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ORIGINAL RESEARCH ARTICLE

The societal costs associated with patients with chronic spontaneous urticaria (CSU) in Italy

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ABSTRACT

Introduction: Chronic spontaneous urticaria (CSU) is a debilitating dermatological disease. The study aimed to estimate the indirect costs and out-of-pocket expenses incurred by CSU patients in Italy.
Methods: The economic model was based on data collected through a survey conducted among patients and caregivers with the support of the Association for the Research and Cure of Urticaria (ARCO). Disease severity was classified into three categories: mild, moderate and severe. Indirect costs were estimated using the human capital approach. Out-of-pocket expenses were estimated in terms of direct healthcare costs borne by the patient and direct non-healthcare costs.
Results: Data were analyzed for 122 patients; 7% of these reported mild CSU, 16% moderate and 78% severe. The average age was 46.8 years, with an average age at diagnosis of 38.2 years. Overall, 50% of employed patients lost workdays due to CSU, and 63.3% reported reduced productivity at work; 45.1% of patients received caregiver support, with 37.9% of employed caregivers reporting workdays lost. The economic model estimated an average annual indirect cost per patient with CSU of €4,281, mainly due to presenteeism (59%). Indirect costs increase with the severity of the disease. Average annual out-of-pocket expenses was €502.7 per patient.
Conclusions: The study conducted based on data directly reported by patients could contribute to a better understanding of CSU, thereby promoting a more efficient approach to the care and support of patients and their families.

Keywords: Chronic spontaneous urticaria, Economic burden, Indirect cost, Out-of-pocket expenditure

Introduction

Chronic spontaneous urticaria (CSU) is a debilitating dermatological disease characterized by the appearance, in the absence of an identifiable trigger, of intensely itchy wheals, angioedema, or both for more than 6 weeks, with individual wheals that may appear and disappear within the same day (1). The condition is caused by the pathogenic activation of mast cells and basophils, which release pro-inflammatory mediators responsible for the appearance of urticaria (2). The wheals associated with CSU appear as well-defined areas of non-pitting edema, with pale centers and raised edges, and are often accompanied by surrounding skin erythema (3). The size varies from a few millimeters to several centimeters, with a tendency to resolve spontaneously within 24 hours. In some patients, CSU may be accompanied by angioedema, a similar process involving the submucosal surfaces of the upper respiratory and gastrointestinal tracts and deeper layers of the skin, including the subcutaneous tissue (2). The condition mainly affects adults between the ages of 20 and 40, and in most patients, it lasts between one and five years, although in severe cases, it can last longer (4). A study conducted at the national level using data from a national database of general practitioners estimated an annual prevalence of CSU that ranged from 0.02% in 2002 to 0.38% in 2013, with a trend towards progressive increase (5). That study also estimated incidence rates of 0.10 to 1.50 per 1,000 person-years for the same period (5). A most recent published study conducted to evaluate the prevalence of CSU in five European countries (France, Germany, Italy, Spain and the United Kingdom (UK)) using data coming from a survey conducted in 2020 and designed to evaluate the health and well-being of the general adult population (the 2020 EU5 National Health and Wellness Survey - NHWS), estimated a prevalence of diagnosed CSU in the EU5 equal to 0.92%; within each EU5 country, the prevalence was 0.76% in France, 0.79% in Germany, 0.79% in the UK, 1.3% in Italy and 1.0% in Spain (6).

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As it is a highly debilitating condition often associated with autoimmune comorbidities and mental disorders such as anxiety, depression, and somatoform disorders (8), it also involves symptoms that significantly affect many aspects of daily life, as well as work and school performance (9).

Regarding treatment options for these patients, first-line therapy is represented by second-generation antihistamines at the lowest effective dose. Antihistamines do not modify the natural history of CSU, but when symptoms control is achieved must be progressively reduced to identify the minimal effective dose (11). However, in patients where symptoms persist despite antihistamine therapy, a biologic drug, omalizumab (anti-IgE monoclonal antibody), is the recommended add-on therapy and the only reimbursed treatment in Italy for exacerbating CSU (11). Up-dosed antihistamines (up to 4× the standard dose) are often used in clinical practice, although they are off-label in Italy. Corticosteroids are also indicated, but only for acute use and for short periods (<10 days). For patients, refractory to both antihistamines and omalizumab, the off-label use of cyclosporine may be considered in the absence of contraindications; however, the use of this drug as a standard CSU therapy, because of the risk of side effects, is not recommended (11). In Italy, omalizumab is prescribed by a therapeutic plan, an official document issued by an authorized specialist to prescribe innovative, high-cost drugs subject to Italian Medicines Agency (AIFA) monitoring with the aim of ensuring the appropriate use and reimbursement of the drug by the National Health Service (NHS).

With reference to the economic burden associated with the disease, a retrospective observational study conducted at the national level analyzed healthcare resource utilization and related economic burden of patients newly diagnosed with CSU using Italian administrative healthcare data. This study estimated an overall mean annual expenditure charged to the NHS of € 1,901, 45.4% of which was due to pharmaceuticals and 39.1% was due to hospitalizations (10).

