ). Meta-analysis using the fixed-effects model indicated that CSU cases were more frequently associated with positive ASST responses than the healthy controls ( $P < 0.01$ , OR=17.16, 95% CI, 9.31-31.63; Fig. 2).

**Comparison of age, duration of disease and UAS in positive and negative ASST cases.** Of all 16 studies, 14 (6,7,14,18,20,24,26,27) and 10 (6,14,16,17,19,22,24,26,27) provided data on age and duration of disease, respectively, in the two groups. A significant heterogeneity was present across the studies (age:  $P < 0.001$ ,  $I^2 = 95\%$ ; duration:  $P < 0.001$ ,  $I^2 = 83\%$ ), necessitating use of the random-effects model. The meta-analysis indicated that the two groups displayed no statistically significant differences in age ( $P = 0.96$ , WMD=0.11, 95% CI, -4.31 to 4.52; Fig. 3) and duration

Table I. Characteristic and methodological quality of included studies.

First author	Year	Area	No. of samples	No. of subjects		Age (years)	Duration (months)	UAS	IgE (IU/ml)	Anti-thyroid	Angioedema	No. of males	NOS score	(Refs.)
				Patients	Controls									
Alpay A	2013	Japan	50	31	5		35.64±67.20			5 (31)	16 (31)		8	(19)
Boonpiyathad T	2016	Thailand	128	19	45		36.24±50.40			2 (19)	10 (19)			
				78		32.60±8.30	6.16±7.26				3 (78)	19	7	(14)
Chen MC	2008	China	100	50		38.10±10.90	5.76±6.60				4 (50)	16		
				58	0			8.03±1.50					8	(25)
Kim JH	2016	Korea	138	42	42			7.07±1.50						
				69		37.00±11.75	6.00±23.63	9.00±2.5	120.00±296.20			16	8	(17)
Krupashankar DS	2012	India	80	69		41.00±13.25	5.50±59.63	10.00±2.50	113.00±247.50			21		
				47		33.81±12.04	21.70±30.65			8 (48)	24 (47)	19	7	(22)
Kumar YH	2016	India	110	33		37.58±14.36	17.42±18.63			5 (62)	9 (33)	17		
				48		28.54±13.50				7 (47)	13 (48)	15	7	(20)
Lee MF	2014	Taiwan	40	62		31.55±14.43				1 (33)	8 (62)	22		
				20		37.00±7.25			174.80±49.50	2 (18)		5	8	(18)
Li MM	2016	China	136	20		46.60±15.00			129.10±16.60	1 (19)		10		
				54		38.52±12.53	45.27±65.67	7.60±4.30	171.20±331.10	9 (54)		10	7	(26)
Aktar S	2015	Japan	50	82		36.60±11.83	35.24±42.54	7.60±3.90	143.90±294.10	16 (82)		24		
				23	3	35.65±9.12		3.09±2.02				5	7	(15)
Song ZQ	2013	China	862	27	20	29.59±9.66		3.15±1.74				13		
				399		35.50±8.80	21.23±10.62	4.20±0.70					8	(6)
Sun WL	2005	China	82	463		23.50±7.60	27.58±18.63	3.80±0.50						
				29		38.30±12.30	41.80±51.40	14.07±2.25		8 (29)	16 (29)	6	7	(27)
Yadav S	2013	India	80	53		33.70±14.40	32.60±40.00	13.13±3.00		3 (53)	13 (53)	15		
				40	4	32.50±8.75		6.80±1.20		8 (40)			7	(21)
Yang SL	2016	China	79	40	40	33.00±8.75		6.20±1.40		6 (40)				
				43	0	39.23±12.24	55.66±38.10	14.64±2.11				14	7	(24)
Ye YM	2016	Korea	75	36	20	38.72±12.65	23.68±20.00	13.16±1.12				16		
				17		38.20±11.80	30.50±26.50	9.50±4.10	238.30±306.60	6 (17)	6 (17)	5	7	(16)
Zhong H	2014	China	390	50		41.10±12.40	13.00±89.50	10.10±3.60	250.20±390.70	9 (47)	21 (50)	19		
				261		34.70±13.80		4.00±1.30			91 (261)	71	7	(7)
				129		32.30±15.30		3.40±1.60			16 (129)	51		

Table I. Continued.

First author	Year	Area	No. of samples	Group	No. of subjects		Age (years)	Duration (months)	UAS	IgE (IU/ml)	Anti-thyroid	Angioedema	No. of males	NOS score	(Refs.)
					Patients	Controls									
Zhou PM	2017	China	154	N1	67	0	36.23±15.14	34.40±73.07	7.30±2.00				25	8	(23)
				N2	87	30	34.94±13.27	24.17±13.17	6.70±1.70				37		

Values are presented as number, mean ± standard deviation or number of positive subjects (total number of subjects). N1, positive autologous serum skin test response; N2, negative autologous serum skin test response; UAS, urticaria activity score; Ig, immunoglobulin; NOS, Newcastle-Ottawa scale.

