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The efficacy of autologous serum therapy in chronic spontaneous urticaria: A systematic literature review and meta-analysis

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Literature Review

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ABSTRACT

Chronic spontaneous urticaria (CSU) is an autoimmune disease characterised by urtica lesions and/or angioedema accompanying an itching sensation, recurring for at least six weeks without any specific trigger. Autologous serum therapy (AST) is an adjuvant therapy for CSU that is resistant to H1 antihistamines. This therapy is an economical option in developing countries. There were a few studies discussing the role of AST in CSU. This systematic review and meta-analysis were conducted to evaluate the efficacy of AST based on urticaria activity scores (UAS or UAS7) and urticaria total severity scores (TSS) so that it can be taken into consideration by clinicians. Data were searched systematically in Cochrane, PubMed, Google Scholar, Willey, and EMBASE from 2000 to March 2023. Data analysis using Excel 2010 (Microsoft Corp) and MedCalc version 20.218. There were 14 studies: 4 randomised controlled trials (RCT), 9 prospective, and 1 cross-sectional. The average improvement in UAS and TSS scores at the end of therapy was 42.24% and 41.24%. Results of subgroup analysis of AST administration in the group autologous serum skin test (ASST) positive and ASST negative based on the end of therapy UAS score (p=0.18). Results of subgroup analysis of AST administration in the positive ASST and negative ASST groups based on the TSS score at the end of therapy (p=<0.001). Results of subgroup analysis of AST administration versus placebo based on TSS score (p=0.861). Based on subgroup analysis, autologous serum therapy improves TSS scores in CSU patients (ASST positive). However, AST is not significantly different from placebo.

INTRODUCTION

Chronic spontaneous urticaria, previously known as chronic idiopathic urticaria, is an autoimmune disease characterised by urtica lesions and/or angioedema accompanying the itching sensation, which subsides within 1 day and recurs for at least 6 weeks or more without any specific trigger.[1] The identification of autoantibodies (Aab) in patients with chronic spontaneous urticaria (CSU) can be facilitated through the in vivo autoimmune serum skin test (ASST). This test is routinely conducted on individuals with CSU to screen for autoantibodies targeting Immunoglobulin E (IgE) or the FcεRI receptor.[1–3]

An alternative therapeutic approach for CSU is AST. This adjuvant treatment is specifically designed for CSU cases exhibiting resistance to H1 antihistamines. The methodology involves the intramuscular administration of autologous serum. Autologous serum therapy promotes tolerance and desensitisation to circulating pro-inflammatory signals in CSU patients. Additionally, other studies have reported a reduction in anti-interleukin-24 (IL-24) Immunoglobulin E (IgE) autoantibodies, which play a role in the pathogenesis of CSU. The safety profile of AST is noteworthy, as it presents minimal side effects.

Furthermore, it stands out as an economically viable option, particularly in developing countries. This cost-effective nature is attributed to the use of basic instruments such as a centrifuge, blood tube, and syringe in the administration of the therapy.[1,3]

The primary objective in managing CSU is to sustain a symptom-free interval through medications with minimal side effects and cost-effectiveness. According to the guidelines outlined by the European Academy of Allergy and Clinical Immunology/European Dermatology Forum/ World Allergy Organization/Indonesian Society of Dermatology and Venereology (EAACI/EDF/WAO/ INSDV) pertaining to urticaria management, 2nd generation H1 antihistamines are recommended as first-line treatment. The dosage can be escalated up to four times if there is no response to the initial dose within 2 to 4 weeks, though this approach may heighten the risk of non-compliance. As a second-line option, immunosuppressant drugs are considered, although they entail a lower safety profile compared to first-line medications. Studies conducted in developing countries have illustrated the ongoing efficacy of AST in sustaining symptom-free intervals, providing an alternative for those facing challenges with conventional treatments.[1–3]

The Urticaria Activity Score (UAS) is reliant on patient-reported outcomes (PRO) and serves as an assessment tool for clinical signs (urtica) and symptoms (pruritus) in CSU. There are two distinct methods for measuring urticaria activity: one within a 24-hour timeframe (UAS) and the other spanning 7 days (UAS7).[4] Meanwhile, the Total Severity Score (TSS) measures the intensity of symptoms and the quantity and type of medication required to manage those symptoms effectively.5

The main concern of CSU is known to have a significant impact on patients' quality of life. Yu et al. demonstrated that CSU patients' quality of life was improved after the last autologous serum injection and further improved after that. Furthermore, on-demand antihistamine consumption was significantly decreased by more than 50%.[2]

Several studies have been conducted to evaluate the efficacy of AST, but the results are inconsistent. Therefore, researchers conducted a systematic literature review and meta-analysis to evaluate the efficacy of AST in positive and negative ASST groups, as well as the efficacy of AST compared to placebo, based on UAS and TSS scores at the end of therapy so that it can be taken into consideration by clinicians.

METHODS

Data search strategy

This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline checklist. A comprehensive data search was conducted assessing the administration of AST therapy in chronic spontaneous urticaria with the keywords "Chronic Spontaneous Urticaria" AND "Autologous Serum Therapy" and its synonyms from year 2000 to March 2023 from several electronic databases PubMed, Cochrane Database Centre, Google Scholar, Willey and Excerpta Medica Database (EMBASE). Search results were evaluated using inclusion and exclusion criteria. The initial search scanned all abstracts to find relevant studies based on content and title. The collected abstracts are screened in full text for further inclusion in the qualitative synthesis. The studies were selected based on the availability of data needed for quantitative synthesis (meta-analysis) (Figure 1).