To the best of our knowledge, there are no national studies conducted to estimate indirect costs and out of pocket expense associated with patients with CSU. Therefore, the aim of this analysis was to estimate the societal costs associated with CSU in Italy using data collected through a cross-sectional survey conducted among patients and caregivers.

Source of data and methods

The study was conducted to estimate the indirect costs associated with CSU and the out-of-pocket expenses incurred by patients for the management and treatment of the disease. The information needed to estimate costs was obtained by administering a questionnaire previously used in economic evaluations published in the literature (7, 12, 13) and adapted to the study context with the support of the Association for the Research and Cure of Urticaria (ARCO). Regarding the methodology for cost calculation, the Human Capital Approach was adopted for the assessment of indirect costs; this methodology allows for the estimation of productivity loss due to the disease by valuing the loss of income by the patient or caregiver for reasons related to the disease or the provision of care to the patient. In particular, the loss of productivity of patients and caregivers (employed) was estimated considering the following employment conditions:

- **absenteeism** - lost productivity due to absence from work by the patient due to illness or by the caregiver due to the provision of care;
- **presenteeism** - reduced productivity at work by the patient who goes to work but, due to illness, produces less than the standard;
- **unemployment** - the lack of employment (and therefore lack of production) of the patient caused by illness or of the caregiver due to the provision of care.

The annual indirect costs of absenteeism are usually estimated by multiplying the average number of working days lost in a year by the average daily income of the employed patient (or caregiver). The annual indirect costs of presenteeism are estimated by multiplying the average number of working days with reduced productivity in a year by the percentage of reduced productivity experienced by the patient and by the average daily income of the employed patient. Patient or caregiver unemployment was valued considering the average annual income of employed individuals. The estimate of the total cost borne by patients for the management and treatment of CSU (out-of-pocket expense) was calculated in terms of:

- **direct healthcare costs borne by the patient**, associated with the management of the disease in terms of diagnosis and treatment (medications, general and specialist visits);
- **direct non-healthcare costs**, which are costs incurred by the patient and related to the disease but not strictly medical (i.e., transportation costs, etc.).

Stage of survey

A cross-sectional, self-administered, internet-based survey was developed following the methodological steps summarized in Figure 1. In particular, the questionnaire was first shared with the ARCO Association to adapt it to the context of the analysis. The final version of the questionnaire, validated by the patient association, was published online on the association's social media channels (Facebook and Instagram) from April 11 to May 12, 2025. The questionnaire was completed by the patients themselves or by their caregivers; patients and caregivers were asked to provide information about each other where available. The data was collected in a completely anonymous form. June and July were spent processing data, while in September, the results were discussed with the Patient Association.

Questionnaire structure

The questionnaire contained, in the introduction, detailed information about the study objectives and data privacy. Consent was considered implicit upon completion of the questionnaire. The 37 questions included in the questionnaire were divided into five different sections:

1. sociodemographic and disease information (severity, age of onset and diagnosis);
2. information on the treatment plan;
3. information on patient absenteeism and presenteeism;

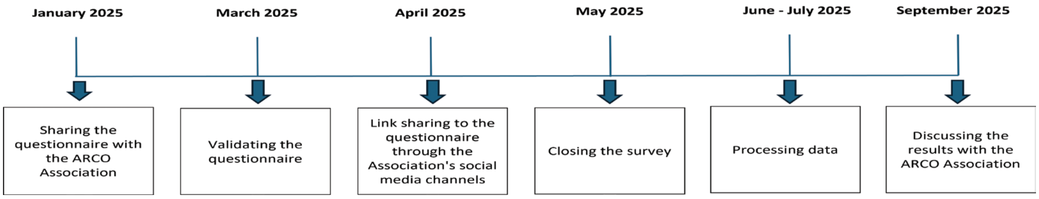

FIGURE 1 - Stages of the survey.

4. information on caregiver absenteeism;
5. information on expenses incurred by the patient.

The first section of the questionnaire was dedicated to collecting sociodemographic information and assessing the severity of the disease at the time of questionnaire completion, which was classified into the following three categories:

- mild (1-5 mostly small hives);
- moderate (5-10 mostly medium hives and with angioedema);
- severe (>10 mostly large hives and with angioedema).

This severity classification, based on the number and dimension of hives and the presence of angioedema, was established in agreement with the ARCO Association, and it was based on the patient's or caregiver's self-assessment; there was no clinical validation. The second section aimed to collect information about any difficulties in accessing the therapeutic plan, therefore the authorization about prescription and reimbursement eligibility of advanced therapies for CSU by the NHS, such as the number of days per year spent managing the treatment plan (1-3 per year), and information about the frequency of disease flare-ups (1-10) before and after accessing the treatment plan. The section dedicated to collecting information on patient absenteeism and presenteeism consisted of questions aimed at identifying the average annual income and the average number of working days lost or with reduced productivity due to illness in the last three months. Patients who reported days of reduced productivity at work were also asked to quantify on a scale of 1 to 10 how much CSU had affected their productivity at work (1 = CSU has no effect on work; 10 = CSU has completely prevented the performance of the work). Similarly, caregivers were asked to indicate their average annual income and the average number of working days lost due to providing care to patients with CSU in the last three months.

