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ORIGINAL RESEARCH ARTICLE

AtopyReg®, the Prospective Italian Patient Registry for Moderate-to-Severe Atopic Dermatitis in Adults: Baseline Demographics, Disease Characteristics, Comorbidities, and Treatment History

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Abstract

Background and Objective AtopyReg® is a multicenter, prospective, observational, non-profit cohort study on moderate-to-severe atopic dermatitis in adults promoted in 2018 by the Italian Society of Dermatology and Venereology (SIDeMaST). We aimed to describe baseline demographics, disease characteristics, comorbidities, and therapeutic data of adult patients affected by moderate-to-severe atopic dermatitis.

Methods Patients were selected based on the following inclusion criteria: age ≥ 18 years; Eczema Area and Severity Index score ≥ 16 or localization in visible or sensitive areas (face, neck, hands, or genitalia), or a Numeric Rating Scale itch score ≥ 7 or a Numeric Rating Scale sleep loss score ≥ 7, or a Dermatology Life Quality Index score ≥ 10. Demographic and clinical data at baseline were recorded and analyzed.

Results A total of 1170 patients (male 51.1%; mean age: 44.7 years; range 18–90 years) were enrolled by 12 Italian Dermatology Units between January 2019 and November 2022. Skin lesions were eczematous in 83.2% of patients, the most involved site were the flexures (53.9%), face (50.9%), and neck (48.0%). Mean Eczema Area and Severity Index score was 22.3, mean Dermatology Life Quality Index value was 17.6, mean Patient Oriented Eczema Measure score was 13.1, and mean Numeric Rating Scale itch and sleep loss scores were 7.6 and 5.9, respectively. Previous systemic therapies were corticosteroids in 77.7% of patients, antihistamines in 50.3% of patients, and cyclosporine A in 42.6% of patients.

Conclusions This baseline data analysis deriving from AtopyReg® provides real-life evidence on patients with moderate-to-severe atopic dermatitis in Italy confirming the high burden of atopic dermatitis with a significant impact on patients' quality of life.

1 Introduction

Atopic dermatitis (AD) is a chronic disease characterized by dysregulation of both acquired and innate immune systems, a cytokine imbalance, activation of inflammatory pathways, impairment of the epithelial barrier function, and microbial dysbiosis [1]. Global AD prevalence is increasing in all ages, up to 20% in children [2] and up to 10% in adults and elderly individuals [2–4]. The increased knowledge of the AD pathomechanism and the continuous evolution of the spectrum of clinical phenotypes reflect an increased accuracy in the diagnosis of AD. In view of AD chronicity and the presence of itch and sleep disorders, AD significantly affects patients' quality of life with a high socioeconomic burden [5]. Therefore, long-term therapy is often required and, currently, the number of treatment options, particularly biologic cytokine and receptor antagonists and Janus kinase (JAK) inhibitors, is continuously increasing [6, 7]. In randomized clinical trials, these new therapeutic options have proven to be highly effective, safe, and, unlike conventional immunosuppressant drugs, suitable also for the long-term management of the disease [8]. However, randomized clinical trials enrol selected patients according to strict inclusion and exclusion criteria, often considering a relatively short

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Key Points

Atopic dermatitis is a chronic inflammatory disease characterized by acquired and innate immune dysregulation, impairment of the epithelial barrier function, and microbial dysbiosis.

Disease registries play an important role in collecting and storing standardized information finalized to scientific, clinical, or policy purposes in public health and medicine.

AtopyReg® is the Italian registry for moderate-to-severe atopic dermatitis in adults promoted by the Italian Society of Dermatology and Venereology (SIDeMaST) aimed to obtain prospective and longitudinal real-world, epidemiologic, clinical, and therapeutic data.

We analyzed real-world data gathered from AtopyReg®concerning baseline patients' demographics and clinical and drug history, confirming the high burden of atopic dermatitis with a significant impact on patients' quality of life.

treatment period. Thus, to improve the diagnostic approach in real-world routine care, to identify predictors of response, and to document long-term treatment safety and effectiveness, specific registries for AD are needed.

AtopyReg®, the Italian registry for moderate-to-severe AD in adults, is a nationwide project promoted in 2018 by the Italian Society of Dermatology and Venereology (SIDeMaST) and supported by the Italian Association of Hospital Dermatologists and the Italian Society of Allergological Dermatology. AtopyReg® aims to be a reliable source of real-world data concerning patients' demographics and clinical and drug history. As the platform permits collection of not only baseline data but also follow-up data up to 60 months from the first visit, therapeutic management and disease outcomes can be also recorded. Here, we analyzed the baseline demographic, clinical, and treatment history collected from January 2019 to November 2022 in the AtopyReg® registry patients.