Inclusion and exclusion criteria

The inclusion criteria for this study were clinical trials and observational studies, which carried out AST injections in CSU patients, comparisons based on ASST status (ASST-positive group vs. ASST-negative) and based on intervention (AST group vs placebo), measurement outcome based on UAS scores (UAS or UAS7) and/or TSS. The exclusion criteria for this study were studies that did not report AST therapy in CSU and such study design review articles, abstracts, case reports, case series, and editorials.

Data extraction, outcome, and bias assessment

Data extraction of studies using standard data extraction protocols. The following data were extracted: first authors, year of publication, study design, number of patients, disease duration, antihistamine use, ASST status, interventions, and outcomes measurement. The primary outcome is the efficacy of AST in CSU patients, assessing efficacy using TSS and UAS scores (UAS or UAS7). Evaluations are carried out at the beginning and end of treatment. The secondary outcome was an analysis of the significance of AST efficacy between the ASST group (ASST positive vs. ASST negative)

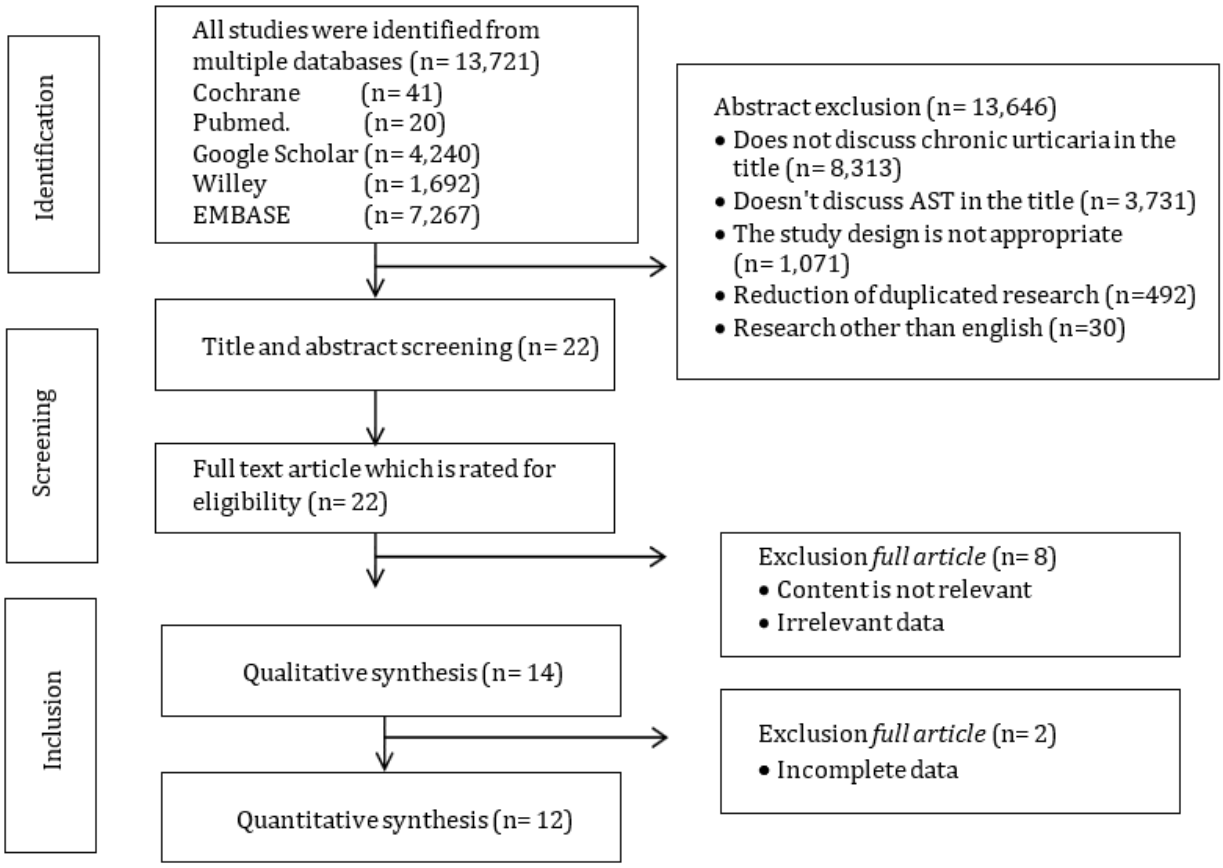

Figure 1. Preferred reporting item for systematic reviews and meta-analyses (PRISMA) diagram flow
AST: Autologous serum therapy; Excerpta Medica Database

and between intervention groups (AST vs. placebo) based on TSS and UAS scores (UAS or UAS7).

Randomised controlled trials (RCT) and non-RCT studies' biases were assessed using the Risk of Bias Tool 2.0 (RoB 2.0) and the Risk of Bias in Non-Randomised Interventions (ROBINS-I) assessment tool. Discrepancies in the assessment were resolved through objective discussion and coordination with the allergy, immunology, and dermatologist consultant at Mohammad Hoesin Hospital, Palembang.

