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Article

The economic Burden of Atopic Dermatitis in Romania: A Broad Perspective

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Abstract: Background: Atopic dermatitis (AD), a common dermatological condition, is often associated with significant economic and social burdens. Despite extensive studies globally, there is a gap in understanding the comprehensive impact of this condition in Romania. Objectives: This study evaluated the economic burden and quality of life impact of AD in Romania, considering both direct and indirect costs. Materials & Methods: A mixed methods cost of illness study was conducted from April to October 2023. A patient survey, expert reviews, and national health data analysis were used to assess direct medical costs (treatments, medical services), direct non-medical costs (transportation, accommodation), and indirect costs (productivity losses). Quality of life was evaluated using the EuroQol EQ-5D-5L instrument. Results: In 2022, the total cost of atopic dermatitis in Romania was 32.983.498 EUR for adults and 31.573.968 EUR for children. Adult costs included 24.534.603 EUR in direct and 8.429.884 EUR in indirect medical costs, with an average annual cost per patient of 447 EUR. Pediatric costs involved 15.026.781 EUR in direct and 16.516.410 EUR in indirect costs, averaging 290 EUR per patient annually. Conclusion: Care expenditure with AD management in Romania is substantially lower than in other countries, posing a significant economic burden, primarily driven by indirect costs. This study provides a foundation for future policy interventions and highlights the need for targeted management strategies for AD.

Keywords: atopic dermatitis; economic burden of disease; cost of illness

Introduction

Atopic dermatitis (AD) is a dermatological disease with a higher attributable burden in terms of disability-adjusted life years/100,000 person-years (99.69 DALYs) than other skin conditions such as contact (28.06 DALYs) or seborrheic dermatitis (3.93 DALYs), or other dermatological diseases such as psoriasis and urticaria ¹⁻³. Despite its relatively low mortality rate, AD significantly impacts patients' lives, affecting their work and personal activities and imposing considerable economic costs ^{2,4,5}.

A growing body of research has highlighted AD's economic and social implications. Studies have identified the high prevalence and impact of AD in specific demographic groups, particularly in children and females, leading to increased healthcare demands and financial burdens. In their comparative study, Toron and colleagues revealed the heightened economic impact on patients with mild-to-moderate AD (as opposed to non-AD patients), including increased healthcare service utilization (for GP visits and dermatology referrals) and associated costs (68.22% higher as compared to non-AD patients) ⁶. Significant out-of-pocket expenses further intensify this trend. In addition, the overall burden of AD is associated with significant mental health challenges, such as anxiety and



depression 6). Simpson and colleagues et al. emphasized the prevalence of moderate to severe AD cases, particularly in younger patients. They highlighted the diverse severity of AD symptoms and their correlation with mental health issues ^{8,9}.

Socioeconomic status is an important variable when quantifying the burden of AD and assessing the trends of co-occurring health problems (such as impaired sleep or mental health pathologies)⁹. A study conducted in Israel underscored socioeconomic disparities among AD patients, with those suffering from severe forms often belonging to lower socioeconomic groups and experiencing higher healthcare burdens. Furthermore, a multinational study across the US and three European countries outlined differences in AD severity, diagnostic age, treatment approaches, and the correlation between disease severity and quality of life (emphasizing that regardless of the scale employed to assess the QoL, severe patients reported poorer QoL) (8,9). A systematic review examining the broader implications of AD on mental health, quality of life, and economic costs revealed a wide range of symptoms and associated costs. The direct costs associated with AD were estimated at around \$4411 (\$940 – \$11.536), with indirect costs reaching approximately \$9068 (\$1289 - \$15650), indicating the extensive economic burden of the disease. As for productivity lost (due to both absenteeism and presenteeism), the total number of days summed up to 68.8 (54 days due to presenteeism and 14.8 due to absenteeism) ¹¹.

A recent prevalence study in Romania represents a landmark achievement in dermatology, mainly atopic dermatitis (AD). The study's achievement in developing and validating a questionnaire used in estimating national prevalence is pivotal for future research initiatives and offers invaluable insights into the demographic and clinical profile of AD within Romania, providing a complementary backdrop to our research and enriching our understanding of the current epidemiological situation of AD ¹². Despite the emergence of this new national epidemiological study and the international literature on the economic impact of atopic dermatitis, there is a gap in the literature regarding the cost of illness and quality of life studies in Romania. Therefore, we aimed to provide the first cost of illness and quality of life study conducted nationally for patients diagnosed with atopic dermatitis.

