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Assessment of Serum Level of IL-6, D-dimer and CRP in Patients with Urticaria

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Abstract

Urticaria is a cutaneous disorder characterized by the recurrent eruption of hives accompanied by redness and itching for less than 6 weeks in acute type and more than 6 weeks in chronic type. Many studies have highlighted the role of activation of coagulation factors, eosinophils and tissue factor pathway with generation of thrombin potentially contributing to an increased vascular permeability. The aim of this work was to assess the serum level of interleukin 6(IL-6), D-dimer and c-reactive protein (CRP), complete blood picture (CBC), prothrombin time (PT), partial prothrombin time (PTT), clotting time (CT) and International Normalized ratio (INR) in patients with urticaria. This case control diagnostic interventional study was carried out on 100 patients (50 patients with acute and 50 patients with chronic urticaria), and 100 normal healthy sex and age matched controls. IL-6, D-dimer ,CRP (were measured by an enzyme-linked immunosorbent assay (ELISA) ,CBC by using (automated haematology analyser) ,CT (by test tube method), PT (by an automated instrument) ,PTT (by citrated plasma, the addition of a platelet substitute , factor 12 activator and CACL2) and INR (=patient PT/ control PT). This study showed significant high levels of whereas CRP, IL-6, D-dimer, PT and PTT were significantly increased in acute group comparing chronic groups (P <0.001, <0.001, <0.001, 0.006 and 0.042). IL-6, CRP, ESR, D-dimer ,PT,PTT and CT could serve as available cheap biomarkers for detection of the coagulation defect that can be encountered in urticaria and this is supposed to be responsible for expected prognosis and marker for the progression of the treatment response .Ther also can serve as a reliable markers in chronic urticaria to indicate disease chronicity and activity .

Keywords: Serum Level, IL-6, D-Dimer, CRP, Urticaria

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1. Introduction

Urticaria is a common inflammatory skin disorder, with a lifetime prevalence of up to 20% worldwide. It is defined as a mast cell-mediated disease that results from the activation and degranulation of skin mast cells, followed by the release of histamine and other mediators that lead to sensory nerve activation, vasodilation, plasma extravasation and cellular recruitment. This process causes the development of the disease-defining signs and symptoms, itchy wheals (hives) and angioedema or both [1]. Mediators and cytokines such as platelet-activating factor, mainly histamine, from mast cells in the tissue, basophils in the blood are released through the immune or non-immune mechanism and may contribute to the pathogenesis of the disease [2]. Associations between activation of coagulation and fibrinolytic systems and the inflammatory response are found in pathogenesis of multiple diseases, yet little is known about the crosstalk between inflammation and thrombotic/fibrinolytic pathways in urticaria especially the chronic type [3]. Activation of endothelial cells (ECs) as well as coagulation cascade; both extrinsic and intrinsic pathways, has been found to play an important role in the pathogenesis of urticaria [4,5]. ECs also play a major role in hemostasis as they regulate the activation of platelets & the coagulation cascade and release pro-fibrinolytic molecules. Chronic spontaneous urticarial (CSU) has been described to be linked to elevated plasma levels of markers of thrombin generation,

which has been proposed to involve EC-derived tissue factor [5]. IL-6, a B-cell differentiation factor secreted by mast cells and T cells, is important for immunological regulation, hematopoiesis, and inflammatory response. Immune disorders and cancer are linked to IL-6. IL-6 may increase mast cell histamine production and inflammation, making it a reliable measure for urticaria severity [6]. High liver acute phase reactant like C-reactive protein are commonly elevated in inflammatory conditions. Researches had linked increased CRP levels to worse chronic urticaria symptoms. Instead of a pathogenic role, it may be a better severity marker [7]. The fibrin degradation product D-dimer can indicate enhanced coagulation and fibrinolysis. Increased concentrations in chronic urticaria patients reflect inflammation-coagulation/fibrinolysis crosstalk [3]. The aim of this work was to assess the serum level of interleukin 6(IL-6), D-dimer and c-reactive protein (CRP), complete blood picture (CBC), prothrombin time (PT) ,partial prothrombin time (PTT) ,clotting time (CT),International Normalized ratio (INR) in patients with urticaria in a trial to find markers for coagulation mechanisms.