2 Patients and Methods

This multicenter observational cohort-based study analyzed baseline data of adult patients affected by moderate-to-severe AD referring to 12 Italian Dermatology Units homogeneously distributed in Northern, Central, and Southern Italy. New recruiting sites are in the process of being added. Data collection by AtopyReg® was approved by the ethics committees of the participating centers and enrollment started in January 2019.

Patients were enrolled according to the following inclusion criteria: age ≥ 18 years; diagnosis of AD according to Hanifin and Rajka criteria [9] by an expert board-certified dermatologist; Eczema Area and Severity Index (EASI) [10] score ≥ 16 or an EASI score < 16 with localization in sensitive areas (face, neck, hands, or genitalia), or a Numeric Rating Scale (NRS) itch [11] score ≥ 7 or a NRS sleep loss [12] score ≥ 7, or a Dermatology Life Quality Index (DLQI) [13] score ≥ 10. Scoring systems and questionnaires used the Italian language according to Harmonising Outcome Measures for Eczema [14] indications. Eligible patients were enrolled in the registry only after they gave their signed informed consent.

The following demographic and clinical data were recorded at baseline: age, sex, level of education (primary, low secondary, high secondary education, or university graduate degree), active smoking and usual use of any alcohol, familial history of atopy (concerning first-degree relatives only), AD age of onset (childhood, age < 12 years; adolescence, aged 12 to < 18 years; adulthood, age 18 to < 65 years; late, age ≥ 65 years), clinical phenotype (eczematous, prurigo nodularis like, eczema nummulare like, erythrodermic, psoriasiform, seborrheic), comorbidities (atopic and non-atopic), and treatments performed before enrollment into the registry. Disease severity was assessed at baseline using the Harmonising Outcome Measures for Eczema criteria [14]: EASI score (range 0–72), Investigator Global Assessment [15] score (range 0–4), and the patient-reported outcome (PRO) scores of NRS itch and sleep loss (range 0–10) evaluated as a peak score during the past 7 days, a DLQI score (range 0–30), and the Patient Oriented Eczema Measure (POEM) [16] (range 0–28). The aforementioned data were registered in the AD Case Report Form as well as the involved skin areas using a simplified iconography. The latter was achieved by a mannequin-shaped diagram that allowed the user to highlight the body surfaces affected by dermatitis. All data regarding patients' AD history were either self-reported or, when possible, documented by patients' records.

In relation to the various data fields that could be filled in the register, some were not completed for all patients as the information was not always available or some patients refused to disclose it (e.g., familial anamnesis, in particularly elderly patients, or usual drinkers of any alcohol) and, therefore, the sample size was not always equal to the total study population. The demographic, clinical, and therapeutic data of patients were recorded by the AtopyReg® website (http://www.atopyreg2.it, managed by Smatech S.r.l., Rome, Italy). With

regard to clinical phenotypes, we considered not only the most frequently encountered phenotypes (eczematous, nodular prurigo like, and nummulare like), but also the less frequently described phenotypes (erythrodermic, psoriasiform, and seborrheic) [17–19]. With regard to AD comorbidities, the registry provided for the inclusion of all possible self-reported non-atopic comorbidities without pre-selection, while specific fields for pre-selected self-reported T-helper 2 comorbidities (rhinitis, conjunctivitis, asthma, food allergy, nasal polyps, eosinophilic esophagitis) were included. The data collection platform is still open for recruitment and structural improvements are being implemented as we aim to further increase the overall potential of the project as a central database.

Data for each category were tested by a normal distribution goodness-of-fit with the Shapiro–Wilk test. Statistical differences between data were studied using non-parametric tests (Mann–Whitney test, chi-squared test, and Kruskal–Wallis test). In all analyses, a two-sided p-value ≤ 0.05 was considered significant. Correlations between data sets were studied using the Spearman's rank correlation (correlation degree: 0–0.19, very weak; 0.20–0.39, weak; 0.40–0.59, moderate; 0.60–0.79, strong; 0.80–1.00, very strong). All statistical analyses were performed using IBM-SPSS Statistics 28.0 (IBM Corp., Armonk, NY, USA, 2022).

3 Results

A total of 1170 patients (male 51.1%) were enrolled in AtopyReg® by 12 Italian Dermatology Units (Perugia, Naples, Rome, Verona, Catanzaro, Brescia, Bari, L'Aquila, Ferrara, Milan Ca' Granda Hospital, Milan Galeazzi Hospital, Pisa) between January 2019 and November 2022. Demographic and clinical baseline characteristics of patients are reported in Table 1. In particular, the mean age was 44.7 (±19.7) years, with 48.2% of patients aged under 40 years. More than half of patients (53.7%) had a higher secondary education, and 26.1% had a university graduate degree. Mean body mass index was 24.6 kg/m^2, with 60.9% (614/1170) of patients having a body mass index < 25. Active smoking and usual use of any alcohol were reported in 243/943 (25.8%) and 121/929 (13.0%) of patients, respectively.