Data analysis

In meta-analysis, the combined effect was calculated using the fixed effect model if heterogeneity is low-moderate and random effect if heterogeneity is high between studies. Heterogeneity between studies was analysed statistically using an intuitive index. Intuitive index value (I^2) used to evaluate heterogeneity of studies ($I^2 < 25\%$, low; $I^2 = 25\%$-50%, moderate; And $I^2 > 50\%$, high). The forest plot incorporates a diamond representing the overall effect across all studies. If the diamond touches the vertical line, it signifies a lack of statistical significance. The funnel plot, designed to detect publication bias, is deemed asymmetrical if $p < 0.05$. Data analysis was conducted using Excel 2016 (Microsoft Corp) and MedCalc version 20.218.

RESULTS

Study identification

Search results based on keywords from 2000-2023 via the Cochrane database obtained 41 articles, PubMed database 119 articles, Google Scholar database 4,240 articles, Willey 1,694 articles, and EMBASE 7,627 articles were obtained. So, the total articles identified based on keywords amounted to 13,646 articles. Then, screened based on suitability with the title/topic and abstract, 22 articles were obtained in full-text. The next step is article screening full text based on the relevance of content and data; 14 articles remain, consisting of 9 prospective, 1 cross-sectional, and 4 RCTs underwent qualitative synthesis, then there were 12 articles consisting of 9 prospective studies and 3 RCTs underwent quantitative synthesis (Figure 1)

Studies characteristics

Characteristics of the 14 included studies: 11 studies consisting of 1 RCT, 1 cross-sectional, and 9 prospective comparing the efficacy of AST in positive and negative ASST groups based on UAS scores (UAS or UAS7) and/or TSS, while 3 other RCT studies compared the efficacy of AST vs placebo based on UAS scores (UAS or UAS7) and/or TSS (Table 1). Assessment using UAS and/or TSS scoring is carried out at the beginning and end of the therapy period.

The inclusion criteria were CSU patients, while the exclusion criteria included pregnancy, breastfeeding, physical urticaria, cholinergic urticaria, suffering from chronic systemic disease or immunocompromised, used systemic steroids or immunosuppressant drugs in the last 6 weeks. The total population was 995 study participants, 599 (60.2%) women and more than 396 (39.8%) men, and the overall mean age of patients was 31.9 years (range 6-63 years). The mean duration of illness for patients in the study was 26.5 months (range 3.9-57.83 months). The number of samples of CSU patients in the ASST-positive and ASST-negative groups in 11 studies was 413 (53,7%) and 357 (46,3%) people, while the number of samples of CSU patients in the AST and placebo groups in 3 studies was 121 and 104 people. The AST therapy in 8 studies used 2 mL of serum for intramuscular injection every week for 8 to 10 injections, 1 study used 2 mL of serum intramuscularly every 2 weeks for 8 injections, 1 study used 0.05 mL/kg BW intramuscularly every week 10 times, 3 studies used 2.5 mL intramuscularly 9 times, 1 study used 2.5 mL initially then continued with 5 mL for 8 to 10 injections (Table 1).

Bias assessment

This study comprises 14 studies divided into an RCT group (4) and a non-RCT group (10). For the bias assessment of the RCT group, we use the risk of bias assessment 2.0 (Rob 2.0) tool for RCTs.20 However, we utilised the risk of bias in non-randomised studies of the intervention I tool (ROBINS-I) for the non-RCT group.[21] The results of the bias assessment of 4 RCTs, 9 prospective studies, and 1 cross-sectional study are visible in the summary plot (Figure 2A and 2B).

