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ORIGINAL RESEARCH

Psychological Wellbeing of Patients with Chronic Spontaneous Urticaria and Its Relation to Their Overall Health-Related Quality of Life

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Purpose: Chronic spontaneous urticaria (CSU) is a chronic skin disease characterized by the appearance of wheals with or without angioedema for more than 6 weeks. Its troublesome symptomatology, recurrent nature, and long-term treatment can be physically, psychologically, and economically challenging to patients adversely affecting their psychological wellbeing and health-related quality of life (HRQoL). This study aimed at (i) measuring the level of anxiety and depression in patients with CSU, (ii) evaluating their HRQoL, and (iii) assessing the relationship between psychological wellbeing and HRQoL in those patients.

Patients and Methods: In this cross-sectional study, patients with CSU (n=114) were recruited by convenience sampling from the dermatology clinic at King Saud University Medical City (KSUMC) between October 2022 and April 2024. Four datasets were collected from each patient: (i) Sociodemographic, disease-, and medication-related characteristics, (ii) anxiety level using the General Anxiety Disorder 7-Item (GAD-7) Scale, (iii) depression level via the 9-item Patient Health Questionnaire (PHQ-9), and (iv) HRQoL using the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL).

Results: The mean age was 42 (SD: 12.5) with 90.4% being females. The majority had mild-to-moderate disease activity. Around 8% reported concomitant inducible urticaria while 53.5% reported angioedema. The prevalence of patients with CSU at risk of either Generalized Anxiety Disorder (GAD) or Major Depressive Disorder (MDD) was around 28% for each. Mean CU-Q_2oL score was 35.3 (SD: 23.4). Several factors were shown to be significantly associated with higher anxiety and depression levels as well as lower HRQoL including, disease activity, presence of angioedema, drug allergy, and the use of sedative antihistamines. Multivariable regression analysis identified high anxiety and depression levels as significant independent predictors of lower HRQoL in patients with CSU.

Conclusion: Clinically significant anxiety and depression are prevalent among patients with CSU and are linked to lower HRQoL in those patients.

Keywords: chronic urticaria, quality of life, anxiety, depression, patient health questionnaire

Introduction

Chronic spontaneous urticaria (CSU) is a skin condition characterized by the spontaneous development of wheals, angioedema or both for >6 weeks.[1] In contrast to chronic inducible (physical) urticaria where a specific trigger can be identified, the cause in CSU may or may not be recognized.[1]

Although CSU is benign in nature, the disease interferes greatly with patients' daily activities which can be emotionally, physically, and economically taxing.[2] This along with the relapsing nature of the disease and its cumbersome symptoms can ultimately affect patients' psychological well-being.[3] In fact, several studies reported higher anxiety and depression levels in patients with chronic urticaria (CU).[3–5] In Saudi Arabia, almost 22 to 29% and 12.6 to 14% of patients with dermatologic conditions were reported to have anxiety and depression, respectively.[6,7] However, these studies did not include patients with CSU.[6,7] The importance of understanding the extent of the problem is underscored

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by the recognition of the bidirectional relationship between CSU and psychiatric comorbidity with each condition feeding into the other.[8–10] Thus, despite the growing global recognition of CSU's psychological burden, studies addressing the weight of the problem in Saudi Arabia are currently lacking.

The past years witnessed an increased interest in patient-reported outcomes,[11] with patient's Health-Related Quality of Life (HRQoL) becoming a fundamental indicator of the efficacy of chronic disease management.[12] A recent systematic review and meta-analysis reported a significant impairment in HRQoL in patients with CU.[13] The occurrence of anxiety and depression[14] along with many other factors such as troublesome symptomatology,[15,16] poor sleep quality,[17] impaired work productivity and absenteeism,[16,18,19] have all been linked to the low HRQoL seen in patients with CSU. Studies investigating HRQoL in patients with CSU in Saudi Arabia are scarce. A study that measured HRQoL in patients with dermatologic diseases reported that urticaria showed the greatest negative impact on HRQoL, however, patients with urticaria constituted only 13.8% of their study population.[20] With a global point prevalence of 0.7%,[21] the lack of data on psychological wellbeing and HRQoL of patients with CSU in Saudi Arabia highlights the need for studies addressing the disease's burden on those parameters.

The current study aimed at measuring (i) the level of anxiety and depression, and (ii) HRQoL in patients with CSU, as well as (iii) assessing the relationship between psychological disturbances and HRQoL in those patients.

Materials and Methods

Study Design and Patient Recruitment

This is a cross-sectional questionnaire-based study conducted at the dermatology clinic at King Saud University Medical City (KSUMC) in Riyadh, Saudi Arabia, from October 2022 to April 2024. Patients were recruited by convenience sampling. Adult patients with CSU diagnosed by a board-certified dermatologist were approached for participation in the study during their follow-up visit. Those fulfilling inclusion and exclusion criteria were invited to participate in the study. Patients were included if they had a primary diagnosis of CSU, while those presenting solely with inducible (physical) urticaria or isolated angioedema were excluded. Patients diagnosed with anxiety and/or depressive disorder, or those on conventional psychotropic medications were also excluded. Prior diagnosis with anxiety and/or depression was determined by self-report and encompassed all types of anxiety and depressive disorders including Generalized Anxiety Disorder (GAD), panic disorder, social anxiety disorder, phobias, separation anxiety, and agoraphobia as well as Major Depressive Disorder (MDD), bipolar disorder, depressive episodes, and chronic depressive disorder. Conventional psychotropic medications included: (1) Anti-depressant medications including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), (2) Anti-anxiety medications including benzodiazepines and all antidepressants mentioned above, and (3) Mood stabilizers including lithium and certain anti-convulsant specifically valproic acid and lamotrigine. Following study explanation, informed consent was obtained from all patients and data collected through face-to-face and/or phone interviews.

Data Collection Tools

Four data sets were collected from each patient, namely, (i) sociodemographic, disease- and medication-related characteristics, (ii) anxiety level using the General Anxiety Disorder 7-Item (GAD-7) Scale, (iii) depression level via the 9-item Patient Health Questionnaire (PHQ-9), and (iv) HRQoL using the Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL).

Sociodemographic, Disease-, and Medication Related Characteristics

Patients were asked about their age, gender, marital, educational, and smoking statuses. Disease-related characteristics such as presence of inducible urticaria, angioedema, coexisting allergic and/or comorbid conditions, and disease activity were also collected. Co-existing allergic and/or comorbid conditions were determined by self-report. Medication-related information was also collected including, current medication use, type of medications used, and ease of obtaining treatment for CSU.