Regarding the section on out-of-pocket expenses, patients were asked to indicate the average amount they spent entirely out of their own pocket in the last 6 or 12 months, respectively, on medications and/or creams and on control visits. Finally, participants were asked to include additional out-of-pocket expenses not explicitly listed in the questionnaire.

Statistical analysis

The collected questionnaires were first evaluated for completeness and plausibility of the collected responses. Outlier values reported in the questionnaires were reported to the ARCO association and excluded from the analysis (only the outlier values; the questionnaire was retained) when deemed unreliable, likely due to a misinterpretation of the question in the questionnaire. Furthermore, questionnaires that did not report the information on disease severity were excluded from the analysis. Descriptive analyses were undertaken. Categorical data were summarized using numbers and percentages, and continuous data as mean and standard deviation (SD).

Additional data sources and assumptions

The average daily income of patients and caregivers, used to calculate indirect costs, was obtained from the average annual income reported by patients or employed caregivers who responded to the questionnaire, considering 254 working days per year, corresponding to the number of working days in 2024. Patients and caregivers who chose not to answer the income question were assigned the estimated average annual income for responding patients.

Since, in some cases, to reduce the memory effect, the questions were referred to the last 3/6 months experienced by the patient or caregiver, a linear trend over time was assumed in order to estimate the annual costs. Therefore, the data referring to the last 3/6 months were also considered for the remaining quarters or for the remaining half of the year. The average annual costs were estimated by disease severity and for the entire sample of patients. Specifically, average costs were calculated by dividing the total estimated costs for each patient subgroup, or for the entire sample, by the number of patients in that subgroup or the total number of respondents, respectively. This approach allows the estimates to be generalized to an average patient with CSU, rather than reflecting only those patients for whom the costs were directly incurred.

Results

General characteristics of the sample

The questionnaires included in the analysis amounted to 122 out of 125. Four of the 122 questionnaires were completed by caregivers who provided information for three minor patients and for one adult patient. In the entire sample, 7% of patients (n = 8 of the entire sample) had a mild form of CSU, 16% (n = 19) had a moderate form, while 78% (n = 95) had a severe form of the disease.

Table 1 shows the general characteristics of patients stratified according to disease severity. The average age of the sample was 46.8 years (SD 13.7), the average age at diagnosis was 38.2 years (SD 14.2), while the average age of onset of the disease was 34.7 years (SD 15.5). Comparing the average age of onset of the disease with the average age of diagnosis, a delay in diagnosis was observed in 63%

of cases; on average, the diagnostic delay was estimated at 6.3 years (SD 6.3). Moreover, the average time from diagnosis to survey completion was estimated to be equal to 9.5 years (SD 10.4). Considering also the disease severity, this average time was estimated equal to 7.8 (SD 11.4), 7.0 (SD 5.5) and 8.7 (SD 6.4), respectively, for patients with mild, moderate and severe forms of CSU. In terms of educational level, most patients had a bachelor's degree, a master's degree, or a doctorate (49.2%; n = 58). From an occupational point of view, 78.9% (n = 90) of patients were employed, while there were no patients who had lost their jobs because of the illness. Finally, the most common marital status was married (58.8%; n = 70).

Therapeutic plan, exacerbation episodes and access to treatment

Among the 122 patients, 77.9% (n = 95) were found to be undergoing a therapeutic plan; for these patients, the average duration of the treatment plan was 4 years. Concerning the number of episodes of disease exacerbation, the majority of patients reported having experienced 10 and between 1 and 2 episodes of exacerbation, respectively, before and after the start of the therapeutic plan (respectively 48% and 38% of responding patients) (Fig. 2). The proportion of patients who did not experience any exacerbations of the disease after the start of the therapeutic plan was 16% (versus 2.2% before the start of the treatment plan) (Figure 2). The number of exacerbation episodes by disease severity before and after the start of the therapeutic plan is reported in Figure A1 in the Appendix. In addition, 46% of the sample of patients reported experiencing difficulties in accessing or renewing their therapy. Among them, 59% indicated problems related to the prescription of the therapy, 41% difficulty in making an appointment at the reference institution and 14% obstacles during visits with the attending physician.

With reference to the time spent by patients on managing their treatment plan, requests for work permits, appointments with clinicians, and renewal requests were the reasons that required the most time commitment from patients (3 days per year) (see Appendix, Fig. A2).

