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The Economic Burden of Alopecia Areata in Romania

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Abstract: Background: Alopecia areata is a skin disease that affects patients' quality of life and social participation. **Objective:** To quantify the economic burden of alopecia areata and to map health services utilization among patients with alopecia areata. **Materials and methods:** Prospective and retrospective data sources, using both top-down and bottom-up approaches to estimate direct and indirect costs and to map health service utilization associated with alopecia areata in Romania in 2022. **Results:** In our study, the total cost of alopecia areata in Romania for 2022 was estimated at 46.289 million EUR for adult patients and 1.89 million EUR for pediatric patients, encompassing both mild and severe cases. The breakdown reveals that both mild and severe cases incurred the highest costs due to associated expenses, medical services, and treatment. As for children, the highest alopecia-related expenses were represented by associated expenses and treatment costs (for both severity levels). **Conclusion:** This is the first study to quantify the burden of alopecia areata in Romania. Additional studies are needed due to a low sample size. However, considering our estimations based on external data sources, alopecia areata should be considered when planning health service distribution.

Keywords: alopecia areata; cost of illness; economic burden

Introduction

Alopecia areata (AA) affects patients of all ages, sexes, and ethnicities, with observed variations among group categories [1]. For example, in terms of sex differences, some studies point out that men are diagnosed earlier by 4.7 years than women, and 11.2% more men exhibit the first signs at the beard level as opposed to the scalp, while other studies have shown contrary results in terms of sex predominance [2,3].

The current burden of alopecia areata in terms of GBD metrics (as opposed to previous estimates) remained approximately constant globally. However, a comprehensive analysis of the epidemiological trends of alopecia areata using global estimates showed slight decreases in global age-standardized incidence rates (ASIRs) compared to 1990 for both men (287.26 vs. 279.16) and women (549.03 vs. 531.68)[4]. Another study highlighted a difference of 0.08% among age-standardized prevalence rates when comparing adults with minor patients (0.18% in adults and 0.10% in pediatric patients). Concerning age predominance, one study reported that patients aged 21–40 were the most affected, while patients aged 40–49 were the second most affected(according to a recent analysis) [5]. Regarding ethnicity, the highest, respectively, and the lowest prevalence were among Asian patients (414/100.000) and White patients (168/100.000)[6]. Regarding the geographical distribution of disease burden, countries with high and high-middle sociodemographic index (SDI) were the most affected (518.91 and 408.62, respectively). In Eastern Europe, ASIRs were similar in 1990 (389.49) and 2019 (387.84)[4].

AA affects patients and their caregivers on multiple fronts. Shi et al. showed in a secondary analysis of registry data that poor quality of life (reported by over 54.7% of the included patients) was associated with age (20-50 years), modification in physical appearance (skin- and hair-related), and sex (female), as well as to several social factors (such as job or family related stress)[7]. A hospital-based multicenter study conducted in Korea reported that quality of life worsened in family members and pediatric patients as the severity of the disease increased. This study also reported that as the disease progressed, the annual cost of treatment in most patients was over 1000 $ [8]. Patients affected by this pathology, both adults and children, were often (compared to controls defined as healthy adults) diagnosed with anxiety and/or depression (or symptoms)[9].

AA also poses an economic burden. A study assessing the healthcare utilization patterns in the US in a sample of adolescent patients with AA listed a total cost per patient of 9397 $ (the highest - 7480 $ was due to payer medical costs, while the lowest was due to payer cost for dermatology appointments - 922 $)[10]. As for the adult patient group (characterized by an average age of 40.3 years and predominantly female - 61%), another US-based study reported healthcare costs of 11241.21 $ (for all causes), while 419.12$ due to alopecia among diagnosed patients with this skin disease[11].

Our study is the first study in Romania to inquire about healthcare utilization, economic burden, and quality of life in patients diagnosed with alopecia areata of different ages, as responses for patients over 18 years were collected from the patients themselves and for patients under 18 were collected from caregivers, which acted as proxies in the data collection process. By focusing on this gap, we aim to offer a policy tool for patients and stakeholders alike, as cost of illness studies (incorporating quality of life instruments) are crucial for policymaking and advocacy, among others.

Methodology

This cost of illness study quantified the medical and non-medical costs associated with alopecia areata over 12 months, considering both direct and indirect components, thus employing a societal perspective. We projected the economic burden by including public (corresponding to the data retrieved on the length of stay and hospitalization costs within public hospitals and data from the GBD study) and private data (taking costs reported in the questionnaire as well as the data from IQVIA), thus incorporating retrospective and prospective data sources.