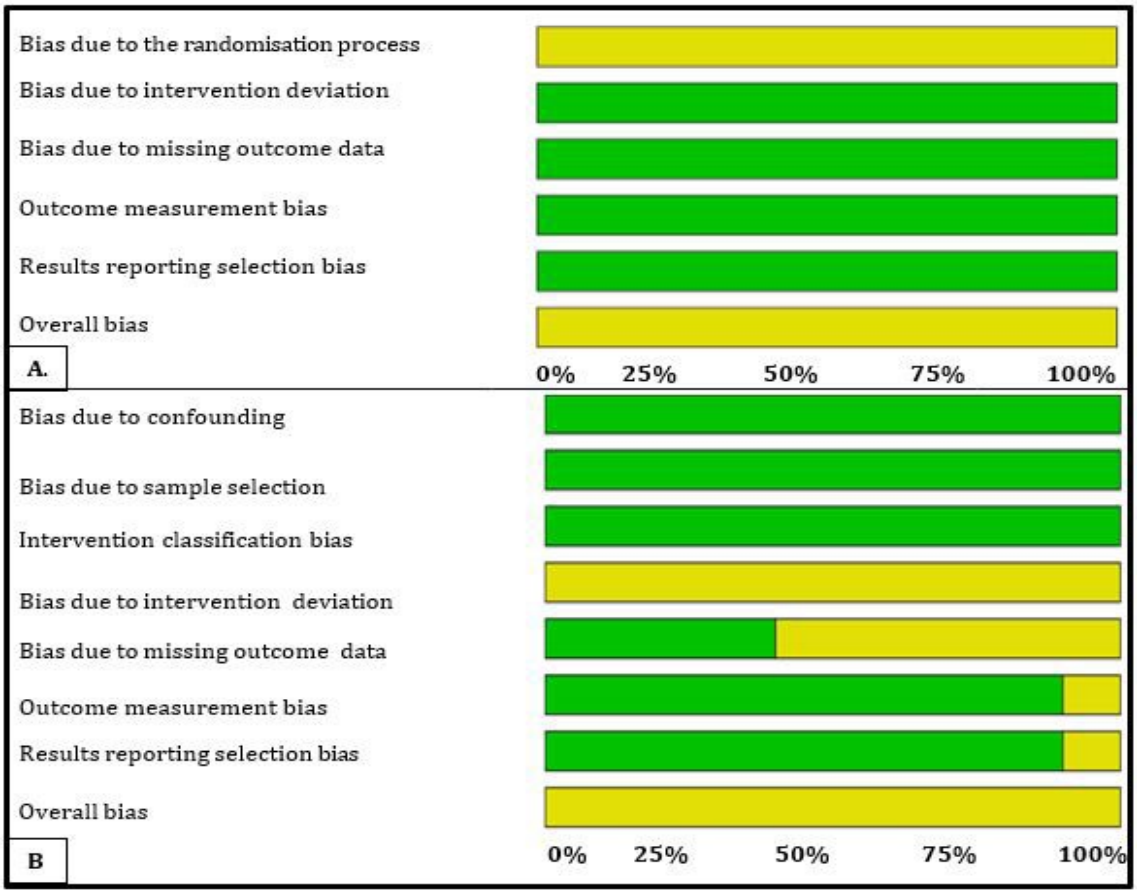

Figure 2. (A) Bias assessment of 4 Randomised Controlled Trials; (B) Bias assessment of 9 prospective studies and 1 cross-sectional study; Green: low; yellow: concern

Successful rate

In Table 2, five studies evaluate the success of AST procedures for the ASST-positive and ASST-negative groups based on the Urticaria Activity Score 7 (UAS7). The ASST-positive group, with the mean baseline UAS7 score of 21.1 (range 14.6-32.4), is categorised as having moderate urticarial activity. Post-therapy, it reduces to 13.57 (range 8.6-26.11), now classified as mild urticarial activity. For the ASST-negative group, the mean baseline UAS7 score is 25.04 (range 16.52-34.3), categorised as moderate urticarial activity, and post-therapy, it is 18.19 (range 8.6-26.31), remaining in the moderate urticarial activity category. Generally, in CSU patients, both ASST-positive and ASST-negative groups show improvement in UAS7 scores, with a percentage change of 35.87% and 27.3%, respectively.

Seven studies evaluate the success of AST actions on ASST-positive and ASST-negative groups based on TSS. In the ASST-positive group, the mean baseline TSS score of 13.9 (range 12.2-15.5) is categorised as severe, and post-therapy, it drops to 6.09 (range 3.8-12.64), now classified as mild. The response level to AST for the ASST-positive group is categorised as very good. For the ASST-negative group, the mean baseline TSS score is 14.12 (range 11.3-15.18), categorised as severe, and post-therapy, it is 9.82 (range 4.93-13.56), now categorised as moderate. The response level to ALST for the ASST-negative group is categorised as good. Generally, in CSU patients, both ASST-positive and ASST-negative groups show improvement in TSS scores, with a percentage change of 56.18% and 30.4%, respectively.

Three studies evaluate the success of the AST group vs placebo based on TSS score. In the AST group, the mean baseline TSS score of 16.77 (range 16.2-17.8) is categorised as severe, and post-therapy is 10.19 (range 9.7-10.94), now categorised as moderate. The response level to TSS development in the AST group is categorised as good. In the placebo group, the mean baseline TSS score of 16.7 (range 16.0-17.71) is categorised as severe, and post-therapy is 10.57 (range 9.29-11.67), categorised as moderate. The TSS development response level for the placebo group is categorised as good. There is an improvement in TSS scores between the AST and placebo groups by 39.2% vs 36.7%.

Overall, 14 studies have measured outcomes based on UAS and/or TSS scores. The overall mean success of therapy shows an improvement in UAS and TSS scores, namely 42.24% and 41.24%, respectively (refer to Table 2).

Meta-analysis

In this segment of the qualitative synthesis, we classified the 13 studies into three subgroups based on the consideration of the heterogeneity of primary research types and outcomes. Each subgroup analysis includes a forest plot and a funnel plot. A forest plot is a graph used to display results from a meta-analysis based on primary studies, while a funnel plot is a diagram showing the possibility of publication bias.

In Figure 3, an analysis of subgroup 1 was carried out on three prospective studies assessing the efficacy of AST in the ASST-positive and ASST-negative groups based on the end-of-therapy UAS7. The analysis results obtained an I2 value of 86.45%, indicating high heterogeneity. Therefore, a random-effects model was employed. The marked standardised mean difference obtained was -0.678 with a 95% confidence interval (CI) value of (-1.675 to 0.319), p=0.181. These findings indicate no significant difference in the efficacy of AST (based on the end-of-therapy UAS7 score) between the positive and negative ASST groups.

The funnel plot suggests publication bias, as the distribution of effect estimates from primary studies leans more to the left of the vertical mean estimate line than to the right. Because publication bias tends to be on the left of the overall vertical line (aligned with the shape diamond on the forest plot), it may overestimate the actual effect of AST on improving UAS scores at the end of therapy between the positive and negative ASST groups (see Figure 3).