TABLE 1 - General characteristics of the sample

	Mild	**Moderate**	**Severe**	**Total**
Severity	6.6% (8)	15.6% (19)	77.9% (95)	122
Age	**Mild**	**Moderate**	**Severe**	**Total**
Average age – years (SD)	50.3 (10.8)	48.3 (16.5)	46.2 (13.7)	46.8 (13.7)
Average age at diagnosis - years (SD)	44.0 (12.3)	40.2 (16.2)	37.3 (13.7)	38.2 (14.2)
Average age of onset of the disease - years (SD)	43.3 (12.1)	37.8 (16.9)	33.4 (15.1)	34.7 (15.5)
Educational qualification of adult patients	**Mild**	**Moderate**	**Severe**	**Total**
2-3 year diploma (patients, n)	0.0% (0)	5.6% (1)	5.4% (5)	5.1% (6)
High school diploma (patients, n)	12.5% (1)	38.9% (7)	44.6% (41)	41.5% (49)
Bachelor's degree, master's degree, doctorate (patients, n)	75.0% (6)	55.6% (10)	45.7% (42)	49.2% (58)
Middle school diploma (patients, n)	0.0% (0)	0.0% (0)	4.3% (4)	3.4% (4)
No qualification (patients, n)	12.5% (1)	0.0% (0)	0.0% (0)	0.8% (1)
Employment status of adult patients	**Mild**	**Moderate**	**Severe**	**Total**
Housewife/househusband (patients, n)	0.0% (0)	5.6% (1)	5.6% (5)	5.3% (6)
Unemployed (patients, n)	14.3% (1)	0.0% (0)	2.2% (2)	2.6% (3)
Employed (patients, n)	71.4% (5)	61.1% (11)	83.1% (74)	78.9% (90)
Retired (patients, n)	14.3% (1)	11.2% (2)	3.3% (3)	5.3% (6)
Withdrawn from work (patients, n)	0.0% (0)	5.6% (1)	2.2% (2)	2.6% (3)
Student (patients, n)	0.0% (0)	16.7% (3)	3.4% (3)	5.3% (6)
Marital status	**Mild**	**Moderate**	**Severe**	**Total**
Single (patients, n)	12.5% (1)	38.9% (7)	32.3% (30)	31.9% (38)
Married (patients, n)	75.0% (6)	55.6% (10)	58.1% (54)	58.8% (70)
Divorced (patients, n)	12.5% (1)	5.6% (1)	6.5% (6)	6.7% (8)
Separated (patients, n)	0.0% (0)	0.0% (0)	3.2% (3)	2.5% (3)

sd: standard deviation

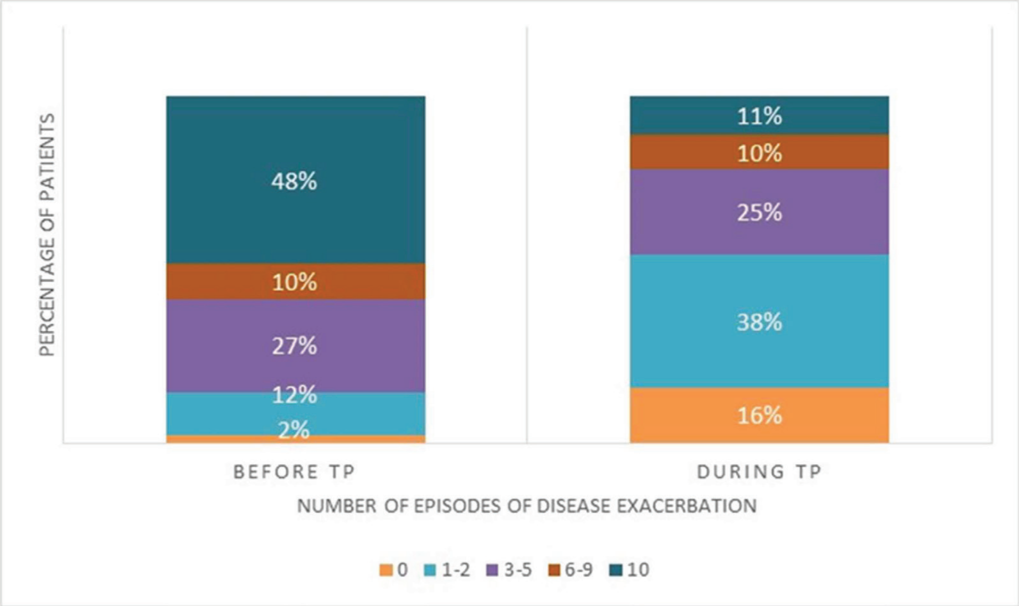

FIGURE 2 - Distribution of patients for each class of number of episodes of disease exacerbation before and after the start of the therapeutic plan. TP: Therapeutic Plan; Estimates calculated on 73% and 66% responding patients, respectively, for the question about the number of episodes before and after the treatment plan.

Indirect costs

To estimate indirect costs, various parameters relating to the impact of the disease on the working lives of patients and caregivers were considered (Tables 2 and 3); in particular, 50% of employed patients reported losing workdays due to the disease, and this percentage increased with disease severity: 40% in mild cases, 45.5% in moderate cases, and 51.4% in severe cases. In addition, 63.3% of employed patients reported working days characterized by reduced productivity at work due to the disease (approximately 66.1% reduced productivity). Furthermore, 45.1% of the patients reported receiving support from a caregiver (25% of patients with mild CSU, 15.8% with moderate CSU, and 52.6% with severe CSU). Among employed caregivers, 37.9% reported losing workdays due to providing care to patients with CSU.