2. Materials and Methods

This prospective cohort study was carried out on 100 patients with urticaria whether acute or acute exacerbation on top of chronic , aged from 18 to 55 years old, both sexes, who were diagnosed on clinical basis of the appearance of spontaneous wheals anywhere on the body, and 100 normal healthy age & sex matched controls. Patients with any cutaneous diseases other than urticarial or systemic diseases (such as autoimmune diseases, blood diseases and malignancy), infections, atopic dermatitis, inflammatory diseases, rheumatoid or receiving any treatment that could affect the studied parameters were excluded from this study. All patients were free of second-generation H1-antihistamine administration within the last 4 days, and glucocorticoids and cyclosporine therapy were withdrawn at least 8 weeks before, no topical application 48 h before sample taking, and none of these patients were previously treated with Omalizumab. Written informed consents were obtained from all participants. The study was conducted at the October 6 University between December 2022 and November 2023 after approval from the Ethical Committee of Dermatology Department, October 6 University. All patients were subjected to complete history taking including personal history, family medical history. Complete physical examination including to confirm the diagnosis, exclude other skin or systemic disease, detect the presence of angioedema and to assess the disease activity as well as severity. All patients underwent clinical investigation including abdominal ultrasonography, chest X-ray, ENT and dental consultations, autologous serum skin test (ASST), and laboratory investigations consist of complete blood count (CBC), kidney and liver functions tests, thyroid profile including TSH, T3, T4, anti-thyroglobulin antibody (Anti-TG) and anti-thyroid peroxidase antibody (Anti-TPO),urine and stool analysis, helicobacter Ag in stool,anti-nuclear antibody (ANA), allergen specific IgE antibodies, and antibodies specific to Hepatitis C and B. All this labs is asked to detect any comorbidities. Disease activity was measured by the number of wheals/24h [(0) no, (1) mild (less than 20),(2)Moderate (between 20 -50) ,(3) Intense (more than 50,or in large area)], and the patient's assessment of itch using a four-point scale [(0) no itch, (1) mild, (2) moderate, (3) severe/intensive)] [8]. Disease severity was assessed using modified urticaria activity score7. The UAS7 was calculated as the sum total of each day's hive score (derived from an exact 24-h hive count) and each day's maximum itch severity score (between morning and evening), over 7 days [8].

2.1. Blood sampling

For all measurements, venous blood was collected from the antecubital vein in the morning after an overnight fast. Sera was obtained by centrifugation that was stored at −85 °C until analysis of concentrations of CRP, IL-6 and D-dimer. Concentration of CRP, D-dimer and interleukin-6 (Il-6) were measured by an enzyme-linked immunosorbent assay (ELISA) using commercially available kits: Quantikine ELISA Human C-Reactive Protein/CRP kit by R&D Systems (MN, USA) for CRP, Human D-Dimer Simple Step ELISA kit ab196269 by Abcam (Cambridge, UK) for D-dimer and Quantikine ELISA Human Il-6 kit by R&D Systems (MN, USA) for Il-6 CBC by using (automated haematology analyser) ,CT (by test tube method), PT (by an automated instrument) ,PTT (by citrated plasma, the addition of a platelet substitute , factor 12 activator and CACL2) and INR (=patient PT/ control PT).

2.1.1. C-reactive protein (CRP) assay

The detection range of the kit was 62.5 - 4000 pg/mL The standard curve concentrations used for the ELISA's were 4000 pg/mL, 2000 pg/mL,1000 pg/mL, 500 pg/mL, 250 pg/mL, 125 pg/mL, 62.5pg/mL. The minimum detectable dose of CRP was typically less than 23.3 pg/mL. The sensitivity of this assay, or Lower Limit of Detection (LLD) was defined as the lowest protein concentration that could be differentiated from zero. Intra-assay precision was 3 samples with low, middle and high level of target were tested 20 times on one plate, respectively. Inter-assay precision was 3 samples with low, middle, and high level of target were tested on 3 different plates, 8 replicates in each plate. CV (%) = SD/meanX100, intra-assay (CV < 10%) and inter-assay (CV < 12%).