Disease activity was assessed using the weekly Urticaria Activity Score (UAS7), a validated patient-reported outcome measure (PROM) in CSU.[1,22] The scale assesses the two major symptoms of CSU, namely, wheals and itch, every day over a period of seven days.[22] Each symptom is evaluated on a scale from 0 to 3, with 0 indicating its absence while 3 indicating more intense presence of that symptom. The sum of wheal and itch scores for each day gives the daily UAS value, while the sum of daily UAS scores over 7 days gives the patient's UAS7 score. The UAS7 score can range from 0 to 42 with higher scores indicating higher disease activity.[22] Itch and wheal scores of the 1st day were filled in by the patient at the time of the interview. Then patients were contacted daily for 6 consecutive days by members of the research team via phone call or WhatsApp message communication to document the scoring of remaining 6 days. The tool has been recommended for disease severity assessment by the international EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline in patients with urticaria.[1] A validated Arabic translation is available[23] and permission to use the Arabic translation of UAS7 has been obtained.

The General Anxiety Disorder 7-Item (GAD-7) Scale

Anxiety level was measured using the GAD-7 scale, a valid and reliable screening tool for generalized anxiety disorder in both psychiatric and general population.[24–27] It is a self-reported measure of 7-items that assesses the frequency of anxiety symptoms over the past two weeks. Each item is scored on a 4-point Likert scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The GAD-7 score is calculated by summing the scores of all seven items and ranges between 0–21. Higher scores indicate greater anxiety symptoms.[24,25] Based on their GAD-7 scores, patients are categorized into 4 anxiety severity levels; 0–4="minimal", 5–9="mild", 10–14="moderate", and 15–21="severe anxiety".[24] In addition to the previously described anxiety severity categories, several investigators proposed cutoff scores that help identify patients at risk for Generalized Anxiety Disorder (GAD).[24,26,27] Although a cutoff score of 8 was reported to have the most acceptable balance between sensitivity and specificity,[26] the same meta-analysis concluded that cutoff scores between 7 and 10 display comparable moderate-to-high pooled estimates for sensitivity and specificity.[26] Based on the above, a cutoff score of 10 was used in the current study to estimate the prevalence of GAD (GAD-7 ≥10), as it was the most widely used by several national[28–30] and international studies[24,31] with a reported pooled sensitivity and specificity of 0.74 and 0.83, respectively.[26] A validated Arabic translation of GAD-7 scale is available and permission for use was obtained.[32]

The 9-Item Patient Health Questionnaire (PHQ-9)

PHQ-9 is a valid and reliable tool for measuring depression severity level.[33] It assesses the frequency of depressive symptoms over the past two weeks using 9-items. Like GAD-7, each item is scored on a 4-point Likert scale (0=not at all to 3=nearly every day). The PHQ-9 score ranges between 0–27 and is calculated by summing the scores of all items with higher scores indicating greater severity.[33] Patients are categorized into 5 depression severity levels based on their PHQ-9 score: 0–4="minimal", 5–9="mild", 10–14="moderate", 15–19="moderately severe", and 20–27="severe depression".[33] Similar to GAD-7, several investigators proposed cutoff scores for PHQ-9 that can detect patients at risk of Major Depressive Disorder (MDD).[33–36] Although there is no agreement on the exact cutoff threshold, a meta-analysis that looked at the pooled sensitivity and specificity of different cutoff scores reported no significant difference in the diagnostic properties of PHQ-9 for scores between 8 and 11.[35] A cutoff score of 10 was used in the current study to estimate patients at risk of MDD (PHQ-9 ≥10). Firstly, it is the conventional cutoff proposed by its developers with a pooled sensitivity and specificity of 0.85 and 0.89, respectively.[33–35] Moreover, it has been used by several studies from Saudi Arabia to estimate the prevalence of MDD at the national level and in disease-specific settings.[28–30] A validated Arabic translation of PHQ-9 scale is available and permission for use was obtained.[32]

Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL)

The CU-Q_2oL is a valid and reliable disease-specific questionnaire that assesses the burden of CU on patients' HRQoL.[37] It is a 23-item questionnaire that taps into six CU-related dimensions, namely, pruritis, swelling, impact on life activities, sleep problems, limits, and looks.[37] Each item is scored on a 5-point Likert scale from 0=not at all to 4=extremely.[15] Item scores are summed up to give an overall score which is then converted to percent of maximum possible score.[15,37] Thus,

CU-Q_2oL scores range between 0–100 with higher scores signifying lower HRQoL.[37] A validated Arabic translation of the questionnaire is available and permission for use was obtained.[23]

Ethical Considerations

The study was approved by King Saud University (KSU) Institutional Review Board (IRB) with ethical approval no. (E-22-7122). Patients eligible for inclusion were identified by a board-certified dermatologist and were invited to participate in the study by members of the research team. Following study explanation, a written informed consent was obtained from those who agreed to participate in the study. All data collected was kept confidential. The study was conducted in accordance with the Declaration of Helsinki. The GAD-7 and PHQ-9 scales are in the public domain and no permission required to reproduce, translate, display or distribute. While the Arabic versions of both questionnaires were obtained from the translator.[32] Permission to use the Arabic version of the CU-Q_2oL was obtained from the translators.[23]

Statistical Analysis

Data were analyzed using SPSS version 29. Continuous variables were described using mean ± SD and/or median and interquartile range (IQR), while frequency and proportions were used to describe categorical variables. Continuous outcome variables (GAD-7, PHQ-9, and CU-Q_2oL scores) were tested for normality. Comparisons between different groups were conducted using independent *t*-test or one-way ANOVA when the outcome variable was normally distributed (CU-Q_2oL score). While Mann–Whitney and Kruskall-Wallis tests were used to conduct group comparisons when outcome variable was not normally distributed (GAD-7 and PHQ-9). To delineate the combined effects of the various variables on HRQoL, ie. CU-Q_2oL score, multiple linear regression (MLR) analysis was conducted. Predictors included in the MLR models are all variables that showed significant association ($p \leq 0.05$) with CU-Q_2oL scores on bivariate analysis. Given non-normality of both GAD-7 and PHQ-9 scores, both variables were log transformed prior to inclusion into the regression model. B coefficients, standard error (SE), and 95% confidence intervals (CI) were used to report the statistical significance and precision of results. *P*-value of <0.05 was considered significant.

Results

A total of 136 patients were recruited. Of those, seven patients did not complete the survey. Two patients had isolated inducible urticaria, while the type of urticaria was not indicated in one patient and as such were excluded. Of the remaining 126 patients, 12 had a prior diagnosis of depression and/or anxiety disorder and were thus excluded. The analysis was conducted on the remaining 114 patients.