Material and Methods

This cost of illness (CoI) study estimated the economic costs of atopic dermatitis over 12 months (using 2022 as a reference year) from a broad perspective, incorporating both direct and indirect costs and elements of a societal perspective. The Institutional Review Board – Public Health (IRB-PH), Babes-Bolyai University (no. 151122-003) approved the submitted protocol for this cost of illness study. The core objective of the study was to accurately determine the economic burden of atopic dermatitis in Romania by triangulating evidence from multiple data sources, including patients and healthcare providers, to influence the calculation of medical costs. We used data from several retrospective sources (public and private) and one prospective source (survey data). Retrospective epidemiological data was retrieved from the Global Burden of Disease study, as well as financial controlling of hospitals, private reports on drug use and other publicly available figures from the National Institute of Statistics (INSSE). From the GBD study¹³, we retrieved incidence and prevalence (for both sexes and for two age groups: “<20 years” and “20+ years”; unit of measure: number of cases) data for 2019 (the latest year for which data was available for Romania). We used prevalence for the main costing exercise and incidence data for sensitivity analyses. The input prevalence data was 112456.9 (95% CI: 105897.8 – 118586.3) for 20+ years and 73719.53 (95% CI: 70706 – 76750.46) and the input incidence data was 7345.723 (95% CI: 6871.783 – 7863.352) for <20 years and 70567.6 (95% CI: 67982.34 – 73079.67)¹⁴. Drug usage data highlighted the average value per medical prescription for AD, which was 40.4 RON. This estimate was based on data retrieved from 3700 pharmacies in 2022. However, the calculation of this average estimate included only medical prescriptions that were partially or fully subsidized and did not include white prescriptions. Data on the average hospital length of stay, the number of hospital discharges, and the average cost per hospitalization in 2022 for both adult (7.95, 30270, 1094) and pediatric patients (4.44, 18942, 1012) was provided by Hospital Consulting, based on financial controlling data collected from a sample of representative hospitals at

the national level, both in terms of profile and catchment areas. From INSSE, we retrieved the mean wages for 2022 (6,126 RON) and the number of working days for 2022 (251 days)¹⁵.

Questionnaire

Based on interviews with doctors and one patient association, the questionnaire was constructed to allow reconstruction of the patient pathway in the national context. In addition, we also reviewed scientific literature and national data sources, categorizing data into significant cost categories. The cross-sectional online survey was used to collect data between the 25th of April 2023 and the 18th of October 2023. The survey was constructed using the Surveyplanet tool¹⁶ and disseminated on social media (Facebook) by APAA (targeted ads were used to enhance its reach). The sampling used for the online cohorts was convenience sampling. The target participants were patients aged over 18 or their caregivers and the caregivers of patients aged under 18 (children and adolescents) who were diagnosed with alopecia areata. The sample size calculated for this study, aiming for a 95% confidence level and a 4% margin of error, was 600 patients (including responses from caregivers). Our survey was composed of questions on sociodemographic characteristics (age, sex, county, settlement type, education, employment), symptom control, self-reported severity, presence of other diseases (chronic urticaria, allergic rhinitis, non-allergic rhinitis, food allergies, eosinophilic esophagitis, contact dermatitis, other autoimmune or inflammatory diseases), type of prescribed treatment (ointment, oral, injection), frequency of prescribed treatment, usage of prescribed medicines, out-of-pocket costs (treatment, medical services, and other types of expenses due to transportation or accommodation), and frequency of the utilization of medical services (visits for primary and secondary care providers - GPs and specialist doctors, inpatient and outpatient admissions, and using the services of a medical laboratory). In addition to these questions, we also collected data on quality of life by employing the generic instrument developed by EuroQoL, EQ-5D-5L. The EQ-5D-5L encompasses the following: five levels rated, descriptive dimensions (mobility, usual activities, self-care, pain and discomfort, anxiety and depression), and a visual analog scale, the EQ-VAS, which provides insights into the patient's self-health assessment that can range from 0 (worst) to 100 (best) health¹⁷⁻²¹. The EQ-5D-5L data generated utilities reported by sex and severity levels. For this part of the analysis, we employed the R package "eq-5d package"²².

Costing approach

We evaluated the economic impact of atopic dermatitis (AD) by incorporating both direct medical (as reported in the survey for treatments and medical services) and direct non-medical costs (including associated expenses). For a subcategory of direct medical costs - treatments - we also provide an additional scenario taking into account the average costs provided by a private consulting firm (IQVIA), thus incorporating a cost comparison for this cost category and evaluating the differences between prospective, self-reported costs and retrospective costs that are collected from a nationally representative sample of pharmacies. In addition, we provide costs for adults (the survey data being self-reported) and minors (the survey data being provided by their caregivers). The bottom-up and top-down approaches are employed by the availability of data to yield the total population cost of the condition.

We used a bottom-up approach to calculate treatment, medical services, hospital, and other associated costs (i.e., transportation, accommodation). We used the data on hospital discharges for 2022 as a multiplier and the GBD crude prevalence for the other costs. We divided the total GBD estimates for the two age groups into mild, moderate, and severe cases based on the corresponding proportion reported in the collected survey data. Thus, there were 22.67% mild cases, 59.17% moderate cases, and 18.17% severe cases. The approach was employed for the sensitivity analyses using the GBD incidence data. As the GBD data stratified the data on different age groups as opposed to the ones mentioned in our survey, we excluded patients aged between 18 – 25 years (n=29) from the dataset when calculating the costs for which we used GBD prevalence as a multiplier.

We included the average costs for the three collected cost categories from the survey. The cost for adults is listed for each severity level for treatment (mild AD: 555 RON, moderate AD: 630 RON,

severe AD: 1292.50 RON), medical services (mild AD: 294 RON, moderate AD: 783 RON, severe AD: 1790 RON), and associated expenses (mild AD: 360 RON, moderate AD: 486 RON, severe AD: 1066 RON). The average costs for children are listed for each severity level for treatment (mild AD: 441 RON, moderate AD: 648 RON, severe AD: 1018 RON, medical services (0 for all severity categories as this item was missed in the survey used to collect data from caregivers), and associated expenses (mild AD: 536 RON, moderate AD: 871 RON, severe AD: 2107 RON).