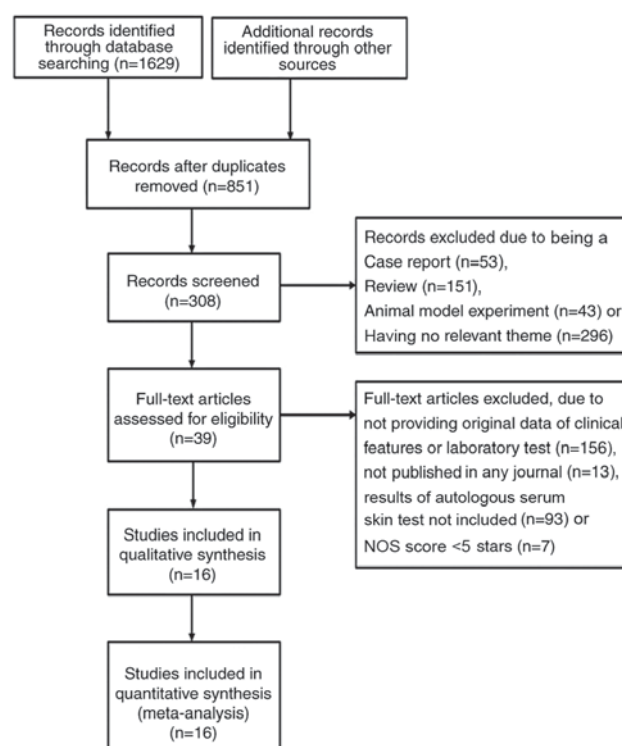


Figure 1. Flow diagram depicting the process of the selection of studies for the present meta-analysis. NOS, Newcastle-Ottawa scale.

( $P=0.08$ ,  $WMD=5.48$ , 95% CI, -0.71 to 11.68; Fig. 4). A subgroup analysis regarding patient age was then performed, in which patients were stratified by region. Results from China and India indicated that the two groups exhibited no difference in age (China:  $P=0.15$ ,  $WMD=3.95$ , 95% CI, -1.49 to 9.39; India:  $P=0.18$ ,  $WMD=-1.88$ , 95% CI, -4.63 to 0.87). Of note, the results from Korea, Thailand and Taiwan indicated that a positive ASST response was associated with younger age (Korea:  $P=0.04$ ,  $WMD=-3.68$ , 95% CI, -7.21 to -0.16; Taiwan:  $P=0.01$ ,  $WMD=-9.6$ , 95% CI, -16.9 to -2.30; Thailand:  $P=0.002$ ,  $WMD=-5.50$ , 95% CI, -9.04 to -1.96), while the opposite result was obtained in Japan ( $P=0.02$ ,  $WMD=6.06$ , 95% CI, 0.85-11.27; Fig. 3). Another subgroup analysis was performed with stratification by duration of disease ( $\leq 30$  vs.  $>30$  months). It was revealed that in patients with a duration of disease of  $\leq 30$  months, the disease duration was not significantly associated with the result of the ASST ( $P=0.59$ ,  $WMD=-1.52$ , 95% CI, -7.03 to 3.99), while in those with a duration of disease of  $>30$  months, a positive ASST response was associated with a significantly increased duration of disease as compared with that in patients with a negative ASST response ( $P=0.002$ ,  $WMD=15.93$ , 95% CI, 56.64-26.22; Fig. 4).

A total of 11 studies provided data on UAS (6,7,15,17,21,23,27). Statistically significant heterogeneity was present across these studies ( $P=0.01$ ,  $I^2=59\%$ ), again resulting in the use of the random-effects model. The meta-analysis revealed that the positive ASST response group had a higher UAS than that of the negative ASST response group ( $P<0.001$ ,  $WMD=0.42$ , 95% CI, 0.35-0.50; Fig. 5). Therefore, a subgroup analysis was performed based on the range of UAS as estimated by employing different guidelines, including European (28) and

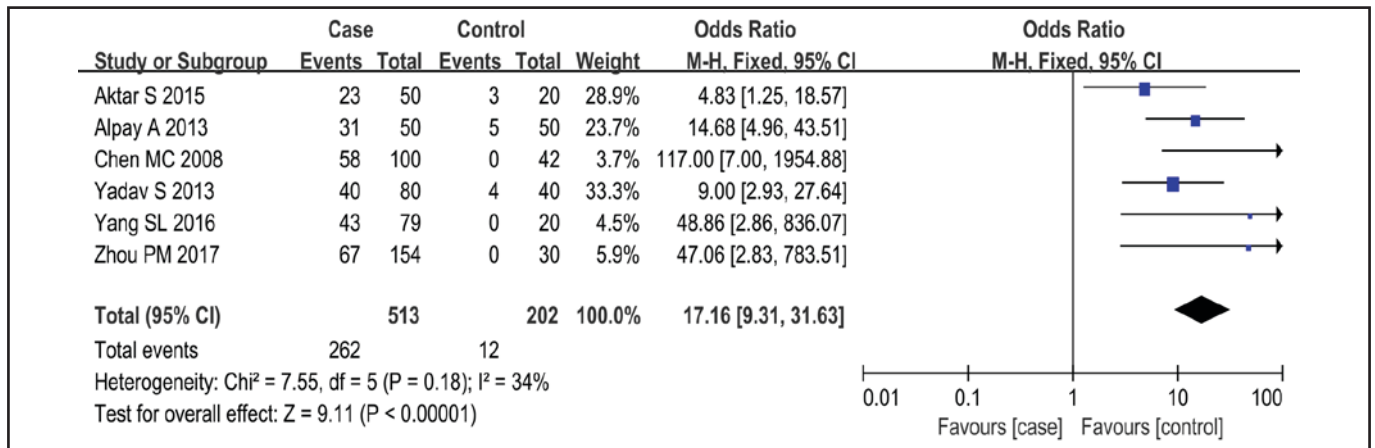


Figure 2. Probability of a positive autologous serum skin test response for subjects with chronic spontaneous urticaria vs. healthy controls. Blue square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; CI, confidence interval; M-H, Mantel-Haentzel; df, degrees of freedom.