Sociodemographic, Disease-, and Medication-Related Characteristics

The average age of studied patients with CSU was 42 (*SD* = 12.5) with 90.4% of them being females. The largest proportion were married (64%) and had university level education (64.9%). Forty-three percent of participants were employed, and most were non-smokers (93.9%) (Table 1).

Disease duration ranged between 1 and 28 years with a median (IQR) of 6 (4–9) years. Most patients had isolated CSU (92.1%) with only ~8% presenting with concomitant inducible urticaria. Approximately 54% of patients reported the presence of angioedema, while 72.8% reported the co-existence of other allergic conditions. The most reported allergic condition was allergic rhinitis (~37%), followed by food allergies (~33%), bronchial asthma (25.4%), eczema (21.1%), and drug allergy (17.5%). Comorbid conditions such as hypertension, diabetes, and hypercholesterolemia were reported in ~21% of patients (Table 1). Most patients (78.1%) were taking medications for CSU with non-sedative antihistamines being the most used class of medication. A third of patients reported difficulty in obtaining treatment for CSU (Table 1).

Using the UAS7 score to assess disease activity, it was found that 33.3 and 26.3% of patients with CSU reported mild-to-moderate urticaria, respectively, while 16.7% reported severe disease (Table 1). Patients with CSU receiving sedative antihistamines and/or mast cell stabilizers showed a significantly higher disease activity (mean (SD) UAS7 score = 24.7 (6.9), and 21.9 (9.8)) compared to patients not receiving those medications (mean (SD) UAS7 score = 14.9 (10.7),

Table 1 Sociodemographic, Disease-, and Medication-Related Characteristics of Patients with CSU[a] (n=114)

Variable	n (%)
Age, mean (SD)	42 (12.5)
Gender	
Female	103 (90.4)
Male	11 (9.6)
Marital status	
Married	73 (64)
Single	30 (26.3)
Widow	5 (4.4)
Divorced	6 (5.3)
Educational level	
No formal education	6 (5.3)
School level	34 (29.8)
University level	74 (64.9)
Employment status	
Unemployed	46 (40.4)
Employed	49 (43)
Student	10 (8.8)
Retired	9 (7.9)
Current smoking status[b]	
Smoker	5 (4.4)
Non-smoker	107 (93.9)
Disease-related characteristics	
Disease duration (years)[c], median (IQR)	6 (4–9)
Type of chronic urticaria	
CSU	105 (92.1)
CSU with inducible urticaria	9 (7.9)
Presence of angioedema	
Yes	61 (53.5)
No	53 (46.5)
Disease activity (UAS7[d] score) (n=111)[e]	
Itch & hive free	3 (2.6)
Well-controlled urticaria	21 (18.4)
Mild urticaria	38 (33.3)
Moderate urticaria	30 (26.3)
Severe urticaria	19 (16.7)
Co-existence of other allergic conditions	
Yes	83 (72.8)
No	31 (27.2)
Types of coexisting allergic conditions[f]	
Allergic rhinitis	42 (36.8)
Food allergy	37 (32.5)
Bronchial asthma	29 (25.4)
Drug allergy	20 (17.5)
Skin (eczema)	24 (21.1)
Presence of comorbid conditions	
Yes	24 (21.1)
No	90 (78.9)

(*Continued*)

Table 1 (Continued).

Variable	n (%)
Types of comorbid conditions	
Hypertension	7 (6.1)
Diabetes	10 (8.8)
Hypercholesterolemia	6 (5.3)
Other[g]	16 (14)
Medication-related characteristics	
Taking medication for CSU	
Yes	89 (78.1)
No	25 (21.9)
Type of medication used for CSU	
Non-sedative antihistamines	81 (71.1)
Sedative antihistamines	11 (9.6)
Mast cell stabilizers	14 (12.3)
Systemic steroids	7 (6.1)
Omalizumab	7 (6.1)
Difficulty obtaining treatment for CSU[b]	
Yes	37 (32.5)
No	75 (65.8)

Notes: [a]CSU = Chronic Spontaneous Urticaria. [b]Data for current smoking status and difficulty obtaining treatment for CSU was missing from two patients (n=112). [c]Disease duration was missing from 4 patients (n=110). [d]The UAS7 = Urticaria Activity Score over 7 days. [e]Data for the UAS7 score was missing from 3 patients (n=111), while 20 patients filled the daily UAS score for some days but not all seven days. For those patients (n=20), the total UAS7 score was calculated by calculating the mean daily UAS score for the days that have been filled and using it to correct for the missing days. [f]Few patients (n=4) missed answering the questions concerning the presence of another allergic condition. [g]Other comorbid conditions include; thyroid disease (n=4), osteoporosis (n=1), rosacea (n=3), rheumatic disease (n=2), polycystic ovarian syndrome (PCOS) (n=2), gastro-esophageal reflux disease (GERD) (n=2), and platelet disorder (n=2).

p =0.004, and 15 (10.7), p =0.026, respectively). No significant difference in disease activity was detected in relation to any of the other sociodemographic, disease-, and medication-related characteristics (Supplementary Table 1).

Anxiety and Depression Levels in Patients with CSU and Their Relation to Sociodemographic, Disease-, and Medication-Related Characteristics

The median anxiety and depression levels in the studied patient population were 6 (IQR = 2–12) and 5 (IQR = 1.75–11), respectively. Most patients (40.4%) had minimal anxiety, while 11.4 and 16.7% of patients with CSU reported moderate and severe anxiety levels, respectively. Comparably, 45.6% had minimal depression while 14, 7.9, and 6.1% of patients reported moderate, moderately severe, and severe depression levels, respectively (Figure 1). A cutoff threshold at 10 for both GAD-7 and PHQ-9 have been used to detect patients at risk of GAD[26,27] and MDD, respectively.[34,35] Patients at risk of GAD (GAD-7 score ≥10) are those that fall collectively within moderate and severe anxiety categories amounting for 28.1% of patients with CSU (Figure 1). Similarly, the percentage of patients at risk of MDD (PHQ-9 ≥10) was 28% representing the sum of patients within moderate, moderately severe, and severe depression categories (Figure 1).

Various sociodemographic, disease-, and medication-related factors were shown to affect anxiety and depression levels in patients with CSU. Higher educational level was significantly associated with lower anxiety and depression levels (p = 0.020 and 0.027, respectively) (Table 2).

