ISSN: 2476 - 2415

Research Article

International Journal of Clinical & Experimental Dermatology

Serum Levels of Interleukin-17, D-Dimer, Immunoglobulin-E and Autologous Serum Skin Test as Severity Markers in Chronic Spontaneous Urticaria

Iman Muhammed Abdelmeniem Metwally[1*], Nouran Abdelaziz Abou Khadr[1], Raghda Saad Zaghloul[2], Doaa Gomaa Ibrahim Salama[1] and Tarek Mahmoud Hussein[1]

[1]*Department of Dermatology, Venerology, and Andrology-Faculty of Medicine, Alexandria University, Egypt*

[2]*Department of Clinical and Chemical Pathology-Faculty of Medicine, Alexandria University, Egypt*

[*]Corresponding Author
MIman Muhammed Abdelmeniem Metwally, Department of Dermatology, Venerology, and Andrology-Faculty of Medicine, Alexandria University, Egypt.

Submitted:2024, Oct 29; **Accepted**: 2024, Nov 04; **Published**: 2024, Dec 13

Citation: Metwally, I. M. A., Khadr, N. A. A., Zaghloul, R. S. Z., Salama, D. G. I., Hussein, T. M. (2024). Serum Levels of Interleukin-17, D-Dimer, Immunoglobulin-E and Autologous Serum Skin Test as Severity Markers in Chronic Spontaneous Urticaria. *Int J Clin Expl Dermatol, 9*(2), 01-07.

Abstract

Background

The evaluation of chronic spontaneous urticaria (CSU) activity is mainly based on subjective assessment. Accordingly, there is an urgent need for objective measurable indicators to evaluate CSU activity and monitor the response to treatment.

Objective

to evaluate Interlukin-17 (IL-17), Immunoglobulin E (IgE), D-dimer, and Autologous Serum Skin Test (ASST) in relation to urticarial activity score (UAS7) and angioedema activity score (AAS) in CSU patients.

Patients and Methods

A comparative study was conducted on 80 CSU patients and 80 healthy age and gender-matched controls. The severity of CSU was assessed using UAS7 and AAS. ASST was done on all patients to determine the group with autoimmune urticaria. A venous blood sample was obtained to measure D-dimer, IL-17, and IgE.

Results

Our data showed elevated serum levels of IL-17, IgE, and D-dimer as well as positive ASST among CSU patients, however, no correlation was reported between these biomarkers. There were high statistically significant correlations between UAS7 with serum IL-17, D-dimer, IgE, ASST, and AAS ($p \leq 0.001$, for all). However, regarding AAS, there's a significant positive correlation between AAS/day with D-dimer ($r=0.245$ and $p=0.029$), and IgE ($r=0.751$ and $p \leq 0.001$).

Conclusion

IL-17, IgE, and D-dimer as well as ASST are related to CSU activity and can be used as useful indicators for diagnosing CSU and for assessing CSU and angioedema activity.

Keywords: IL-17, D-Dimer, IgE-E, ASST, Chronic Spontaneous Urticaria

1. Introduction

Chronic spontaneous urticaria (CSU) is a skin disorder, in which the spontaneous appearance of wheals (hives), may be or not accompanied by angioedema, that remains above six weeks on most days of the week without any apparent trigger is characteristic [1]. At any time, the prevalence of CSU has been suggested to be 0.5% to 1%. The evaluation of disease activity is mainly based on medical history and clinical assessment, besides, using a number of validated questionnaires, including urticarial activity score (UAS7) and angioedema activity score (AAS).

However, these questionnaires are subjective with a retrospective design. Accordingly, there is an urgent need for objective measurable indicators to assess the disease activity and monitor the treatment response [2,3]. Owing to the suggested autoimmune nature of CSU that is defined by functional Immunoglobulin (Ig) autoantibodies that are present in the blood and target either IgE or the alpha chain of IgE receptor, IgE was investigated to assess its actual role in the disease severity and activity [4]. Additionally, the Autologous Serum Skin Test (ASST), a simple, office-based screening test for serum auto-reactivity in patients with CSU that detects autoantibodies was assessed [5,6]. The imbalance between T lymphocyte subgroups and cytokines is one of the underlying causes of the majority of autoimmune and allergy disorders [7]. In many autoimmune diseases, including CSU, elevated Interlukin-17 (IL-17) was reported [,8].