2.1.2. D-dimer assay

We determined the concentration of the target protein in the sample by interpolating the blank control subtracted absorbance values against the standard curve and the resulting value was multiplied by the appropriate sample dilution factor, if used, to obtain the concentration of target protein in the sample. Samples generating absorbance values greater than that of the highest standard were further diluted and reanalysed. Similarly, samples, which measured at an absorbance value less than that of the lowest standard, should be retested in a less dilute form. The calculated minimal detectable dose (MDD) is 71 pg/mL. The MDD was determined by calculating the mean of zero standard replicates (n=25) and adding 2 standard deviations then extrapolating the corresponding concentrations.

2.1.3. Interleukin-6 (Il-6) assay

The mean absorbance for each set of duplicate standards, controls and samples was calculated and the average zero standard optical density was subtracted. A standard curve must be run with each assay [9]. The primary outcome was assessment of the serum levels of IL-6, D-dimer, and CRP in patients with urticaria. The secondary outcome was to correlate the serum level of IL-6, D-dimer and CRP with disease severity.

2.2. Sample size calculation

This study base on study carried out by Grzanka et al., [3] Epi Info STATCALC was used to calculate the sample size by considering the following assumptions: 95% two-sided confidence level, with a power of 80%. & alpha error of 5% odds ratio calculated (1.115). The final maximum sample size taken from the Epi- Info output was 60.

2.3. Statistical analysis

Statistical analysis was done by SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by unpaired student t-test. Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analysed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analysed using the Chi-square test or Fisher's exact test when appropriate. Linear Correlation coefficient (r): It was used for detection of correlation between two quantitative variables in one group. A two-tailed P value < 0.05 was considered statistically significant.