History of AD and atopic and non-atopic comorbidities of patients are reported in Table 2. In particular, the mean age at diagnosis was 25.3 years: disease onset occurred in equal distribution in childhood (47.9%) and adults/elderly individuals (46.7%). A family history of atopy was recorded in 45.3% of patients: AD resulted was the most frequent (24.3%), followed by rhinitis (18.5%) and conjunctivitis (9.6%). Among personal atopic comorbidities (43.2%), rhinitis was the most frequent (31.1%), followed by conjunctivitis (27.1%), asthma (18.0%), and food allergy (2.2%). Non-atopic comorbidities (48.9%) were mainly systemic hypertension (21.2%), dyslipidemia (7.6%), and type 2 diabetes mellitus (5.4%). Concerning the relationship between the age of onset of disease and the education level (Table 3), patients with a long AD history had more frequently a higher education level, while those with a shorter AD history had a lower education level.

Applying an odds ratio (OR) calculation, the early-onset group was considered as the reference group, comparing frequencies of atopic comorbidities with the adult-onset and late-onset groups (Table 4). A significant inverse association between atopic comorbidities and AD onset was observed: adult-onset AD was less likely to be associated with atopic comorbidities [OR: 0.45, 0.34–0.59]; this is further reduced for late-onset AD with an OR of 0.23 [0.14–0.37].

Clinical phenotypes, involved sites, AD severity, and PRO scores at baseline are reported in Table 5. Almost all patients presented with a single clinical phenotype, while 24 (2.4%) presented with more than one phenotype. The majority of the study population presented with an eczematous phenotype (83.2%), but a non-negligible percentage of patients showed both prurigo-nodularis-like (11.1%) and eczema nummulare-like (5.7%) phenotypes. Other clinical

Table 1 Baseline sociodemographic characteristics

	N	%
Age, years (mean ± SD)	44.7 ± 19.7	
18 to < 40	564	48.2
40 to < 65	363	31.0
65 to < 75	138	11.8
≥ 75	105	9.0
n_{total}	1170	
Sex (male)	598	51.1
Level of education		
Primary	46	5.1
Low secondary	135	15.1
High secondary	482	53.7
University	234	26.1
n_{total}	897	
BMI, kg/m^2 (mean ± SD)	24.6 ± 4.1	
< 25	614	60.9
25 to < 30	311	30.9
≥ 30	83	8.2
n_{total}	1008	
Active smokers	243	25.8
n_{total}	943	
Usual alcohol drinkers	121	13.0
n_{total}	929	

BMI body mass index, *SD* standard deviation

Table 2 Atopic dermatitis history and comorbidities

	N	%
Age at diagnosis, years (mean ± SD)	25.3 ± 25.3	
n_{total}	910	
Age of onset, years (mean ± SD)	24.5 ± 25.1	
0 to < 12	473	47.9
12 to < 18	54	5.5
18 to < 65	366	37.0
≥ 65	95	9.6
n_{total}	988	
Family history of atopy[a]	343	45.3
Atopic dermatitis	184	24.3
Rhinitis	140	18.5
Conjunctivitis	73	9.6
Asthma	66	8.7
Food allergy	17	2.2
Nasal polyps	1	0.1
n_{total}	757	
Atopic comorbidities	430	43.2
Rhinitis	309	31.1
Conjunctivitis	216	27.1
Asthma	179	18.0
Food allergy	22	2.2
Nasal polyps	7	0.7
Eosinophilic esophagitis	1	0.1
n_{total}	995	
Non-atopic comorbidities	447	48.9
Systemic hypertension	194	21.2
Dyslipidemia	71	7.6
Type II diabetes mellitus	49	5.4
Thyroiditis	37	4.0
Anxious and/or depressive symptoms	34	3.7
Cancer[b]	31	3.4
Type I diabetes mellitus	2	0.2
n_{total}	915	

SD standard deviation

[a]First-degree relatives

[b]Hematological 4, breast 4, colorectal 3, bladder 3, prostate 2, lung 1, others 14

phenotypes included psoriasiform, seborrheic, and erythrodermic AD. The most involved sites were the flexures (53.9%), face (50.9%), and neck (48.0%), while the hands, scalp, and genital areas were involved in 37.1%, 14.5%, and 14.1% of patients, respectively. Atopic dermatitis was severe in most patients, documented by an Investigator Global Assessment score ≥ 3 in 61.2% of patients and an EASI score ≥ 24 in 69.1% of patients.

