

# Association between Clinico-epidemiological Features in Chronic Urticaria with Autologous Serum Skin Test: A Cross-sectional Observational Study

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## ABSTRACT

**Introduction:** Urticaria is a frequent and heterogeneous skin disease characterised by the development of wheals (hives), angioedema, or both. Chronic urticaria is characterised by the occurrence of wheals lasting less than 24 hours, with or without angioedema occurring daily or almost daily lasting more than six weeks. The two subtypes of chronic urticaria are Chronic Spontaneous Urticaria (CSU) and Chronic Inducible Urticaria (CIU). Autologous Serum Skin Test (ASST) is the simplest and the best in-vivo clinical test for the detection of basophil histamine-releasing activity. ASST has a sensitivity of approximately 70% and a specificity of 80%.

**Aim:** To study the association between clinico-epidemiological features of CSU with positive and negative ASST.

**Materials and Methods:** The cross-sectional study was conducted on 80 clinically diagnosed cases of CSU attending the Department of Dermatology Venereology Leprology Outpatient Department at Mahatma Gandhi Memorial Hospital (Kakatiya Medical College), Warangal, Telangana, India; during the period of January 2016 to

September 2017. The detailed history was taken; complete physical and cutaneous examination and laboratory investigations like Complete Blood Picture (CBP), Absolute Eosinophil Count (AEC), Erythrocytic Sedimentation Rate (ESR), Thyroid Function Test (TFT) were carried out. ASST was done and read after 30 minutes. Chi-square test was applied and the results analysed using Statistical Package for the Social Sciences (SPSS) version 10.0.

**Results:** Out of total 80 patients included in the study, ASST was positive in 36 (45%) and negative in 44 (55%). ASST positive patients showed longer duration of the disease with increased frequency of attacks and longer duration of wheals. However, both ASST positive and negative groups did not show statistically significant difference in the age of occurrence, gender, angioedema, dermatographism.

**Conclusion:** Autoimmune urticaria has no distinctive clinical features. ASST positive, autoimmune urticaria patients have more severe disease with greater impact on quality of life. Thus, they may need more aggressive treatment.

**Keywords:** Autoimmune urticaria, Chronic idiopathic urticaria, Chronic spontaneous urticaria

## INTRODUCTION

Urticaria is a frequent and heterogeneous skin disease characterised by the development of wheals (hives), angioedema, or both. Wheals are transient, well-demarcated, superficial erythematous or pale swellings of dermis. Angioedema are the swellings that affect the deeper dermal, subcutaneous and submucosal tissues [1]. Urticaria is generally classified as acute or chronic, depending on the duration of symptoms. Acute urticaria is characterised by occurrence of wheals with/without angioedema presenting daily or almost daily lasting for less than six weeks. Chronic urticaria is characterised by the occurrence of wheals lasting less than 24 hours, with or without angioedema occurring daily or almost daily lasting more than six weeks [2]. Chronic urticaria is further divided into CSU and CIU depending on the inciting agent [3]. CSU was formerly also known as CIU as there is no inciting agent identified. CSU may be due to known (e.g., auto antibodies) or unknown causes. A patient may well have more than one type of urticaria. Most of these conditions are mainly mediated by histamine. The pathogenesis of urticaria is complex and has many features in addition to the release of histamine from dermal mast cells [4]. Wheals result from localised capillary vasodilation as a result of release of pro-inflammatory mediators predominantly histamine by activation of cutaneous mast cells, followed by transudation of protein-rich fluid into surrounding tissues; they resolve when the fluid is slowly reabsorbed [1]. The inappropriate activation and degranulation of mast cells in CSU

may be attributed to autoimmunity. Autoimmune urticaria is a distinct subset of urticaria whose clinico-epidemiological features may be different from other CSUs.

The ASST is used as a screening test. ASST is a simple, in vivo clinical test which helps in the detection of histamine release phenomenon in the body. It is a test for autoreactivity rather than autoimmunity. Autoreactivity does not define autoimmune urticaria but may be an indication of mast cell activating auto antibodies in ASST positive patients. ASST may be used as a fairly reliable test for the detection of circulating functional autoantibodies since basophil histamine release assay is not widely available and is expensive [5]. A number of studies were conducted both in India and also abroad, showed difference in the ASST positivity among patients of CSU [6-11]. Kulthanan K et al., in a study from, Thailand showed ASST positivity as 24.7% [6]. Various Indian studies showed ASST positivity ranging from 34%-50% [7-10].