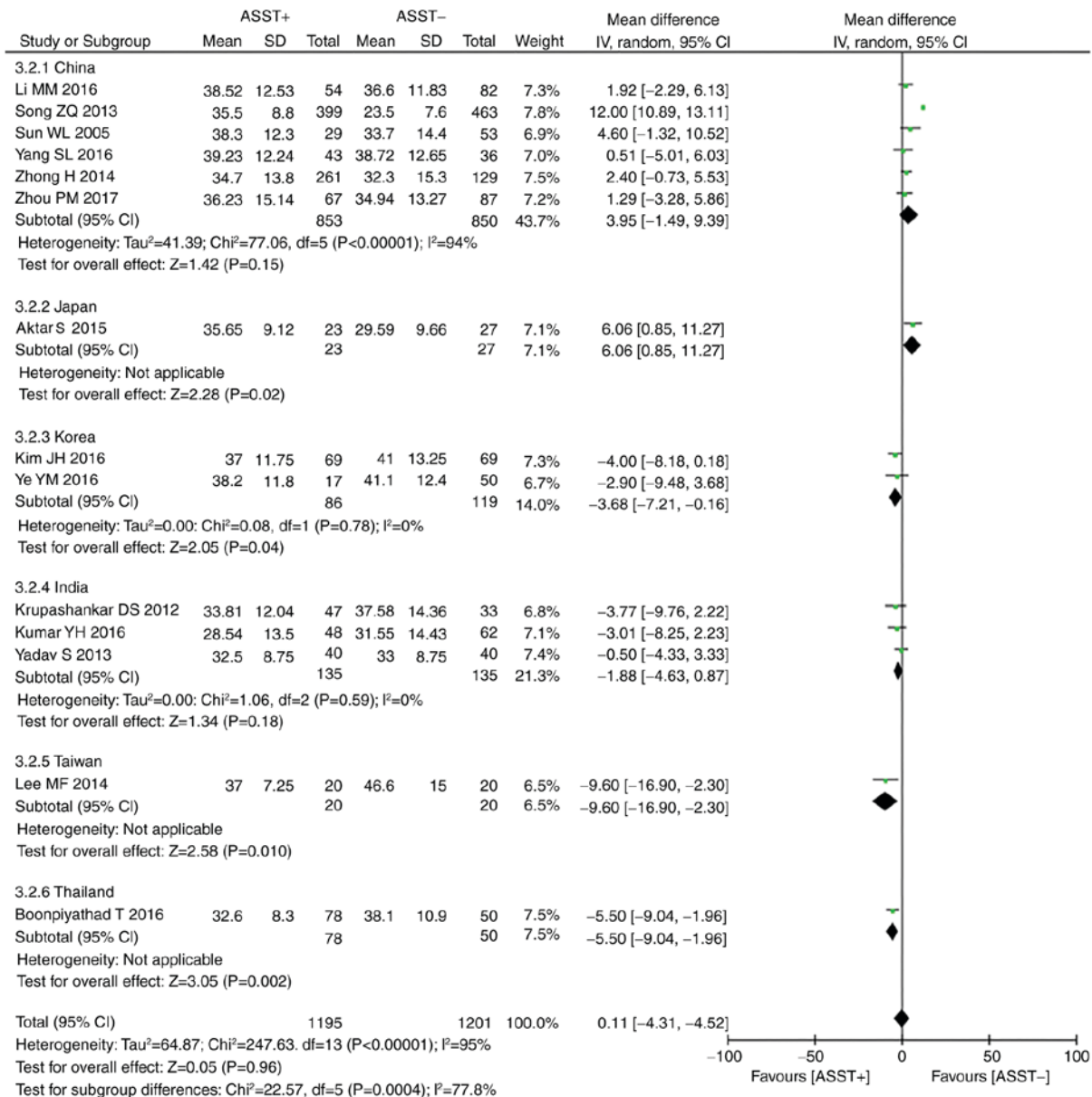


Figure 3. Difference in age between chronic spontaneous urticaria cases with positive vs. negative ASST responses. Green square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; SD, standard deviation; IV, inverse variance; CI, confidence interval; ASST, autologous serum skin test; df, degrees of freedom.



