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 ANXIETY AND DEPRESSION IN PREDICTING THE RISK OF CHRONIC SPONTANEOUS  
 URTICARIA (CSU) AND ATOPIC DERMATITIS (AD)

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 შფოთვა და დეპრესია ქრონიკული სპონტანური ურტიკარიის (CSU) და ატოპიური დერმატიტის  
 (AD) რისკის პროგნოზირებაში

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის, ალერგოლოგიისა და კლინიკური  
 იმუნოლოგიის დეპარტამენტი, თბილისი, საქართველო

### რეზიუმე

წინა კვლევებმა აჩვენა, რომ შფოთვა და დეპრესია დაკავშირებულია კანის ბევრ ქრონიკულ დაავადებასთან, მათ შორის ქრონიკულ სპონტანურ ურტიკარიასა (CSU) და ატოპიურ დერმატიტთან (AD). ამ ფენომენებს შორის მიზეზ-შედეგობრივი კავშირი ჯერ კიდევ არ არის დადგენილი. ავტორთა უმეტესობა თვლის, რომ ეს ქავილით მიმდინარე მგომარეობები ხშირად იწვევს შფოთვას, დეპრესიას და უძილობას. ჩვენ შევეცადეთ შეგვეფასებინა შფოთვისა და დეპრესიის, როგორც CSU-ისა და AD-ის რისკის ფაქტორების, პროგნოზირებადი მნიშვნელობა. მიზნის განსაზოციელებლად ჩატარებული იქნა პროსპექტული ობსერვაციული კლინიკური კვლევა ლოგისტიკური რეგრესიის გამოყენების საშუალებით. კვლევაში მონაწილეობდა თსსუ-ის საუნივერსიტეტო კლინიკებში 2018-2021 წ.წ. რეგისტრირებული CSU-ით დაავადებული 120 და AD-ით დაავადებული 110 პაციენტი. შესწავლილ ჯგუფებში რისკის კონცენტრაციის შედარება განხორციელდა ლორენცის მრუდის მიხედვით და ჯინის კოეფიციენტის გაანგარიშებით. კვლევის შედეგად დადგინდა, რომ დეპრესია და შფოთვა განიხილება მნიშვნელოვან რისკ-ფაქტორებად CSU-ის და, ნაკლებად, AD-ის განვითარებისთვის. ლორენცის მრუდი ახასიათებს ავადობის რისკის კონცენტრაციას ყველაზე მნიშვნელოვანი საფრთხის მქონე პირებში. მისი წარმატებით გამოყენება შესაძლებელია CSU-ის განვითარების პროგნოზირებისთვის.

**Introduction.** Previous research has shown that anxiety and depression are associated with many chronic skin diseases, including chronic spontaneous urticaria (CSU) and atopic dermatitis (AD) [1, 8, 13, 17, 18]. A causal relationship between these phenomena has not yet been established [7, 14, 19]. Most authors believe that these itchy conditions cause anxiety, depression, and insomnia rather than the other way around. The publications consider several possible mechanisms to explain the coexistence of CSU/AD with anxiety and depression. However, the inverse relationship between these states has not yet been studied. Therefore, the predictive value of these neuropsychiatric conditions in developing atopic dermatitis and chronic spontaneous urticaria is still unknown. In our work, we attempted to assess the predictive value of anxiety and depression as risk factors for chronic urticaria and atopic dermatitis.

Developing risk prediction new tools have become an important research topic for methodologists in recent years [15]. The most commonly used methods are disease risk variation, which evaluates whether the disease burden for a particular subgroup exceeds a selected threshold. One of the research methods is logistic regression by constructing the Lorenz curve [4]. When predicting disease risk using this method, the cumulative proportion of individuals at risk (y-axis) is ranked from lowest to highest. The abscissa represents the cumulative percentage of risk, and the cumulative number of people predicted to have a particular disease (i.e., the estimated total disease burden) [9].

We aimed to investigate the impact of depression and anxiety as risk factors for atopic dermatitis and urticaria. We also assessed the predictive value of the logistic regression method in prospective observational clinical trials.