To calculate indirect costs related to productivity (for patients aged over 18 years and for caregivers), we incorporated the following elements: age threshold, the number of participants who were considered active in the job market (under the age threshold) either full-time or part-time employed, the mean wage for 2022 (6126 RON), and the number of working days for 2022 (251 days)²³. We report average and total patient costs; severity level and descriptive characteristics are reported as totals and percentages.

Data processing

The initial dataset comprised 826 questionnaires. During the data cleaning process, the following exclusions were made. Twenty-six questionnaires were removed due to the absence of informed consent. Thirty-four entries were excluded because participants were minors. Three test entries were identified and removed. Thirty-three entries were excluded as they did not meet the self-diagnosis criteria for dermatitis. Following these exclusions, the dataset was narrowed down to 656 questionnaires from adult patients. Thirty-four questionnaires for which the disease severity was listed as unknown were excluded. Seventy-four questionnaires were collected from caregivers, among which, four questionnaires for which the disease severity was listed as unknown were excluded. Sixty were for minors. Fourteen were for adults who had a proxy respondent.

Subsequent modifications and checks were applied to the database. Meta-variables irrelevant to the analysis were removed to streamline the dataset. Instances with only one FALSE/TRUE were recorded for consistency. For Q19: Outlier values (e.g., 98 visits to a general practitioner) were corrected, and the lowest plausible value was selected. For Q14 and a similar question for caregivers: Due to varying interpretations (total number of applications vs. types of medications used), these were converted to binary format indicating whether the respondent had received treatment. For questions Q15-Q17, if Q14 indicated no treatment, artifact entries from these questions were removed. A similar approach was applied to caregiver responses. All cost entries were rounded to the nearest 50 RON to address inconsistencies likely caused by slider input errors (e.g., 998 RON). Cells were split for questions Q19-23 and corresponding caregiver questions to record the number of visits separately. Question Q15 and similar items were clustered based on open-ended answers, though few such cases were noted. Several variables were checked for consistency, leading to corrections in cases of evident errors (e.g., in Bucharest Municipality, some entries incorrectly marked rural locations; among caregivers, retirees reported missing work; in caregiver data, some reported the highest level of education completed by the child instead of themselves, leading to implausible entries such as a 10-year-old with a university degree). Various other aberrant or missing values were corrected, such as undeclared doctor visits being defaulted to one visit.

Results

The results stratified by the severity of atopic dermatitis (AD), with data collected from patients and caregivers, are presented in Tables 1 and 2.

Table 1. Socioeconomic features of questionnaire respondents.

	Data collected from patients			Data collected from proxies/caregivers		
	Mild AD	Moderate AD	Severe AD	Mild AD	Moderate AD	Severe AD
Gender						
Male	35 (5.6%)	80 (12.9%)	34 (5.5%)	-	9 (12.9%)	12 (17.1%)
Female	106 (17%)	286 (46%)	79 (12.7%)	-	17 (24.3%)	15 (21.4%)
Other option	-	2 (0.3%)	-	-	-	-

Age interval (patients)			Age interval (caregivers)			
18-25 years	6 (1%)	18 (2.9%)	5 (0.8%)	16 (22.9%)	13 (18.6%)	7 (10%)
26-35 years	10 (1.6%)	17 (2.7%)	5 (0.8%)	6 (11.4%)	8 (11.4%)	7 (10%)
36-45 years	28 (4.5%)	90 (14.5%)	25 (4%)	18-25 years	2 (2.9%)	3 (4.3%)
46-55 years	47 (7.6%)	114 (18.3%)	39 (6.3%)	26-35 years	2 (2.9%)	1 (1.4%)
56-65 years	32 (5.1%)	71 (11.4%)	23 (3.7%)	36-45 years	1 (1.4%)	-
66-75 years	16 (2.6%)	53 (8.5%)	14 (2.3%)	46-55 years	1 (1.4%)	1 (1.4%)
75+ years	2 (0.3%)	5 (0.8%)	2 (0.3%)	-	-	-
Settlement type (patients)			Settlement type (caregivers)			
Urban	118 (19%)	309 (49.7%)	99 (15.9%)	21 (30%)	20 (28.6%)	15 (21.4%)
Rural	23 (3.7%)	59 (9.5%)	14 (2.3%)	7 (10%)	4 (5.7%)	3 (4.3%)
Education level (patients)			Education level (caregivers)			
Primary school	2 (0.3%)	8 (1.3%)	2 (0.3%)	Kindergarte n/nursery	12 (17.1%)	8 (11.4%)
Gymnasium	1 (0.2%)	2 (0.3%)	-	Primary school	7 (10%)	3 (4.3%)
High school	43 (6.9%)	120 (19.3%)	37 (5.9%)	Gymnasium	2 (2.9%)	3 (4.3%)
Post-secondary school	12 (1.9%)	28 (4.5%)	10 (1.6%)	High school	2 (2.9%)	5 (7.1%)
University	83 (13.3%)	210 (33.8%)	64 (10.3%)	University	5 (7.1%)	3 (4.3%)
Employment status (patients)			Employment status (caregivers)			
Employed full time	71 (11.4%)	188 (30.2%)	55 (8.8%)	Employed	16 (22.9%)	11 (15.7%)
Employed part-time	3 (0.5%)	23 (3.7%)	5 (0.8%)	part-time	1 (1.4%)	4 (5.7%)
Unemployed	7 (1.1%)	13 (2.1%)	4 (0.6%)	Unemployed	1 (1.4%)	2 (2.9%)
Student	8 (1.3%)	12 (1.9%)	7 (1.1%)	Student	6 (8.6%)	1 (1.4%)
Retired (age limit)	28 (4.5%)	79 (12.7%)	26 (4.2%)	Retired (age limit)	3 (4.3%)	5 (7.1%)
Retired (due to sickness)	12 (1.9%)	22 (3.5%)	8 (1.3%)	Retired (due to sickness)	1 (1.4%)	2 (2.9%)
Other option	12 (1.9%)	31 (5%)	8 (1.3%)	Other option	-	-