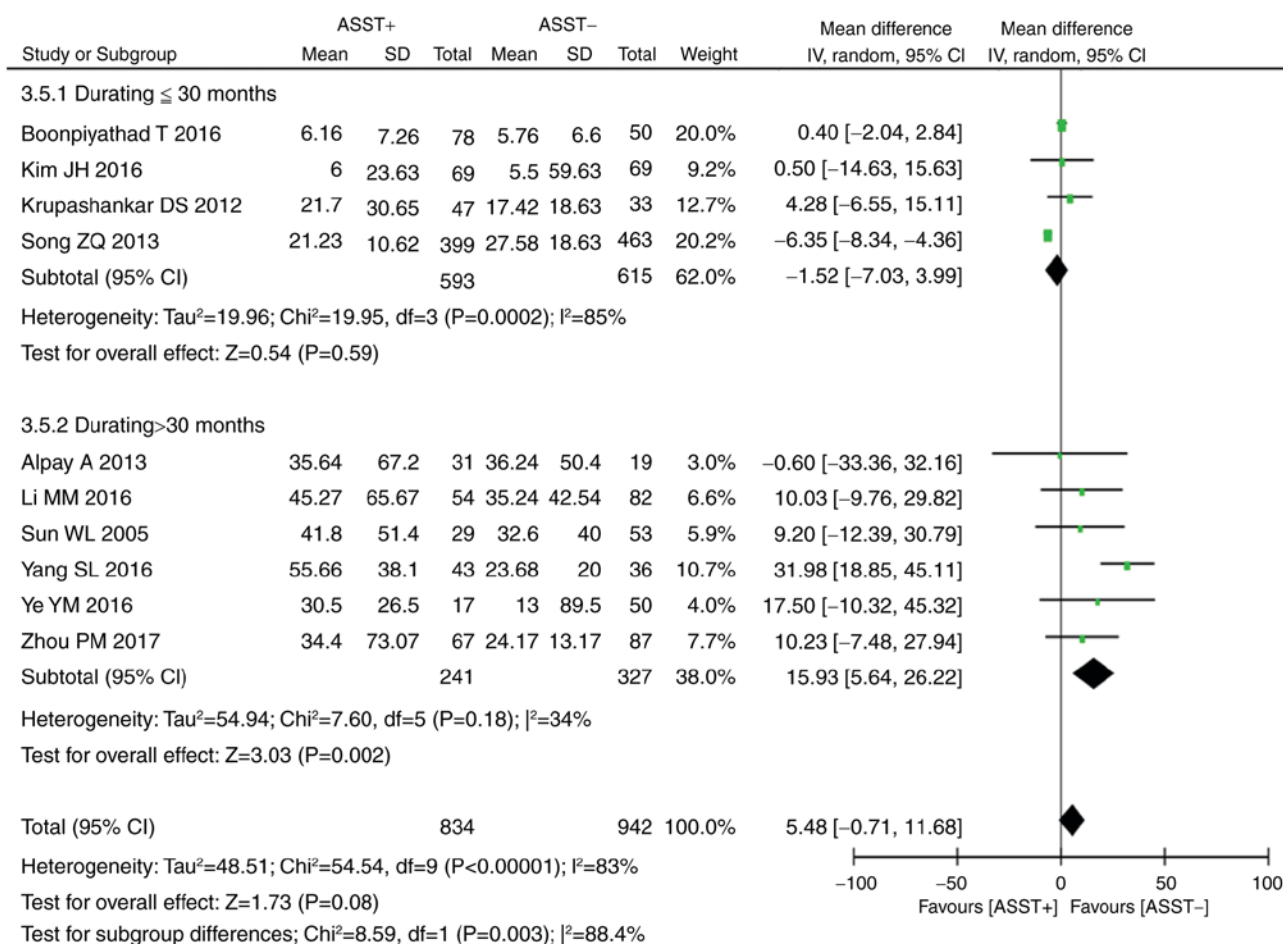


Figure 4. Differences in duration of chronic spontaneous urticaria in cases with positive vs. negative ASST responses. Green square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; SD, standard deviation; IV, inverse variance; CI, confidence interval; ASST, autologous serum skin test; df, degrees of freedom.

Korean guidelines (29). The results of this subgroup analysis also indicated that the positive ASST response group had a higher UAS than the negative ASST response group [UAS (0-6):  $P<0.001$ , WMD=0.41, 95% CI, 0.33-0.49; UAS (0-9):  $P<0.001$ , WMD=0.77, 95% CI, 0.36-1.18; UAS (0-18):  $P=0.00$ , WMD=1.18, 95% CI, 0.57-1.80]. However, the results of UAS of 0-12 was at the verge of statistical significance, however it was not statistically significant ( $P=0.05$ , WMD=0.60, 95% CI, 0.00-1.20, and an inverse result was observed for UAS of 0-15 ( $P=0.04$ , WMD=-0.73, 95% CI, -1.41 to -0.05). In addition, two studies provided the median and range of UAS but no standard deviation (SD) (25,27). The SD was then calculated using an established formula (30).

*Comparison of total serum IgE, angioedema and anti-thyroid autoantibodies in positive and negative ASST groups.* Of all studies included in the present review, 4 (16-18,26) provided data on total serum IgE and 8 (16,18-22,26,27) on the presence of thyroid autoantibodies in the two groups. Statistical analysis indicated that a significant homogeneity was present across these studies (serum total IgE:  $P=0.78$ ,  $I^2=0\%$ ; anti-thyroid autoantibodies:  $P=0.38$ ,  $I^2=7\%$ ). Meta-analysis using the fixed-effects model indicated that a positive ASST result was associated with higher levels of total serum IgE ( $P<0.001$ , WMD=41.99, 95% CI, 20.40 to 63.58; Fig. 6) and thyroid

autoantibodies ( $P<0.01$ , OR=1.87, 95% CI, 1.19-2.94; Fig. 7) than a negative ASST result.

Data from 7 studies provided information on angioedema in the two groups. As the results on angioedema displayed a statistically significant heterogeneity across studies ( $P=0.03$ ,  $I^2=57\%$ ), it was necessary to use the random-effects model. Meta-analysis revealed that a positive ASST result was associated with a higher risk of angioedema than that of a negative ASST result ( $P=0.03$ , OR=1.92, 95% CI, 1.08-3.40; Fig. 8). Angioedema is a subjective index of urticaria and manifests in a relatively short-lived edema in the skin. The occurrence of angioedema is affected by inherited and environmental factors; furthermore, physical stimulators, including shock and pressure, may also induce angioedema (31). As a result, a substantial heterogeneity in angioedema data may be present.