On the other hand, the coagulation cascade role in CSU pathogenesis was proposed. Inflammation and the coagulation cascade are intimately related, and they both activate and propagate one another [9]. Recently, D-dimer, a fibrin degradation product, was noticed to be elevated in CSU patients [10]. Herein, this study aimed to evaluate D-dimer, IL-17, IgE, and ASST in relation to UAS7 and AAS in patients with CSU.

2. Patients and Methods

This study involved two groups of subjects recruited from the outpatient Clinic of the Dermatology, Venerology, and Andrology Department in Alexandria Main University Hospital. Sample size software (PASS 2020) and power analysis were used to determine the sample size. Group A consisted of 80 patients with CSU (Itchy wheals, angioedema, or both that appeared spontaneously, lasting ≥6 weeks from recognized causes), and group B comprised 80 age and sex-matched healthy control subjects.

Approval of the Medical Ethics Committee of Alexandria Faculty of Medicine was obtained on the 20th of January 2022. An informed written consent was taken from each participant included in this study.

We excluded 1) patients on antihistamines for at least 3 days and corticosteroids or any immunosuppressive medications for 4 weeks prior to the study, 2) patients with any disease or medication used that affects the coagulation cascade (e.g. anticoagulants), 3) patients with an uncertain diagnosis of CSU during physical examination, 4) patients with any suspected case of chronic inducible urticarial [11].

• CSU Severity

In order to assess the disease severity, UAS7 and AAS were used. UAS7 is the summation of daily symptom scores for 7 consecutive days. UAS7 was categorized into absent (0), well-controlled (1–6), mild (7–15), moderate (16–27), and severe (28–42). With the AAS, a patient can rate their angioedema on a scale of 0 to 3 for each of the five major aspects (duration, physical discomfort, impact on activities during the day, impact on patient appearance, and the general severity of the swelling), for a total daily score ranging from 0 to 15 [12,13].

• ASST

ASST was done on all patients to determine the group with autoimmune urticarial. In order to perform ASST, two milliliters of venous blood were drawn, stored in a non-heparinized plain tube, and left for clotting at room temperature. Then, in order to separate the serum, the blood was centrifuged for ten minutes at 2000 revolutions per minute. The patient's serum (0.05 mL) is administrated by intradermal injection on the volar aspect of the subject forearm at a location that hasn't experienced a wheal in the previous 24 hours. Simultaneously, as a control test, injection of the same volume of normal saline is administrated at least 5 centimeters away from the site of the serum injection. The response is measured after 30 minutes. If there was a wheal and flare at the testing location with a diameter of at least 1.5 millimeters greater than the wheal and flare caused at the control site, the test is deemed positive and the patient is diagnosed with chronic autoimmune urticaria. (Figure 1)

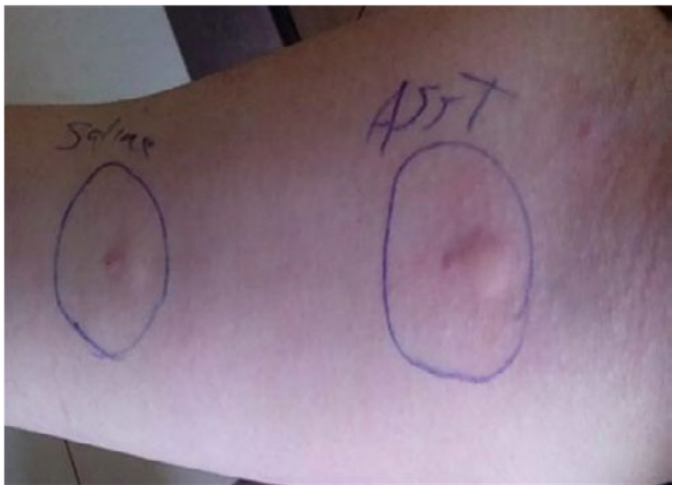

Figure 1: Positive ASST

3. Mesurment of IL-17, Total Ige, And D-Dimer

Venous blood samples (6ml) were collected (from both groups) on fasting from elbow veins and divided into 3 samples. The first and the second samples are for serum IL-17 and total IgE respectively and left for clotting for one hour at room temperature before centrifugation for 15 min at 1000xg. Sera were stored frozen at -85 °C until assayed. The third one is added to an anticoagulant and used as a plasma sample for the detection of D-dimer level.