Table 2. Self-reported clinical features of questionnaire respondents.

	Data collected from patients			Data collected from proxies/caregivers		
	Mild atopic dermatitis	Moderate atopic dermatitis	Severe atopic dermatitis	Mild atopic dermatitis	Moderate atopic dermatitis	Severe atopic dermatitis
Time since diagnosis						
Under 1 year	27 (4.3%)	93 (15%)	18 (2.9%)	-	1 (1.4%)	1 (1.4%)
1 - 3 years	42 (6.8%)	102 (16.4%)	36 (5.8%)	7 (10%)	9 (12.9%)	4 (5.7%)
4 - 6 years	33 (5.3%)	62 (10%)	23 (3.7%)	10 (14.3%)	10 (14.3%)	4 (5.7%)
7 - 9 years	8 (1.3%)	13 (2.1%)	2 (0.3%)	4 (5.7%)	2 (2.9%)	1 (1.4%)
Over 10 years	31 (5%)	98 (15.8%)	34 (5.5%)	7 (10%)	2 (2.9%)	8 (11.4%)
Level of symptom control						
Not at all under control	7 (1.1%)	17 (2.7%)	27 (4.3%)	-	2 (2.9%)	2 (2.9%)
Often under control	60 (9.6%)	98 (15.8%)	9 (1.4%)	10 (14.3%)	8 (11.4%)	2 (2.9%)
Sometimes under control	65 (10.5%)	253 (40.7%)	61 (9.8%)	6 (8.6%)	12 (17.1%)	12 (17.1%)
All the time under control	9 (1.4%)		16 (2.6%)	12 (17.1%)	2 (2.9%)	2 (2.9%)

Patients

Two hundred fifty-four patients reported being diagnosed with other autoimmune diseases, 214 with contact dermatitis, 127 with allergic rhinitis, 87 with non-allergic rhinitis, 81 with chronic urticaria and food allergies, and 8 with esophagitis. Lastly, 117 reported not being diagnosed with any of the listed diseases. Treatment modalities varied: 507 patients used ointments, 191 oral treatments, 57 injections, and 24 other forms, including medical devices (n=15) and medicated

shampoos or shower gels (n=9). Most patients were using their treatment multiple times per day (n=241), once per day (n=145), or when needed (n=139), while a minority of patients were using it once per week (n=24). During the 12 months, 46 patients reported having made 2 visits to their GP's office, 2 groups of 40 patients reported 1, respectively 5 visits, 39 patients made 3 visits, 36 patients made 4 visits, while 311 patients reported 0 visits (overall range: 0-16 visits). As for visits to the specialist doctor, 71 patients reported having made 1 visit, 57 patients 2 visits, 53 patients 5 visits, 47 patients 6 visits, and 216 patients 0 visits (overall range 0 - 30 visits). During the study period, 27 patients with atopic dermatitis reported having 2 outpatient discharges, 23 patients 1 outpatient discharge, 22 patients 3 visits, and 20 patients 4 outpatient discharges, while 511 patients have not reported any outpatient discharges (overall range: 0-45 outpatient discharges). As for inpatient discharges, most patients (n=23) had 5 discharges, and two groups of 19 patients had 1 and 3 discharges, respectively. In comparison, 525 patients have not reported any inpatient discharges during the 12 months (overall range of 0 - 12 inpatient discharges). Laboratory services were underutilized, with 409 patients not using them at all— 59 patients reported using these services once, while 41 patients used them thrice. Additionally, two groups of 37 patients reported four and two utilizations during the 12 months (overall range: 0-15 utilizations). The impact of AD on work was significant, with most patients (n=337) reporting some days off. Patients with a mild form (n=141) of atopic dermatitis took between 1 and 5 days from work (with a total of 66 days), patients with a moderate form (n=368) between 1 and 12 days (with a total of 249 days), and patients with a severe form (n=113) between 1 and 10 days (with a total of 339 days).

Table 3. Frequency of issues reported by AD patients in Romania by EuroQol dimension and age group.