Both quality-of-life and subjective symptoms scores (DLQI and NRS itch/sleep loss, respectively) were reported as severe, with 78.8% of patients having a DLQI score ≥ 10 (Table 5). Confirming the disease severity, mean NRS itch and sleep loss scores were 7.6 and 5.9, respectively, while the mean POEM score was 13.1, falling in the "moderate" category (Table 5).

An association between EASI/PROs (POEM, NRS itch, NRS sleep loss, and DLQI) and the age of onset is reported in Fig. 1. Baseline NRS itch, NRS sleep loss, and DLQI scores were significantly higher in patients with adult-onset and late-onset AD, except for NRS itch in patients with adult-onset AD.

An association between EASI/PRO (POEM, NRS itch, NRS sleep loss, and DLQI) and atopic comorbidities is reported in Table 6. Atopic comorbidities were significantly associated with lower EASI, NRS itch, and NRS sleep loss, and DLQI scores.

A multiple Spearman rank correlation coefficient R among EASI and PROs was calculated (Table 7). A strong significant correlation was documented between sleep loss and itching (0.67) and DLQI and itching (0.60), while a weak correlation (0.29) was observed between POEM and DLQI. All other correlations among EASI and PROs reached a moderate correlation degree (from 0.40 to 0.57).

In analyzing correlations between EASI/PROs and the education level (Fig. 2), patients with AD with a lower education level presented with a significantly higher EASI score, whereas the POEM value was lower in patients with AD with a primary education level, without statistical significance. Regarding PROs, a significant association was documented for DLQI and NRS itch.

Data on systemic treatments for AD before inclusion into the registry were available in three quarters of patients

Table 3 Association between onset age of atopic dermatitis and education level (Mann–Whitney U test)

	Age of onset (years) Median [IQR]		University	Upper middle school	Lower middle school	Primary
University	5 [1–24]	Difference between medians		5*	30**	45**
Upper middle school	10 [2–40]		5*		25**	40**
Lower middle school	35 [10–57]		30**	25**		15
Primary	50 [10–73]		45**	40**	15	

IQR interquartile range, *$p < 0.01$; **$p < 0.0001$

Table 4 Association between atopic comorbidities and atopic dermatitis onset (early-onset group was considered as the reference group)

	Atopic comorbidities			
	OR	SD	*p*-value	95% CI
Early onset (< 18 years)	ref			
Adult onset (18 to < 65 years)	0.45	0.14	0.0001	0.34–0.59
Late onset (≥ 65 years)	0.23	0.25	0.0001	0.14–0.37

CI confidence interval, *OR* odds ratio, *ref* reference, *SD* standard deviation

(74.7%) [Table 8]. Among these, the most prescribed drugs were corticosteroids, antihistamines, and cyclosporin A (77.7%, 50.3%, and 42.6%, respectively). Among patients who previously received at least one systemic drug (869), 306 (35.2%) received one systemic drug and 563 (64.8%) received two or more systemic drugs. Among the latter, 434 (77.1%) received two systemic drugs, 110 (19.5%) received three systemic drugs, 14 (2.5%) received four systemic drugs, and five (0.9%) received five systemic drugs. Phototherapy was previously used in 12.9% of patients.

4 Discussion

AtopyReg®, the first Italian registry on adult patients with moderate-to-severe AD, is a study project by SIDeMaST [20] to obtain prospective and longitudinal real-world epidemiologic, clinical, and therapeutic data. This approach could supply the information derived from cross-sectional and retrospective studies. Moreover, sharing a core set of domains and domain items regarding demographic, clinical, and therapeutic scenarios of AD, AtopyReg® participates in the European TREatment of ATopic eczema (TREAT) Registry Taskforce, an international network of AD registries collecting data from the national registries from Denmark, France, Germany, Italy, Spain, Sweden, the Netherlands, and the UK [20, 21]. This project aims to create a common ground to compare information and data from different European countries to harmonize the existing discrepancies regarding AD diagnostic criteria, severity definition, and therapeutic management. According to the national healthcare scenarios and regulations, this project attempts to improve patients' outcomes regarding this disease, which significantly impacts on the quality of life and mental well-being [22, 23].