Serum IL17 level was measured by ELISA technique (E0142Hu Human IL-17 ELISA Kit, China, with a sensitivity of 1.06 ng/L) while the measurement of serum total IgE was done by means of electrochemiluminescence immunoassay "ECLIA" technique (Cobas, USA), Finally, using an automated latex agglutination method (STA-R Evolutionâ; Diagnostica Stago, Asnieres, France), plasma D-Dimer level was measured.

4. Statistical Analysis Of The Data

The computer was provided with data, and IBM SPSS software package version 27.0 was used for analysis. IBM Corp., Armonk, NY). For descriptive analysis, numbers and percentages were used to define the qualitative data, whereas, range, mean, and standard deviation (SD) were used to illustrate quantitative data. For analytic analysis, the used tests were Pearson's Chi-square test ($\chi 2$), Fisher-Freeman-Halton Exact Test, Kruskal-Wallis H test, and Mann-Whitney test. For the correlation of the ordinal data, Pearson's correlation test was utilized. At the 5% level ($P \leq 0.05$), the significance of the acquired results was judged [14].

5. Results

Age ranged between 18-78 years with a mean of 43.34 ± 13.52 years. Males were 9 (11.2%) and females were 71 (88.8%). No statistical difference was found between the CSU patients and controls in terms of their gender (p=0.127) and age (p=0.088). Table (1). The urticaria was gradual in 68 (85%) of cases and sudden in 12 (15%). The majority of cases (56 patients; 70%) had a progressive course of the disease and 24 (30%) were stable. Among the 80 enrolled patients, the mean disease duration was 6.81 ± 6.06 years (range; 2 to 24 years) A positive family history was reported in 4 (5%) of cases. Diurnal variation was in 32 (40%) of cases. Antihistaminic therapy was received in 23 (28.7%) of cases, 18 (22.5%) received corticosteroids, 4 (5%) received Omalizumab, and one case (1.3%) received Cyclosporine. Other patients received combined therapy 29 (36.1%). Stress was reported in 15 (18.8%) and 4 (5%) had urticaria as one of the manifestations of post-covid syndrome.

	Patient (n = 80)		**Control (n = 80)**		**Test of Sig.**	**p**
	No.	%	No	%		
Sex						
Male	9	11.3	16	20.0	$\chi 2$= 2.323	0.127
Female	71	88.8	64	80.0		
Age(years)						
Min. – Max.	18.0 – 78.0		20.0 – 75.0		t= 1.717	0.088
Mean ± SD.	43.34 ± 13.52		47.31 ± 15.69			
t: Student t-test x2: Chi-square test						

Table 1: Demographic data of CSU patients and controls.

UAS7 was mild in 19 (23.8%) of cases, moderate in 36 (45%) of cases, and severe in 25 (31.3%) of cases. AAS ranged between 0 to 14 with a mean value of 3.2 ± 4.03.

UAS7	No.	%
Mild	19	23.8
Moderate	36	45
Severe	25	31.3
AAS/day	No.	%
Yes	44	55
No	36	45
Range	0-14	
Mean ± S.D.	3.2 ± 4.03	

Table 2: Assessment of disease severity in the studied cases by UAS7 and AAS

Table 3 shows the results of IL-17, D-Dimer, IgE, and ASST of CSU patients and controls. Serum IL-17 was significantly higher among CSU patients than in controls (356.4 ± 510.3 pg/ml vs. 0.76 ± 0.42 pg/ml, p <0.001). The total serum D-Dimer level was significantly higher among CSU patients (783.27 ± 801.26 IU/ml) compared to controls (109.44 ± 54.98 IU/ml), (p <0.001). The total serum IgE level among the cases was (330.3 ± 270.4 IU/ml) significantly higher than in the controls (55.66 ± 26.90 IU/ml) (p <0.001). ASST among the cases was positive in 22 cases (27.5%) and negative in 58 cases (72.5%) while all controls were negative (100%) (p <0.001).

