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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 study was conducted from April to October 2023, involving 826 responses from AD patients and caregivers. Surveys, interviews, 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:* The total cost of AD in Romania for 2021 was 30.418.896 EUR, with a significant proportion attributed to indirect costs. The average per-patient cost was approximately 164 EUR. The average cost per patient was 33 EUR (n=42.206) for mild cases, 355 EUR (n=110.160) for moderate cases, and 2448 EUR (n=33828) for severe cases. The data revealed a higher burden in patients with moderate to severe AD, predominantly female, with significant impacts on daily life and mental health. *Conclusion:* The expenditure on AD management in Romania is substantially lower compared to other countries, thus posing a significant economic burden, largely 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 than other skin conditions such as contact or seborrheic dermatitis, or other dermatological diseases such as psoriasis and urticaria (1). Despite its relatively low mortality rate, AD significantly impacts patients' lives, affecting their work and personal activities and imposing considerable economic costs (2–4).

A growing body of research has highlighted the economic and social implications of AD. Studies have identified an increased prevalence and impact of AD in specific demographic groups, particularly in children and females, leading to escalated healthcare demands and financial burdens. In their comprehensive study, Toron and colleagues revealed the heightened economic impact on patients with mild-to-moderate AD, including increased healthcare service utilization and associated costs. This trend is further intensified by significant out-of-pocket expenses and is associated with significant mental health challenges, such as anxiety and depression, in affected patients (5,6). Similarly, Sampson et al. emphasized the prevalence of moderate to severe AD cases, particularly in

younger patients, and highlighted the diverse severity of AD symptoms and their correlation with mental health issues (7).

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 costs. Furthermore, a multinational study across the U.S. and three European countries outlined differences in AD severity, treatment approaches, and the significant correlation between disease severity and quality of life (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, with indirect costs reaching approximately \$9068, indicating the extensive economic burden of the disease (9).

The recent prevalence study in Romania represents a landmark achievement in dermatology, mainly atopic dermatitis (AD). The study's achievement in developing a validated questionnaire and 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 AD (10). 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. We aim to provide the first cost of illness and quality of life study conducted at a national level for patients diagnosed with atopic dermatitis.

Material and Methods

The study measured medical and non-medical expenditures for atopic dermatitis and alopecia areata over 12 months, incorporating both direct and indirect costs from a societal perspective. The specific timeframe was adjusted based on data availability during the COVID-19 pandemic. Service volumes in Romania decreased by 40% on average after the onset of the pandemic, not counting the initial lockdown in March 2020. The study acknowledged 2019 as the last standard reference year but also considered the "new normal" in the health system post-pandemic for the economic analysis. Sensitivity analyses were employed to assess the pandemic's impact on atopic dermatitis and alopecia areata care.

The socio-economic burdens explored included public and private health insurance costs, other medical out-of-pocket expenses, loss of productivity costs for patients and caregivers, informal care costs, opportunity costs related to disease consequences, quality of life impacts using EuroQol standards, and estimating Disease-Adjusted Life Years (DALYs) for the diseases. The study employed a mixed-method approach, engaging physicians and patient organizations to reach patients and caregivers through interviews, focus groups, and surveys. We also reviewed scientific literature and national data sources, categorizing data into major cost categories. Data collection tools included a cross-sectional online patient/caregiver survey disseminated via social media and snowball/convenience sampling methods, public health insurance claims, anonymized patient data, and information from private medical suppliers and the National Institute of Statistics. The data was supplemented by peer-reviewed literature on epidemiology and economic disease burden, along with expert interviews and focus groups. 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.

Questionnaire

A questionnaire protocol was submitted and approved by the Institutional Review Board - Public Health (IRB-PH), Babes-Bolyai University (no. 151122-003). This cost of illness (CoI) study was built using prospective data gathered with a cross-sectional, online survey between 25th of April 2023 and the 18th of October 2023. The survey was constructed using the Surveyworld tool, disseminated on social media (Facebook) by APAA, and employing targeted ads. 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 (response rate %), aiming for a 95% confidence level and a 4% margin of error, was 600 patients (including responses from caregivers). Our final sample comprised N participants, consisting of x patients and y caregivers. We excluded responses with incomplete EQ-5D-5L data (x patients, y caregivers) and those lacking severity level information (x patients, y caregivers). Consequently, our final sample size was x respondents, with only % being caregivers.

Our survey is 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, OOPs (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 incorporated the EQ-5D-5L, a generic instrument, to collect health-related quality-of-life data. The collected data was analyzed in R using the “eq-5d” package.