Analysis of subgroup 2 was conducted on seven prospective studies assessing the efficacy of AST in the ASST-positive and ASST-negative groups based on the TSS at the end of therapy. The analysis results obtained an I2 value of 98.10%, indicating high heterogeneity. Thus, a random-effects model was employed. The marked standardised mean difference was -5.433 with a 95% CI value of (-7.401 to -3.465), p<0.001. These results show a significant difference in the efficacy of AST (based

Table 1. Study characteristics based on ASST status (ASST positive vs ASST negative) and intervention (AST vs placebo)

No	Researcher, Year, Type of Study	Age in Years (Mean ± SD)		Number of Samples (male/female)		Duration of illness in months		Therapy	Dose (serum)	Time, Total
		ASST (+)	ASST (-)	ASST (+)	ASST (-)	ASST (+)	ASST (-)			
1	Kocaturk et al.[6], 2012, RCT	39.36±11.95	39.07±14.13	59 (24/35)	29 (6/23)	56.10+88.40	58.88+133.03	Fexofenadine; AST IM	2.5 mL week 1 5 mL week 2-10	1 time/1 week, 10x
2	Bajaj et al.[7], 2008, Prospective	25	24	62 (30/32)	13 (6/7)	N/A	N/A	Pheniramine 25 mg; AST IM	2 mL	1 time/1 week, 9x
3	Nageswaramma et al.[8], 2017, Prospective	N/A	N/A	29 (11/18)	21 (5/16)	N/A	N/A	Antihistamine H1; AST IM	2.5 mL	1 time/1 week, 9x
4	Valapil et al.[9] 2020, Prospective	35.03±13.44	36.64±12.48	32 (12/20)	78 (30/48)	N/A	N/A	Antihistamine H1; AST IM	2 mL	1 time/1 week, 9x
5	Sundaresh et al.[10] 2021 Prospective	34.8±10.2		23 (9/14)	27 (11/16)	N/A	N/A	Levocetirizine 5 mg; AST IM	2.5 mL	1 time/1 week, 9x
6	Karn et al.[11], 2017, Cross-sectional	22.5±9.7	25.2±11.2	37 (12/35)	65 (19/46)	12.9+10.84	16.3+14.86	Antihistamine H1; AST IM	0.05 mL/kgBW	1 time/1 week, 10x
7	Elazab et al.[12], 2017, Prospective	34.7±6.5	36.3±8.2	20 (3/17)	20 (5/15)	4.7 + 5.6	3.9+6.1	Antihistamine H1; AST IM	2 mL	1 time/1 week, 10x
8	Agarwal et al.[13], 2023, Prospective	12.78±1.88	13.12±2.94	14(8/6)	8 (2/6)	6.21+2.15	7.75+1.38	Levocetirizine 5 mg; AST IM	2 mL	1 time/1 week, 9x
9	Patel et al.[14], 2016, Prospective	N/A	N/A	74 (32/42)	39 (19/20)	N/A	N/A	Levocetirizine 5 mg; AST IM	2 mL	1 time/2 week, 8x
10	Majid et al.[15], 2015, Prospective	30	37	19 (2/17)	40 (28/12)	12	24	Antihistamine H1; AST IM	2 mL	1 time/1 week, 10x
11	Chintaginjala et al.[16], 2017, Prospective	36.18±9.8	38.8±7.4	44 (15/29)	17 (8/9)	25.02	59.75	Antihistamine H1; AST IM	2 mL	1 time/1 week, 8x

Table 1. Study characteristics based on ASST status (ASST positive vs ASST negative) and intervention (AST vs placebo)

No	Researcher, Year, Type of Study	Age in Years (Mean ± SD)		Number of Samples (male/female)		Duration of illness in months		Therapy	Dose (serum)	Time, Total
		AST	Placebo	AST	Placebo	AST	Placebo			
12	Debbarman et al.[17], 2014, RCT	39.56±0.74	38.21±9.56	54 (28/26)	57 (40/17)	N/A	N/A	AST (Cetirizine 5 mg; AST IM) Placebo (Cetirizine 5 mg; Normal Saline)	2 mL	1 time/ week, 9x
13	Abonezhadian et al.[18], 2016, RCT	34.80±3.15	37.87±10.58	35 (4/31)	15 (6/9)	3.6±3.50	4.53±3.93	AST (Cetirizine 10-40 mg; AST IM) Placebo (Cetirizine 10-40 mg; Normal Saline)	2,5 mL	1 time/week, 9x
14	Datta et al.[19], 2020, RCT	36.7±2.05	33.90±13.31	32 (10/22)	32 (11/21)	24.62±43.36	43.43±61.98	AST (Cetirizine 10 mg; AST IM) Placebo (Cetirizine 10 mg; Normal Saline)	2 mL	1 time/ week, 9x

RCT: Randomised Controlled Trials, N/A: Not available, SA: Short Acting, ASST: autologous serum skin test; AST: Autologous serum therapy; IM: Intramuscular

Table 2. Outcome based on ASST status (ASST positive vs ASST negative) and intervention (AST vs placebo)