The present study was undertaken to study the clinico-epidemiological features of CSU with positive and negative ASST. This knowledge may have a significant bearing on the long-term management of these patients in terms of need for anti-histamines, immunomodulators and even immunotherapy.

## MATERIALS AND METHODS

The present cross-sectional observational study was carried out between January 2016 to September 2017, after obtaining Ethical

Committee approval (M151005025). Eighty clinically diagnosed cases of CSU attending the Department of Dermatology Venereology Leprology OPD at Mahatma Gandhi Memorial Hospital (Kakatiya Medical College), Warangal, Telangana, India, were enrolled.

Diagnosis was made based on detailed history and clinical examination. All these patients were subjected to relevant laboratory investigations like CBP, AEC, ESR and TFT. All the data was recorded on predesigned proforma after taking written informed consent.

**Inclusion and Exclusion criteria:** Patients clinically diagnosed of CSU, willing to give written informed consent were included in the study. Patients less than 12 years of age, pregnant and lactating women, patients with physical urticaria (other than simple dermatographism), urticarial vasculitis were excluded. ASST procedure was performed on all enrolled patients and the readings were recorded.

## STATISTICAL ANALYSIS

Descriptive statistics was used to summarise data for comparison between ASST positive and ASST negative groups. Chi-Square test was used for categorical variables. Statistical Package for the Social Sciences (SPSS) version 10.0 for windows was used for analysis significant p-value <0.05.

## RESULTS

Out of 80 patients, ASST was positive in 36 patients (45%) and negative in 44 patients (55%). The youngest patient enrolled was 14 years and the oldest was 66 years. The mean age of the ASST positive patients was 30.11 years, and for negative patients it was 34.46 years. ASST positivity was most commonly observed in the age group of 21-30 years. The p-value was not significant being 0.12356. Out of total 80 patients enrolled in the study, 46 (57.5%) were females and 34 (42.5%) were males. Among females, 22 were ASST positive (48%) and among males, 14 (41%) were ASST positive (p-value=0.554525) [Table/Fig-1].

Variable	ASST +ve (n=36)	ASST -ve (n=44)	Total	p-value
Male	14 (38.8%)	20 (45.5%)	34 (42.5%)	0.554525
Female	22 (61.1%)	24 (54.5%)	46 (57.5%)	
Mean age (years)	30.11	34.46	32.54	0.12356

[Table/Fig-1]: Association of epidemiological features with ASST.

In the present study, duration of the disease ranged from three months to five years. The mean duration of the disease was 24.35 months. The mean duration of the disease in ASST positive and negative patients is shown in [Table/Fig-2]. Out of 80 patients, 30 (37.5%) patients had 3 episodes of urticaria per week and 26 (32.5%) had almost daily episodes. Frequency of attacks were significantly higher in ASST positive patients than negative patients with p-value 0.017434 as shown in [Table/Fig-2]. In the present study, duration of wheal lasted from 30 seconds to >10 hours. Wheal duration was found to be longer in ASST positive than negative patients with a p-value 0.034929 which is significant as shown in [Table/Fig-3].

Clinical features	ASST +ve	ASST -ve	p-value
	n=36 (%)	n=44 (%)	
Mean duration of disease (months)	28.30	21.12	0.378888
Frequency of attacks (daily)	17 (47.2%)	9 (20.4%)	0.017434
Duration of wheals (2-10 hrs)	24 (66.6%)	15 (34%)	0.034929
Angioedema	18 (50%)	13 (29.5%)	0.061728
Dermatographism	5 (13.8%)	6 (13.6%)	0.97397
Thyroid abnormality	7 (19.4%)	2 (4.54%)	0.035895

[Table/Fig-2]: Association of clinical features with ASST.

Duration of wheals	ASST +ve (n=36)	ASST -ve (n=44)	Total (n=80)	p-value
30 sec-2 hours	9 (25%)	22 (50%)	31 (38.7%)	0.034929
2-5 hours	11 (30.5%)	8 (18.1%)	19 (23.7%)	
5-10 hours	13 (36.1%)	7 (15.9%)	20 (25%)	
>10 hours	3 (8.3%)	7 (15.9%)	10 (12.5%)	

[Table/Fig-3]: Duration of wheals.