The average number of working days lost per year by employed patients with CSU (equal to 17.5 days) also increased with the severity of the disease: 4 working days lost due to illness in patients with mild CSU, 6.2 days in patients with moderate CSU, and 20.3 days in patients with severe CSU. A similar trend was observed for working days characterized by reduced productivity at work, which were estimated for patients with CSU regardless of the severity, equal to 37.2 and equal to 2.4, 21.5 and 42.1 days per year, respectively, in patients with mild, moderate and severe CSU. Regarding the absenteeism of caregivers, an average of 10.1 working days lost per year by caregiver was estimated, with an unusual trend in relation to patients' severity (20, 0 and 9.6 in patients with mild, moderate and severe CSU), probably influenced by the small number of patients with mild and moderate disease.

The average annual cost per patient with CSU in terms of indirect costs was estimated to be equal to €4,281.2 (Table 4).

TABLE 2 - Parameters for calculating indirect costs

Parameters	**Severity**			
	Mild	**Moderate**	**Severe**	**Total**
Employed patients who lost work days - % (patients, n)	40.0% (2)	45.5% (5)	51.4% (38)	50.0% (45)
Employed patients with work days characterized by reduced productivity - % (patients, n)	20.0% (1)	36.4% (4)	70.3% (52)	63.3% (57)
Average reduced productivity at work by employed patients who reported days with reduced productivity % (SD)	30.0% (0%)	60.0% (18.3%)	67.3% (23.2%)	66.1% (23.1%)
Patients receiving caregiver assistance - % (patients, n)	25.0% (2)	15.8% (3)	52.6% (50)	45.1% (55)
Employed caregivers who lost work days due to caregiving - % (patients, n)	100.0% (2)	0.0% (0)	37.5% (9)	37.9% (11)

TABLE 3 - Number of work days lost or with reduced productivity

Work days lost/with reduced productivity	Mild		Moderate		Severe		Total	
	Average	(Min - Max); SD	Average	(Min - Max); SD	Average	(Min - Max); SD	Average	(Min - Max); SD
Average annual number of work days lost by employed patients due to illness	4	(0.0-12.0); 5.7	6.2	(0.0-40.0); 11.9	20.3	(0.0-152.0); 30.8	17.5	(0.0-152.0); 28.6
Average annual number of work days with reduced productivity for employed patients due to illness	2.4	(0.0-12.0); 5.4	21.5	(0.0-160.0); 47.8	42.1	(0.0-200.0); 45.9	37.2	(0.0-200.0); 45.9
Average annual number of work days lost by caregivers due to caregiving	20	(12.0-28.0); 11.3	0	(0.0-0.0); 0	9.6	(0.0-40.0); 13.7	10.1	(0.0-40.0); 13.7

In particular, this cost increased with severity: €812 in mild cases, €1,124.7 in moderate cases, and €5,204.7 in severe cases. As shown in Figure 3, the average cost per patient with CSU in terms of absenteeism, presenteeism, and caregiver absenteeism was €1,497.2, €2,520, and €264, respectively.

Out-of-pocket expenditure

Regarding treatments (topical and oral), the majority of the patients sample incurred private spending in the last 6 months on topical products (43% of patients); regarding oral treatments, 32% of patients incurred outofpocket expenses for antihistamines, 20% for "other" treatments, mainly referred to lactic ferments, vitamins, and supplements, 18% for corticosteroids and 7% for cyclosporine. Even stratified by disease severity, most patients incur the highest out-of-pocket expenses for topical products (63%, 32% and 43% of patients with mild, moderate and severe CSU) compared to oral treatments (see Appendix, Fig. A3).

The total annual expenditure incurred by a patient with CSU to purchase treatments was €166.2 (€133.1, €115.5 and €179.2, respectively, for a patient with mild, moderate and severe CSU) (Figure 4 and Table 4). The major expenditure is associated with topical products and antihistamines (€62.9 and €51.2, respectively).

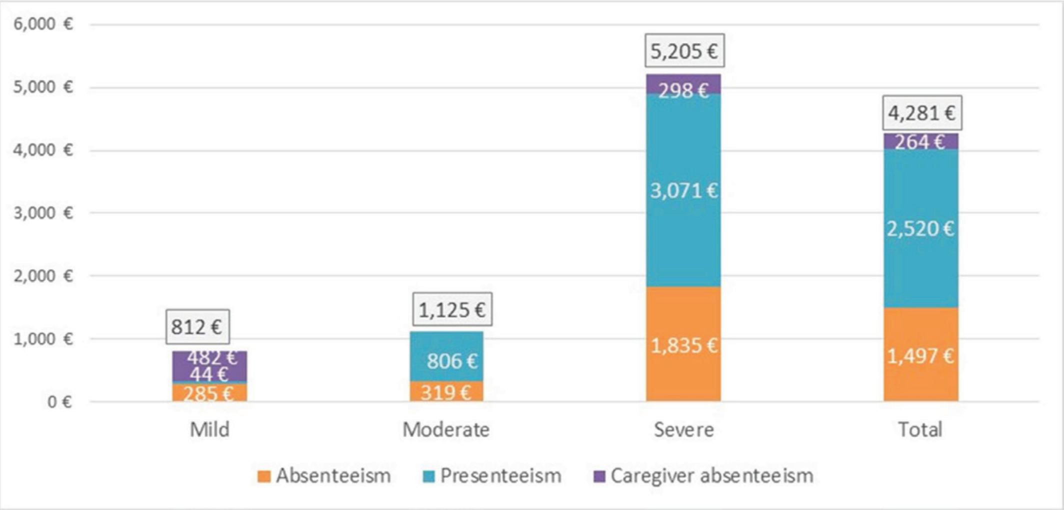

FIGURE 3 - Average annual indirect cost per patient with CSU in relation to disease severity.