*Sex differences among subjects with positive ASST responses.*

An included study demonstrated that females are more likely to have a positive ASST response as rates of ASST were 78% and 22% in females and males, respectively (15). Of all studies included in the present review, 12 (7,14,18,20,22,24,27), which accounted for 1462 cases, contained 756 cases with positive responses to ASST. Of these 756 cases, 210 were males and 546 were females. Statistical analysis of positive ASST

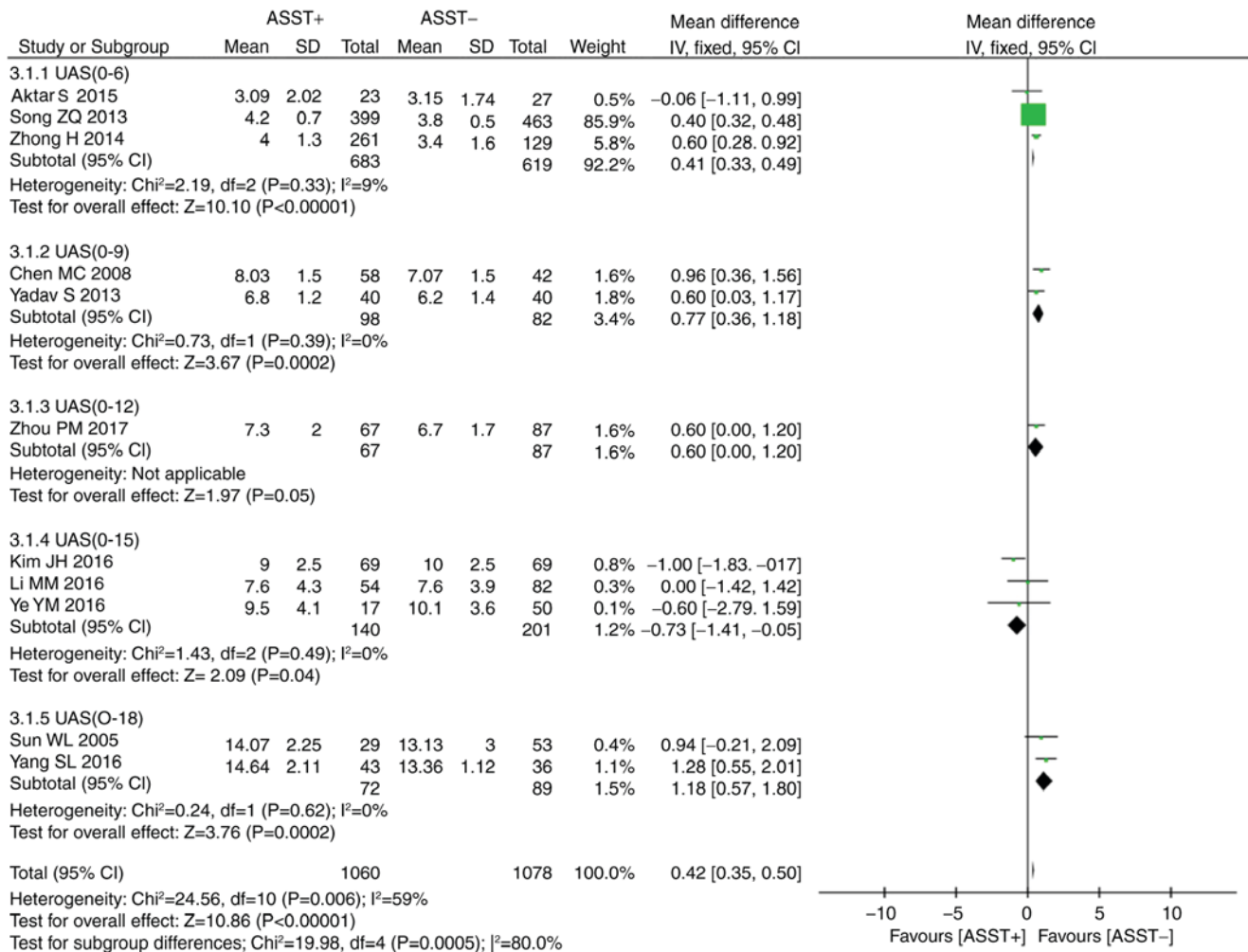


Figure 5. Differences in UAS in chronic spontaneous urticaria cases with positive vs. negative ASST responses. Green square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; SD, standard deviation; IV, inverse variance; CI, confidence interval; ASST, autologous serum skin test; df, degrees of freedom; UAS, urticaria activity scores.