Here, the current status of demographic and clinical baseline data of 1170 adult patients with moderate-to-severe AD from 12 Italian recruiting Dermatologic Units are presented. One fifth of these patients were aged older than 65 years, confirming that the prevalence of AD is increasing not only in children and adults, but also in elderly individuals [4, 24]. AtopyReg® patients had an overall average education rate: more than half of the patients had a high secondary education, with only one quarter having a university degree, in line with the Italian general population rate [25]. Recently, a higher

Table 5 Atopic dermatitis characteristics, severity, patient-reported outcome measures at baseline

	n	%
Clinical phenotype		
Eczematous	823	83.2
Prurigo nodularis-like	110	11.1
Eczema nummulare-like	56	5.7
Other	24	2.4
n_{total}	989	
Involved sites		
Flexures	630	53.9
Face	595	50.9
Neck	562	48.0
Hands	434	37.1
Scalp	170	14.5
Genital area	165	14.1
Feet	116	9.9
Diffuse	61	5.2
IGA		
0	22	3.8
1	47	8.2
2	154	26.8
3	279	48.5
4	73	12.7
n_{total}	575	
EASI (mean ± SD)	22.3 ± 9.6	
< 6	121	10.4
6 to < 24	239	20.5
24 to 72	804	69.1
n_{total}	1164	
DLQI (mean ± SD)	17.6 ± 8.9	
< 10	234	21.2
≥ 10	871	78.8
n_{total}	1105	
POEM (mean ± SD)	13.1 ± 7.6	
Clear/almost clear (0–2 points)	48	7.7
Mild (3–7 points)	144	23.2
Moderate (8–16 points)	206	33.2
Severe (17–24 points)	184	29.7
Very severe (25–28 points)	58	9.4
n_{total}	620	
NRS itch (mean ± SD) n_{total} = 1083	7.6 ± 2.7	
NRS sleep-loss (mean ± SD) n_{total} = 959	5.9 ± 3.3	

DLQI Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IGA* Investigator Global Assessment, *NRS* Numerical Rating Scale, *POEM* Patient Oriented Eczema Measure, *SD* standard deviation

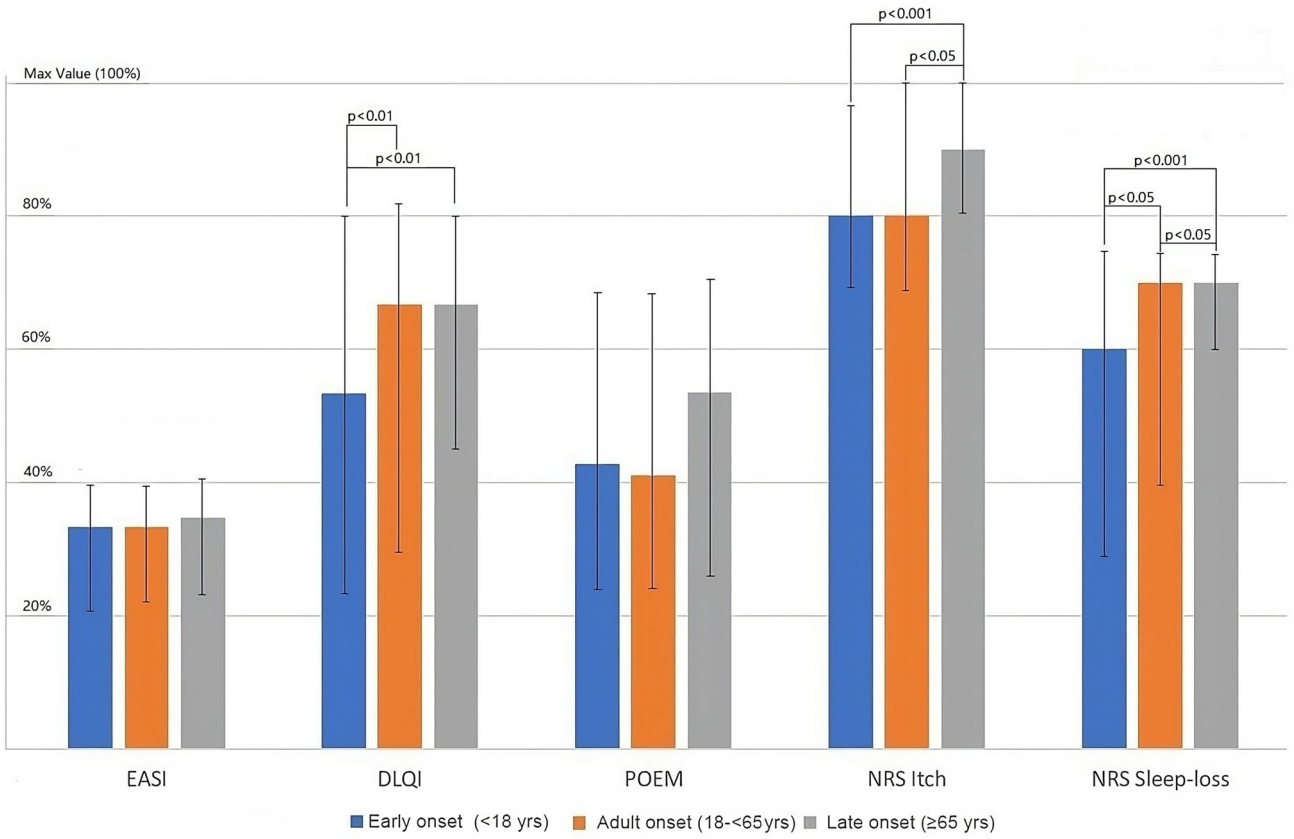

Fig. 1 Clinical and patient-reported outcome scores of atopic dermatitis across patients subgrouped by the age of disease onset. *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *Max* maximum, *NRS* Numeric Rating Scale, *POEM* Patient Oriented Eczema Measure, *yrs* years