Patients with CSU who reported angioedema and the presence of another allergic condition displayed significantly higher anxiety and depression levels when compared to those without these conditions (Table 2). Whereas, patients with

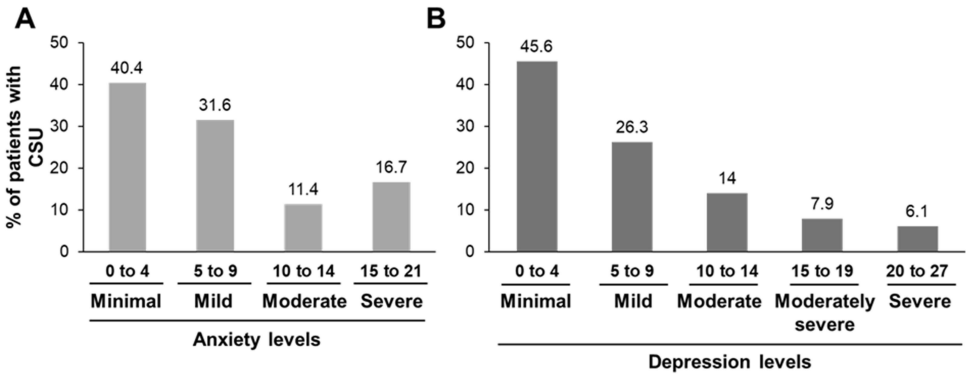

Figure 1 Levels of anxiety (**A**) and depression (**B**) in patients with CSU (n=114) measured using the GAD-7 and PHQ-9 questionnaires, respectively. (**A**) shows the percentage of patients with CSU in the different anxiety severity categories. The x axis depicts GAD-7 score ranges and their corresponding anxiety severity levels. Patients with GAD-7 scores ≥ 10, ie those within the moderate to severe categories, are at risk of GAD. (**B**) shows the percentage of patients with CSU in the different depression severity categories. The x axis depicts PHQ-9 score ranges and their corresponding depression severity levels. Patients with PHQ-9 scores ≥ 10, ie those within the moderate to severe categories, are at risk of MDD.

concurrent inducible urticaria had a significantly higher anxiety level only compared to those with isolated CSU (median (IQR) = 14 (8–19.5) vs 6 (1.5–9.5), p =0.0005). Looking at the different allergic conditions, significantly higher anxiety and depression levels were reported in patients who have concomitant drug allergies and eczema, whereas those with concurrent allergic rhinitis and food allergy displayed a significant increase only in depression level (Table 2). Use of sedative antihistamines was associated with a significant increase in both anxiety and depression levels (median (IQR) = 9 (6–17) and 13 (5–18), respectively) compared to patients not using them (median (IQR) = 6 (1–11), p = 0.037 and 5 (1–10), p = 0.008, respectively) (Table 2).

There was a noticeable increase in both anxiety and depression levels as disease activity increased (p = 0.007 and $p <$ 0.001), respectively (Table 2). Whereas, no significant correlation was detected between disease duration and anxiety (r_s =0.108, n = 110, p = 0.263) nor with depression levels (r_s = 0.107, n = 110, p = 0.266) in the current patient population (Table 2). To ease the comparison with other studies, corresponding mean (SD) values for GAD-7 and PHQ-9 scores were included in Supplementary Table 2.

HRQoL in Patients with CSU

HRQoL and Its Relation to Sociodemographic, Disease-, and Medication-Related Characteristics

The average CU-Q_2oL score in patients with CSU included in the current study was 35.3 (*SD* = 23.4) (Table 2). The factors identified to be significantly associated with lower HRQoL included, presence of angioedema, higher disease activity, concomitant food and drug allergy, as well as the presence of bronchial asthma (Table 2). Additionally, patients taking sedative antihistamines and/or mast cell stabilizers had a significantly lower HRQoL compared to those not taking

Table 2 Differences in the Levels of Anxiety, Depression, and HRQoL in Patients with CSU in Relation to the Various Sociodemographic, Disease-, and Medication-Related Characteristics (n=114)

Variable	n	Anxiety Level (GAD-7 Score[a])		Depression Level (PHQ-9 Score[a])		HRQoL (CU-Q2oL Score)[b]	
		Median (IQR)	p[c]	Median (IQR)	p[c]	Mean (SD)	p[d]
Overall	114	6 (2–12)	–	5 (1.75–11)	-	35.3 (23.4)	
Gender							
Female	103	6 (2–12)	0.180	5 (2–11)	0.171	36.0 (23.5)	0.368
Male	11	4 (0–7)		2 (0–7)		29.3 (22.2)	

(*Continued*)

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Table 2 (Continued).

Variable	n	Anxiety Level (GAD-7 Score[a])		Depression Level (PHQ-9 Score[a])		HRQoL (CU-Q2oL Score)[b]	
		Median (IQR)	p^c	Median (IQR)	p^c	Mean (SD)	p^d
Marital status							
Married	73	6 (1.5–12)	0.876	5 (1–11)	0.530	36.4 (25.2)	0.832
Single	30	7 (2–13.25)		6.5 (2–12.25)		33.1 (21.8)	
Widow	5	9 (2–17.5)		9 (3.5–14)		39.1 (16.9)	
Divorced	6	6 (4–8)		5 (1.5–5.5)		29.9 (12.8)	
Educational level							
No formal education	6	11.5 (3–16.25)	0.020	9.5 (5.5–17.25)	0.027	29.7 (9.0)	0.265
High school level or less	34	8 (5–13.5)		7.5 (2.75–11.25)		40.7 (21.3)	
University graduate	74	4 (1–9.25)		3.5 (1–8.25)		33.3 (24.8)	
Employment status							
Unemployed	46	5.5 (1.75–13.25)	0.968	5 (2–9.5)	0.702	39.4 (24.3)	0.197
Employed	49	7 (0.5–13)		6 (1–11.5)		33.8 (22.3)	
Student	10	6.5 (2.75–7.25)		2.5 (0.75–8.25)		22.4 (17.8)	
Retired	9	5 (2.5–6.5)		4 (1.5–15)		37.2 (27.2)	
Current smoking status[e]							
Smoker	5	7 (2.5–15)	0.615	7 (2.5–15.5)	0.484	42.2 (25.3)	0.477
Non-smoker	107	6 (2–12)		5 (1–11)		34.5 (23.3)	
Disease-related characteristics							
Disease duration	110	6 (2–12)	0.263[f]	5 (2–11)	0.266[f]	35.8 (23.6)	0.217[f]
Type of chronic urticaria							
CSU	105	6 (1.5–9.5)	0.005	5 (1.5–11)	0.134	34.2 (22.8)	0.085
CSU with inducible urticaria	9	14 (8–19.5)		9 (2–20.5)		48.2 (28.2)	
Presence of angioedema							
Yes	61	7 (3–15)	0.034	6 (2–12.5)	0.016	42.1 (25.3)	<0.001
No	53	4 (1–9.5)		3 (1–8.5)		27.5 (18.2)	
Disease activity (UAS7 score)[g]							
Itch & hive free	3	0 (0–0)	0.007	0 (0-)	<0.001	3.6 (4.5)	<0.001
Well-controlled urticaria	21	2 (0–7)		2 (0–4)		18.9 (15.6)	
Mild urticaria	38	6 (1–9)		4.5 (1.75–9)		29.6 (19.8)	
Moderate urticaria	30	7 (3.5–12.5)		6.5 (2–12)		42.7 (19.9)[#]	
Severe urticaria	19	8 (3–14)		8 (4–13)		57.4 (22.9)*	
Co-existence of allergic conditions							
Yes	83	7 (3–13)	0.006	6 (2–11)	0.004	37.8 (22.3)	0.06
No	31	3 (0–7)		2 (0–7)		28.6 (25.3)	
Types of co-existing allergic conditions							
Allergic rhinitis[h]							
Yes	42	7 (4–13.25)	0.079	7 (3–12)	0.011	39.0 (21.2)	0.212
No	71	5 (1–10)		4 (1–9)		33.3 (24.6)	
Food allergy[e]							
Yes	37	7 (4–13)	0.105	7 (2.5–14)	0.013	41.2 (20.8)	0.048
No	75	5 (1–11)		4 (1–8)		32.0 (24.0)	
Bronchial asthma[e]							
Yes	29	8 (3–15.5)	0.101	7 (2–15)	0.066	45.1 (22.0)	0.011
No	83	6 (2–9)		5 (1–9)		32.39 (23.04)	
Drug allergy[e]							
Yes	20	12 (4.5–15)	0.007	8 (3.25–13)	0.037	46.0 (21.7)	0.018
No	92	5 (1–8.75)		4.5 (1–9)		32.5 (23.1)	