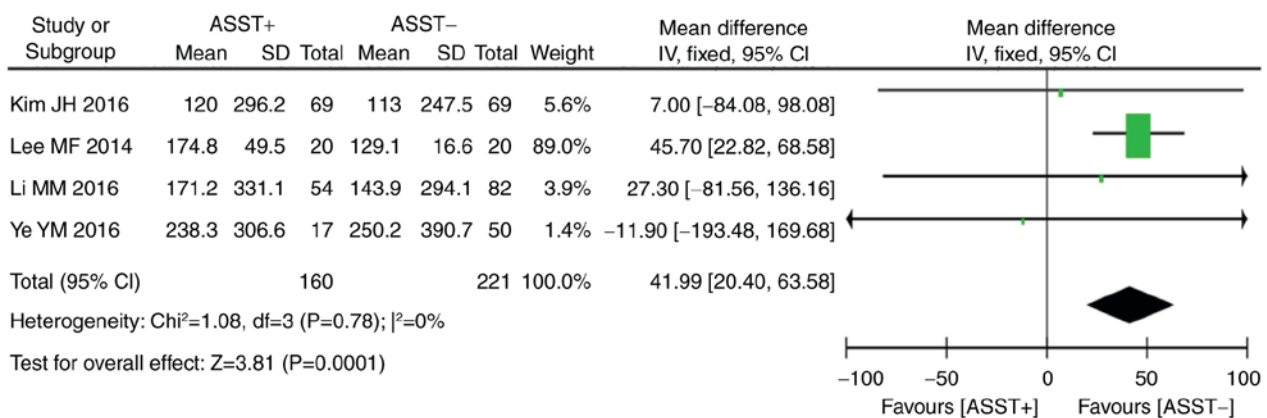


Figure 6. Differences in serum total immunoglobulin E levels in chronic spontaneous urticaria cases with positive vs. negative ASST responses. Green square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; SD, standard deviation; IV, inverse variance; CI, confidence interval; ASST, autologous serum skin test; df, degrees of freedom.

responses in CSU cases indicated that a statistically significant homogeneity was present across studies ( $P=0.97$ ,  $I^2=0\%$ ), and the fixed-effects model was therefore used. The meta-analysis revealed that females had a higher prevalence of positive ASST responses ( $P<0.001$ ,  $OR=0.63$ , 95% CI, 0.50-0.79; Fig. 9). The

detailed results of the meta-analysis for the above indexes are presented in Table I.

**Sensitivity analysis.** Studies that failed to satisfy the criterion of high quality were excluded from the present review. In

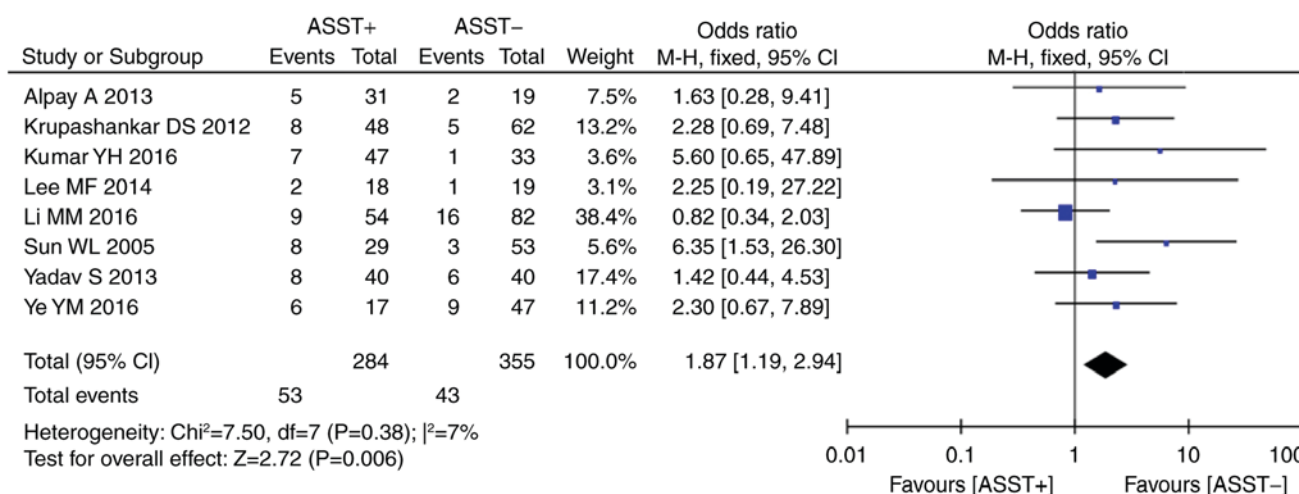


Figure 7. Probability of the presence of anti-thyroid antibodies in chronic spontaneous urticaria cases with positive vs. negative ASST responses. Blue square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; M-H, Mantel-Haentzel; CI, confidence interval; ASST, autologous serum skin test; df, degrees of freedom.

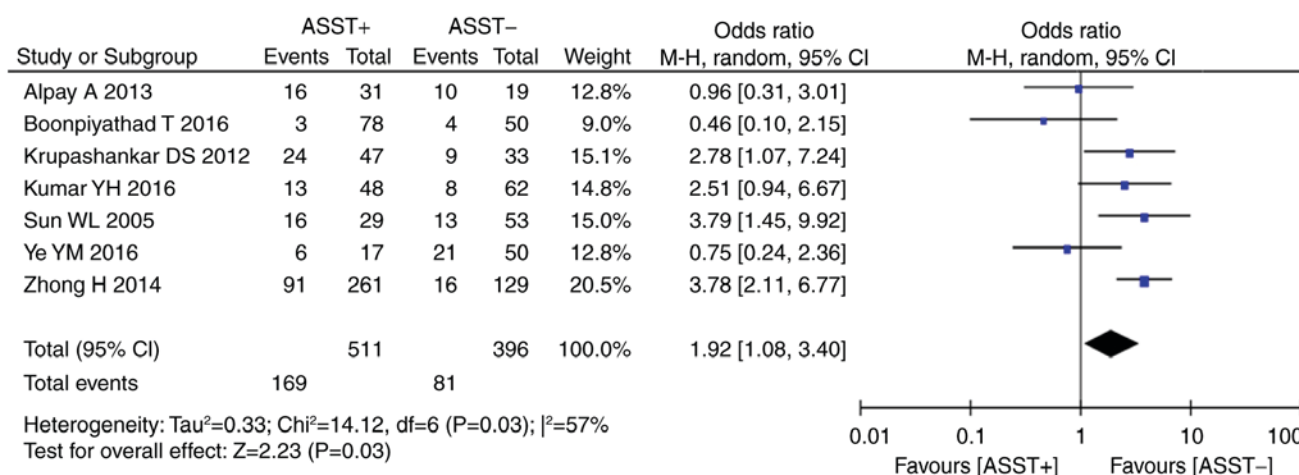


Figure 8. Probability of angioedema in chronic spontaneous urticaria cases with positive vs. negative ASST responses. Blue square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; M-H, Mantel-Haentzel; CI, confidence interval; ASST, autologous serum skin test; df, degrees of freedom.