Table 6 Association between EASI/patient-reported outcomes (POEM, NRS itch, NRS sleep loss, and DLQI) and atopic comorbidities

	EASI Median [IQR]	POEM Median [IQR]	NRS itch Median [IQR]	NRS sleep loss Median [IQR]	DLQI Median [IQR]
Atopic comorbidities					
Yes	24 [17–28]*	13 [7–19]	8 [7–10]**	6 [33–8]***	18 [10–25]**
No	25 [19–28]	12 [7–20]	9 [7–10]	7 [4–10]	20 [11–25]

DLQI Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *IQR* interquartile range, *NRS* Numerical Rating Scale, *POEM* Patient Oriented Eczema Measure, $p < 0.05$; *$p < 0.001$; ***$p < 0.0001$

educational level was reported to be related to a higher socioeconomic status, consistent with a higher prevalence of skin and atopic diseases in patients with a middle or high socioeconomic status compared with those with a low socioeconomic status [26, 27]. Nevertheless, there is no consensus on whether a higher socioeconomic status has a net positive or negative effect on AD [28, 29].

An interesting finding emerged from comparing the education level with AD severity, as clinical scores are generally lower in patients with a higher education than in those with a lower education. In fact, patients with a university degree had lower EASI, DLQI, and NRS itch scores than those with a primary education ($p < 0.01$, $p < 0.00001$, and $p < 0.001$, respectively). Moreover, a university education was associated with a better quality of life even with respect to an upper-middle or lower-middle education ($p < 0.00001$). Our data showed an inverse association between the age of AD onset, lower than 12 years of age in almost half of the study population, and education level with the most educated patients having more frequently early-onset AD, whereas patients with a primary education had more frequently late-onset AD. This seems in contrast with findings that severe

Table 7 Spearman's rank correlation coefficient R calculated between clinical and patient-reported outcome scores

	EASI	POEM	NRS itch	NRS sleep loss	DLQI
EASI		0.46	0.48	0.41	0.57
POEM	0.46		0.40	0.40	0.29
NRS itch	0.48	0.40		0.67	0.60
NRS sleep loss	0.41	0.40	0.67		0.55
DLQI	0.57	0.29	0.60	0.55	

DLQI Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *NRS* Numerical Rating Scale, *POEM* Patient Oriented Eczema Measures

All values have a statistical significance level of $p < 0.00001$

childhood AD is associated with both learning disabilities [30] and difficulties attain a superior education in later life [31, 32], even if these aspects are debated in the literature [33].

Active smoking and usual use of any alcohol, well-known risks for public health that often coexist in the same patient, were reported in 25.8% and 13.0% of our patients with AD, respectively. The rate of active smokers is in line with the national data (24.5%) [34], while usual use of any alcohol was much lower than reported by the Italian National Statistical Institute (21.4%) [35], although this difference does not reach statistical significance.

A family history of atopy was reported in a large percentage (45.3%) of the study population, much higher than that reported by a large Italian epidemiologic study on a general population [36]. Personal atopic comorbidities were encountered in 43.2% of patients with AD, confirming previous studies [37, 38]. As reported by other authors [38, 39], we documented an inverse association between atopic comorbidities and age of onset, with an OR of 0.45 in patients with adult-onset AD. This is further reduced in patients with late-onset AD who had an OR of 0.23.

Morphology of AD lesions was eczematous in most patients with AD (83.2%), but the relatively large prevalence of prurigo nodularis like and eczema nummulare like (11.1% and 5.7%, respectively) is noteworthy. Although these two phenotypes are now effectively included in the AD clinical spectrum [39–41], no consensus exists on AD exclusivity of these two phenotypes as they have difficult-to-discern etiologies or result from a coexistence with other dermatologic conditions, especially when other AD clinical