3. Results and discussion

There was an insignificant difference between the studied groups regarding age and sex (Table 1). Regarding the disease parameters, the disease duration was significantly longer in chronic groups compared to acute group (P<0.001), whereas other parameters (Course and angioedema) were insignificantly different between both groups. There was insignificant difference between chronic and acute groups as regard the disease severity (once daily UAS, itching severity, hives severity, severity according to UsA-7 and the median UAS-7). Regarding the comorbidities, a significant difference was detected between groups as regard thyroid disease and autoimmune CT disease (P=0.022, <0.001) (Table 2). ANA, Anti thromboantithyroid were significantly elevated in chronic group comparing acute groups (P <0.001, 0.041), whereas CRP, IL-6, ESR, D-dimer, PT and PTT were significantly increased in acute group compared to chronic groups (P <0.001, <0.001, <0.001, <0.001, 0.006, 0.042, and 0.02). There was insignificant difference between both groups regarding total IgE level and other vital signs (diastolic and systolic blood pressure, temperature and pulse). (Table 3). The Case group showed a of CRP, IL-6, ESR, D dimer, clotting time, PT, PTT and INR compared to controls, with insignificant difference between both groups as regard the platelet count (Table 4). There are significant linear strong positive correlations between IL-6 and D dimer, IL-6 , ESR and CRP (r=0.83, r=0.77 and 0.78) respectively, CRP, D dimer, CRP and ESR& IL-6 (r=0.79 r=0.77&0.77) respectively, age and CRP , IL-6 and ESR (r=-0.76 ,r=-0.70 and r=-0.31) respectively, age and D dimer, IL-6 and itching, moderate correlation between IL-6 and hives &UAS-7 (r=0.75,r=0.63 &0.67) respectively. There are significant linear moderate correlation between IL-6 and different coagulation parameter, PT, CT (r=0.52 and r=0.61) respectively, CRP and different coagulation parameter, PT (r=0.54) and CT (r=0.54 and r=0.60) respectively, CRP as well as ESR and different disease parameter ; itching & UAS-7, while mild correlation was with PTT, age and INR, between age and PT (r=-0.82, r=-0.31 and r=-0.21) respectively, hives (r=0.60, r=0.55 and r=0.38) respectively and weak correlation with INR, For angioedema there are weak positive correlation with IL-6 (r=0.21). There was no significant correlation between inflammatory markers and sex, sex and coagulatory markers (Table 5). Although the pathogenesis of AU is almost clear and although autoimmunity explains some aspects of CU pathogenesis, several points remain unclear. It is generally accepted that autoantibodies to IgE or to the high-affinity IgE receptor, FceRI, which are commonly regarded as the most relevant pathogenic factors in this disease, can be detected in sera of only 25–50% of patients with CU [10-11]. Thrombin is able to activate mast cell and trigger their degranulation [12-13]. Activation of the tissue factor (TF) can produce an elevation of plasma levels of D-dimer, the last being regarded as a sign of fibrinolysis [14, 15]. In the current study, cases exhibit significantly elevated levels of all inflammatory markers and all coagulation markers except platelet count compared to the control group. This was supported by the findings of Grzanka et al. [3] who reported that the CRP and IL-6 concentrations were significantly increased in the CSU patients than in the control group. In addition, our findings matched with Plavsic et al, [16] who reported that CSU participants had statistically significant increased D-dimer and PT in comparison to controls. This may highlight the possibility of using D-dimer and PT as biomarkers for coagulation/fibrinolysin in urticarial. Our results stated that a significant positive correlation between the inflammatory markers that had been studied with disease the coagulation markers. Grzanka et al., [3], supported this. Henceforth, we propose that the fundamental process responsible for the heightened functionality of the coagulation/fibrinolysis system in CSU may arise due to both localized and/or systemic inflammatory reaction, alongside the plausible involvement of the coagulation procedure in the occurrence of urticaria. Evaluation of PT and aPTT may play a crucial role in the assessment of primary coagulation pathways, specifically the activation of thrombin synthesis. Furthermore, these tests offer valuable insights into the significance of both intrinsic and extrinsic pathways in urticarial. We found a significant positive correlation between the inflammatory markers that had been studied with disease parameter (as itching, hives, and UAS-7). Consistent with the findings of Kasperska-Zajac et al., [17]. It was also in agreement with Criado et al., [18] and Kuna et al., [19] who reported positive correlation between CRP and UAS.

Table 1. Demographic data between the studied groups

		Cases (n=100)	Control (n=100)	P value
Age (years)		33.8 ± 10.5	33.9 ± 10.6	0.380
Gender	**Female**	55 (55%)	55 (55%)	1
	Male	45 (45%)	45 (45%)	

Data are presented as mean ± SD or frequency (%).

Table 2. Disease parameter, severity and comorbidities of the studied cases

		Acute (n=50)	Chronic (n=50)	P value
Disease parameter				
Duration of disease (weeks)		3.1 ± 0.7	21.2 ± 4.6	**<0.001***
Course	**Remission and exacerbation**	50 (100%)	50 (100%)	1.0
	Static	0 (0%)	0 (0%)	
Angioedema (n=38)	**With**	14 (28%)	13 (26%)	0.821
	Without	6 (12%)	5 (10%)	
Disease severity				
Once daily UAS	**No disease (0 score)**	0 (0%)	0 (0%)	0.990
	Well controlled (1 score)	13 (26%)	13 (26%)	
	Mild (2 score)	9 (18%)	9 (18%)	
	Moderate (3-4 score)	15 (30%)	15 (30%)	
	Severe (5-6 score)	13 (26%)	13 (26%)	
Itching severity	**No**	5 (10%)	5 (10%)	0.967
	Mild	17 (34%)	16 (32%)	
	Moderate	19 (9.5%)	18 (9%)	
	Intense	9 (18%)	11 (22%)	
Hives severity	**No**	7 (14%)	8 (16%)	0.984
	Mild	23 (46%)	23 (46%)	
	Moderate	14 (28%)	14 (28%)	
	Severe	6 (12%)	5 (10%)	
Severity according to UsA-7	**No disease (score=0)**	0 (0%)	0 (0%)	0.994
	Well controlled (1-6)	12 (24%)	11 (22%)	
	Mild (7-15)	10(20%)	10 (20%)	
	Moderate (16-27)	13 (26%)	14 (28%)	
	Severe (28-42)	15 (30%)	15 (30%)	
UAS-7		24 (3:40)	24 (2:40)	0.967
Comorbidities				
Diabetes mellitus		9 (18%)	8 (16%)	0.789
Hypertension		7(14%)	6 (12%)	0.766
Thyroid disease	**Hashimoto disease**	0 (0%)	3 (6%)	**0.022***
	Hyperthyroidism	0 (0%)	0 (0%)	
	Graves' disease	0 (0%)	1 (2%)	
	No thyroid disease	50 (100%)	46 (92%)	
Autoimmune CT disease		0 (0%)	10 (20%)	**<0.001**