The study used 2022 as a reference year; however, incidence and prevalence data were retrieved from the GBD 2019 study (this being the latest available estimations for Romania)[12]. For the primary analyses, we used the crude prevalence (<20 years – 4002.547, 20+ years – 40540.68), as for the sensitivity analyses, we used the crude incidence (<20 years – 7345.723, 20+ years – 70567.6), for both sexes, retrieved from the GBD 2019 study (within the category "skin and other subcutaneous diseases")[13]. Other data utilized in the Global Burden of Disease Study 2019, which was included in the principal costing analysis, was the prevalence data for Romania. We used these two age bands since, compared to our study, there were different age bands. Therefore, to cover most age groups, we employed the under and over 20+ GBD age bands, and we excluded one patient aged between 18 and 25 years only from our cost projects that used GBD data.

In addition, we complement the economic cost of illness by collecting data on the health-related quality of life with EQ-5D-5L. This instrument is composed of five descriptive dimensions (mobility, usual activities, self-care, pain and discomfort, anxiety, and depression) that are measured on five levels (no, mild, moderate, severe, and extreme) and form the first part of the instrument. In contrast, the second part is represented by EQ-VAS, a visual analog scale that provides data on the patient's self-health assessment that can range from 0 (worst) to 100 (best) health[14]. The EQ-5D-5L instrument has been widely used in studies with different study designs, such as population health surveys, observational studies, or clinical trials [15–18]. We used this tool to collect primary data to generate utilities. The analysis was performed in R using the "eq-5d" package[19]. We report the generated utilities stratified by severity and sex (for adult and pediatric patients). As the EQ-5D-5L user manual recommends, we divide the EQ-5D-5L levels into two categories: "no problems" corresponding to level 1 and "problems" corresponding to levels 2, 3, 4, and 5. For EQ VAS, we report the mean, standard deviation, and the 25th and 75th percentile by age groups[20].

This cost of illness (CoI) study was also built by collecting data via a cross-sectional, online questionnaire (start date of collection process: 25 April 2023; end date of the collection process: 18 October 2023). The survey was constructed using the Surveyplanet tool[21] and disseminated on Facebook (using targeted ads) by APAA. The type of sampling for this survey was convenience sampling, with a target population composed of patients over 18 years old and caregivers (of patients under and over 18 years old).

Our prospective data source (online questionnaire) contained, in addition to EQ-5D-5L, a set of open and multiple-choice questions. We developed this questionnaire based on a literature review of the cost of illness and health service utilization studies and, to account for the national context of the patient pathway for alopecia areata; we further refined it with the help of other stakeholders (i.e., doctors and patients' association).

Our questionnaire encompassed a range of questions regarding sociodemographic factors (such as age, gender, county, settlement type, education, and employment) as well as symptom control, self-reported severity, and the presence of other health conditions (including chronic urticaria, allergic rhinitis, non-allergic rhinitis, food allergies, eosinophilic esophagitis, contact dermatitis, and other autoimmune or inflammatory diseases). Additionally, the survey covered the types of prescribed treatments (ointments, oral medications, injections), their frequency, the usage of prescribed medications, and out-of-pocket expenses (such as treatment, medical services, and expenses related to transportation or accommodation). Lastly, the questionnaire assessed the frequency of utilization of medical services in the last twelve months, including visits to primary and secondary care providers (general practitioners and specialist doctors), inpatient and outpatient admissions, and the use of medical laboratory services. From the questionnaire, we incorporated (for each level of GBD severity for alopecia areata) for the costing exercise the following items: treatment costs, medical services costs, associated expenses, number of missing days from work (both part-time and full-time employment) for both active patients and caregivers. We excluded missing days reported for patients under 18 years old from patients and caregivers over 65 years (thus being considered retired), and from patients and caregivers under 65 but have checked (retired due to illness) when completing the survey. In addition, we also excluded data (for a group of 4 patients) on the number of days representing leave from work as it exceeded the number of days within a year.

Further, we incorporated data from IQVIA, which helped us ascertain the average cost of treatment for alopecia areata based on data collected from 3,700 pharmacies. This excluded "white prescriptions," and the average cost amounted to 52 RON (with partial or total reimbursed prescriptions included).