EQ-5D Dimension	18 – years	25 – years	35 – years	45 – years	46 – years	55 – years	56 – years	65 – years	66 – years	75 – years	75+ – years
Mobility – no problems	82.8%	90.6%	88.8%	80.5%	88.9%	83.1%	88.9%				
Mobility – problems	17.2%	9.4%	11.2%	19.5%	11.1%	16.9%	11.1%				
Self-care – no problems	55.2%	31.3%	35.7%	32%	36.5%	32.5%	55.6%				
Self-care – problems	44.8%	68.8%	64.3%	68%	63.5%	67.5%	44.4%				
Usual activity – no problems	82.8%	90.6%	87.4%	80.5%	85.7%	83.1%	66.7%				
Usual activity – problems	17.2%	9.4%	12.6%	19.5%	14.3%	16.9%	33.3%				
Pain/discomfort – no problems	37.9%	34.4%	31.5%	26%	39.7%	24.1%	33.3%				
Pain/discomfort – problems	62.1%	65.6%	68.5%	74%	60.3%	75.9%	66.7%				
Anxiety/depression – no problems	27.6%	21.9%	26.6%	23.5%	34.9%	33.7%	55.6%				
Anxiety/depression – problems	72.4%	78.1%	73.4%	76.5%	65.1%	66.3%	44.4%				

Table 4. EQ-VAS collected from AD patients in Romania.

EQ VAS	18 – 25 years	26 – 35 years	36 – 45 years	46 – 55 years	56 – 65 years	66 – 75 years	75+ years
Mean – Std Dev	67.24 (24.98)	70.56 (22.30)	66.26 (22.12)	67 (21.13)	66.80 (20.16)	59.09 (21.54)	65.33 (14.65)
Median	70	72.5	70	70	70	65	60
25th percentile	55	53.75	50.5	53.75	55	40	53
75th percentile	85	90	82.5	85	80	75	70

Proxies and caregivers

The surveyed caregivers reported the following distribution of comorbidities for patients with atopic dermatitis: 25 cases of food allergies, 14 of allergic rhinitis, 12 of contact dermatitis, 8 of autoimmune diseases, 5 cases of chronic urticaria, and 4 of non-allergic rhinitis. In addition, esophagitis was absent in this patient group, and 31 caregivers indicated that the patients they cared for did not suffer from any listed comorbid conditions. All 70 caregivers reported that the patients they cared for were undergoing treatment, all of whom were using ointment, and 26 were using oral treatment. None of the patients were using injectable treatments. Other forms of treatment, such as UV therapy, skincare products (medicated shower gels and shampoos), and mud packs, were used in two cases. Two groups of 24 caregivers reported that the patient they cared for was using their treatment once and multiple times per day, 20 only when needed, and 2 once per week. During study period, 7 caregivers reported that the patients they were taking care of made 2 visits to their GP's office, and five groups of 4 responded reported that the patients they were taking care of made 1, 3, 5, 6, respectively 7 visits to their GPs office, while 39 caregivers reported 0 visits (overall range 0-21 visits). As for visits to the specialist doctor, 15 caregivers reported that the patients they care for made 2 visits, 7 reported 1 visit, two groups of 5 caregivers reported 3 and 5 visits, and two groups of 3 caregivers reported 4 and 7 visits. In comparison, 26 caregivers reported 0 visits (overall range of 0 - 12 visits). Outpatient hospitalizations were relatively less frequent. Three groups of 2 caregivers reported 1, 2, and 4 outpatient admissions, while three reported that the patients they cared for had 3, 7, and 8 outpatient discharges (an overall range of 0-8 outpatient discharges). Inpatient hospitalizations were reported in a few cases, with 5 caregivers noting 1 inpatient hospitalization and others reporting 2 and 3 discharges (overall range: 0 - 3 discharges). Regarding medical laboratories, two groups of 5 caregivers reported that the patients they care for used the services of a medical laboratory 2-4 times, 4 patients used it 3 times, and one patient used it 6, 7, and 10 times (overall range: 0-10 utilizations). The number of missing days attributable to atopic dermatitis ranged between 1 and 98 days (average: 6.4 days) for caregivers (n=22) and between 1 and 95 days for patients with atopic dermatitis (average: 8.3 days). Regarding the missing days reported for patients, there were 567 missing days for patients aged between 1 and 17 years and 13 for patients aged between 18 and 35 years.

Costs

The total cost of atopic dermatitis in Romania during 2022 for adult patients was **32.983.498 EUR**, of which **10.991.053 EUR** were attributable to treatment costs, **12.800.839 EUR** were attributable to costs of medical services, **742.711 EUR** to inpatient hospitalization (all of these three categories corresponding to direct medical costs) and **8.429.884 EUR** were attributable to associated expenses (transportation, hotel, or other types of expenses made when they had to travel for a doctor's appointment of treatment; which is an indirect medical cost), and **16.040 EUR** due to medical leave for full-time employed, and **2970 EUR** for part-time employment (indirect cost). The utilities for mild cases range between 0.017 and 1, moderate cases between 0.136 and 1, and severe cases between 0.483 and 0.947 (See appendix). The yearly average per patient cost for atopic dermatitis in Romania in 2022

for patients aged 20+ years was approximately **447 EUR**, based on Global Burden of Disease prevalence estimates. The average cost per patient was **1.941 EUR** (n=16992.35) for mild cases, **765 EUR** (n=43125.92) for moderate cases, and **2.426 EUR** (n=13593.88) for severe cases. In the cost scenario for which we have replaced the collected cost for treatment with the IQVIA cost, the total cost decreased to **22.596.496 EUR**, with the total corresponding cost for treatment being **604.051 EUR**.