Data are presented as mean ± SD, median (range) or frequency (%), UAS: urticaria activity score, *: statistically significant as p value <0.05.

Table 3. ANA, total IGE, anti thromboantithyroid, general examination, and vital signs of the studied cases

		Acute (n=50)	Chronic (n=50)	P value
ANA	**Positive**	0 (0%)	10 (20%)	**<0.001***
	Negative	50 (100%)	40 (80%)	
Total IGE		180.82 ± 36.44	181.25 ± 36.23	0.938
Anti thromboantithyroid		0 (0%)	4 (8%)	**0.041***
General examination				
Cyanosis		0 (0%)	1 (2%)	0.310
Pallor		0 (0%)	1 (2%)	0.410
Jaundice		1 (2%)	1 (2%)	0.560
LN enlargement		2 (4%)	2 (2%)	0.400
Vital signs				
Systolic blood pressure (mmHg)		129.18 ± 12.46	128.48 ± 14.86	0.799
Diastolic blood pressure (mmHg)		82.62 ± 6.33	81.14 ± 6.24	0.241
Pulse (beats/min)		90.92 ± 11.35	91.3 ± 8.69	0.851
Respiratory rate (breath /min)		17.4 ± 1.41	16.8 ± 1.12	**0.02***
Temperature (ºC)		37.11 ± 0.2	37.1 ± 0.42	0.879

Data are presented as mean ± SD, or frequency (%), ANA: Anti-nuclear antibody, LN : Lymph node, *: statistically significant as p value <0.05.

Table 3. Inflammatory and coagulation markers of the studied cases

		Cases (n=100)	Control (n=100)	P value
Inflammatory marker	**CRP (mg/dl)**	5.1 ±2.1	1.7 ± 0.5	**0.001***
	IL-6 (pg/ml)	216.6 ±29	53 ±12.6	**0.001***
	ESR (mm/hr.)	22.9 ±7.2	5.8 ± 3.7	**0.001***
Coagulation marker	**D dimer**	730 ±211	253 ± 31.4	**0.001***
	Clotting time (min)	9.7±1.6	6.4 ±1.5	**0.001***
	PT (sec)	11.6 ±1.2	9.9 ±0.87	**0.001***
	PTT (sec)	33.8±3.4	30.4 ±3.9	**0.001***
	INR	0.98 ±0.09	0.93±0.07	**0.001***
	Platelets (*10^9/L)	264 ±76	267 ±79	0.820
		Acute (n=50)	**Chronic (n=50)**	**P value**
Inflammatory marker	**CRP (mg/dl)**	7 ± 1.3	3.4 ± 1.2	**<0.001***
	IL-6 (pg/ml)	240.2 ± 21.6	193.1 ± 10	**<0.001***
	ESR (mm/hr.)	25.4 ± 6	20.6 ± 7.5	**<0.001***
Coagulation marker	**D dimer**	908.6 ± 72	551.6 ± 142.5	**<0.001***
	Clotting time (min)	9.8 ± 1.5	9.6 ± 1.8	0.545
	PT (sec)	12 ± 1.1	11.3 ± 1.4	**0.006***
	PTT (sec)	34 ± 3.8	33.8 ± 3.3	**0.042***
	INR	1 ± 0.1	1 ± 0.1	0.777
	Platelets (*10^9/L)	252.9 ± 80.7	274.8 ± 70.4	0.151

Data are presented as mean ± SD, CRP: C-reactive protein, Il-6: Interleukin-6, ESR: erythrocyte sedimentation rate, *: statistically significant as p value <0.05.