Additional information sources

For this study, we used retrospective data from the Global Burden of Disease Study 2019 (G.B.D.), IQVIA, National Institute for Management of Health Services and Hospital Consulting Romania. The epidemiological input for this cost of illness study on the burden of atopic dermatitis was based on all ages, for both sexes, prevalence data (total crude number) modeled for 2019, for Romania, encompassed in the “Skin and other subcutaneous diseases” causes category, retrieved from the G.B.D. estimates publicly available (<https://vizhub.healthdata.org/gbd-results/>). The all ages for both sexes prevalence for 2019 for atopic dermatitis was 186176.4 cases (95% CI:178959.7 - 193499.4). We also retrieved disability weights corresponding to the levels of severity for atopic dermatitis from the G.B.D. study (<https://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights>): mild - 0.027 (0.015 - 0.042), moderate - 0.188 (0.125 - 0.267), and severe - 0.576 (0.401 - 0.731). Health state names and descriptions are available in the supplementary material. Data obtained from IQVIA highlighted that an individual category for atopic dermatitis was lacking. Therefore, we assumed that patients with atopic dermatitis were under the category “other dermatitis”. For our costing exercise, we included the median value/medical prescription, which had the value of 40.4 RON. This estimate was based on data retrieved from 3700 pharmacies in 2022; however, in calculating this estimate, there were medical prescriptions that were partially or totally subsidized.

Costing approach

We evaluated the economic impact of atopic dermatitis (AD) and alopecia areata 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 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. The bottom-up and top-down approaches are employed in accordance with the availability of data to yield the total population cost of the condition. In addition to the costs incurred by atopic dermatitis, this study determined the health-related quality of life for patients with these two conditions. This approach will provide an additional layer of clarity regarding the impact of alopecia areata and atopic dermatitis on society, offering an insight into the intangible burden of AD – often difficult to quantify in cost of illness studies.

Data processing

The initial dataset comprised 826 questionnaires. During the data cleaning process, the following exclusions were made:

- 26 questionnaires were removed due to the absence of informed consent.
- 34 entries were excluded because participants were minors.
- 3 test entries were identified and removed.
- 33 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.
- 74 questionnaires from caregivers, among which:
 - 60 were for minors.
 - 14 were for adults who had a proxy respondent.

Subsequent modifications and checks were applied to the database, as detailed below:

- *Meta-variable Removal:* Meta-variables irrelevant to the analysis were removed to streamline the dataset.
- *Recoding of Boolean Variables:* Instances with only one FALSE/TRUE were recoded for consistency.
- *Questionnaire Item Corrections:*
 - Q19: Outlier values (e.g., 98 visits to a general practitioner) were corrected, and the lowest plausible value was selected.
 - 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.
- *Artifact Removal:* For questions Q15-Q17, if Q14 indicated no treatment, artifact entries from these questions were removed. A similar approach was applied to caregiver responses.
- *Cost Adjustments:* All cost entries were rounded to the nearest 50 R.O.N. to address inconsistencies likely caused by slider input errors (e.g., 998 RON).
- *Splitting and Reorganizing Data:*
 - For questions Q19-23 and corresponding caregiver questions, cells were split to separately record the number of visits.
 - Question Q15 and similar items were clustered based on open-ended answers, though few such cases were noted.
- *Consistency Checks:* Several variables were checked for consistency, leading to corrections in cases of evident errors, such as:
 - In Bucharest Municipality, some entries incorrectly marked rural locations.
 - Among caregivers, retirees who reported missing work.
 - In caregiver data, some reported the highest level of education completed by the child instead of themselves, leading to implausible entries (e.g., 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.

Aggregation and analysis

The study employed a methodical, analytical approach to comprehensively understand the impact of atopic dermatitis (AD) in Romania. The primary step involved stratifying the collected data by demographic and clinical characteristics. This stratification process categorized the data according to various criteria, such as age, sex, severity of AD, and comorbid conditions. This categorization was essential to analyze how AD affects different population segments. An analysis of treatment patterns and healthcare utilization was then conducted. This involved examining the types of treatments patients use, their frequency, and the overall pattern of healthcare service engagement. The analysis included assessing visits to general practitioners and specialists, hospital admissions, and utilizing laboratory services. This examination provided insights into the healthcare-seeking behaviors of individuals affected by AD and the resulting demands on the healthcare system. The economic

impact of AD was also a critical focus of the study. The research involved a detailed calculation of the direct medical and non-medical costs and indirect costs associated with productivity losses due to medical leaves. This economic assessment aimed to quantify the overall economic burden of AD. Furthermore, the study assessed the quality of life for patients with AD using the EuroQol EQ-5D-5L instrument. This assessment involved correlating the quality-of-life data with factors such as the severity of AD and various demographic characteristics. In addition to these analyses, a comparative analysis was conducted. This comparison involved juxtaposing self-reported cost data with retrospective data collected nationally. The purpose of this comparison was to offer a multidimensional perspective on the economic implications of AD. The statistical methods used in the study focused on providing a clear representation of the data. Descriptive statistics were employed, including calculating means, ranges, and total values for each cost category. The study also involved calculating utilities for different severity levels of AD to further understand the impact of the disease.