Angioedema was present in 18 (50%) ASST positive patients and 13 (29.5%) ASST negative patients. The p-value was 0.061728 which is insignificant. Dermatographism was present in 5 (13.8%) ASST positive patients and 6 (13.6%) ASST negative patients. The p value was not significant being 0.97397.

Seven (19.4%) ASST positive patients and 2 (4.54%) ASST negative patients were hypothyroid. Thyroid function abnormalities were more common in ASST positive group and this was significant with a p-value of 0.035895.

Three patients (8%) had leucocytosis in the ASST positive group whereas 4 (9%) in the ASST negative group. ESR was raised in 7 (9%) patients out of which 2 (5%) were ASST positive and 5 (11%) ASST negative. Raised AEC was seen in 3 (8%) ASST positive and 6 (14%) ASST negative patients.

## DISCUSSION

The present study aimed to associate clinical and epidemiological features in CSU with ASST positivity. By knowing this relationship, one can understand the pattern of the disease better, thereby helping in its long-term management. 45% (36 out of 80) patients with CSU were ASST positive in the present study. Studies by Vohra S et al., Kumar YHK et al., Pokhrel K et al., showed ASST positivity as 46%, 43.62%, 42.2%, respectively which were in concordance with the present study [9-11]. On the contrary, Kulthanan K et al., George M et al., study showed ASST positivity as 24.7% and 34%, respectively [Table/Fig-4] [6,7]. Differences could be attributable to patient selection, methodology and response interpretation or even to geographic and ethnic variations in the prevalence of autoimmune urticaria. Genetic factors are probably responsible for this variation [12].

**Epidemiological features:** The mean age of presentation of CSU patients in the present study was 32.54 years. Majority {26 (33%)} of the patients were in the 21-30 years age group. The mean age of the ASST-positive patients was 30.11 years and ASST-negative patients were 34.46 years. In the present study, 58% were females (46 out of 80). Some other studies also [6-8,11], showed that there was no statistical difference in age and sex distribution among the ASST positive and negative groups, thus consistent with the present study. All the above studies, including present study show that CIU is common among the reproductive age group [Table/Fig-4].

**Clinical features:** In the present study, mean duration of the disease in ASST positive patients was 28.30 months and in ASST negative patients was 21.12 months. Thus, ASST positive patients had longer duration of disease than ASST negative patients. The p value however was statistically insignificant. Studies conducted by Kulthanan K et al., Krupashankar DS et al., Vohra S et al., also found duration of disease longer in ASST positive than negative patients [6,8,9]. These studies were in congruence with the present study.

In the present study, frequency of wheals was more in the ASST positive group compared to ASST negative group which was statistically significant. ASST positive group were more likely to have daily attacks (47% vs 20%). In Kulthanan K et al., George M et al., Kumar YHK et al., Pokhrel K et al., studies patients

Variable	Present study (n=80)		Kulthanan K et al., [6] (n=85)		George M et al., [7] (n=100)		Vohra S et al., [9] (n=100)		Krupashankar DS et al., [8] (n=80)		Kumar YHK et al., [10] (n=110)		Pokhrel K et al., [11] (n=90)	
	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve	+ve	-ve
ASST positivity	36 (45%)	44	21 (24.7%)	64	34 (34%)	66	46 (46%)	54	47 (58.75%)	33	48 (43.62%)	62	38 (42.12%)	52
Male/female ratio	14/22	20/24	5/16	11/53	16/18	28/38	1:2.07	1:1.25	19/28	17/16	15/33	22/40	11/27	16/36
Mean age of presentation (years)	30.11	34.46	38.8	33.7	-	-	29.65	30.43	33.81	37.58	28.54	31.55	31.59	
Duration of disease (months)	28.30	21.12	27.4	26.7	12	15	43.37	37.52	21.70	17.42	16.34		10	13
Frequency of attacks (daily)	17 (47.2%)	9 (20.4%)	4.1 (3.1%)	4.6 (2.9%)	24 (71%)	34 (51.5%)	-	-	22 (46.8%)	19 (57.5%)	20 (41.66%)	19 (30.6%)	26 (51%)	25 (49%)
Duration of wheals (2-10 hours)	24 (66.6%)	15 (34%)	-	-	-	-	-	-	-	-	-	-	-	-
Angioedema	18 (50%)	13 (29.5%)	2	4	-	-	27 (59%)	28 (52%)	24 (51.1%)	9 (27.3%)	13 (33.33%)	8 (14.51%)	-	-
Dermographism	5 (13.8%)	6 (13.6%)			3	29								