Table 4. Correlation between inflammatory and coagulation markers and demographic data and disease parameter

		IL-6	CRP	ESR
Inflammatory and coagulation markers				
IL6	**r**	---	0.770**	0.780**
	P	---	<0.001*	<0.001*
CRP	**r**	0.770**	---	0.771**
	P	<0.001*	---	<0.001*
ESR	**r**	0.780**	0.771**	---
	P	<0.001*	<0.001*	---
D-dimer	**r**	.833**	0.790**	0.765**
	P	<0.001*	<0.001*	<0.001*
Pt	**r**	0.528**	.547**	0.436**
	P	<0.001*	<0.001*	<0.001*
CT	**r**	0.612**	.607**	00.590**
	P	<0.001*	<0.001*	<0.001*
INR	**r**	.154*	0.111	0.092
	P	0.03*	0.118	0.194
PTT	**r**	.351**	.310**	.310**
	P	<0.001*	<0.001*	<0.001*
platelet	**r**	-0.031	-0.057	0.084
	P	0.662	0.42	0.238
Disease parameters and Inflammatory markers				
Duration	**r**	-0.79**	-0.72**	-0.40**
	P	<0.001*	<0.001*	<0.001*
Type (acute, chronic)	**r**	-0.85**	-0.79**	-0.29**
	P	<0.001*	<0.001*	0.003*
Angioedema	**r**	0.21	0.01	-0.03
	P	0.03*	0.90	0.75
Itch	**r**	0.75**	0.60**	0.53**
	P	<0.001*	<0.001*	<0.001*
Hives	**r**	0.63**	0.38**	0.41**
	P	<0.001*	<0.001*	<0.001*
UAS daily	**r**	0.67**	0.49**	0.44**
	P	<0.001*	<0.001*	<0.001*
UAS7	**r**	0.67**	0.55**	0.48**
	P	<0.001*	<0.001*	<0.001*

Inflammatory marker and demographic data		**Age**	**Sex**
IL-6	**r**	-.708**	0.033
	P	<0.001*	0.741
CRP	**r**	-.768**	-0.176
	P	<0.001*	0.079
ESR	**r**	-.318**	-0.06
	P	<0.001*	0.553
Coagulation markers and demographic data			
D dimer	**r**	-.826**	0.01
	P	0.001*	0.89
PT	**r**	-.212*	-0.001
	P	0.03*	0.98
CT	**r**	0.04	-0.02
	P	0.691	0.84
INR	**r**	.319**	-0.16

	r	0.001*		0.10		
PTT	**P**	-0.02		0.11		
	r	0.795		0.25		
Platelet count	**P**	0.166		0.07		
	r	0.099		0.43		
		D -dimer	**PTT**	**CT**	**INR**	**PTT**
Duration of disease	**r**	-.756**	-.269**	-0.047	0.186	-0.025
	P	<0.001*	0.007*	0.643	0.06	0.803
Type of urticaria	**r**	-.846**	-.278**	-0.07	0.184	-0.044
	P	<0.001*	0.005*	0.49	0.06	0.662
Angioedema	**r**	.270**	.228*	-0.023	-.347**	0.02
	P	0.007*	0.02*	0.822	<0.001*	0.845
Itch	**r**	.766**	0.138	0.003	-.328**	0.083
	P	<0.001*	0.172	0.979	0.001	0.409
Hives	**r**	.551**	0.015	-0.163	-0.11	0.135
	P	<0.001*	0.88	0.104	0.277	0.18
UAS daily	**r**	.741**	0.051	-0.069	-.314**	0.081
	P	<0.001*	0.61	0.494	0.001*	0.422
UAS7	**r**	.815**	0.034	-0.068	-.351**	0.068
	P	<0.001*	0.73	0.50	<0.001*	0.50

r: correlation coefficient, UAS: urticaria activity score, CRP: C-reactive protein, Il-6: Interleukin-6 , ESR: erythrocyte sedimentation rate, *: statistically significant as p value <0.05. ** Correlation is significant at the 0.01 level (2 tailed). * Correlation is significant at the 0.05 level (2-tailed).