(*Continued*)

Table 2 (Continued).

Variable	n	Anxiety Level (GAD-7 Score[a])		Depression Level (PHQ-9 Score[a])		HRQoL (CU-Q2oL Score)[b]	
		Median (IQR)	*p*[c]	Median (IQR)	*p*[c]	Mean (SD)	*p*[d]
Skin allergy (eczema)[i]							
Yes	24	8.5 (5.25–14.5)	0.009	7.5 (3.25–12)	0.039	40.8 (23.0)	0.171
No	86	5 (1–9)		4 (1–9)		33.36 (23.53)	
Presence of comorbid conditions							
Yes	24	6 (1.5–14.25)	0.447	6.5 (2.25–12)	0.238	38.7 (21.6)	0.423
No	90	6 (2–12)		5 (1–11)		34.4 (23.9)	
Types of comorbid conditions							
Hypertension							
Yes	7	15 (5–17)	0.099	11 (6–18)	0.073	46.4 (14.4)	0.195
No	107	6 (2–11)		5 (1–11)		34.6 (23.7)	
Diabetes							
Yes	10	10 (4.5–16.5)	0.085	8 (5.5–13.25)	0.111	40.6 (13.9)	0.461
No	104	6 (2–11.5)		5 (1–11)		34.8 (24.1)	
Hypercholesterolemia							
Yes	6	6.5 (4.5–12)	0.721	6.5 (3–9.75)	0.760	42.9 (17.1)	0.414
No	108	6 (2–12)		5 (1.25–11)		34.9 (23.7)	
Medication-related characteristics							
Taking medication for CSU							
Yes	89	6 (1.5–12)	0.665	5 (1–11)	0.353	36.5 (23.3)	0.299
No	25	7 (3–11)		6 (2–11.5)		31.0 (23.7)	
Type of medication used for CSU							
Non-sedative antihistamines							
Yes	81	6 (1.5–12.5)	0.799	5 (1–11)	0.656	36.8 (23.0)	0.298
No	33	7 (3–9.5)		5 (2–11)		31.7 (24.3)	
Sedative antihistamines							
Yes	11	9 (6–17)	0.037	13 (5–18)	0.008	58.3 (19.7)	<0.001
No	103	6 (1–11)		5 (1–10)		32.9 (22.5)	
Mast cell stabilizers							
Yes	14	7 (1.5–12.5)	0.729	5 (1.75–17.25)	0.532	48.5 (21.2)	0.024
No	100	6 (2–12)		5 (1.25–11)		33.5 (23.2)	
Systemic steroids							
Yes	7	8 (4–14)	0.403	6 (3–12)	0.631	32.6 (11.9)	0.754
No	107	6 (2–12)		5 (1–11)		35.5 (24.0)	
Omalizumab							
Yes	7	7 (0–14)	0.836	2 (0–13)	0.340	39.3 (35.5)	0.644
No	107	6 (2–12)		5 (2–11)		35.1 (22.6)	
Difficulty obtaining treatment for CSU[e]							
Yes	37	7 (2.5–12.5)	0.214	6 (2–11)	0.128	45.1 (23.6)	<0.001
No	75	5 (1–12)		4 (1–9)		29.8 (21.7)	

Notes: [a]The levels of anxiety and depression were measured using the 7-item GAD-7 and the 9-item PHQ-9 questionnaires, respectively. The questionnaires assess symptoms of anxiety and depression over the past two weeks, respectively. Each item is scored on a 4-point Likert scale. The total score reflects the sum of scores with higher scores indicating higher anxiety and depression levels. [b] The CU-Q2oL is a 23-item disease-specific questionnaire. Each item is scored on a 5-point Likert scale from 0–4 reflecting the intensity of that item over the past 14 days. A raw total score is calculated by summing the individual scores for all 23 items, which is then converted to a score from 0–100. Higher scores indicate lower HRQoL. [c]*p*-value was calculated using the Mann–Whitney test when comparing between two groups and the Kruskal–Wallis test when comparing between three or more groups. [d]*p*-value was calculated using the independent *t*-test when comparing between two groups, while one-way ANOVA test was used for comparisons between 3 groups or more followed by Bonferroni's multiple comparison test when significant. The significance level was set at *p*-value <0.05. [e]Data for smoking status, food allergy, bronchial asthma, drug allergy, and difficulty obtaining treatment was missing from two patients (n=112). [f]*p*-value calculated using Spearman correlation. [g]UAS7 = Urticaria Activity Score over 7 days. Data for the UAS7 score was missing from 3 patients (n=111), while 20 patients filled the daily UAS score for some days but not all seven days. For those patients (n=20), the total UAS7 score was calculated by computing the mean daily UAS score for the days that have been filled by the patient and using it to correct for the missing days. [h]Datum for allergic rhinitis was missing from one patient (n=113). [i]Data for skin allergy (eczema) was missing from 4 patients (n=110). *Showed significant difference (*p*-value <0.001) compared to itch and hive free, well-controlled urticaria, and mild urticaria groups following Bonferroni's multiple comparisons test. #Showed significant difference (*p*-value =0.013 and *p*-value <0.001) compared to itch and hive free, and well-controlled urticaria, respectively.

those medications (Table 2). A significantly lower HRQoL was also seen in patients who reported difficulty obtaining treatment for CSU (Table 2).