Hospital Consulting Romania was another used source. It provided data on the average cost for inpatient hospitalizations for both adult and pediatric patients with alopecia areata in 2022 – 1,094 RON for adults and 1,012 RON for children – as well as the estimates for the average length of hospital stays (7.95 days for adults and 4.44 days for children).

Lastly, we looked at productivity costs, for which we used data on the mean wage for 2022 (6,126 RON) from INSSE and the number of working days in 2022, amounting to 251. These comprehensive data sources collectively informed our analysis, providing a robust foundation for our study on the economic impact of alopecia areata. We calculated the costs using both top-down and bottom-up approaches, considering the multiple data sources.

The final questionnaire sample consisted of 41 patients and 7 caregivers. We report crude numbers and proportions (stratified for severity levels: S0-S6) for each descriptive category reported in the survey. For costs, we report total costs and corresponding percentages for each cost item from the total costs; we also report the mean cost per GBD severity levels (L1 and L2; per expert opinion, severity levels S0 to S2 were incorporated in L1, while S3 to S5 in L2, while a case for which the severity was unknown was excluded from all analyses). All costs were converted into EUR (1 EUR = 4.9313), based on an average exchange rate for 2022[22].

The Institutional Review Board - Public Health (IRB-PH), Babes-Bolyai University (no. 151122-003) submitted and approved a research protocol.

Results

Descriptive for each of the collected variables were stratified by severity (Tables 1–4).

Most patients with alopecia areata were female, aged between 46 and 55 years old, resided in the urban area, graduated from university, were employed full-time, and were diagnosed within the last 1-3 years or over ten years.

Table 1. Data collected from patients.

Severity	**S0**	**S1**	**S2**	**S3**	**S4**	**S5**
Sex						
Male	2 (5%)	1 (2%)	2 (5%)	2 (5%)	-	1 (2%)
Female	1 (2%)	9 (22%)	5 (12%)	8 (20%)	3 (7%)	7 (17%)
Age intervals						
18-25 years	-	-	1 (2%)	-	-	-
26-35 years	1 (2%)	1 (2%)	2 (5%)	-	-	1 (2%)
36-45 years	1 (2%)	3 (7%)	2 (5%)	2 (5%)	1 (2%)	4 (10%)
46-55 years	1 (2%)	3 (7%)	2 (5%)	1 (2%)	1 (2%)	3 (7%)
56-65 years	-	1 (2%)	-	3 (7%)	1 (2%)	-
66-75 years	-	2 (5%)	4 (10%)	-	-	-
Settlement type						
Urban	-	6 (15%)	6 (15%)	6 (15%)	2 (5%)	2 (5%)
Rural	3 (7%)	4 (10%)	1 (2%)	4 (10%)	1 (2%)	6 (15%)
Education level (patients)						
Primary school	1 (2%)	-	1 (2%)	1 (2%)	1 (2%)	-
Gymnasium	-	1 (2%)	-	2 (5%)	-	-
High school	1 (2%)	2 (5%)	-	1 (2%)	-	2 (5%)
Post-secondary school	-	3 (7%)	3 (7%)	3 (7%)	1 (2%)	2 (5%)

University	1 (2%)	4 (10%)	3 (7%)	3 (7%)	1 (2%)	4 (10%)
Employment status						
Employed full time	1 (2%)	6 (15%)	6 (15%)	2 (5%)	2 (5%)	6 (15%)
Employed part-time	-	-	1 (2%)	-	1 (2%)	-
Unemployed	1 (2%)	-	-	1 (2%)	-	-
Retired (age limit)	-	3 (7%)	-	7 (17%)	-	-
Retired (due to sickness)	1 (2%)	-	-	-	-	2 (5%)
Other option (maternity leave)	-	1 (2%)	-	-	-	-

Table 2. Data collected from patients.

	Data collected from patients					
	S0	**S1**	**S2**	**S3**	**S4**	**S5**
Time since diagnosis						
Under 1 year	-	1 (2%)	-	-	-	1 (2%)
1 - 3 years	2 (5%)	4 (10%)	2 (5%)	4 (10%)	1 (2%)	1 (2%)
4 - 6 years	-	1 (2%)	1 (2%)	-	1 (2%)	-
7 - 9 years	1 (2%)	1 (2%)	3	1 (2%)	-	2 (5%)
Over 10 years	-	3 (7%)	1 (2%)	5 (12%)	1 (2%)	4 (10%)

Thirteen of the surveyed patients were diagnosed with autoimmune thyroiditis, 8 with atopic dermatitis, 7 with psoriasis, 4 with systemic lupus erythematosus, 3 with anemia, and 10 had none of the listed options.