Also, our results matched with Carvallo et al., [20] who reported that UAS7 correlated positively with D-dimer levels. According to the finding of the current study, We suggested that utilizing measurements of IL-6, CRP ,ESR and D-dimer could be beneficial in the clinical practice for assessing the efficacy of therapy and the progression of disease, given its correlation with disease activity and severity. Nevertheless, the application of CRP and ESR in a clinical context needs careful consideration, as it should be taken into account that certain patients with CSU may present with comorbid conditions, wherein elevated CRP levels could also be observed [18]. The result of our research indicated a positive correlation between angioedema and D dimer. In contrast to the findings of Carvallo et al., [20] and Dabas et al., [21]. The occurrence of angioedema in CSU has been associated with a prolonged duration of the disease, whereas the presence of coexisting D-dimer has been correlated with heightened disease activity. Consequently, it was observed to be elevated in patients with uncontrolled CSU [22].

4. Conclusions

IL-6, CRP, ESR, D-dimer, PT, PTT and CT could serve as available cheap biomarkers for detection of the coagulation defect that can be encountered in urticarial. This is supposed to be responsible for expected prognosis and marker for the progression of the treatment response. They also can serve as reliable markers in chronic urticaria to indicate disease chronicity and activity.

References

[1] P. Kolkhir, A.M. Giménez-Arnau, K. Kulthanan, J. Peter, M. Metz, M. Maurer. (2022). Urticaria. Nature Reviews Disease Primers. 8 (1) 61.

[2] E. Celik, E. Dirican. (2020). Can we predict the duration of treatment requirement by complete blood count in chronic spontaneous urticaria patients receiving omalizumab?. Dicle Tıp Dergisi. 47 (3) 568-577.

[3] R. Grzanka, A. Damasiewicz-Bodzek, A. Kasperska-Zajac. (2018). Interplay between acute phase response and coagulation/fibrinolysis in chronic spontaneous urticaria. Allergy, Asthma & Clinical Immunology. 14 1-8.

[4] P.I. Uysal, Y. Hayran, N. Akdoğan, A. Öktem, A. Atılan, G.G. Aksoy, B. Yalçın. (2018). Effect of omalizumab therapy on coagulation parameters and total immunoglobulin E levels in patients with chronic idiopathic urticaria and bullous pemphigoid. Turk Dermatoloji Dergisi. 12 (4) 159.

[5] Y. Mostmans, K. De Smedt, B. Richert, D. Elieh Ali Komi, M. Maurer, O. Michel. (2021). Markers for the involvement of endothelial cells and the coagulation system in chronic urticaria: A systematic review. Allergy. 76 (10) 2998-3016.

[6] Y. Zhang, H. Zhang, S. Du, S. Yan, J. Zeng. (2021). Advanced biomarkers: therapeutic and diagnostic targets in urticaria. International archives of allergy and immunology. 182 (10) 917-931.

[7] L.F. Ensina, A.P. Cusato-Ensina, R. Cardona. (2019). Advances in the pathogenesis representing definite outcomes in chronic urticaria. Current Opinion in Allergy and Clinical Immunology. 19 (3) 193-197.

[8] R.A. Sabroe, E. Fiebiger, D.M. Francis, D. Maurer, P.T. Seed, C.E. Grattan, R.M. Barr. (2002). Classification of anti-FcєRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. Journal of Allergy and Clinical Immunology. 110 (3) 492-499.

[9] R. Cuchacovich, J. Hagan, T. Khan, A. Richert, L.R. Espinoza. (2011). Tumor necrosis factor-alpha (TNF-α)-blockade-induced hepatic sarcoidosis in psoriatic arthritis (PsA): case report and review of the literature. Clinical rheumatology. 30 133-137.