	Patient (n = 80)		**Control (n = 80)**		**U**	**P**
IL-17						
Min. – Max.	222.3 – 4830.0		0.09 – 1.40		0.000*	<0.001*
Mean ± SD.	356.4 ± 510.3		0.76 ± 0.42			
Median (IQR)	272.5 (256.0 – 337.1)		0.79 (0.39 – 1.12)			
D-Dimer						
Min. – Max.	1.30 – 2921.0		10.0 – 199.0		791.000*	<0.001*
Mean ± SD.	783.27 ± 801.26		109.44 ± 54.98			
Median (IQR)	407.5(160.5 –1422.5)		112.5 (60.50 – 153.5)			
IgE						
Min. – Max.	1.12 – 1276.0		10.0 – 99.0		696.000*	<0.001*
Mean ± SD.	330.3 ± 270.4		55.66 ± 26.90			
Median (IQR)	283.5 (130.5 – 460.0)		57.0 (29.0 – 78.0)			
ASST	**Patient (n = 80)**		**Control (n = 80)**		**χ2**	**P**
	No.	%	No.	%		
Negative	58	72.5	80	100.0	25.507*	<0.001*
Positive	22	27.5	0	0.0		
U: Mann Whitney test X^2: Chi-square test			**: Statistically significant at p ≤ 0.05*			

Table 3: IL-17, D-Dimer, and IgE of CSU patients and controls.

There were high statistically significant relations between UAS7 with serum IL-17, D-dimer, IgE, ASST, and AAS (p ≤0.001, for all). (Table 4)

Regarding AAS, there's a significant positive correlation between AAS/day with D-dimer (r=0.245 and p=0.029), and IgE (r=0.751 and p ≤0.001). However, there was no significant correlation between AAS/day with IL-17 (p =0.748). In addition, no statistically significant correlation between ASST and AAS was found (p= 0.452). (Table 4)

	UAS7 AAS		**AAS**	
	Kruskal-Wallis test	P value		P value
IL-17	28.964	≤0.001**	0.036	0.748
D-dimer	16.812	≤0.001**	0.245*	0.029*
IgE	36.753	≤0.001**	0.751**	≤0.001**
ASST	Pearson Chi-Square	P value		P value
	21.953	≤0.001**	0.914	0.452

Table 4: Correlations between UAS7 with serum IL-17, D-dimer, IgE, ASST, and AAS

No correlation was found between serum levels of IL17 and D-Dimer (p= 0.316). No correlation was found between serum levels of IL17 and IgE (p= 0.561). No correlation was reported between serum level of IgE and D-Dimer (p= 0.938). (Table 5)

	IL-17	
	rs	P
D-Dimer	0.114	0.316
IgE	0.066	0.561
	D-Dimer	
	rs	P
IgE	-0.009	0.938
rs: Spearman coefficient		

Table 5: Correlations between serum levels of IL17, D-Dimer, and IgE rs: Spearman coefficient

6. Discussion

The current study found elevated serum levels of IL-17, IgE, and D-dimer as well as positive ASST among CSU patients, however, no correlation was reported between these biomarkers, supporting the heterogeneity of the CSU pathogenesis. Both autoimmunity and the coagulation cascade are among the heterogeneous pathways. Moreover, all studied parameters, IL-17, IgE, D-dimer, and ASST, were linked with the disease activity. Concerning the disease activity in the work, UAS7 and AAS were applied. The results of USA7 indicated that the majority of our cases had moderately active disease. Similarly, Atwa et al.(2) mentioned that based on UAS7, nearly half of CSU patients (50.7%) were moderately active. On the other hand, the mean AAS was 3.2 ± 4.03 (range; 0 to 14), while Rodríguez-Garijo et al.(14) reported a lower angioedema score (median AAS =1) among 63 CSU patients. Following previous studies, Expectedly, a high statistically significant relation between AAS and UAS7 ($p \leq 0.001$) was found [15-17].

Serum IL-17, in the present work, was significantly higher in CSU patients than in controls ($p < 0.001$), suggesting a potential role of IL-7 in CSU pathogenesis. The present work also found a high statistically significant relation between serum IL-17 and UAS7 ($p \leq 0.001$), indicating the role of IL-17 not only in the pathogenesis of CSU but also in the disease activity. However, we observed a weak positive correlation between AAS/day and IL-17 ($r = 0.036$ and $p = 0.748$), suggesting no association between IL-17 and angioedema activity.