Treatment utilization

24 patients were using ointment, 17 oral treatments, 8 injections, and 7 other forms (Shampoo/shower gel – n=2, infusions – n=1). Most patients are using their treatment once per day (n=15), multiple times per day (n=10), or once per week (n=6), while the fewest patients are using it when needed (n=4).

Health services utilization

During the last 12 months, 15 patients reported that they were using their treatment once per day (four patients with S2 and S3, three with S5, and two with S1 and S4 each), 10 reported that they were using their treatment multiple times per day (three patients with S0 and S1 each, one with S2 and S3 each, and two from S5), one group of six patients once per week (two with S2 and one with S1, S3, S4, and S5), and another group of six patients stated that they did not know the time they were using their treatment (two with S1, S3, and S5). Four patients reported using their treatment when needed (2 from S1 and 2 from S3).

Regarding GP visits, 15 patients reported visits during the last 12 months (five patients with S1, four with S5, three with S3, two with S0, and one with S4). Three groups at 12 months reported 3, 6, and 9 visits, respectively. The other reported values per patient were 0, 1, 2, 5, and 10. In addition, one patient reported visiting their GP (without specifying the number) but for other reasons. As for specialist doctors, 23 patients reported visiting the specialist doctor (3 with S0, 7 with S1, 2 with S2, 4 with S3, 1 with S4, and 6 with S5).

Seven patients reported day hospitalization (two with S0, one with S1, three with S3, and one with S4). The number of hospitalizations ranged from 12 (S3) to two (S1 and S2). Twelve patients (S3) reported having made 6-day hospitalizations, 8 patients (S4) 8-day hospitalizations, and 9 patients (S3) reported 9-day hospitalizations during the past 12 months, while four patients (two with S0 and two with S1) reported 2-day hospitalizations and five patients (S0) reported 5-day hospitalizations during the past 12 months. Regarding inpatient hospitalizations, only six patients reported being admitted in an inpatient setting (three patients with S3 and one with S0, S4, and S5 each). Two patients (one with S3 and one with S4) reported seven hospital admissions, and two (both with S3) reported nine. Lastly, one patient (with S0) reported five hospital admissions and one (with S5) 9 hospital admissions during the past 12 months.

Eleven patients reported using the services of a medical laboratory for alopecia areata during the past 12 months, and the maximum number of utilizations was 98 (one patient with S3 and one with S4). Patients with S0 (n=2) reported 2, respectively 5 utilizations, two patients with S1 reported 2 utilizations, and another with the same severity level reported 3. Patients with S3 (n=2) reported 7 and 8 utilizations, respectively, and patients with S5 (n=2) reported 2 and 1 utilization, respectively.

Leave from work

The number of days the patients took from work ranged between 1 (n=2) and 174 (n=1). Other patients took 3, 5, 6, 10, 12, 13, 16, and 20 days, respectively.

Table 3. Data collected from proxies - caregivers.

Severity	**S0**	**S1**	**S2**	**S3**	**S4**	**S5**
Sex						
Male	-	2 (29%)	2 (29%)	-	-	-
Female	-	2 (29%)	-	1 (14%)	-	-
Age intervals						

1 - 10 years	-	-	1 (14%)	-	-	-
11 - 17 years	-	1 (14%)	1 (14%)	1 (14%)	-	-
26-35 years	-	1 (14%)	-	-	-	-
36 - 45 years	-	1 (14%)	-	-	-	-
56 - 65 years	-	1 (14%)	-	-	-	-
Settlement type						
Urban	-	3 (43%)	2 (29%)	1 (14%)	-	-
Rural	-	1 (14%)	-	-	-	-
Education level (patients)						
Primary school	-	-	1 (14%)	1 (14%)	-	-
Gymnasium	-	1 (14%)	-	-	-	-
High school	-	1 (14%)	-	-	-	-
University	-	2 (29%)	-	-	-	-
Kindergarten/nursery	-	-	1 (14%)	-	-	-
Employment status - caregiver						
Employed full time	-	1 (14%)	1 (14%)	1 (14%)	-	-
Student	-	1 (14%)	-	-	-	-
Retired (age limit)	-	1 (14%)	1 (14%)	-	-	-
Retired (due to sickness)	-	1 (14%)	-	-	-	-

Table 4. Data collected from caregivers – proxies.