Results

The results are stratified by the severity of atopic dermatitis (AD), with data collected from patients and caregivers under 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	80	34	11	9	6	
Female	106	286	79	17	15	12	
Other option	-	2	-	-	-	-	
Age interval (patients)			Age interval (caregivers)				
18-25 years	6	18	5	1-10 years	16	13	7
26-35 years	10	17	5	11-17 years	6	8	7
36-45 years	28	90	25	18-25 years	2	3	1
46-55 years	47	114	39	26-35 years	2		2
56-65 years	32	71	23	36-45 years	1		1
66-75 years	16	53	14	46-55 years	1		
75+ years	2	5	2	-			
Settlement type (patients)			Settlement type (caregivers)				
Urban	118	59	14		21	20	15
Rural	23	309	99		7	4	3
Education level (patients)			Education level (caregivers)				

Primary school	2	8	2	Kindergarten/nursery	12	8	5
Gymnasium	1	2		Primary school	7	10	3
Post-secondary school	12	28	10	Gymnasium	2	3	5
University	83	210	64	University	5	3	3
Employment status (patients)				Employment status (caregivers)			
Employed full time	71	188	55		16	11	8
Employed part-time	3	23	5		1	4	
Unemployed	7	13	4		1	2	
Student	8	12	7	Other option	6	1	3
Retired (age limit)	28	79	26		3	1	5
Retired (due to sickness)	12	22	8		1	5	2

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 year	1 27	93	18	-	1	1
1 - 3 years	42	102	36	7	9	4
4 - 6 years	33	62	23	10	10	4
7 - 9 years	8	13	2	4	2	1
Over years	10 31	98	34	7	2	8

Level of symptom control						
Not at all under control	7	17	27	-	2	2
Often under control	60	98	9	10	8	2
Sometimes under control	65	253	61	6	12	12
All the time under control	9		16	12	2	2

Comorbidities

Eighty-one patients reported being diagnosed with chronic urticaria and food allergies, 177 with allergic rhinitis, 87 with non-allergic rhinitis, 8 with esophagitis, 214 with contact dermatitis, and 254 with other autoimmune diseases. Lastly, 117 reported not being diagnosed with any of the listed diseases.

Treatment utilization

Treatment modalities varied: 507 patients used ointments, 191 oral treatments, 57 injections, and 24 other forms, including medical devices (n=15) and specialized 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).

Health services utilization

During the past 12 months, 46 patients reported having made 2 visits to their G.P.'s office, 2 groups of 40 patients reported 1, respectively 5 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). Patients reported having 2 outpatient discharges (n=27), followed by 1 (n=23), respectively 3 (n=22) and 4 outpatient discharges (n=20), while 452 patients reported 0 outpatient discharges during the past 12 months (overall range 0-45 discharges). As for inpatient discharges, most patients had 5 discharges *n=23), two groups of 19 patients had 1, respectively 3 inpatient discharges and 464 had 0 inpatient discharges (overall range 1 - 12 inpatient discharges). Laboratory services were underutilized, with 362 patients not using these services at all (overall range of 0-15 utilizations). A total of 59 patients reported using these services once, while 41 patients used them three times. Additionally, two separate groups of 37 patients each reported four and two utilizations, respectively.

Leave from work

The impact of AD on work was significant, with all patients reporting some days off. The majority took one day (n=239), two groups of 90 patients took 5, respectively 6 days, 68 patients took 4 days, while fewer patients took 8 days off from work.

Proxies and caregivers

Among the caregivers surveyed, they reported a range of comorbidities in addition to atopic dermatitis in patients. 9 caregivers noted that the patients they care for also have bronchial asthma. Additionally, there were reports of chronic urticaria (5 cases), allergic rhinitis (14 cases), non-allergic rhinitis (4 cases), and food allergies (25 cases). Contact dermatitis and autoimmune diseases were also noted in 12 and 8 cases, respectively. Esophagitis was absent in this patient group, and 31 caregivers indicated that the patients they cared for did not suffer from any of the listed comorbid conditions.

Treatment utilization

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 U.V. therapy and specialized skincare products like shower gels, shampoos, and 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 in need, and 2 once per week.