addition, a sensitivity analysis was applied for each index involving ASST comparisons. The sensitivity analysis demonstrated that the results obtained using the random- and fixed-effects models were in accordance with each study included in the review. These results suggested that no individual studies significantly affected the pooled results. This indicated that the meta-analysis performed provided reliable results.

**Detection of publication bias.** An analysis of publication bias was performed by using Egger's regression test. The results indicated that no publication bias was present regarding the UAS and sex differences among patients with positive ASST responses (UAS:  $Z=-2.18$ ,  $P=0.06$ ; sex differences among patients with positive ASST response:  $Z=-0.73$ ,  $P=0.48$ ). However, publication bias was present with regard to age and duration of CSU (age:  $Z=-3.93$ ,  $P=0.002$ ; duration of CSU:  $Z=4.23$ ,  $P=0.003$ ). Although the above results revealed that studies included in the present review displayed an

inconformity in publication bias, the funnel plots had typical shapes, and the funnel plot of anti-thyroid autoantibodies is presented in Fig. 10.

## Discussion

To the best of our knowledge, the present study is the first systematic review comparing ASST responses in patients with CSU. The results obtained by the meta-analysis suggest that cases with positive ASST responses had higher UAS and higher levels of serum total IgE than those of cases with negative ASST responses. In addition, cases with positive responses to ASST were more likely to have accompanying angioedema and were positive for thyroid autoantibodies. CSU was more prevalent in females, who were also more likely to exhibit a positive response to ASST. It was also confirmed that a greater incidence of ASST was present in CSU patients as compared with that in healthy controls. No statistically significant differences were present between cases with



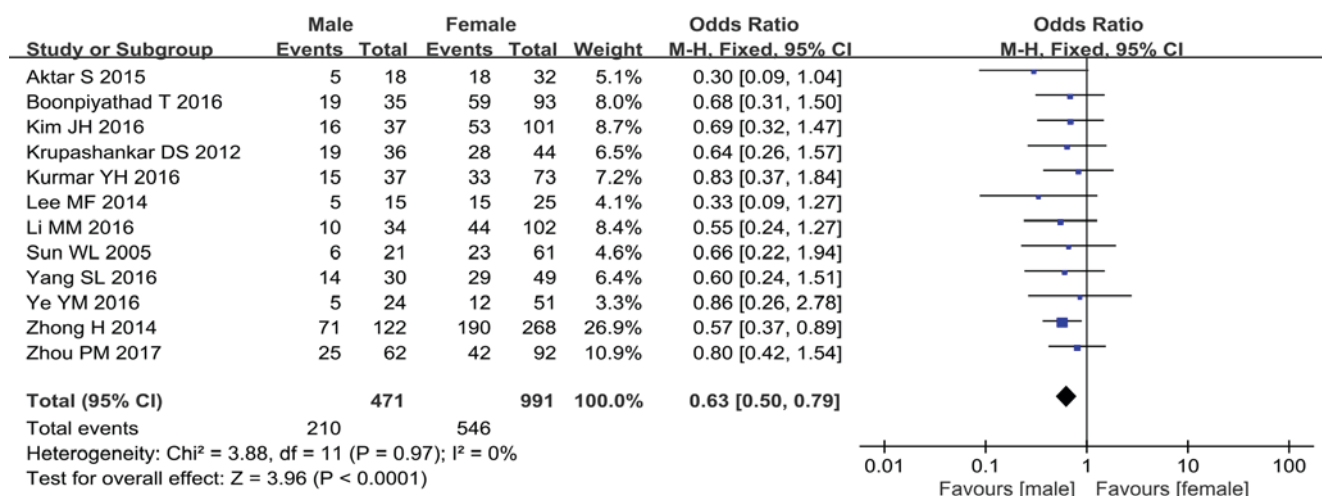


Figure 9. Probability of a positive autologous serum skin test response in males vs. females with chronic spontaneous urticaria. Blue square, weight of each study; black diamond, weighted mean difference; horizontal lines, 95% CI of each study; M-H, Mantel-Haentzel; CI, confidence interval; df, degrees of freedom.