No	Researcher, Year Type of Study	Frequency of Antihistamine Baseline		Frequency of Antihistamine End of Therapy		UAS Baseline (Mean ± SD)		UAS End of Therapy (Mean ± SD)		TSS Baseline (Mean ± SD)		TSS End of Therapy (Mean ± SD)	
		ASST(+)	ASST(-)	ASST(+)	ASST(-)	ASST(+)	ASST(-)	ASS (+)	ASST(-)	ASST(+)	ASST(-)	ASST(+)	ASST(-)
1	Kocaturk et al.[6], 2012, RCT	N/A	N/A	N/A	N/A	16±7*	16.52±5.78*	8.6±6.6*	N/ AL	N/A	N/A	N/A	N/A
2	Bajaj et al.[7], 2008, Prospective	2.9±0.1	2.9±0.1	N/A	N/A	N/A	N/A	N/A	N/A	15.5±0.2	14.1±0.8	7.1±0.6	10.9±0.5
3	Nageswaramma et al.[8], 2017, Prospective	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	12.2±0.81	11.3±0.78	6±1.2	8.5±1.4
4	Valapil et al.[9], 2020, Prospective	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	14.78±1.36	15.12±1.21	3.81±0.69	5.45±0.74
5	Sundaresh et al.[10],2021, Prospective	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	13.4±1.1	N/A	4.56±0.993	4.93±1.9
6	Karn et al.[11], 2017, Cross-sectional	N/A	N/A	N/A	N/A	14.6±6.3*	16.9±7.8*	10.2 ±5.1*	8.6±4.8*	N/A	N/A	N/A	N/A
7	Elazab et al.[12], 2017, Prospective	3±0	3±0	2.3±0.5	3±0.5	32.4±5.6*	34.3±9.1*	11.9±7.2*	23.5±6.8*	N/A	N/A	N/A	N/A
8	Agarwal et al.[13], 2023, Prospective	N/A	N/A	N/A	N/A	30.42 ±2.73*	29.37±1.92*	11.0±6.9*	14.3±8.39*	N/A	N/A	N/A	N/A
9	Paltel et al.[14], 2016, Prospective	3	3	2.38	2.55	28±3.29*	28.13±3.31*	26.1±3.96*	26.3±3.86*	14.3±1.57	14.82±1.7	12.6±1.19	13.5±3.21
10	Majid et al.[15], 2015, Prospective	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	13±2.2	14.2±2	4.7±0.4	12.5±0.5
11	Chintaginjala et al.[16], 2017, Prospective	2.5	N/A	0.455	N/A	N/A	N/A	N/A	N/A	14.68± 1.2	15.1±1.32	3.8±0.62	12.9±0.4

Table 2. Outcome based on ASST status (ASST positive vs ASST negative) and intervention (AST vs placebo)

No	Researcher, Year Type of Study	Frequency of Antihistamine Baseline		Frequency of Antihistamine End of Therapy		UAS Baseline (Mean ± SD)		UAS End of Therapy (Mean ± SD)		TSS Baseline (Mean ± SD)		TSS End of Therapy (Mean ± SD)	
		AST	Placebo	AST	Placebo	AST	Placebo	AST	Placebo	AST	Placebo	AST	Placebo
12	Debbarman et al.[17], 2014,RCT	N/A	N/A	N/A	N/A	5.74±0.44	5.49±0.57	2.7±1.19	3.84±0.95	17.8± 0.41	17.7±0.46	9.7±3.15	9.29±2.80
13	Abonezhadian et al.[18], 2016, RCT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	16.2±1.49	16.0±1.19	10.9±3.92	11.6±2.7
14	Datta et al.[19], 2020, RCT	12.0±4.17	13.3±6.19	4.0±4.43	6.3±6.58	38.0±5.31*	37.8±5.85*	15.9±10.5*	18.5±12.52	16.3±1.63	16.6±1.03	9.93± 4.10	10.75±4.71

RCT: Randomised Controlled Trials; N/A: Not available; *: UAS7; IM: Intramuscular; UAS: Urticaria Activity Score; TSS: Urticaria Total Severity Score; AST: Autologous Serum Therapy

on the TSS score at the end of therapy) between the positive and negative ASST groups.

The funnel plot indicates publication bias, with the distribution of effect estimates from primary studies leaning more towards the left of the vertical mean estimate line than the right. Because publication bias tends to be on the left of the overall vertical line, aligning with the shape diamond on the forest plot, it may overestimate the actual effect of AST on improving TSS values at the end of therapy between the positive and negative ASST groups (refer to Figure 3).

Analysis of subgroup 3 was conducted on three RCT studies assessing the efficacy of AST and placebo based on the TSS score at the end of therapy. The analysis results obtained an I2 value of 0%, indicating homogeneity. Therefore, a fixed-effects model was employed. The marked standardised mean difference obtained was -0.023 with a 95% confidence interval (CI) value of (-0.028 to 0.242), p=0.861, and the diamond on the forest plot touches the vertical mean line. These results indicate a significant difference and improvement in TSS scores at the end of therapy between the AST and placebo groups.

The funnel plot for this subgroup shows no publication bias, and the distribution of effect estimates from primary studies is more to the left of the vertical mean estimate line than to the right (see Figure 3).