Health services utilization and work leave

During the last 12 months, 7 caregivers reported that the patients they were taking care of made 2 visits to their G.P.'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 G.P.s office (overall range 1-21 visits). As for visits to the specialist doctor, 15 caregivers reported that the patients they care for made 2 visits, 7 reported 1 visit, 5 reported 5 visits, and 4 caregivers reported 8, 9, 10, respectively 12 visits during the last twelve months (overall range 1 - 12 visits). Outpatient hospitalizations were relatively less frequent, with a few caregivers reporting 1 to 4 outpatient admissions, while three caregivers reported that the patient they were taking care of had 3, 7, respectively 8 outpatient discharges (overall range 1 - 8 outpatient discharges). Inpatient hospitalizations were reported in a small number of cases, with 5 caregivers noting 1 inpatient hospitalization and others reporting 2 or 3 discharges (overall range 1 - 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, respectively 4 times, 4 patients used it 3 times, and one patient used it 6, 7, respectively 10 times (overall). The number of days attributable from the range between 1 day (reported by two caregivers) and over 30 days (reported by six caregivers).

Costs

The total cost of atopic dermatitis in Romania during 2021 was **30.418.896 EUR**, of which 329.639 EUR were attributable to treatment costs, 9.220.864 EUR were attributable to costs of medical services, 1.305.807 EUR to inpatient hospitalization (all of these three categories corresponding to direct medical costs) and 19.545.615 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 16.972 EUR due to medical leave (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 2021 was approximately **164 EUR**, based on Global Burden of Disease prevalence estimates (1%). The average cost per patient was **33 EUR** (n=42.206) for mild cases, **355 EUR** (n=110.160) for moderate cases, and **2448 EUR** (n=33828) for severe cases.

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. Our study corroborates these findings, demonstrating similar trends in the Romanian context. The proportion of patients suffering from anxiety and depression, the high prevalence of AD in females, and the marked increase in healthcare service usage align with these international observations.

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 healthcare services' volume, coupled with 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 key 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 ability of the study to disseminate results across scientific communities, dermatologists, policymakers, and the public further amplifies its impact and sets a benchmark for future research in this domain. 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 the economic and social burdens of AD, 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 Romania.

Consistent with the multinational study findings (6), our results also indicated a strong correlation between AD severity and quality of life. The lower socioeconomic status observed in patients with severe AD forms echoes the findings from the study conducted in Israel (5), emphasizing the multidimensional impact of AD on various aspects of life.

In Romania, the total cost for AD in 2021 was 30.418.896 EUR. The breakdown of these costs reveals a significant proportion (19.545.615 EUR) attributed to associated expenses, such as transportation and accommodation for medical appointments, indicating the indirect costs that significantly impact patients' financial burden. Direct medical costs, including treatment, medical services, and inpatient hospitalization, accounted for a smaller portion of the total costs. Interestingly, the cost due to medical leave was relatively minor (16.972 EUR). The per-patient cost, calculated based on the prevalence estimates from the Global Burden of Disease, was approximately 164 EUR annually.

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 (€ 5229 ± € 7538) than mild cases (€ 1466 ± € 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 € 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 (11).

A comparative analysis of our study on atopic dermatitis (AD) in Romania and a retrospective cohort study focusing on the direct and indirect costs of AD among adults in the U.S. in 2018 highlights several key aspects and differences in the approach and findings (12). 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 U.S. 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 U.S. 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 U.S. 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 U.S. 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 U.S. 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 therapies (13). 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 that could potentially mitigate these financial implications, both in Romania and globally.

Our study also finds interesting parallels and contrasts with a cost-of-illness study conducted in Hungary (14). 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, an aspect that 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.

In comparing our study's findings with those presented in the European White Paper on atopic dermatitis (AD), several noteworthy contrasts and parallels can be drawn (15). Our study on Romania indicates a total AD cost of €30.4 million in 2021, substantially lower than the €30 billion annual societal cost estimated across Europe in the White Paper. This variance likely mirrors differences in the scale of the populations, healthcare systems, and economic conditions between a single country and the continent at large. Both studies highlight AD's significant economic burden, encompassing direct medical costs and indirect expenses such as lost workdays and personal expenditures. Our study further separates these costs and provides detailed breakdowns for different severity levels of AD, offering a more nuanced view of its economic impact within Romania. Despite the differences

in magnitude, our research corroborates the extensive financial and humanistic toll of AD, underscoring the pressing need for enhanced management and treatment approaches.

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 certain demographics over others. Additionally, the sample size, though adequate for our analysis, may not capture the full 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 selectively report their experiences and expenditures related to AD. Our economic analysis was based on cost data that might not fully encapsulate all the 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 the economic and social impact of AD 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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