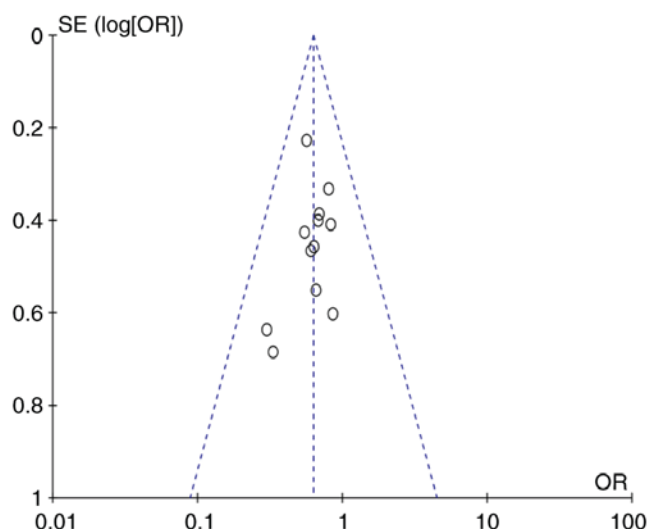


Figure 10. Funnel plot of studies on anti-thyroid autoantibodies for chronic spontaneous urticaria cases with positive and negative autologous serum skin test responses. OR, odds ratio; SE, standard error; log OR, logarithm of OR.

positive vs. negative responses to ASST with regard to patient age and duration of disease.

Angioedema, which is the clinical manifestation of urticaria, develops when urticaria is located within the subcutis. It is a syndrome characterized by a sudden and limited subcutaneous and/or submucous swelling. Angioedema in CU is caused by a non-specific histamine release from activated mast cells (32). The occurrence of angioedema in CU, while not an indication for disease severity, is associated with a longer duration of urticarial disease. Non-steroidal anti-inflammatory drugs and/or systemic corticotherapy are classic triggers of angioedema in CU (33). Mast cells may be activated primarily by IgE-dependent (allergen, anti-IgE) as well as by IgE-independent mechanisms (34). Increased levels of IgE are thought to provoke urticaria. Auto-antibodies for IgE and the  $\alpha$ -chain of Fc $\epsilon$ RI contribute to the occurrence of CU (35). It has been reported that one third of patients with

CU have significantly elevated levels of total IgE and levels of serum total IgE are associated with disease severity and duration (36). The severity of CSU was also identified to be associated with a positive response in the ASST (37), which is in accordance with the results of the present meta-analysis.

CSU is linked with thyroid diseases, which are the most commonly reported autoimmune condition in patients with CSU. Patients with thyroid dysfunction and CSU have a more severe and prolonged course of urticaria than those without thyroid dysfunction. A significantly greater number of anti-thyroid antibodies are present in CSU patients. Even in clinically euthyroid CSU patients, anti-thyroid antibodies remain present and are considered to be associated with CSU. Thyroid disease may worsen urticaria through activation of the complement system (2).

CU is characterized by mast/basophil cell activation, which initiates an inflammatory response. Sex hormones modulate immune and inflammatory cell functions, including mast cell secretion. Of note, urticaria may be associated with certain diseases and conditions associated with hormonal changes, including endocrinopathy, the menstrual cycle, pregnancy, menopause and hormonal contraceptives or hormone replacement therapy. Dehydroepiandrosterone (DHEA) is a modulator of endocrine and immune functions and depletion of DHEA may lead to adverse events (38). Serum concentrations of DHEA sulfate in CSU patients are significantly lower than those in healthy subjects and are associated with positive responses to ASST (39). This is in accordance with the results of the present meta-analysis, which indicate a female predominance for CSU and a positive response in the ASST (6-8,15).

Although the average NPV of the ASST was 92.8%, a negative ASST was identified as a significant determinant of urticaria remission and a negative ASST serves as a good predictor for achieving urticaria remission within 2 years (8,14,40). A positive ASST response is a significant predictor of CSU in controls (14).

While the studies included in the present meta-analyses were selected based on strict inclusion and exclusion criteria, certain unavoidable limitations and bias remain. As compared

with a randomized controlled trial, the quality of observational studies is low, which represents a limitation of the present meta-analysis. However, all subjects enrolled in the present meta-analysis were patients with CU who voluntarily underwent an ASST. The major observational endpoints were UAS, serum total IgE and anti-thyroid autoantibodies, all of which are objective parameters. Furthermore, all of the studies included were on Asian populations, which is a cause of publication bias. Although ASST has a high specificity to test for functional autoantibodies, their absence has a high specificity for CU. According to the European expert consensus from 2009 (8), the value and meaning of the ASST remains to be fully established. Furthermore, skin testing requires the collection of venous blood and separation of serum prior to hypodermic injection. It is essential that failsafe precautions are taken to ensure that the patient's own serum is used for skin testing and aseptic procedures are required. Commercial ELISA is now sufficiently mature for testing for functional autoantibodies, including IgE. The dermatologists of developed countries may be more likely to identify anti-IgE antibodies using ELISA compared with certain Asian dermatologists. An additional source of potential bias may be differences within health care providers and hospitals regarding the techniques applied for detecting ASST and the conditions of the patients. Although all studies included in the present review involved comparisons of/within case groups with positive and negative ASST responses, inherent differences in researchers' approaches to, and interpretations of, CSU may exist. Finally, the limited sample size and resultant data available for the present meta-analyses may have affected the final results obtained. The conclusions require verification by subsequent studies and the resolution of remaining issues.

In conclusion, the results of the present analyses of pooled data indicate that CSU patients with a positive ASST response have more severe clinical features and are more likely to have an accompanying autoimmunity condition as compared with those with a negative response to the ASST.

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## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

XLN analyzed autologous serum skin test data of all involved studies and drafted the manuscript. LLZ searched the literature and collected the data associated with chronic urticaria. MHS and YJZ performed the statistical analysis. XHG and RQQ critically revised the manuscript for important intellectual

content. All authors have read and approved the final version of the manuscript prior to submission.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors have no competing interests to declare.

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