This result supports the findings of previous studies. Atwa et al. demonstrated that serum IL-17 was significantly higher in CSU patients than in that of controls, besides, serum IL-17 in CSU patients was significantly correlated to the disease activity measured by UAS ($r = 0.677$, $p < 0.001$), highlighting a functional contribution of IL-17 in the pathogenesis and progression of CSU. Also, Grzanka et al. reported elevated IL-17 levels in CSU patients compared to controls, concluding that elevated serum IL-17 level may serve as an independent indicator, unrelated to elevated C-reactive protein (CRP) concentration, for the systemic inflammatory response in CSU [2,18].

Likewise, Lin et al. quantified IL-17, IL-31, and IL-33 to assess their role in CSU and their relation to the disease severity. All studied cytokines were noticed to be significantly elevated in CSU patients and, particularly, IL-17 was significantly higher in severe CSU than in mild to moderate CSU [19].

Furthermore, Sabag et al. found raised IL-17 in the lesional skin biopsies of 20 CSU patients and concluded a potential role of IL-17 in the pathogenesis of CSU. They also found a significant reduction in urticaria activity after receiving secukinumab, an anti-IL-17A antibody [8].

Among our subjects, the total serum D-Dimer level was significantly higher among CSU patients than in controls ($p < 0.001$). Additionally, there was a high statistically significant relation between D-dimer and UAS7 ($p \leq 0.001$). There's a positive significant correlation between AAS/day and D-dimer ($r = 0.245$ and $p = 0.029$), suggesting an association between D-dimer and angioedema activity.

The current findings support the role of coagulation cascade in the development and progression of CSU which was consistent with previous works. In a retrospective study, Dabas et al. reported higher D-dimer levels in 32.6% of their population (141 CSU patients). The D-dimer was highest in patients with severe CSU compared to mild and moderate CSU ($p < 0.001$).

Likewise, Triwongwaranat et al. retrospectively investigated the D-dimer level in 120 chronic urticaria patients and its correlation to the severity of the disease. They observed that D-dimer was elevated in nearly of patients (48.3%). In addition, they found that D-dimer is positively correlated with disease severity ($r = 0.537$; $p < 0.05$) which agreed with our results [20,21].

Contrary to our findings, Rodríguez-Garijo et al. found no correlation between D-dimer and AAS among CSU patients, yet a significant correlation was established between D-dimer and AAS among chronic histaminergic angioedema patients in their study. This may be due to the presence of hives and itch which may influence the higher severity of angioedema in CSU patients and the impact on quality of life (QoL) is subject to patients' individual interpretations of symptoms [15].

In the current work, we found that the total serum IgE level among the cases was ($p < 0.001$). There's a high statistically significant

relation between IgE and UAS7 (p ≤0.001). There's a strong positive significant correlation between AAS/day and IgE (r=0.751 and p ≤0.001). These results explain the autoimmune nature of CSU.

This was in alignment with Altrichter et al. who stated that although normal or extremely low total IgE levels occasionally happened, CSU patients typically exhibited high total IgE blood levels (up to 50%). They added elevated total IgE indicates more disease activity, a longer course of the illness, and a higher possibility of responding to omalizumab therapy [22].

In the current study, ASST among the cases was positive in 22 cases (27.5%) and negative in 58 cases (72.5%) while all controls were negative (100%) (p <0.001). There's a high statistically significant relation between ASST and UAS7 (p ≤0.001). However, there's no statistically significant relation between ASST and AAS (p= 0.452). This suggests that people with chronic autoreactive urticaria have more intense symptoms that are difficult to manage.

Supporting the work findings, Atwa et al. reported that ASST was positive in 44% of CSU patients with a reported significant association between ASST and disease activity assessed via UAS7 (p= 0.002). Also, El-Sharkawy et al. noticed that ASST was positive in 38% of chronic urticaria patients. They added that the relationship between the urticaria activity score7 (UAS7) and the positivity of the ASST showed a high statistical significance [2,23].

This is consistent with research conducted by Caproni et al. on chronic urticaria patients which found that ASST-positive individuals had more extensive lesions as well as much more severe itching and overall discomfort [24].