The total cost of atopic dermatitis in Romania during 2022 for pediatric patients was **31.573.968 EUR**, of which **15.026.781 EUR** were attributable to treatment costs, **8.203 EUR** to inpatient hospitalization (all of these categories corresponding to direct medical costs) and **16.516.410 EUR** were attributable to associated expenses (transportation, hotel, or other types of expenses made when they had to travel for a doctor's appointment of treatment; which is an indirect medical cost), and **3.267 EUR** due to medical leave for caregivers that reported being full-time employed, and **19.307 EUR** for part-time employment (indirect cost). The yearly average per patient cost for atopic dermatitis in Romania in 2022 for patients aged <20 years was approximately **290 EUR**, based on Global Burden of Disease prevalence estimates. The average cost per patient was **727 EUR** (n=43.408) for mild cases, **762 EUR** (n=41.429) for moderate cases, and **1.143 EUR** (n=27.619) for severe cases. In the cost scenario for which we have replaced the collected cost for treatment with the IQVIA cost, the total cost decreased to **17.468.740 EUR**, with the total corresponding cost for treatment being **921.553 EUR**.

The utilities for female patients (adult segment) ranged between 0.017 and 1, while for male patients, between 0.581 and 1. As for the pediatric population, utility values ranged between 0.349 and 1 for females and -0.025 and 1 for male patients.

Discussion

Our study presents a comprehensive analysis of the economic and social burdens of atopic dermatitis (AD) in Romania, marking a significant contribution to understanding the condition's impact on a national scale. The findings resonate with previous research indicating the substantial costs associated with AD, both direct and indirect, affecting patients and their caregivers alike. The global literature on AD highlights its pervasive impact on quality of life, mental health, and economic costs. Studies from various regions, including those by Toron et al. (2), Sampson et al. (4), and multinational research (6) underline the increased prevalence in childhood, the significant healthcare utilization, and the higher costs borne by AD patients compared to non-AD individuals.

The unique aspect of our study lies in its focus on the Romanian healthcare landscape after the COVID-19 pandemic. The pandemic's effect on the volume of healthcare services and the "new normal" in the health system provided a novel backdrop for our analysis. The sensitivity analyses performed to measure the pandemic's impact on AD care revealed vital insights into how healthcare utilization and costs have been reshaped in this period.

The Romanian prevalence study of atopic dermatitis, focusing on estimating AD prevalence across diverse geographic regions and demographic groups, deserves special mention for its innovative approach and significant contributions to the field. By employing a robust probabilistic stratified sampling method and combining questionnaire data with clinical examinations, this study has set a high standard for epidemiological research in dermatology. Though not directly used in our analysis due to differing research objectives and methodologies, the detailed demographic and clinical profiles captured in the prevalence study provide a valuable context. They underscore the variability and complexity of AD as a public health issue, reinforcing the need for targeted interventions and policies. The prevalence figures from the Romanian study, indicating a 9.41% prevalence of AD in the sample with a confidence interval ranging from 6.22% to 12.6% for the general population, offer valuable context for our study's findings. This prevalence rate, notably higher than international estimates and extrapolations, highlights the urgent need for targeted healthcare interventions and policies. Our study, focusing on AD's economic and social burdens, found that international estimates are nine times lower than these prevalence figures, indicating a significant underestimation of costs, suggesting a broad and underrecognized burden of AD in Romania¹⁴.

A study conducted in Germany between 2017 and 2019 highlights a notably higher economic burden of AD. The annual costs per patient vary greatly depending on the severity, with moderate-to-severe cases costing substantially more ($\text{€} 5229 \pm \text{€} 7538$) than mild cases ($\text{€} 1466 \pm \text{€} 3029$). This variance demonstrates the significant impact of disease severity on healthcare costs. The total annual costs for all patients were estimated to be more than $\text{€} 2.2$ billion, a figure significantly higher than that in Romania. This difference could be attributed to various factors, including differences in healthcare systems, cost of living, and the availability of treatment options, in addition to differences in study methodology²⁴.

A comparative analysis of our study on atopic dermatitis (AD) in Romania and a retrospective cohort study focusing on the direct and indirect AD costs among adults in the US in 2018 highlights several key aspects and differences in the approach and findings²⁵. Our study, conducted in Romania, encompassed both adult and pediatric populations and considered a broader range of costs, including direct medical costs and substantial indirect costs such as transportation and accommodation. In contrast, the US study was a retrospective cohort analysis specifically targeting adults with AD, matched 1:3 with controls without AD. This focus on adults aligns with the objective of understanding the healthcare burden of AD beyond its common perception as a childhood illness. The US study utilized commercial and Medicare-insured adults, which provided a substantial and specific dataset.