	Data collected from proxy/caregivers					
	S0	**S1**	**S2**	**S3**	**S4**	**S5**
Time since diagnosis						

Under 1 year	-	1 (14%)	-	-	-	-
1 - 3 years	-	2 (29%)	1 (14%)	1 (14%)	-	-
4 - 6 years	-	1 (14%)	1 (14%)	-	-	-

The surveyed caregivers stated that the patients they care for were also diagnosed with atopic dermatitis (n=1) or anemia (n=1), while most (n=5) stated that the patients were not diagnosed with any of the listed options (n = 5)

Treatment utilization

All surveyed caregivers (n=7) reported that the patients with alopecia areata they are taking care of are using ointment as a form of treatment administration, only one stated that the patient in their care was also using a treatment with oral administration, and one reported an injectable treatment. As for other options, one caregiver listed the usage of anti-hair fall serum. Most caregivers (n=3) reported that the patients used the treatment multiple times or once per day (n=3), and only one patient used the treatment when needed.

Health services utilization

As for visits to the specialist doctor, the ranges are the same as for the GP visits - between 2 and 13 visits; however, one caregiver who reported 0 visits to the GP's office reported that the patient under their care made 3 visits to the specialist doctor during the last twelve months.

Regarding outpatient hospitalizations, most caregivers (n=6) reported 0-day hospitalizations and only one reported 2-day hospitalizations made by the patient they cared for. Similar results have been reported on inpatient hospitalizations.

Most caregivers (n=5) responded that the patients diagnosed with alopecia areata have used the services of a medical laboratory, with the number of usages ranging between 2 and 12 during the last twelve months.

Leave from work

For the number of days missed from education or work, caregivers have reported that patients with alopecia areata have missed 3, 13, 15, 19, and 300 days. In contrast, caregivers reported 2, 3, 20, and 50 days missed from work or a form of education due to the patients' alopecia areata.

Costs

The total cost of alopecia areata for adult patients in Romania in 2022 was **46.288.586 EUR** for mild and severe cases. The costs for mild cases were **12.345 EUR** for hospitalizations, **7.454.855 EUR** for treatment, **8.256.504 EUR** for medical services, **10.384.775 EUR** for associated expenses, and **4.157 EUR** for productivity loss. The severe cases cost **5.058.266 EUR** for treatment, **6.622.416 EUR** for medical services, **8.414.346 EUR** for associated expenses, **72.311 EUR** for hospitalizations, and **1.739 EUR** for productivity loss. The average costs range between **268 EUR** (treatment, L2 cases) and **478 EUR** (associated expenses, L1 cases). The mean cost per patient ranges between **2.864 EUR** (L2 cases) and **3.037 EUR** (L1 cases).

The scenario for which the cost associated with the treatment (collected via the survey) was replaced with the average provided by IQVIA decreased the total cost by 26.14% to **34.196.090 EUR**. The cost of treatment was **228.657 EUR** for mild cases and **198.835 EUR** for severe cases.

The total cost of alopecia areata for pediatric patients in Romania in 2022 was **1.893.368 EUR** for mild and severe patients. The costs of mild cases were **310.460,5 EUR** for treatment, **695.796 EUR** for associated expenses, and **127 EUR** for caregiver productivity costs. The cost for severe cases was

378.844 EUR for treatment, **507.290 EUR** for associated expenses, and **848,45 EUR** for caregiver productivity costs. The scenario for which the cost associated with the treatment (collected via the survey) was replaced with the average provided by IQVIA decreased the total cost by 34.18% to **1.246.269 EUR**. The cost of treatment was **31.654 EUR** for mild cases and **507.290 EUR** for severe cases.

Utilities

Adult population

Calculated utilities ranged between 0.136 and 1 for females and 0.738 and 0.083 for males. When stratified by disease severity, the corresponding ranges for each severity are between 0.711 and 0.801 for S0, 0.083 and 1 for S1, 0.701 and 0.962 for S2, 0.205 and 0.947 for S3, 0.803 and 0.941 for S4, and between 0.671 and 0.909 for S5.

Pediatric population

Calculated utilities ranged between 0.734 and 1 for female and 0.704 for male patients (n=1). When stratified by disease severity, the corresponding ranges for each severity are 0.734 for S1, between 0.941 and 1 for S2, and 0.704 for S3.