The Association Between HRQoL and Anxiety and Depression Levels in Patients with CSU

CU-Q_2oL scores were found to rise as the levels of anxiety and depression increase, indicating lower HRQoL. In fact, when compared to patients reporting minimal depression, patients with moderate, moderately severe, and severe depression showed significantly lower HRQoL ($p < 0.001$) (Figure 2). Moreover, patients with severe depression had significantly lower HRQoL when compared to those patients reporting lower depression levels (Figure 2). Patients with CSU showing severe anxiety had significantly lower HRQoL compared to patients with minimal ($p < 0.001$), mild ($p < 0.001$), and moderate ($p < 0.05$) anxiety levels (Figure 2).

Predictors of HRQoL in Patients with CSU

From the above, it becomes clear that the HRQoL in patients with CSU is negatively correlated with their anxiety and depression levels. However, a few disease- and medication-related factors were shown to be linked to patients' HRQoL as well as their psychological status, namely, the presence of angioedema, disease activity, presence of drug allergies, and use of sedative antihistamines. Thus, to investigate the independent effect of these various factors on the HRQoL of patients with CSU a multivariable regression analysis was conducted. Given the strong correlation between anxiety (GAD-7 scores) and depression (PHQ-9 scores) levels (r_s=0.841, n=114, $p < 0.001$), two separate models were employed (Table 3). Both models included all variables that showed a significant association with HRQoL in addition to either anxiety level in model 1 or depression level in model 2.

Model 1 explained 56.8% of the variation seen in HRQoL (CU-Q_2oL score), $r^2_{adjusted}$= 0.568, F (4,101) = 35.55, $p < 0.001$ (Table 3). While model 2 explained 57.2% of the variation seen in patients HRQoL (CU-Q_2oL score), $r^2_{adjusted}$= 0.572, F (4,101) = 36.03, $p < 0.001$ (Table 3). Anxiety and depression levels were shown to have a significant independent effect on HRQoL in patients with CSU. In addition, both models have shown that disease severity, presence of angioedema, and difficulty obtaining treatment for CSU are significant independent predictors of HRQoL in patients with CSU (Table 3).

Discussion

The troublesome symptoms of CSU along with its recurring nature can place a burden on both the psychological well-being as well as the HRQoL of patients suffering from the disease. The current study aimed at measuring the prevalence

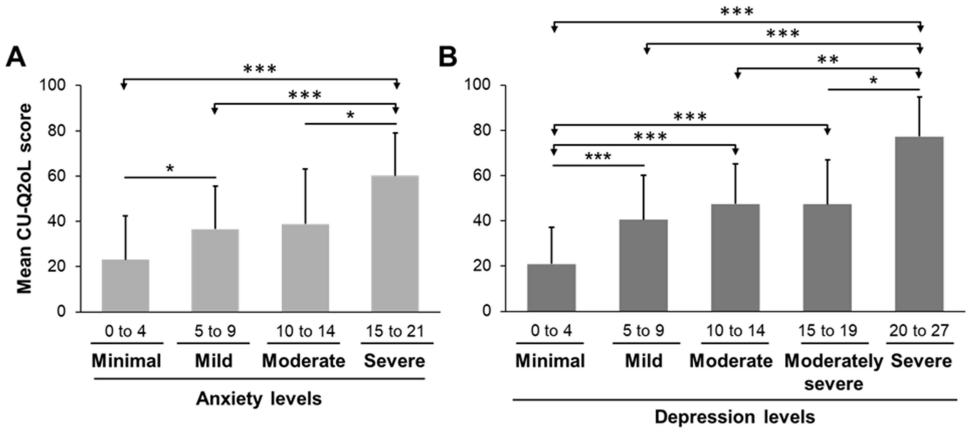

Figure 2 Differences in HRQoL in relation to (**A**) anxiety and (**B**) depression levels in patients with CSU. HRQoL was measured using the disease specific CU-Q_2oL questionnaire with a score range between 0–100. Higher scores indicate lower HRQoL. (**A**) Anxiety level was measured using GAD-7 questionnaire. GAD-7 score ranges along with their corresponding anxiety severity levels are shown on the x axis. (**B**) Depression level was measured using PHQ-9 questionnaire. PHQ-9 score ranges and their corresponding depression severity levels are shown on the x axis. Comparisons between CU-Q2oL scores among the various anxiety and depression levels were assessed using one-way ANOVA test followed by Bonferroni's multiple comparison test when significant. A significant difference in CU-Q2oL scores in relation to anxiety and depression levels were detected using one-way ANOVA, F (3,110) = 16.122, p <0.001; and F (4,109) = 21.927, p <0.001, respectively. Significance level was set at p <0.05. *p <0.05, **p <0.01, ***p <0.001.

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Table 3 Multivariable Regression Analysis of Predictors of HRQoL in Patients with CSU (n=106)

Predictors	B Coefficient	*SE*	95% CI		*p*-value
			LL	*UL*	
Model 1					
(Constant)	−2.22	3.47	−9.11	4.66	0.523
GAD-7 score	25.29	3.68	17.99	32.60	<0.001
UAS7 score	0.68	0.15	0.38	0.98	<0.001
Presence of angioedema	10.10	3.01	4.14	16.06	0.001
Difficulty obtaining treatment for CSU	9.38	3.23	2.97	15.79	0.005
Model 2					
(Constant)	−0.59	3.35	−7.24	6.07	0.862
PHQ-9 score	27.52	3.96	19.67	35.37	<0.001
UAS7 score	0.58	0.16	0.27	0.89	<0.001
Presence of angioedema	9.01	3.02	3.03	15.00	0.004
Difficulty obtaining treatment for CSU	8.63	3.23	2.22	15.04	0.009