[10] D. Terhorst, I. Koti, K. Krause, M. Metz, M. Maurer. (2018). In chronic spontaneous urticaria, high numbers of dermal endothelial cells, but not mast cells, are linked to recurrent angio-oedema. Clinical and Experimental Dermatology. 43 (2) 131-136.

[11] M. Columbo, E.M. Horowitz, L.M. Botana, D.W. MacGlashan Jr, B.S. Bochner, S. Gillis, L.M. Lichtenstein. (1992). The human recombinant c-kit receptor ligand, rhSCF, induces mediator release from human cutaneous mast cells and enhances IgE-dependent mediator release from both skin mast cells and peripheral blood basophils. Journal of immunology (Baltimore, Md.: 1950). 149 (2) 599-608.

[12] T. Jasinska, A. Kasperska-Zając. (2012). Soluble CD40 ligand is not elevated in plasma of patients with chronic spontaneous urticaria. British Journal of Dermatology. 167 (2) 450-452.

[13] A. Szegedi, B. Irinyi, M. Gal, J. Hunyadi, K. Danko, E. Kiss, E. Gyimesi. (2006). Significant correlation between the CD63 assay and the histamine release assay in chronic urticaria. British Journal of Dermatology. 155 (1) 67-75.

[14] B. Hermes, M. Worm, F. Nowak, R.A. Kroczek, H. Stein, B.M. Henz. (1997). Upregulation of CD40 and CD40 ligand expression in IgE-associated cutaneous diseases. Acta dermato-venereologica. 77 (6) 441-445.

[15] L. Zhang, R. Qi, Y. Yang, X. Gao, H. Chen, T. Xiao. (2019). Serum miR-125a-5p and CCL17 upregulated in chronic spontaneous urticaria and correlated with treatment response. Acta Dermato-Venereologica. 99 (6) 571-578.

[16] A. Plavsic, V. Tomic-Spiric, S. Arandjelovic, R. Miskovic, M. Dimitrijevic, A. Peric-Popadic. (2021). Biomarkers of disease activity in patients with chronic spontaneous urticaria. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii. 38 (6) 1017-1022.

[17] A. Kasperska-Zajac, A. Grzanka, A. Damasiewicz-Bodzek. (2015). IL-6 transsignaling in patients with chronic spontaneous urticaria. PloS one. 10 (12) e0145751.

[18] R.F. Criado, C.G. Bensi, P.R. Criado, M.T. Henriques, B.A.R. de Espindola, C.D.A. Machado Filho. (2021). Evaluation of serum levels of C-reactive protein, D-Dimer and Autologous Serum Skin Test in patients with Chronic Spontaneous Urticaria in a Brazilian tertiary center: a cross-sectional study. Anais Brasileiros de Dermatologia. 96 148-154.

[19] M. Kuna, M. Štefanović, B. Ladika Davidović, N. Mandušić, I. Birkić Belanović, L. Lugović-Mihić. (2023). Chronic Urticaria Biomarkers IL-6, ESR and CRP in Correlation with Disease Severity and Patient Quality of Life—A Pilot Study. Biomedicines. 11 (8) 2232.

[20] A. Carvallo, B. Veleiro, M. Sabaté-Brescó, M.L. Baeza, M. Guilarte, V. Herrera-Lasso, M. Ferrer. (2024). Serum Amyloid A as a Potential Biomarker for Disease Activity in Chronic Spontaneous Urticaria. The Journal of Allergy and Clinical Immunology: In Practice. 12 (1) 195-200.

[21] G. Dabas, V. Thakur, A. Bishnoi, D. Parsad, A. Kumar, M.S. Kumaran. (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.

[22] A.M. Giménez-Arnau, L. de Montjoye, R. Asero, M. Cugno, K. Kulthanan, Y. Yanase, A.P. Kaplan. (2021). The pathogenesis of chronic spontaneous urticaria: the role of infiltrating cells. The Journal of Allergy and Clinical Immunology: In Practice. 9 (6) 2195-2208.