Table 5. Frequencies of patients reporting problems and no problems per each EQ-5D domain - data collected from patients.

EQ-5D Dimension	**18 - 25 years**	**26 - 35 years**	**36 - 45 years**	**46 - 55 years**	**56 - 65 years**	**66 - 75 years**
Mobility - no problems	1 (100%)	3 (100%)	12 (100%)	5 (100%)	2 (100%)	4 (100%)
Mobility - problems	0	0	0	0	0	0
Self-care - no problems	1 (100%)	3 (100%)	9 (75%)	4 (80%)	2 (100%)	4 (100%)
Self-care - problems	0	0	3 (25%)	1 (20%)	0	0
Usual activity - no problems	1 (100%)	3 (100%)	6 (50%)	2 (40%)	2 (100%)	4 (100%)
Usual activity - problems	0	0	6 (50%)	3 (60%)	0	0
Pain/discomfort - no problems	0	2 (66.66%)	2 (16.66%)	1 (20%)	0	3 (75%)
Pain/discomfort - problems	1 (100%)	1 (33.33%)	10 (83.66%)	4 (80%)	2 (100%)	1 (25%)
Anxiety/depression - no problems	0	2 (66.66%)	0	0	1 (50%)	3 (75%)
Anxiety/depression	1 (100%)	1 (33.33%)	12 (100%)	5 (100%)	1 (50%)	1 (25%)

- problems						

Table 6. Frequencies of patients reporting problems and no problems per each EQ-5D domain - data collected from caregivers.

EQ-5D Dimension	**1 - 10 years**	**11 - 17 years**	**26 - 35 years**	**36 - 45 years**	**56 - 65 years**
Mobility - no problems	1 (100%)	1 (100%)	0	0	1 (100%)
Mobility - problems	0	0	1 (100%)	1 (100%)	0
Self-care - no problems	1 (100%)	1 (100%)	0	0	1 (100%)
Self-care - problems	0	0	1 (100%)	1 (100%)	0
Usual activity - no problems	1 (100%)	1 (100%)	0	0	1 (100%)
Usual activity - problems	0	0	1 (100%)	1 (100%)	0
Pain/discomfort - no problems	1 (100%)	1 (33.33%)	0	0	0
Pain/discomfort - problems	0	2 (66.66%)	1 (100%)	1 (100%)	1 (100%)
Anxiety/depression - no problems	0	1 (33.33%)	0	0	0
Anxiety/depression - problems	1 (100%)	2 (66.66%)	1 (100%)	1 (100%)	1 (100%)

Table 7. EQ-VAS collected from patients.

EQ VAS	**18 - 25 years**	**26 - 35 years**	**36 - 45 years**	**46 - 55 years**	**56 - 65 years**	**66 - 75 years**
Mean - Std Dev	70 - only one entry	45.6 (36.10)	45.46 (29.4)	59.64 (22.7)	66 (16.3)	48.5 (37.3)
Median		50	50	70	60	70
25th		10	10	41	54	18.25

percentile						
75th percentile		80	70	75.5	75	73.75

Table 8. EQ-VAS collected from caregivers.

EQ VAS	**1 - 10 years**	**11 - 17 years**	**26 - 35 years**	**36 - 45 years**	**56 - 65 years**
Mean - Std Dev	100 - only one entry	45 (35)	91 - only one value	30 - only one value	70 - only one value
Median	-	60	-	-	-
25th percentile	-	32.5	-	-	-
75th percentile	-	65	-	-	-

Discussion

This is the first study to assess the costs and self-rated health in patients (children and adults alike) diagnosed with alopecia areata. The highest share was attributable to associated expenses for mild and severe cases, followed by medical services and treatment. In this cost of illness study, only slightly over half of the cases were mild, while the rest were severe. Regarding productivity, patients with mild cases had slightly more than double the number of lost days due to alopecia areata (translated into lost productivity). The difference between the average cost of mild versus severe cases is € 138 €, with less severe cases being slightly more costly. The number of reported days of work-related absence did not exceed 20 days when reported by patients. As for the number of days reported by caregivers, the maximum was 300 (including the missing number of days from work and the educational process). Our study only inquires about the number of missing days. Thus, future studies should add a more detailed instrument on absenteeism and presenteeism. An alternative tool would be previously validated WPAI – Work Productivity and Activity Impairment [23]. Gandhi et al. emphasize in their study how the burden of AA highly affects productivity and cognitive activity when in working environments[24]. Other studies also point out that patients with AA, in addition to having a higher level of work absenteeism, also have a higher risk of losing their job/having difficulties in finding one (which are further explained by the mental health-related complications posed by this pathology)[25–27].