Notes: HRQoL was assessed using the disease-specific CU-Q_2oL questionnaire that measures HRQoL in patients with CSU. Scores range between 0–100 with higher scores indicating lower HRQoL. Variables included in the model are all variables that showed a significant association with CU-Q_2oL on one-way ANOVA and independent t testing, namely, presence of angioedema, disease activity (UAS7 score), co-existing food and drug allergy, presence of bronchial asthma, sedative antihistamine and mast cell stabilizer use, difficulty obtaining treatment for CSU, and either GAD-7 score (anxiety level) in model 1 or PHQ-9 score (depression levels) in model 2. Using Spearman's rank correlation testing, a strong significant correlation (r_s=0.841, n=114, p <0.001) was detected between GAD-7 and PHQ-9, hence they were not included in the same model. GAD-7 was included in model 1 while PHQ-9 was included in model 2. Using the forward method, model 1 explained 56.8% of the variation seen in patients HRQoL (CU-Q_2oL score). $R^2_{adjusted}$= 0.568, F (4,101) = 35.55, p <0.001. While model 2 explained 57.2% of the variation seen in patients HRQoL (CU-Q_2oL score). $R^2_{adjusted}$= 0.572, F (4,101) = 36.03, p <0.001. In both models, excluded variables are: use of sedative antihistamine, use of mast cell stabilizers, presence of food and drug allergy, and presence of bronchial asthma. Log transformed GAD-7 and PHQ-9 scores were used in model 1 and 2, respectively. p <0.05 was considered significant.
Abbreviations: SE, Standard error; CI, confidence interval; LL, lower limit; UL, upper limit.

of anxiety and depression in patients with CSU and their association with patients' HRQoL. A total of 28.1% of CSU patients reported moderate-to-severe anxiety (GAD-7 ≥ 10) putting them at risk for GAD. Similarly, 28% were found to have moderate to severe depression (PHQ-9 ≥ 10) and at risk for MDD. Higher anxiety and depression levels were associated with lower HRQoL in patients with CSU. After correcting for confounders, higher anxiety and depression along with presence of angioedema, higher disease activity, and difficulty obtaining treatment for CSU were identified as independent predictors for lower HRQoL in patients with CSU. These findings emphasize the importance of assessing mental health of patients affected by CSU during clinic visits and follow up to allow early detection and proper intervention aiming to improve patients' HRQoL.

Although higher anxiety and depression in patients with CSU have been clearly described in the literature, the reported burden is greatly variable. This variability stems from differences in study design, patient population characteristics, methodology and tools used to assess anxiety and depression. A case–control study conducted using a national database reported that 9.6 and 11% of their CSU patients had anxiety and depression, respectively.[4] While another smaller scale case–control study reported values as high as 92 and 72% for anxiety and depression, respectively.[17] The latter included a small number of participants with higher disease activity, as judged by their raised mean (SD) UAS7 score of 39.7 (2.8).[17] While, the former lacked description of their population's disease-related parameters to enable such extrapolations.[4] Using data from the 2020 National Health and Wellness Survey (NHWS) from 5 European countries, Balp et al found that 72.4 and 75.7% patients with CSU had some form of anxiety and depression, respectively compared to 39.6 and 45.1% of adults from the full NHWS sample.[38] However, they used a cutoff of 5 for GAD-7 and PHQ-9 which is lower than the cutoff used in the current study.[38] Two case–control studies from Turkey found higher anxiety and depression scores in patients with CSU compared to controls with 48 to almost 59% of CSU patients having anxiety and/or depression.[5,39] Although a prevalence of 28% for moderate-to-severe anxiety and/or depression is lower than

those reported in the above studies,[5,17,38,39] it is comparable to the overall prevalence reported in a systematic review (SR) and meta-analysis (MA) that included a total of 25 studies.[40] This SR and MA reported an overall prevalence of 31.6% for any psychiatric comorbidity in patients with CSU with anxiety and mood disorders being reported in 30.6 and 29.4% of patients.[40] Moreover, the current study aligns with other real-life studies that reported anxiety and depression among the most common comorbidities observed in patients with CSU with a prevalence ranging between 23 to 24.6%.[38,41] At the national level, two studies reported the occurrence of anxiety and depression in 22.1–29% and 12.6–14% of dermatologic patients, respectively.[6,7] However, neither of the studies included patients with CSU.[6,7] To the knowledge of the authors, this is the first report on the prevalence of anxiety and depression in patients with CSU from Saudi Arabia. The demonstration that ~28% of CSU patients were at risk of MDD or GAD is much higher than the reported national prevalence for both conditions in Saudi Arabia.[28,29] The national prevalence for developing MDD and GAD reported by BinDhim et al and Alhabeeb et al ranged between 14.9–12.7% and 12.4–11.4%, respectively.[28,29] It is worth noting that both studies used the same tools used in the current study and implemented the same cutoff point to assess both conditions.[28,29] This highlights the burden of psychiatric comorbidities in patients with CSU.

Several factors were significantly associated with higher anxiety and depression levels in patients with CSU in the current study, namely, lower education level, concomitant presence of inducible urticaria and angioedema, higher disease activity, co-existing allergic condition especially eczema and drug allergy, as well as use of sedative antihistamines. The higher anxiety and depression levels observed in patients receiving sedative antihistamines may be attributed to higher disease activity compared to those not receiving them (mean UAS7 (SD) = 24.7 (6.9) vs 14.9 (10.7), respectively). Higher disease activity was shown to be associated with higher anxiety and depression levels in the current study and by other investigators.[3,39,42] The negative impact of angioedema on patients' psychological wellbeing aligns with those documented by Badura and Brzoza[43] and should be taken seriously especially that it occurs in half or more of patients with CSU as reported in the current study and many others.[18,39,41,44] Fear of suffocation secondary to involvement of the upper airway[45] along with the emotional and social distress incited by it affecting a visible and sensitive area like the face may underlie such an association. In fact, patients with concomitant angioedema were shown to have lower sense of coherence, a measure that reflects a person's ability to cope with stress, which correlated negatively with their anxiety level.[46] CSU patients with drug allergy constituted 17.5% of the study sample and displayed significantly higher anxiety and depression level compared to those not reporting drug allergy. The co-occurrence of drug allergy with CSU[47,48] and its negative impact on the psychological wellbeing of patients is well documented.[49–51] Allergy to more than one drug was reported in 38% of patients with CU.[48] Patients with drug allergy/hypersensitivity were shown to display significantly higher neuroticism, anxiety, and depression compared to controls.[50–53] Moreover, in a recent UK population-based retrospective cohort, patients with drug allergy had significantly higher risk for anxiety and depression with an adjusted hazards ratio (aHR) of 1.36 (95% CI=1.34–1.37, $p<0.001$) and 1.27 (95% CI=1.25–1.28, $p<0.001$), respectively compared to matched individuals without atopy.[49] Many factors have been proposed to explain the association between drug allergy and psychological disturbances. Vigilance and increased restrictions imposed by drug allergy, along with the unpredictability of the episodes can put patients under heightened psychological stress especially that the consequent effects can be life-threatening.[49,54] The picture is further complicated by sleep disturbances that generally accompany atopic reactions negatively impacting the mental wellbeing of patients.[39,55–57] A body of literature has also proposed a biological link between CSU and psychological status. The activation of mast cells (MCs) in the skin, a key player in CSU pathogenesis, causes its degranulation and subsequent release of several compounds including histamine, serotonin, and inflammatory cytokines.[9,58] Apart from their role in bringing about disease manifestations of swelling and redness, some of these mediators can stimulate nearby sensory nerve endings leading to the release of substance P (SP).[9,58] SP can bind receptors on MCs inducing degranulation and release of more inflammatory mediators that exacerbate the condition.[9,58,59] Moreover, chronic allergic conditions are associated with a low grade chronic inflammatory state that have been linked to increased risk of depression.[60–62] Additionally, stress via its activation of the hypothalamic-pituitary and sympatho-adrenomedullary axes modulates the immune system which may play a role in precipitating or aggravating atopy.[9,10,58] Although the above represents an oversimplified view of the complex interplay that occur between immune cells and sensory nerves in the skin, it highlights the bidirectional nature of the relationship.[9,10] Taken together, the