About expenditure incurred by patients for visits in the last 12 months, 70% of the patients in the sample incurred private expenses for visits to allergists, immunologists, and dermatologists, 23% for visits to pulmonologists, and 48% for other specialist visits. Also considering the disease severity, the greatest number of patients incurred expenses for visits to allergist, immunologist, dermatologist (50%, 68%, and 73% respectively for a patient with mild, moderate and severe CSU) (see Appendix, Fig. A4).

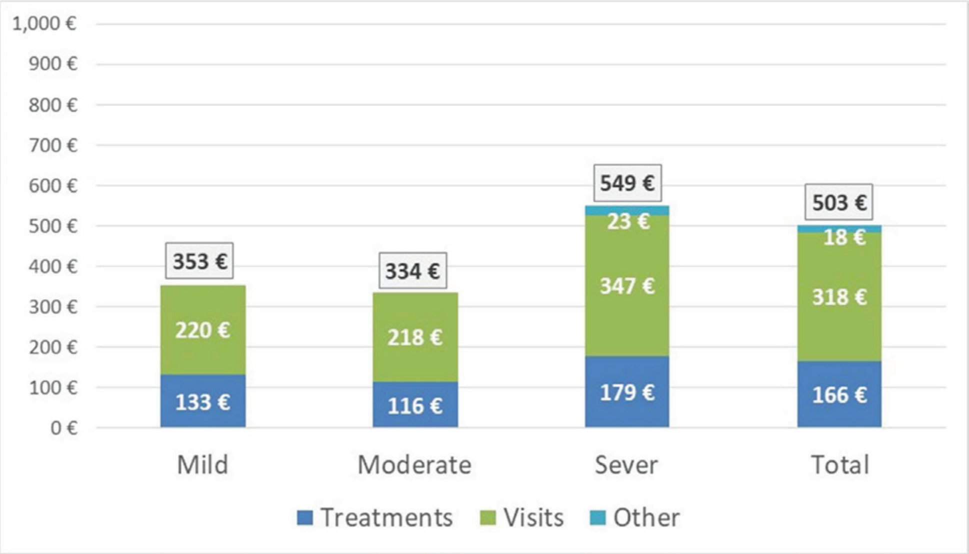

FIGURE 4 - Average annual expenditure incurred by patients with CSU in relation to disease severity.

TABLE 4 - Average annual indirect costs and out-of-pocket expenses per patient with CSU in relation to disease severity

		Mild	Moderate	Severe	Total
	Number of patients	8	19	95	122
	Total – mean (SD)	**812.0 €** (621.4 €)	**1,124.7 €** (3,782.3 €)	**5,204.7 €** (9,043.2 €)	**4,281.2 €** (8,304.0 €)
Indirect costs	Absenteeism – mean (SD)	285.4 € (528.9 €)	319.1 € (908.2 €)	1,834.9 € (3,682.5 €)	1,497.2 € (3,328.4 €)
	Presenteeism – mean (SD)	44.3 € (125.3 €)	805.6 € (2,884.0 €)	3,071.3 € (5,749.4 €)	2,520.0 € (5,292.2 €)
	Caregiver absenteeism – mean (SD)	482.3 € (1,364.1 €)	0.0 € (0.0 €)	298.4 € (1,381.0 €)	264.0 € (1,267.2 €)
	Total – mean (SD)	**352.8 €** (409.8 €)	**334.0 €** (335.8 €)	**549.1 €** (410.5 €)	**502.7 €** (402.8 €)
Out-of-pocket expenses	**Treatments** – mean (SD)	**133.1 €** (152.7 €)	**115.5 €** (175.3 €)	**179.2 €** (202.8 €)	**166.2 €** (195.8 €)
	Antihistamine – mean (SD)	7.6 € (43.1 €)	31.8 € (75.2 €)	58.7 € (82.3 €)	51.2 € (84.9 €)
	Corticosteroid – mean (SD)	7.6 € (24.9 €)	7.5 € (22.9 €)	17.4 € (61.7 €)	15.2 € (54.5 €)
	Cyclosporine – mean (SD)	0.0 € (0.0 €)	5.3 € (24.5 €)	5.7 € (33.9 €)	5.3 € (30.7 €)
	Creams, ointments, etc. – mean (SD)	82.9 € (92.2 €)	48.6 € (87.5 €)	64.1 € (88.9 €)	62.9 € (88.4 €)
	Other – mean (SD)	35.0 € (77.8 €)	22.3 € (55.9 €)	33.2 € (67.6 €)	31.6 € (66.0 €)
	Visits – mean (SD)	**219.7 €** (287.7 €)	**218.5 €** (202.6 €	**346.7 €** (316.3 €)	**318.4 €** (301.3 €)
	Allergist/Immunologist/ Dermatologist – mean (SD)	123.3 € (159.3 €)	100.8 € (107.7 €)	170.7 € (154.8 €)	156.7 € (150.1 €)
	Pulmonologist – mean (SD)	18.8 € (53.2 €)	18.5 € (59.0 €)	35.2 € (90.2 €)	31.5 € (84.0 €)
	Other– mean (SD)	77.6 € (147.1 €)	99.1 € (148.7 €)	140.8 € (167.6 €)	130.2 € (163.1 €)
	Other – mean (SD)	**0.0 €** (0.0 €)	**0.0 €** (0.0 €)	**23.2 €** (70.5 €)	**18.1 €** (62.7 €)