**[Table/Fig-4]:** Comparison of the present study variables with various studies [6-11].

with positive ASST had more frequent attacks which was statistically significant as compared to the ASST-negative group [6,7,10,11]. These results were consistent with the present study. Krupashankar DS et al., also reported frequency of urticarial attacks to be lower in ASST positive than negative group, unlike the present study [8].

Present study showed significantly longer duration of wheals in ASST positive (5-10 hrs) than ASST negative (30 sec-2 hrs) patients [Table/Fig-3]. George M et al., observed that wheals lasted for significantly longer duration in patients with positive ASST [7]. The median duration being 4 hours for ASST-positive patients compared to 2 hours in ASST-negative individuals (p-value=0.001), which was statistically significant. In the Pokhrel K et al., study wheals lasted for significantly longer duration in patients with positive ASST [11], the median duration being 3 hours for ASST-positive as compared to 1 hour in ASST-negative individuals. The above studies are in concordance with the present study.

Although the frequency of angioedema was higher in the ASST positive group than the negative group in the present study, this was not statistically significant. In George M et al., study there was no significant difference in the frequency of angioedema between ASST positive and negative patients which was in accordance with the present study [7].

In the present study, 9 (11%) patients had thyroid function abnormalities. Of which 7 (19%) were ASST positive and 2 (5%) were ASST negative. This was statistically significantly. In the Kulthanan K et al., study the prevalence of thyroid auto antibodies in patients with positive ASST was 9.5% and in those with negative ASST 3.1% [6]. However, there was no statistically significant difference (p-value=0.23). Krupashankar DS et al., study did not find significant difference of thyroid profile among the ASST positive and ASST negative groups [8]. George M et al., observed abnormal TFT values in three ASST-positive patients out of 34, this study did not find any difference in the incidence of thyroid disease [7]. The association of chronic urticaria with autoimmune thyroiditis strengthens the autoimmune theory. Larger scale studies and case control studies are required to confirm the association between autoimmune thyroiditis and autoimmune urticaria.

The CSU patients with positive ASST may have more severe disease with greater impact on quality of life. Thus, they may need more aggressive treatment.

### Limitation(s)

As single investigator performed ASST and recorded history, there was a possibility of bias in the measurement of wheal diameter. Histamine was not used as a positive control due to the risk of anaphylaxis, so few cases of false negative ASST cases may have been missed due to this. Pseudoallergy as a cause of chronic urticaria was not ruled out. Tests for anti-thyroid antibodies were not carried out.

### CONCLUSION(S)

The ASST is a simple inexpensive in vivo test for the detection of autoreactivity. It may be used as a fairly reliable test for autoimmune urticaria especially since basophil histamine release assay is not widely available and is expensive. Therefore, ASST positive (autoimmune urticaria) patients have more severe disease with longer duration of disease, increased frequency of attacks and longer duration of wheals. As there are no other clinical tests to predict the severity of CSU, ASST can help in delineating a subgroup requiring more anti histaminics and even immunomodulatory drugs.

More widespread studies are required to understand the variations in ASST positivity in different geographical areas. Long-term follow-up studies are required to better understand the clinical outcome in ASST positive and negative patients. The procedure and interpretation of ASST should be standardised.

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**PLAGIARISM CHECKING METHODS:** [\[Jain H et al.\]](#)

- Plagiarism X-checker: Feb 19, 2021
- Manual Googling: Apr 21, 2021
- iThenticate Software: May 26, 2021 (20%)

**ETYMOLOGY:** Author Origin**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 01, 2021**Date of Peer Review: **Mar 02, 2021**Date of Acceptance: **May 05, 2021**Date of Publishing: **Jul 01, 2021**