On the other hand, our study was more general in its approach, incorporating a broader population base and not limiting to insured patients only. In the US study, the unadjusted annual healthcare costs for adults with AD were significantly higher than for matched controls, primarily driven by outpatient services and pharmacy costs. Our study also found a significant economic burden of AD in Romania, with indirect costs, such as those associated with travel and accommodation, forming a substantial part of the total costs. This indicates that while the direct medical costs are a crucial component, the indirect costs can also significantly impact the overall economic burden of AD. The US study highlighted greater utilization of outpatient and pharmacy services among adults with AD. This aligns with our findings, suggesting high healthcare service usage, though our study did not specifically differentiate between adults and children. A notable limitation in the US study was the potential underrepresentation of mild AD cases, as these individuals may not seek medical treatment. This limitation points to the possibility of an even broader impact of AD when considering mild cases that may not be captured in healthcare utilization data. Our study, while comprehensive, also faced limitations in sampling and potential biases in self-reported data.

The IQVIA Health Plan Claims study provides valuable insights into the economic burden of managing severe cases of atopic dermatitis (AD), particularly in the context of advanced therapies²⁶. The significant annualized total cost for patients transitioning to advanced treatments like dupilumab and systemic immunosuppressants is particularly noteworthy. These findings resonate with our study's insights into the multifaceted nature of AD's impact, albeit from a different healthcare perspective. They highlight the escalating costs associated with more intensive AD treatments and reinforce the need for effective management strategies to mitigate these financial implications in Romania and globally.

Our study also finds exciting parallels and contrasts with a cost-of-illness study conducted in Hungary²⁷. Both studies underscore the significant societal and economic impact of AD. The Hungarian study, focusing on adult AD patients, highlights the considerable costs arising from treatments, outpatient visits, hospital admissions, and indirect costs such as productivity losses due to absenteeism and presenteeism. These findings align with our study's revelation of the substantial indirect costs, including transportation and accommodation for medical appointments in Romania. However, the Hungarian study's use of the Work Productivity and Activity Impairment (WPAI) questionnaire provides a more quantified view of the impact of AD on work productivity. This aspect enriches the understanding of AD's broader socioeconomic impact. While both studies illuminate the high cost of managing AD, the Hungarian study's detailed analysis of the relationship between disease severity, duration, quality of life, and economic burden offers additional insights into how

these factors interplay to escalate costs, a perspective that complements our broader findings in the Romanian context.

The difference between the total costs for adult and pediatric patients was not high. However, there were differences of over 4 million EUR for treatment costs, while the cost for associated expenses was more than double that for adult patients. The cost for inpatient hospitalizations was 90 times higher for adult patients. Slightly higher was encountered for the days off caregivers had to take to take care.

Most patients (for both GP visits and dermatology referrals) made 2 or 1 during the past twelve months. As for outpatient and inpatient hospitalizations, although they were less frequent in the survey cohort, most patients reported one admission during the past twelve months. This low number might be explained by the fact that our study did not incorporate hospital records and that most cases were moderate and severe. A secondary analysis focusing on the utilization of ambulatory services showed that over 17 years (1993-2010), there were 3.7 million visits due to AD (the rates were similar when comparing sex and season)²⁸. In another study by Al Hammadi et al., patients with AD had 1.8 inpatient visits/year, 22.7 outpatient visits/year, and 3.8 emergency visits/year²⁹. In a study conducted in the UK, there were only 13 hospital admissions (with the average LoS ranging between 2 and 11 days)³⁰.

The difference between the average number of days due to work or medical leave was 2.9 days (6.4 days – caregivers; 8.3 days – patients). In a sample composed of patients with AD from Europe (France, Germany, and the UK) and the US diagnosed with moderate-to-severe AD, impairment in work productivity (measuring using the concept of absenteeism) was higher in the patients with severe AD. The number of working days lost due to absenteeism per study sample was 0.5 days/week³¹. Another study focusing on patients with AD living in Japan showed that the percentage of time missed from work per day in the group with mild AD was slightly higher than the percentage reported by the moderate/severe AD group; however, the difference was not statistically significant³².

Most patients (for all AD severity levels) were aged between 46 and 55 years, whereas only a few patients were aged over 75 years. The data collected from the caregivers indicated that the age group of 1-10 years was the most common, while the least was between 46-55 years. Our results agree with some of the previously published estimates, stating that the prevalence in the adult population is between 1% and 3%, while among the population segment under 18 years, it is up to six times higher³³. A study on the global prevalence indicates that these percentages can vary (0.2%–22.6%), depending on the country (i.e., India, Ecuador, Columbia, among others) and the studied age group (i.e., 13-14 years, 6-7 year)³⁴. Different prevalence estimates have been reported in studies conducted in Switzerland (14% - 18.4%), Japan (7.4%-15%), and the USA (6%)³⁵⁻³⁷. A systematic analysis of the GBD study (2017) showed that the four age groups with the highest prevalence rates (100,000 inhabitants) were aged between 1-4 years, 5-9 years, 10-14 years, and 15-19 years⁴. A review published in 2021 highlighted the epidemiological differences between countries and years (which could be explained by the diagnostic criteria)^{38,39}. Lastly, the results of a systematic review and meta-analysis showed that in 64% (out of 25) of the included studies, the patients were aged over 16 years, and the reported proportion of adult patients was 26.1% (95% CI: 16.5% - 37.2%)⁴⁰.