The total annual expenditure incurred by patients for private visits was €318.4 (€219.7, €218.5, and €346.4, respectively, for patients with mild, moderate and severe CSU) (Fig. 4 and Table 4).

The average annual expenditure incurred by patients for items not included in the questionnaire emerged only for patients with severe disease. This expenditure was characterized mainly by the purchase of products for personal care (clothing, cosmetics, detergents), testing and diagnostics (tests, skin and tissue biopsies), transportation and logistics (fuel, tolls, overnight stays). The total average annual expenditure per patient with severe CSU for items not included in the questionnaire was estimated to be equal to € 23.2. Table 4 summarizes the estimated cost items described earlier

Total societal burden

As shown in Figure 5, the average annual cost per patient with CSU increases with severity of the disease, both in terms of indirect costs (€812, € 1,125, and €5,205 for mild, moderate, and severe cases, respectively) and out-of-pocket expenditure (€353, €334, and €549 for mild, moderate, and severe cases, respectively). These results should certainly be interpreted with caution due to the small sample size of patients with mild (N = 8) and moderate (N = 19) CSU; therefore, the estimated total costs are strongly influenced by the high proportion of patients with severe disease (N = 95).

Discussion

The present analysis was conducted to estimate the societal costs associated with CSU, a condition already recognized for its significant clinical burden. Data on the prevalence of CSU is limited, with reported estimates varying based on study design (i.e., data came from clinical databases or from a patient- reported survey). The study conducted by Lapi et al. 2016 using data from a national database of general practitioners estimated an annual prevalence of CSU that ranged from 0.02% in 2002 to 0.38% in 2013, with a trend towards progressive increase probably attributed to the improvement of data quality in data recording over recent years, as reported by the authors (5). The most recent published study conducted by Balp et al. to evaluate the prevalence of CSU in five European countries using data coming from a survey conducted to evaluate the health of the general adult population estimated a prevalence of diagnosed CSU in the EU5 and in Italy equal to 0.92% and 1.3%, respectively (6). The true prevalence of CSU is likely intermediate between the estimates reported by studies using healthcare databases and survey-based studies.

Regarding the economic burden evaluated from a societal perspective, the analysis estimated an average annual cost for patients with CSU in terms of indirect costs equal to €4,281.2, characterized mainly by presenteeism (59%) and followed by patient absenteeism (35%) and caregiver absenteeism (6%). The expenditure increased proportionally with disease severity, amounting to €812.0, €1,124.7, and €5,204.7 for patients with mild, moderate, and severe CSU, respectively.

The average annual expenditure borne by the patient also represented a high-cost component, amounting to €502.7 per patient with CSU. Most of this expenditure was attributable to visits (63% of the total estimated expenditure borne by the patient), followed by expenditure on treatments (33% of the total) and 4% for other costs (for personal care, testing and diagnostics, transportation and logistics). In particular, out-of-pocket expenditure was €352.8, €334.0, and €549.1 for patients with mild, moderate, and severe CSU, respectively.

Several studies conducted in Europe have shown that CSU entails a significant economic burden, particularly through