Our results show a female predominance among patients who have collected the survey as (slightly) opposed to the data collected from the caregivers. The literature on the epidemiological distribution by sex shows conflicting results, as female or male predominance was reported[5]. Other sex differences include age, AA severity, and other symptoms (affecting nails)[28–36].

Most patients had three age bands: 66-75, 36-45, and 46-55. The burden of alopecia areata study performed by Mesinkovska is in line with our results, as 25% of the included patients (82% of the total being female) were aged between 46-55 years and 21% between 55-65 years. In contrast, patients over 65 were the fourth group with most patients. Regarding hair loss degree, over three-quarters characterized their hair loss as severe[26]. A recent epidemiologic assessment focusing on alopecia totalis and universalis, in addition to alopecia areata, in the adult and pediatric population within the US, reported increases in the prevalence (2016: 0.199%, 2019: 0.222%) and incidence (2017: 87.39/100,000 person-years, 2019: 92.90/100,000 person-years) of alopecia areata[37]. In another study, based on secondary registry data, most patients were females (73%), more than half were over 40 years old, and 43% reported having poor quality of life (mediated by five risk factors, such as age, sex, degree of hair loss, stress and work-related factors)[7]. In another study, with patients enrolled from 22 hospitals, most AA patients were of mild severity (followed by severe and moderate severity), were male (53.7%), and most were aged between 10 and 14 years (38.1%). This study also pointed out that patients with severe AA (as well as their families) are experiencing a poor quality of life[8]. Another retrospective observational study shows that 34.8% have moderate-to-severe forms, and only 15.1% are mild. As for sex distribution, 61% were female. As for comorbidities, most reported were hyperlipidemia (baseline: 20.4%, follow-up: 22.4%), followed by hypertension (baseline: 20.2%, follow-up: 21.8%), and thyroid disorder (baseline: 11.1%, follow-up: 13.1%). Other comorbidities were asthma (baseline: 6.6%, follow-up: 6.9%), atopic dermatitis (baseline: 2%, follow-up: 2.8%), psoriasis (baseline: 1.3%, follow-up: 2.1%), chronic urticaria (baseline: 1.3%, follow-up: 1.5%), as well as mental health-related comorbidities, such as depression (baseline: 8.1%, follow-up: 9.5%), anxiety (baseline: 6.5%, follow-up: 8.4%), or suicidal ideation (baseline: 0.6%, follow-up: 0.7%)[11]. In our study, most patients suffer from autoimmune thyroiditis, atopic dermatitis, psoriasis (as data collected from patients), or atopic dermatitis and anemia (as data collected from the caregivers).

GPs and dermatologists provided the most used medical services, while the least were outpatient and inpatient hospitalizations. In the migration of medical doctors, retirement due to the age of current professional, patients with alopecia areata should be taken into account when planning retention and distribution strategies of healthcare professionals, considering that this pathology is utterly dependent on health workers within the primary and secondary care strata[38].

The highest costs for both mild and severe cases of alopecia corresponded to the same categories (and order) associated expenses, followed by medical services and treatment. This highlights how burdening can be an unequal distribution of health services and (lack of) treatment reimbursement for treatment options. Out-of-pocket costs have been an essential component of the economic burden of AA in German-speaking countries as well (such as Germany, Switzerland, or Austria), and in the sample consisting of patients that were mainly employed and female, over three-quarters of them reported monthly (non-reimbursed) AA-related OOP costs. The average ranged between 38.4 ± 59.8€ (for hair-related items – i.e., wigs – and cosmetic products) and 15.3± 32.9€ (for medicines)[39].

Settlement type, defined as rural or urban, is a variable of interest regarding access to medical services, diagnosis, and survey response rate. In Romania, the problem of unequal distribution and access to healthcare services has been widely documented and debated in scientific and gray literature[40].

Most respondents to our questionnaire (patients and caregivers combined) came from the urban area. Although cities such as Bucharest, Cluj-Napoca, Iasi, and Timisoara are overpopulated and have some of the highest rates in terms of available medical services (coming from both public and private areas), cities with significantly lower numbers of inhabitants suffer severe lacks in terms of available services. Still, they should not be deprived of funds and support in reorganizing health services to make them available and affordable. Although Romania has a universal social health insurance system, funds are scarce, and the burden of unmet needs for communicable and noncommunicable diseases is increasing[40,41].