Contrary to the present findings, Lee et al. and Al Hammamy et al. showed that there was no statistically significant association between ASST and the UAS. This may be due to the small sample size, auto-reactivity accounted only partially for the etiology of CIU (still 41% of patients with CIU had no identified factor, these autoantibodies were also detected in subjects in remission and even in normal subjects and ASST does not actually prove the presence of antibodies, but rather shows histamine-releasing properties of the tested serum [6,25].

In the present work, the correlations between the studied parameters were assessed. We found no correlation between serum levels of IL17 and D-Dimer (p= 0.316). No correlation was found between serum levels of IL17 and IgE (p= 0.561). No correlation was found between serum level of IgE and D-Dimer (p= 0.938). Our findings support the heterogeneity of the CSU pathogenesis.

In addition to being a prospective case-control study, studying these different biomarkers with different mechanisms of action in CSU and their relations with the disease activity strengthens our work. However, the small sample size is the main limitation of this study. Additionally, the utility of these biomarkers in monitoring the treatment follow-up wasn't assessed, so we recommended further studies to investigate the usefulness of the studied parameters in monitoring the treatment response.

7. Conclusion

The current study data showed elevated serum levels of IL-17, IgE, and D-dimer as well as positive ASST among CSU patients, however, no correlation was reported between these biomarkers, supporting the heterogeneity of the CSU pathogenesis. Both autoimmunity and the coagulation cascade are among the heterogeneous pathways.

Moreover, all IL-17, IgE, D-dimer, and ASST were related to the disease activity. These biomarkers can be used as useful indicators for the diagnosis of CSU and for the evaluation of the disease activity and may be helpful in the diagnostic workup of CSU patients.

References

1. Maheshwari, A., Garg, T., Chander, R., & Debnath, E. (2022). Chronic spontaneous urticaria: an etiopathogenic study. *Indian Journal of Dermatology, 67*(1), 92.
2. Atwa, M. A., Emara, A. S., Youssef, N., & Bayoumy, N. M. (2014). Serum concentration of IL-17, IL-23 and TNF-α among patients with chronic spontaneous urticaria: association with disease activity and autologous serum skin test. *Journal of the European Academy of Dermatology and Venereology, 28*(4), 469-474.
3. Termeer, C., Staubach, P., Kurzen, H., Strömer, K., Ostendorf, R., & Maurer, M. (2015). Chronic spontaneous urticaria–a management pathway for patients with chronic spontaneous urticaria. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 13*(5), 419-428.
4. Sánchez, J., Sánchez, A., & Cardona, R. (2018). Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. *Allergy, asthma & immunology research, 11*(1), 29-42.
5. Degirmenci, P. B., Kırmaz, C., Vatansever, S., Onur, E., Nal, E., Erdin, S., & Ozyurt, B. (2017). Analysis of the association of chronic spontaneous urticaria with interlekin-4,-10, transforming growth factor-β1, interferon-γ, interleukin-17A and-23 by autologous serum skin test. *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii, 34*(1), 70-76.
6. Al-Hamamy, H. R., Hameed, A. F., & Abdulhadi, A. S. (2013). Autologous serum skin test as a diagnostic aid in chronic idiopathic urticaria. *International Scholarly Research Notices, 2013*(1), 291524.
7. Zhao, G., Zhou, S., Davie, A., & Su, Q. (2012). Effects of moderate and high intensity exercise on T1/T2 balance. *Exercise immunology review, 18*.
8. Sabag, D. A., Matanes, L., Bejar, J., Sheffer, H., Barzilai, A., Church, M. K., ... & Vadasz, Z. (2020). Interleukin-17 is a potential player and treatment target in severe chronic spontaneous urticaria. *Clinical & Experimental Allergy, 50*(7), 799-804.