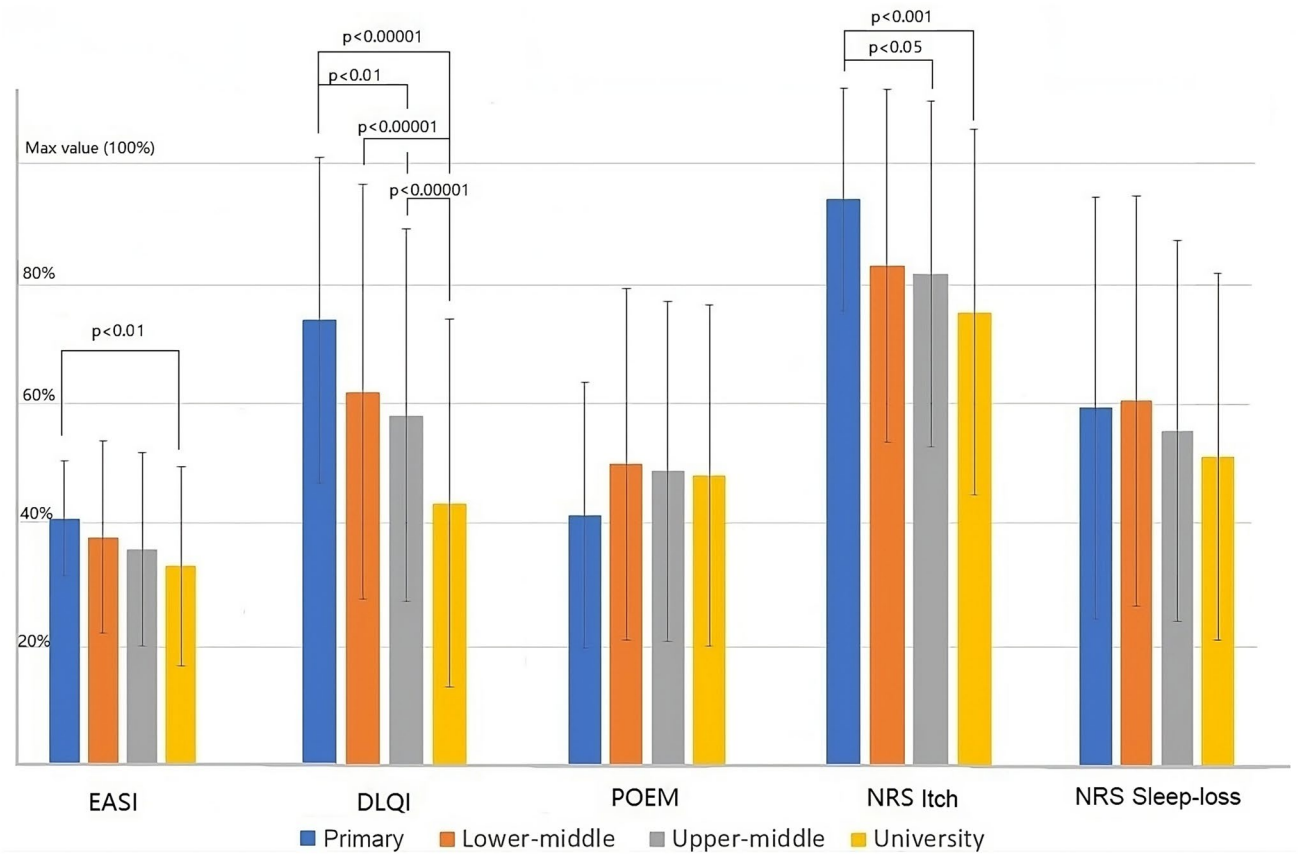

Fig. 2 Clinical and patient-reported outcome scores of atopic dermatitis according to the education level. *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *Max* maximum, *NRS* Numeric Rating Scale, *POEM* Patient Oriented Eczema Measure, *yrs* years

Table 8 Treatment history in patients with atopic dermatitis before inclusion in AtopyReg®[a]

	n	%
Treatment history (patients who received any systemic drug) $n_{total} = 869$		
Corticosteroids	675	77.7
Antihistamine	437	50.3
Cyclosporin A	370	42.6
Dupilumab	41	4.7
Azathioprine	25	2.9
Methotrexate	25	2.9
Omalizumab	5	0.6
Tralokinumab	4	0.5
Montelukast	2	0.3
Upadacitinib	1	0.1
Treatment history (patients who received a single systemic drug) $n_{total} = 306$		
Corticosteroids	177	57.8
Antihistamine	57	18.6
Cyclosporin A	62	20.3
Dupilumab	4	1.3
Azathioprine	2	0.7
Methotrexate	2	0.7
Omalizumab	2	0.7
Treatment history (patients who received >1 systemic drug) $n_{total} = 563$		
Corticosteroids	498	88.5
Antihistamine	380	67.5
Cyclosporin A	308	54.7
Dupilumab	37	6.6
Azathioprine	23	4.1
Methotrexate	23	4.1
Omalizumab	3	0.5
Tralokinumab	4	0.7
Montelukast	2	0.4
Upadacitinib	1	0.2