DISCUSSION

Chronic spontaneous urticaria represents an autoimmune ailment that profoundly impacts the patient's quality of life and socioeconomic well-being. For individuals unresponsive to initial therapy involving H1 Antihistamines, as per the current CSU management protocols, immunosuppressive interventions are considered, bearing a lower safety profile compared to H1 antihistamines. Such alternatives may involve substances like cyclosporine, methotrexate, steroids, or omalizumab.[1–3] In this meta-analysis, we focused on studies employing ALST as an adjunct to the first-line treatment with H1 Antihistamines for individuals with CSU who did not achieve remission.

In terms of gender, the majority of studies

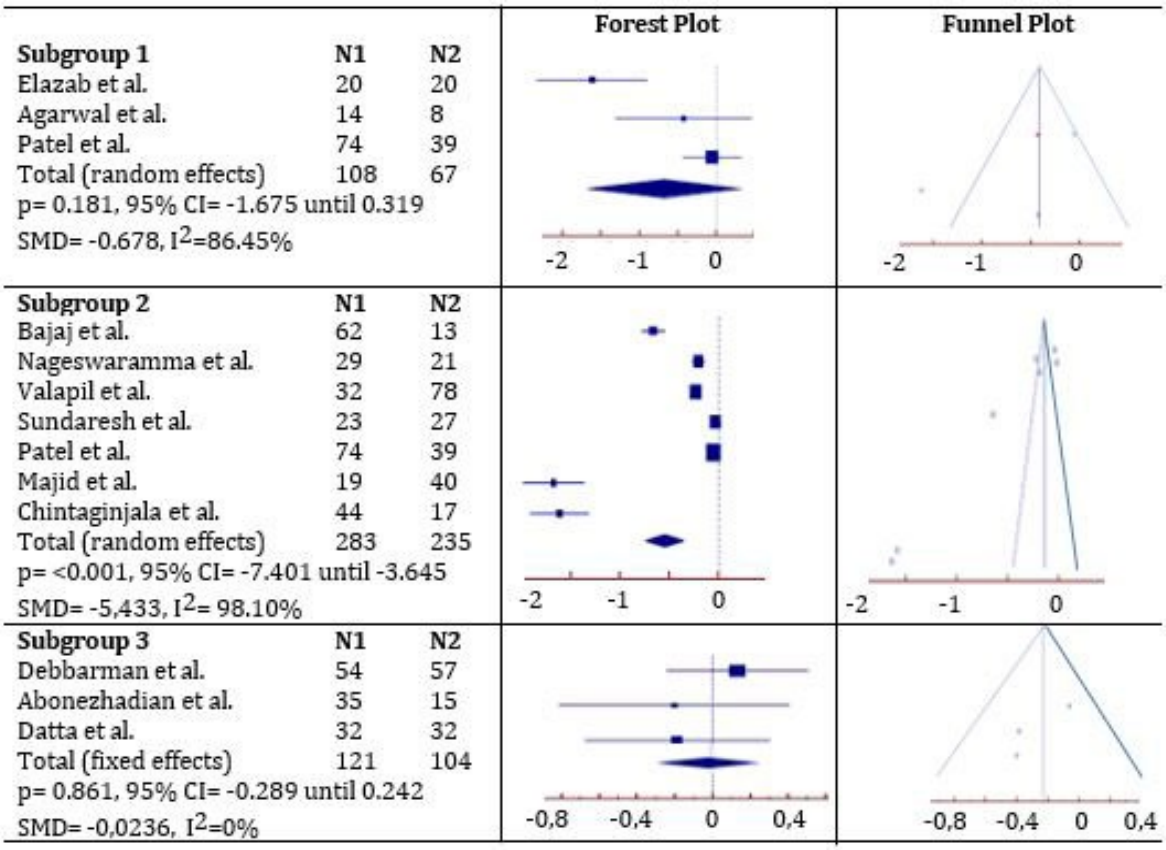

Figure 3. Forest plot and funnel plot of 3 subgroups; SMD=Standardized Mean Differences; CI: Confidence Interval

indicate that women are nearly twice as likely to experience urticaria compared to men. This trend is observed not only in CSU but also in many other forms of urticaria. Furthermore, the prevalence of a positive ASST result in CSU patients is reported to be higher in women than in men. Across most studies, the peak age of CSU patients falls between 20 and 40 years. A survey on office-based practices in the United States, encompassing all types of urticaria, revealed a bimodal age distribution in patients aged newborn to 9 years and 30 to 40 years.1 In the current study, comprising 995 participants, the majority were women (60.2%), and the overall mean age of patients was 31.9 years.

In the pursuit of novel modalities to enhance urticaria pharmacotherapy, the age-old practice of AST warrants investigation to alleviate the pill burden while maintaining a symptom-free interval. This consideration holds particular significance for individuals unresponsive to a single daily dose of antihistamines. Typically, AST involves an intramuscular injection of 2 mL of autologous serum using a 24G needle.19 This systematic literature review categorises primary studies into five treatment methods. First, 2 mL of serum was administered via intramuscular injection every week for 8 to 10 sessions (8 studies). Second, 2 mL of serum was delivered intramuscularly every two weeks for eight injections (1 study). Third, injecting 0.05 mL/kg body weight intramuscularly every week for ten sessions (1 study). Fourth, 2.5 mL was administered intramuscularly for nine sessions (3 studies). Fifth, initiating with 2.5 mL and then continuing with 5 mL for 8 to 10 injections (1 study).