presence of CSU can disturb the psychological wellbeing of a person suffering from the disease, which in turn aggravates the inflammatory process inciting a vicious cycle that negatively impacts both the patients' disease and their mental state.

This calls for a more holistic bio-psycho-social approach when managing patients with CSU.[8,63,64] In fact, psychological intervention in the form of brief behavioral activation treatment in patients with CSU and depression reduced depression and improved urticaria control.[65]

Apart from its effect on patients' psychological well-being, CSU has a considerable impact on their HRQoL.[13,15] A recent meta-analysis of 123 studies involving more than 23,000 patients showed that CU causes moderate-to-severe HRQoL impairment.[13] In Saudi Arabia, two studies reported low HRQoL in patients with dermatologic disease. One of which did not include patients with CSU while in the other they constituted 13.8% of enrolled dermatologic patients.[6,20] Yet Alotaibi et al showed that patients with CSU were among those showing the largest effect on HRQoL.[20] Contrary to the generic tool used by Alotaibi et al, the current study applied a disease-specific tool to measure HRQoL in patients with CSU and reported a mean (SD) CU-Q_2oL score of 35.3 (23.4).[20] This figure is comparable to that reported by Dias et al (36 ± 22) but lower than those described by others.[3,15,23,66] The study by Almeida et al had a higher proportion of CSU patients with concomitant angioedema compared to the current study[15] While Tawil et al enrolled a higher proportion (46.2%) of patients with severe disease activity compared to 16.7% in the current study.[23] Both of these factors were shown in the current study to negatively affect patients' HRQoL which may explain the differences in reported scores. In addition to angioedema and disease activity, the presence of bronchial asthma and drug allergy, use of sedative antihistamines and mast cell stabilizers, as well as difficulty obtaining treatment for CSU were also found to be significantly associated with decreased HRQoL in patients with CSU in the current study. Patients taking sedative antihistamines and mast cell stabilizers displayed significantly higher UAS7 scores, indicating more active disease, compared to those not taking those medications, which may explain the lower HRQoL observed in those patients. Apart from that, no significant difference in disease activity was detected in patients having any of the above-mentioned factors compared to those without. These findings agree with those reported by other investigators. Angioedema,[43] increased disease activity,[3,39] bronchial asthma,[67,68] and drug allergy[54] were all linked to lower HRQoL.

The occurrence of anxiety and depression in patients with CSU has also been linked to lower HRQoL.[15,69–71] The findings of the current study corroborated these earlier reports with the demonstration of a significant decrease in HRQoL as the level of anxiety and depression increases. Given that many factors that were linked to lower HRQoL in patients with CSU in the current study were also shown to be associated with higher anxiety and depression levels, correcting for confounders was important. Using multivariable regression analysis, an independent effect for anxiety and depression levels on HRQoL of patients with CSU was demonstrated. These findings are consistent with previous research indicating that psychiatric comorbidities, including anxiety and depression, negatively affect the HRQoL in patients with CSU.[69–71] Depression has been linked to low adherence in chronic diseases.[72] In the case of CSU, poor adherence may lead to worsening symptoms and inadequate disease control inciting a vicious cycle of events that will further worsen patients' psychological status and HRQoL. These findings stress the importance of incorporating mental state assessment in the management of patients with CSU.

Unfortunately, the current study did not assess sleep quality which is known to be affected in patients with CSU and to influence both psychological status and HRQoL. However, adding an additional scale to the multiple questionnaires used in the current study would have made it even more challenging to recruit patients and maintain consistent follow-up throughout the study period. The use of questionnaires constitutes a limitation given their potential inaccuracy and susceptibility to social desirability and recall bias. Moreover, the temporal relationship between the different variables and hence causality cannot be established in view of the cross-sectional nature of the study. Selection bias cannot be ruled out given that patients were recruited by convenience sampling from one clinic in a tertiary care center.

Conclusion

In conclusion, the findings of the current study highlight the burden of CSU on the psychological wellbeing of patients suffering from the disease and underscore its independent negative effect on patients' perceived HRQoL. In addition to anxiety and depression levels, the presence of angioedema, higher disease activity, and difficulty finding treatment were also identified as independent predictors of lower HRQoL in patients with CSU. It is recommended that patients' clinical

evaluation includes a careful assessment of these factors to help identify those at risk of developing psychological disturbances and low HRQoL allowing for early intervention and aiming to alleviate the disease's impact on their HRQoL.

Abbreviations

CSU, Chronic Spontaneous Urticaria; CU, Chronic Urticaria; HRQoL, Health-Related Quality of Life; KSUMC, King Saud University Medical City; GAD-7, General Anxiety Disorder 7-Item Scale; PHQ-9, 9-item Patient Health Questionnaire; CU-Q_2oL, Chronic Urticaria Quality of Life Questionnaire; UAS, Urticaria Activity Score; UAS7, Urticaria Activity Score over 7 days; PROM, Patient-reported Outcome Measure; EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI, European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/Asia Pacific Association of Allergy, Asthma and Clinical Immunology; KSU, King Saud University; IRB, Institutional Review Board; SE, Standard Error; CI, confidence intervals; IQR, interquartile range; SD, Standard Deviation; NHWS, National Health and Wellness Survey; SR, Systematic Review; MA, Meta-analysis; aHR, Adjusted Hazards Ratio; MCs, Mast cells; SP, substance P.

Data Sharing Statement

Data supporting the results reported in the manuscript are available with the corresponding author and can be shared upon request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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