9. Asero, R., Tedeschi, A., Coppola, R., Griffini, S., Paparella, P., Riboldi, P., ... & Cugno, M. (2007). Activation of the tissue factor pathway of blood coagulation in patients with chronic urticaria. *Journal of Allergy and Clinical Immunology, 119*(3), 705-710.
10. Criado, P. R., Antinori, L. C. L., Maruta, C. W., & Reis, V. M. S. D. (2013). Evaluation of D-dimer serum levels among patients with chronic urticaria, psoriasis and urticarial vasculitis. *Anais brasileiros de dermatologia, 88*(3), 355-360.
11. Abd El-Azim, M., & Abd El-Azim, S. (2011). 8 Chronic Autoimmune Urticaria: Frequency and Association With Immunological Markers. *Journal of Investigational Allergology and Clinical Immunology, 21*(7), 546.
12. Göncü, E. K., Aktan, Ş., Atakan, N., Başkan, E. B., Erdem, T., & Koca, R. (2016). The Turkish guideline for the diagnosis and management of urticaria-2016. *Turkderm, 50*(3), 82-98.
13. Weller, K., Zuberbier, T., & Maurer, M. (2015). Chronic urticaria: tools to aid the diagnosis and assessment of disease status in daily practice. *Journal of the European Academy of Dermatology and Venereology, 29*, 38-44.
14. Feeney, Brooke C. *A Simple Guide to IBM SPSS® Statistics: For Version 23.0.* Cengage learning, 2016.
15. Rodríguez-Garijo, N., Sabaté-Brescó, M., Azofra, J., Baeza, M. L., Donado, C. D., Gaig, P., ... & Ferrer, M. (2022). Angioedema severity and impact on quality of life: Chronic histaminergic angioedema versus chronic spontaneous urticaria. *The Journal of Allergy and Clinical Immunology: In Practice, 10*(11), 3039-3043.
16. Metz, M., Bernstein, J. A., Giménez-Arnau, A. M., Hide, M., Maurer, M., Sitz, K., ... & Severin, T. (2022). Ligelizumab improves angioedema, disease severity and quality-of-life in patients with chronic spontaneous urticaria. *World Allergy Organization Journal, 15*(11), 100716.
17. Sussman, G., Abuzakouk, M., Bérard, F., Canonica, W., Oude Elberink, H., Giménez-Arnau, A., ... & Balp, M. M. (2018). Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU. *Allergy, 73*(8), 1724-1734.
18. Grzanka, A., Damasiewicz-Bodzek, A., & Kasperska-Zajac, A. (2017). The relationship between circulating concentrations of interleukin 17 and C reactive protein in chronic spontaneous urticaria. *Allergy, Asthma & Clinical Immunology, 13*, 1-5.
19. Lin, W., Zhou, Q., Liu, C., Ying, M., & Xu, S. (2017). Increased plasma IL-17, IL-31, and IL-33 levels in chronic spontaneous urticaria. *Scientific reports, 7*(1), 17797.
20. Dabas, G., Thakur, V., Bishnoi, A., Parsad, D., Kumar, A., & Kumaran, M. S. (2021). Causal relationship between D-dimers and disease status in chronic spontaneous urticaria and adjuvant effect of oral tranexamic acid. *Indian Dermatology Online Journal, 12*(5), 726-730.
21. Triwongwaranat, D., Kulthanan, K., Chularojanamontri, L., & Pinkaew, S. (2013). Correlation between plasma D-dimer levels and the severity of patients with chronic urticaria. *Asia Pacific Allergy, 3*(2), 100-105.
22. Altrichter, S., Fok, J. S., Jiao, Q., Kolkhir, P., Pyatilova, P., Romero, S. M., ... & Maurer, M. (2021). Total IgE as a marker for chronic spontaneous urticaria. *Allergy, asthma & immunology research, 13*(2), 206.
23. El-Sharkawy, R. E. E. D., Abd-Elmaged, W. M., Ahmed, D. A., & Abdel-Wahed, S. A. E. F. (2018). Pattern of chronic urticaria and value of autologous serum skin test in Sohag Province, Upper Egypt. *Electronic Physician, 10*(5), 6781.
24. Caproni, M., Volpi, W., Giomi, B., Cardinali, C., Antiga, E., Melani, L., ... & Fabbri, P. (2004). Chronic idiopathic and chronic autoimmune urticaria: clinical and immunopathological features of 68 subjects. *Acta dermato-venereologica, 84*(4).
25. Lee, H. C., Hong, J. B., & Chu, C. Y. (2011). Chronic idiopathic urticaria in Taiwan: a clinical study of demographics, aggravating factors, laboratory findings, serum autoreactivity and treatment response. *Journal of the Formosan Medical Association, 110*(3), 175-182.