### Methods

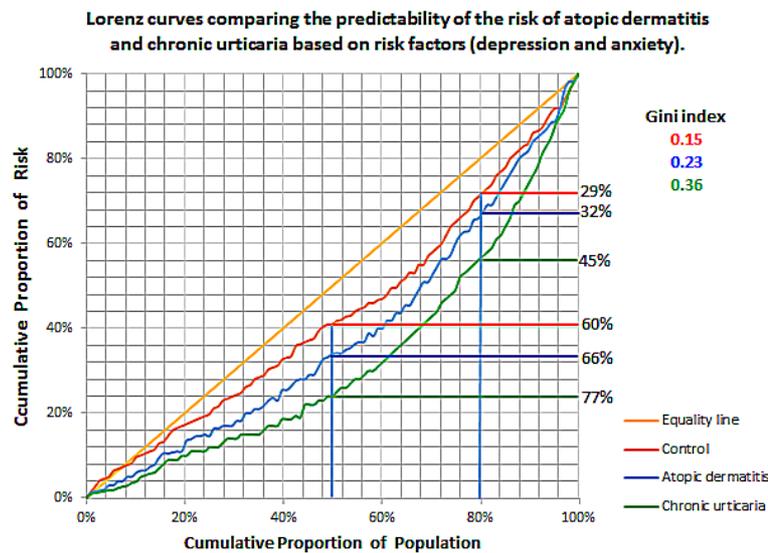
**Study population.** The study was conducted at the Department of Allergology and Clinical Immunology, Tbilisi State Medical University. The study used a case-control observation protocol. The

control group (I-group) consisted of 160 healthy individuals (aged 18-69 years) (5th-year students, as well as academic staff and their relatives). The study included 120 patients suffering from chronic spontaneous urticaria (II-group) and 110 patients with atopic dermatitis (III-group) registered at the university clinics for three years (2018-2021). Anxiety and depression were identified using appropriate questionnaires (GAD-7 and PHQ-9) by allergists, dermatologists and general practitioners.

**Statistical analysis.** We used conventional logistic regression and built a Lorenz curve that estimates risk concentration to demonstrate the association between CSU and AD and anxiety and depression. A comparison of risk concentration in the studied groups was carried out according to the Lorenz curve and by calculating the Gini coefficient. All statistical analysis was performed using SPSS software, version 25 IL, USA), Excel and RevMan 5.4.

**Results.** Our study showed how well propensity measures distinguish patients from healthy individuals. The upper half of patients with the highest risk of disease manifestation accounted for 77% of all patients with urticaria and 67.3% with atopic dermatitis. Quantification of the predictive value of risk factors (depression and anxiety) using the Lorenz curve and the Gini coefficient revealed a persistent increase in the concentration of risk factors in the groups of atopic dermatitis and CSU. In patients with the highest risk of developing the disease, atopic dermatitis develops in 32% (Gini=0.23 - blue line) and chronic urticaria in 45% (Gini=0.36 - green line). The control group's risk of developing these diseases does not exceed 29% (Gini=0.15 - red line), see Table. 1.

Table 1.



The statistical significance of the risk intensity distribution on the Lorenz curve is represented in the forest plot (see Table 2).

Table 2. The statistical significance of the risk intensity distribution

Study or Subgroup	CSU		Control		Odds Ratio (Non-event) M-H, Random, 95% CI	Odds Ratio (Non-event) M-H, Random, 95% CI
	Events	Total	Events	Total		
<b>1.1.1 The concentration of risks at 50% levels of the Lorenz curve</b>						
Risk conc. up 50% CSU vs Control	92	120	64	160	0.20 [0.12, 0.34]	
Risk conc. up 50% AD vs Control	73	110	64	160	0.34 [0.20, 0.56]	
Risk conc. up 50% CSU vs AD	92	120	73	110	0.60 [0.34, 1.07]	
<b>1.1.2 The concentration of risks at 20% levels of the Lorenz curve</b>						
Risk conc. up 20% CSU vs Control	54	120	46	160	0.49 [0.30, 0.81]	
Risk conc. up 20% AD vs Control	35	110	46	160	0.86 [0.51, 1.47]	
Risk conc. up 20% CSU vs AD	54	120	35	110	0.57 [0.33, 0.98]	
<b>1.1.3 The concentration of risk factors at 50% vs 20% levels on the Lorenz curve</b>						
Risk conc. up 50% vs 20% CSU	92	120	54	120	0.25 [0.14, 0.43]	
Risk conc. Up 50% vs 20% AD	73	110	35	110	0.24 [0.13, 0.42]	
Risk conc. up 50% vs 20% control	64	160	46	160	0.61 [0.38, 0.96]	