One of the characterizing symptoms of alopecia areata is hair loss (in varying degrees). Patients with severe types of hair loss (and those with a lower level of hair loss) report health-related quality of life impairments that interfere with their daily activities, social life, and work life, in addition to causing emotional stress[42]. The study by Cartwright et al. has shown that a more significant impact of the disease is reported in female patients in aspects related to emotional and personal life. In contrast, men reported a more significant impact of the disease in work-related activities[43].

A systematic review and meta-analysis highlight that patients with AA are suffering from anxiety (between 8% and 19.1%) as opposed to non-AA controls or healthy controls. As for pediatric patients with AA, up to 8% suffer from separation anxiety and up to 16% from generalized anxiety disorder. The results of the meta-regression pointed out that, based on the data (affected by heterogeneity from fourteen studies, AA had a moderate effect on the quality of life in patients with AA (when measured with DLQI)[9].

One of the limitations of our cost of illness study is the decreased number of respondents for both patients and caregivers. This decreased survey reach could be explained by several factors: high differences between the reported prevalence rates for alopecia areata compared to other skin diseases, such as atopic dermatitis or chronic urticaria or psoriasis, undiagnosed cases (as most patients are diagnosed at the age of 20+ years or patients are not searching for medical care in the case of mild cases up until they experience a more severe form; with a higher difference in health-seeking behavior related to diagnosis being reported for female patients)[5,37]. In addition, another explanation would be that since we disseminated the survey by employing only one social media platform (Facebook) and have not collected data employing other popular platforms in Romania (i.e., Instagram, TikTok), we have not reached all potential patients [44].

Another limitation (as well as a strength) is represented by the fact that the instrument used to measure the quality of life in patients with alopecia areata was EQ-5D-5L. We included only one health-related quality-of-life measure to avoid respondent fatigue[45,46], as our survey already had over 20 items. Although this instrument has been validated and used in different populations (values in Romania have been made recently available[47]) and study designs, taking into account the multidimensional impact of the disease (on adult and pediatric patients), an instrument that is dermatology specific (such as DLQI - Dermatology Life Quality Index[48], the most common scale used in patients diagnosed with dermatologic diseases), hair disease-specific (such as Scalpdex - with a scoring system between 0 and 4; composed of 23 items contained in 3 subscales[49]) or disease-specific (such as Alopecia Areata Symptom Impact Scale - with a scoring system based on a visual analog scale with 10 points; composed of 13 items contained in 3 subscales[50]). In addition, instruments quantifying the impact of the alopecia-related burden on mental health (due to anxiety or depression), such as the Hospital Anxiety and Depression scale (for hospitalized patients), Beck Depression and Anxiety Inventories, should be included to capture all the possible impacts[25]. Studies incorporating costs and multiple instruments on the quality of life and co-occurring psychiatric diagnoses (anxiety and depression) as an increasing burden can be translated into an increased cost of auxiliary services which are currently being reimbursed under strict conditions (such as counseling) and would require advocacy efforts for appropriate planning and financing to meet the unmet needs of patients with alopecia areata. However, patients are not the only ones experiencing anxiety, depression, and an overall decreased quality of life[25]. Studies have shown that caregivers (of children diagnosed with more severe cases) are experiencing a decreased quality of life and feelings of helplessness, guilt, or depression[51].

Another limitation of our study is represented by the fact that although we gathered data on the burden of alopecia areata for minors under 18) from their formal/informal caregivers, we have not collected to avoid respondent fatigue (except the number of days taken to take care of the patient - which has been used as input in our costing exercise to quantify an indirect cost generated by alopecia areata), caregiver-related burden in terms of quality of life and other potential costs (psychological counseling for caregivers). Our study collected data on the cost of treatment, medical services, and associated costs (transportation, hotel, or other non-medical expenses). Still, it did not distinguish between formal and informal caregivers and does not account for the economic burden generated due to paid care of patients with alopecia areata. These items should be considered in future works. These findings provide insight into the economic burden of alopecia areata and its impact on Romania's health-related quality of life in 2022. Although it is low prevalence, this disease yields considerable costs burdening an already resource-scarce health system.

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