This systematic literature review and meta-analysis aimed to evaluate the efficacy of AST in CSU. Considerations guiding the use of AST in numerous studies were taken into account.[6–19] Firstly, it is noteworthy that circulating auto-reactive factors exist in the serum rather than in the cellular components of the blood. Secondly, AST exhibits several mechanisms of action, including the induction of tolerance and immune desensitisation, anti-idiotype properties, and alterations in the Th1 response to Th2. Thirdly, the therapy employs simple equipment such as syringes, centrifuges, and blood tubes, ensuring cost-effectiveness for clinicians. Additionally, using thinner needles for serum injection has been suggested, potentially reducing discomfort and enhancing compliance.

The ASST test serves as a diagnostic procedure in CSU, employing intradermal injection of a small amount of autologous serum to screen for autoantibodies against IgE or FcεRI (high-affinity IgE receptor).[22] Approximately one-third to one-half of CSU patients yield positive results in the ASST.[6–23] According to Kumalr et al., individuals with positive ASST values often present with more severe disease and require prolonged treatment durations.[24] Studies by Majid et al. and Mohammed et al. revealed that ASST-positive patients possess anti-FcRI antibodies ranging from 40% to <20%, and not all ASST-positive individuals exhibit anti-FcRI antibodies. Additionally, less than 2% of ASST-negative patients tested positive for anti-FcRI. This fact underscores the reason ASST is positive in the presence of anti-FcRI antibodies, and ASST-negative patients experience significant clinical improvement with AST.[15,22–26] In this meta-analysis, most of the 11 studies involved ASST-positive CSU patients (53.7%).

Based on the data extracted from the studies, there was an overall average success in therapy, with improvements noted in both UAS and TSS, specifically 42.24% and 41.24%, respectively. A decrease in the disease severity was observed, where moderate activity urticaria transformed into mild urticaria in the UAS scoring, and severe cases became moderate in the TSS scoring. Consequently, the response to AST was deemed categorically good. These findings align with prior studies assessing the efficacy of AST in CSU.[6–19]

The results of subgroup one analysis, evaluating the efficacy of AST in positive and negative ASST groups based on UAS7 scores, demonstrated no significant difference in end-of-therapy UAS7 scores between positive ASST and negative ASST groups. These findings are in line with studies conducted by Mohammed et al., Minni et al., and Luthral et al.[26–28] Similarly, the results of subgroup two analysis, assessing the efficacy of AST in positive and negative ASST groups based on TSS scores, revealed no significant difference in end-of-therapy TSS scores between positive ASST and negative ASST groups. This outcome is consistent with studies carried out by Surendraln et al. and Walnnous et al.[29,30]

The disparity in results observed in the meta-analysis across the two subgroups mentioned

above can be attributed to the variance in the scoring systems employed, specifically UAS14 and TSS.[14] In UAS7, the assessment spans an entire week and is conducted based on the number of lesions and the degree of subjective complaints regarding itching that interfere with daily activities.[4] On the other hand, the evaluation in TSS tends to be more intricate as it considers factors such as the number and size of urticaria lesions, the intensity of pruritus, duration of persistence, frequency of appearance of lesions, and the use of H1 Antihistamines.[5]

The results of the subgroup 3 analysis, evaluating the efficacy of AST compared to placebo based on end-of-therapy TSS scores, indicated no significant difference in changes in end-of-therapy TSS scores between the AST and placebo groups. These outcomes align with a study conducted by Chalng et al. However, it is crucial to note that the placebo group utilised subcutaneous administration of AST and still employed Antihistamine treatment.[31] Additionally, two of the three analysed studies did not specify the frequency of Antihistamine use, introducing a potential bias.[17–19]

Several differences were identified when compared to previous systematic literature reviews on similar topics, such as Chang et al.'s study.[31] Firstly, in this study, the researcher incorporated several relevant studies that were relatively new and published after 2019. Secondly, the researcher provided more specific information about differences in means and standard deviations for each type of outcome scoring. Additionally, the analysis focused on the efficacy of AST at the end of therapy, aligning closely with the real clinical scenario and offering insights into immediate efficacy post-treatment. To enhance the robustness of findings, future studies should consider larger sample sizes, RCT designs, and long-term follow-up, contributing to a more comprehensive understanding and validation of the efficacy of this therapy in CSU.

CONCLUSION

Based on subgroup analysis, Autologous serum therapy improves TSS in CSU patients (ASST positive). However, AST is not significantly different from placebo. More studies need to be conducted regarding the efficacy of AST in chronic spontaneous urticaria, multicenter, standard intervention protocols, measurement outcome uniformity, and an RCT design to confirm the conclusions of the current study.

CONFLICT OF INTEREST

The authors have no competing interests to declare.

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AUTHOR CONTRIBUTIONS

Conceptualisation: ALS, N, and P; writing original draft preparation, ALLS; writing review, interpreted data and analysis, ALLS, N and P. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

CSU: Chronic Spontaneous Urticaria; AST: Autologous Serum Therapy; ASST: Autologous Serum Skin Test; UAS/UAS7: Urticaria Activity Score/Urticaria Activity Score 7 days; TSS: Urticaria Total Severity Score; RCT: Randomised Controlled Trial; EAACI: The European Academy of Allergy and Clinical Immunology; EDF: European Dermatology Forum; WAO: World Allergy Organization; INSDV: Indonesian Society of Dermatology and Venereology

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