Most of the patients were female. When stratified by AD severity and sex, most male and female patients reported moderate AD, and most minor patients had severe AD. Regarding the data collected from caregivers, most of the cared AD female patients had mild AD, whereas most AD male patients had mild AD. A study conducted in the Israeli population (using a provider database) showed that AD burden was higher among men by 25.8 in terms of new AD cases/1000 person-years in the group aged under 6 months, while in the following two analyzed groups (6 months \leq 12 years, 12 years \leq 18 years) the sex differences were lower (1.4 and 0.9). For the last analyzed age group, \geq 18 years, the number of new AD cases/1000 person-years was 1.1 higher in the female group. Overall, 52.3% of the patients with AD were female¹⁰. A nested case-control study conducted in Sweden, focusing on AD patients aged between 0-14 years, reported that 67.5% of the pediatric population diagnosed with a form of mild-to-moderate AD was aged between 0-4 years, and 56.5% having a severe form were from the same age group. Patients aged between 10-14 years were the least from

the mild-to-moderate group (12.6%) as well as from the pediatric group (19.1%)⁶. Lastly, the results of an epidemiological survey published in 2018, focusing on eight countries (US, Canada, France, Germany, Italy, Spain, UK, and Japan) showed that – except for the US, where the AD prevalence was higher by 0.5 in males, and for the UK, where the prevalence by sex was equal – prevalence of AD in women was higher. Differences ranged between 0.5 (Japan) to 4 (Italy)⁴¹.

Some co-occurring diseases the surveyed patients with atopic dermatitis reported being diagnosed were other autoimmune diseases, contact dermatitis, or allergic rhinitis. In contrast, other autoimmune diseases were more common among adult patients, and food allergies were more common among pediatric patients. Results of the National Health and Wellness Survey, which collected data from 5 European countries (France, Germany, Italy, Spain, and the UK), showed that most patients reported suffering from "allergic rhinitis and asthma" or that were not diagnosed with allergic rhinitis nor asthma⁴². Another study using the Japanese data of the same survey reported nasal allergies/hay fever in 36.91% of AD patients, asthma in 12.62%, high cholesterol in 8.99%, and arthritis in 3.79%³². Another study, having a multicenter observational design, conducted in Italy, gathered data on atopic and metabolic comorbidities that were further stratified by severity. Among adult AD patients of all degrees of severity, hypercholesterolemia was most common (26.1% – mild, 22.6% - moderate, 21.2% - severe), and hypertension the second most common in patients with mild (10.4%) and severe (15.3%) AD, while in patients with moderate the second most reported metabolic comorbidity was hypertriglyceridemia (3.2%). As for atopic comorbidities, rhinitis and sleep disorders were most common in patients suffering from moderate and severe AD, while conjunctivitis (together with rhinitis) was most common in patients suffering from mild AD. Alopecia was reported in 3% of mild AD patients, 27.5% of moderate AD patients, and 8.1% of severe AD patients⁴³. In the study by Hagerstrom et al., patients with AD were prone to be diagnosed with infections of the skin, allergic rhinitis, pruritus, and alopecia areata⁴⁴.

Some limitations of our study must be discussed. We used convenience sampling, which may not fully represent the entire population affected by AD. This sampling method could introduce bias, as it might disproportionately represent specific demographics over others. Additionally, the sample size, though adequate for our analysis, may not capture the total variability and complexity of AD cases across Romania. A substantial portion of our data was collected through self-reported questionnaires. While this approach is valuable for gathering personal experiences and perceptions, it is subject to recall and social desirability biases. Respondents may not accurately remember or may choose to report their experiences and expenditures related to AD selectively. Our economic analysis was based on cost data that might only partially encapsulate some indirect costs associated with AD, such as long-term loss of productivity or unreported out-of-pocket expenses.

Moreover, the economic data were influenced by the fluctuating economic conditions in Romania, especially during the COVID-19 pandemic, which might limit the generalizability of our findings to other periods. Given the study's focus on Romania, the findings might not be generalizable to other countries or regions with different healthcare systems, economic conditions, and demographic compositions. The specificities of the Romanian healthcare landscape and the societal context play a significant role in shaping the outcomes of our study. Our study did not include clinical data such as disease severity assessed by healthcare professionals, which could provide a more comprehensive view of the disease burden.

Nevertheless, the methodological rigor of the present study, employing a mix of surveys, interviews, and analysis of national data, ensured a comprehensive capture of the economic burden of AD. Furthermore, the dynamic nature of healthcare service utilization during the pandemic suggests that our results might be specific to this period, necessitating ongoing research to track these trends over time.

The substantial economic burden and the profound impact on quality of life highlighted in this study underscore the need for targeted healthcare policies and interventions in Romania. These should aim at reducing the direct and indirect costs of AD, improving access to effective treatments, and addressing the associated mental health issues. Integrating our findings into healthcare planning and resource allocation could lead to more effective management of AD, ultimately enhancing patient

outcomes and reducing the societal burden of this condition. In conclusion, this study provides a pivotal understanding of AD's economic and social impact in Romania, enriching the global discourse on the burden of dermatological diseases. The insights gleaned from this research could serve as a foundation for future studies and inform healthcare strategies to mitigate the multifaceted challenges posed by atopic dermatitis.

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