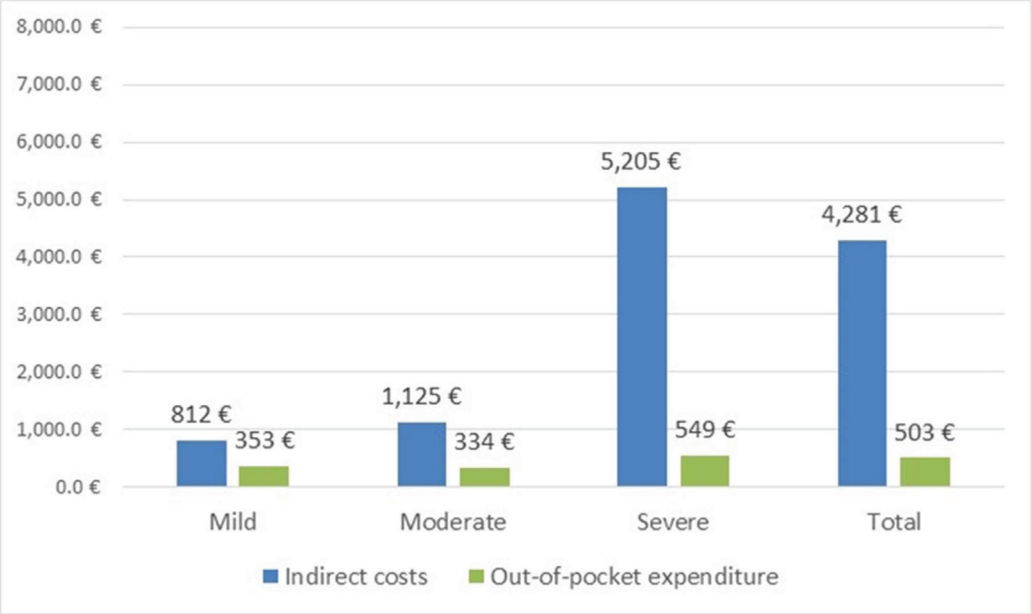

FIGURE 5 - Average annual cost per patient with CSU in terms of indirect costs and out-of-pocket expenditure.

indirect costs related to productivity loss. A study conducted by Lacour et al. (2018) (14) to characterize the clinical and economic burden of CSU in symptomatic patients in France (of 101 of patients analyzed, 43.4% were with moderate to severe disease and 72.3% with angioedema), estimated a mean absenteeism and presenteeism equal to 6.4% and 20.8% based on data collected from a patient survey. Additionally, the study estimated, over a 4-week period, indirect costs due to presenteeism and work productivity loss equal to €421 and €420, respectively.

A recent systematic literature review conducted by Pagada et al. (15) to summarize the published evidence on the direct and indirect costs associated with adult patients with CSU who were symptomatic/inadequately controlled with H1-antihistamine treatment, reported average indirect costs for CSU over four weeks ranging from PPP$ 544.8 in France to PPP$ 1,287.4 in Germany (Italy PPP$ 613.9), mainly due to absenteeism. The same study estimated that in Europe, the mean absenteeism score varied from 10.5% to 17.9%, and the presenteeism score varied from 27.4% to 39.5%. Therefore, the literature confirms that presenteeism is the principal contributor to productivity impairment in individuals affected by CSU.

At the national level, a retrospective observational cohort study conducted in patients newly diagnosed with CSU from 2016 to 2021 using administrative healthcare data (Ronconi et al. (8)) estimated an average annual direct cost per patient with CSU borne by NHS was €1,901, with drugs accounting for 45.4% (about one quarter for CSU-specific drugs) and hospitalizations for 39.1%. By integrating the findings of the study conducted by Ronconi et al. with those of the present study, it seems that indirect costs constitute the largest component of expenditure associated with patients with CSU, followed by direct costs and out-of-pocket expenses.

It is important to note that the average annual cost estimates provided in this study per patient with CSU are inevitably influenced by the distribution of disease severity within the enrolled population (78% of participants presenting with severe CSU). Furthermore, considering the distribution of patients within the study sample, the estimates for individuals with mild CSU should be interpreted with caution due to the limited representation of this subgroup (6.6%, N = 8). This inevitably limits the robustness of the findings, especially for this patient subgroup; however, given the exploratory nature of the analysis, we considered it important to retain and report all available data. Regarding the distribution of disease severity, in the published literature, the study conducted at the national level by Lapi et al. (5) to explore the epidemiology of CSU in Italy via questionnaires administered to 537 patients reported that 22.3%, 60.1%, and 10,4% have respectively mild, moderate and severe CSU. In that study as well, disease severity was assessed solely through patient self-assessment, and, to our knowledge, no published national observational studies have clinically validated the severity of CSU to accurately characterize the epidemiology of this condition in the Italian clinical setting. Considering the limitations outlined above, this study attempted to provide, for the first time, national estimates of indirect costs and out-of-pocket expenditures associated with CSU, with the objective of quantifying the societal burden imposed by this condition. Further studies on a larger patient sample could be able to provide more representative estimates, especially for the patient subgroups that were underrepresented in this analysis.

Conclusions

Chronic spontaneous urticaria in Italy is associated with a significant societal burden both in terms of indirect costs and out-of-pocket expenditure. This burden often remains silent, since it is mainly related to loss of work productivity and expenses incurred directly by patients. The study, conducted based on data directly reported by patients, could contribute to a better understanding of CSU, thereby promoting a more efficient approach to the care and support of patients and their families.

Disclosures

Conflict of interest: CB, AM, VS, and ER declare that they have no conflicts of interest. LC is an employee of Novartis Italy.

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Author contributions: CB, AM, VS, and LC participated in the design of the analysis. ER participated in patient recruitment and data collection. All authors analyzed and interpreted the data. CB was the statistician responsible for the analyses. All authors were members of the writing group and participated in the development of the report, agreed on the content, reviewed drafts, and approved the final version.

Data availability statement: The data are not publicly available due to their being collected and used exclusively for the purposes of this study.

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