[a]All the reported drugs were used for atopic dermatitis

and topographical features, increased immunoglobin E, or personal atopic comorbidities are lacking [17]. Conversely to that reported by the TREATgermany registry where the neck, face, and hands were the most involved sites (80.5%, 80.3%, and 77.7%, respectively) [26], in our patients, the flexures, face, and the neck were mostly involved (53.9%, 50.9%, and 48.0%, respectively). The involvement of the genital area is non-negligible (14.1%) and higher than that previously reported in other work [42]. This is likely because of the selection criteria that we implemented in the registry: we also enrolled patients with an EASI score < 16 with involvement of sensitive areas, including the genital area, as in these patients the AD burden is often high.

In this analysis of baseline data, AD was mostly severe as confirmed by Investigator Global Assessment and EASI scores (≥ 3 in 61.2% and ≥ 24 in 69.1%, respectively), as well as by PRO scores. In fact, the DLQI score was ≥ 10 in 78.8% of patients and mean NRS itch and sleep loss scores were 7.6 and 5.9, respectively. As demonstrated by the Spearman's rank correlation coefficient R, EASI and PRO scores showed a moderate-to-strong correlation, except for POEM, the least correlated with other scores. Analyzing the association between EASI/PROs and the age of onset, baseline NRS itch, NRS sleep loss, and DLQI scores were significantly higher in patients with adult and late AD onset than in those with early onset, highlighting that a more recent AD history had a higher disease burden [43]. However, EASI, NRS itch, and NRS sleep loss scores, and DLQI scores were significantly lower in patients with atopic comorbidities, probably owing to the less frequent presence

of atopic comorbidities in patients with adult and late-onset AD characterized by the aforementioned higher PRO scores.

Data on systemic treatments before inclusion in the registry detected a high percentage of patients (77.7%) reporting previous use of systemic corticosteroids, despite prescription of this drug class being rarely recommended and only in cases of a severe AD flare-up [6, 44]. Similarly, antihistamines are frequently prescribed (50.3%), even if not included in the guidelines because of a lack of proven efficacy, except for sleep disturbance control when sedative molecules are chosen [45]. In accordance with the guidelines [6], cyclosporine A was frequently reported (42.6%) as the prescription of this drug, in the absence of contraindications (i.e., uncontrolled hypertension, malignancy, kidney failure), is a mandatory step required by the Italian Drug Agency before biologic and small-molecule prescription. Biologics and JAK inhibitors were reported by only 5.9% of the study population at baseline, likely owing to the fact that patients were mostly enrolled into the registry at the moment of first biologic or JAK inhibitor prescription. Moreover, in Italy, reimbursability by the Italian Drug Agency was approved for the first two JAK inhibitors (abrocitinib and upadacitinib) in January 2023, after the enrollment period (November 2022) of the present study.

4.1 Limitations

There are some limitations in this study. First, the outcomes might have been influenced by selection bias. In fact, our investigation was conducted on patients referred to 12 Italian Dermatology Units that, although uniformly distributed throughout the country, represent only a part of the Italian Dermatology Units dealing with the clinical and diagnostic management of AD. At the cut-off date (30 November, 2022), some Italian Dermatology Units had completed the activation process but they had not yet started recruitment. Second, patients were entered into the registry in a non-consecutive manner, as only patients who provided signed informed consent participated in the study and no data were available on patients unable to provide informed consent. However, given the hypothetical small number of patients who fit into this category compared with the large sample size of patients enrolled in the study, this is unlikely to have created a bias. Third, AD comorbidities might have been underestimated because these data were self-reported by the patients, therefore some diseases might have been under-reported. Fourth, some data fields of the register were not completed for all patients as the information to be entered was not always available or some patients refused to disclose it. Therefore, the sample size for much information did not correspond to the total study population.

5 Conclusions

The AtopyReg® registry provides real-life evidence of baseline demographic, clinical, and therapeutic data of patients with moderate-to-severe AD in Italy. These data confirmed the high burden of AD with a significant impact on patients' quality of life and, therefore, the importance of therapeutic decision making and management improvement based on effective and safe treatments. Finally, AtopyReg® data are updated regularly, new recruiting sites are continuously initiated, and the patient pool is continuously expanded. Additionally, further findings concerning both baseline data that might appear with more statistical power and information regarding follow-up will be analyzed in the future.

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Declarations

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Ethics Approval AtopyReg® project was approved by the Ethical Committee of Brescia (Italy), the Study Coordinator Center (approval number: 0013530).

Consent to Participate All patients provided written informed consent.

Consent for Publication Not applicable.

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