The first subgroup consisted of patients whose risk of disease manifestation exceeded 50%. This subgroup observed a significant difference (compared to control) in patients with chronic spontaneous

urticarial (OR= 0.20, 95% CI 0.12-0.34) and atopic dermatitis (OR= 0.34, 95% CI 0.20-0.56). **The second subgroup** consisted of patients whose risk of disease manifestation exceeded 20%. In this subgroup, a significant difference was found in patients with CSU compared with the control group (OR= 0.49, 95% CI 0.30-0.81) and CSU vs AD (OR= 0.57, 95% CI 0.33-0.98). In **the third subgroup**, the predictive value of the concentration of risk factors at various levels (50% vs 20%) was compared. It turned out that, the concentration of risk factors (anxiety and depression) is significantly higher with an average concentration (above 50%) compared with a high concentration (20%) with CSU (OR= 0.25, 95% CI 0.14-0.43) and AD (OR= 0.24, 95% CI 0.13-0.42).

**Discussion.** Many authors believe that the accuracy of risk prediction depends on the concentration of risk, as it reflects the likelihood of disease in a predictable, ideally small subset of the population. That is why Pepe and his colleagues [5, 9, 12] offer graphical forecasting methods, one of which is the estimation of the Lorenz curve [6]. We used this method in our work and have shown that the Lorenz diagram well differentiates the predisposition of patients to various diseases, and more often, there are persons with the highest predisposition score to the illness (CSU and AD).

By quantifying this discrimination using the Gini index, we showed to what extent the level of predisposition to disease reflects the likelihood of their (urticaria and atopic dermatitis) actual manifestation in the population. In our case, in 50% of patients with the highest predisposition score, urticaria occurs in 77% of all patients with urticaria, and in the 20% of patients with the highest score, it occurs in 45%.

Although in our work we confirmed the predictive value of depression and anxiety in the development of CSU, we were unable to determine exactly the direction of causal relationships with these psychopathological and skin diseases since they can be associated with many medical, economic and socio-psychological factors [1, 8, 13], for example, mood disorders are associated with chronic inflammation caused by cytokines [10], changes in neurotransmitter activity [16], as well as abnormalities of the immune system. Of course, a more straightforward theory has the right to exist, according to which the manifestations of skin diseases cause social isolation and aggravate the condition of patients.

Since the early publications used completely different predictive methods to identify the relationship of CSU with anxiety and depression [3, 11], the current study has theoretical and clinical significance. We first used the Lawrence graphical method to identify predictive risk factors (anxiety and depression) in the development of CSU. It turned out that the current study's results can be helpful in solving such scientific hypotheses and in many other areas of modern clinical medicine [2, 16]. It is also interesting to further study the role of psychiatric diseases in developing urticaria and other chronic skin diseases.

#### **Conclusion.**

It is concluded that depression and anxiety are considered significant risk factors for developing chronic spontaneous urticaria and, to a lesser extent, atopic dermatitis.

The strongest association between anxiety and depression was found in patients suffering from chronic spontaneous urticaria (CSU). This relationship was less pronounced in the control group and individuals with atopic dermatitis. The Lorenz curve characterizes the concentration of the risk of morbidity in individuals with the most significant threat. It can be successfully used to predict the development of chronic spontaneous urticaria. We believe further research is needed to shed light on the pathophysiological interaction pathways between these clinical conditions.

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**SUMMARY**

Previous research has shown that anxiety and depression are associated with many chronic skin diseases, including chronic spontaneous urticaria (CSU) and atopic dermatitis (AD). A causal relationship between these phenomena has not yet been established. Most authors believe that these itchy conditions cause anxiety, depression, and insomnia rather than the other way around. In our work, we attempted to assess the predictive value of anxiety and depression as risk factors for chronic urticaria and atopic dermatitis. We aimed to investigate the impact of depression and anxiety as risk factors for atopic dermatitis and urticaria. We also assessed the predictive value of the logistic regression method in prospective observational clinical trials. The study included 120 patients suffering from chronic spontaneous urticaria and 110 patients with atopic dermatitis registered at the university clinics of TSMU for 2018-2021 years. A comparison of risk concentration in the studied groups was carried out according to the Lorenz curve and by calculating the Gini coefficient. It is concluded that depression and anxiety are considered significant risk factors for developing chronic spontaneous urticaria and, to a lesser extent, atopic dermatitis. The Lorenz curve characterizes the concentration of the risk of morbidity in individuals with the most significant threat. It can be successfully used to predict the development of chronic spontaneous urticaria.

**Keywords:** anxiety, depression, chronic spontaneous urticaria, atopic dermatitis