# Impact of demographic features and clinical factors on quality of life of patients with alopecia areata

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Received: 16 December 2021
Accepted: 19 September 2022

**Background:** Alopecia areata is a non-cicatricial alopecia that profoundly affects patients' quality of life. In this study, we evaluated the influence of demographic and clinical features of alopecia areata patients on their quality of life.

**Methods:** This cross-sectional study was performed on alopecia areata patients at the Dermatology Clinic of Afzalipour Hospital, Kerman. Firstly, demographic features and clinical data were collected. Then, the severity of alopecia areata [based on the severity of alopecia tool (SALT) score] and quality of life of the patients [using dermatology life quality index (DLQI) and child dermatology life quality index (CDLQI)] were calculated. Finally, the impacts of the patient's demographic and clinical features on quality of life were evaluated via multivariate logistic regression.

**Results:** One hundred and thirty-five patients with alopecia areata were enrolled in the study. The mean SALT score was 6.63 ± 6.34 (range 2–64). Mean DLQI scores for mild and moderate cases of AA were 7.4 and 12.5, respectively ($P = 0.57$). Females had significantly higher DLQI scores compared to males. Furthermore, patients with negative family history of alopecia areata had significantly higher DLQI scores than patients with positive family history ($P = 0.03$).

**Conclusion:** We found no significant difference in quality of life between patients with different alopecia areata severities. However, females and patients with a negative family history of alopecia experienced significantly greater negative impacts on quality of life than males and those with a positive family history.

**Keywords:** alopecia areata, quality of life, demography

Iran J Dermatol 2023; 26: 127-133

DOI: 10.22034/ijd.2022.320141.1479

## INTRODUCTION

Alopecia areata (AA) is an autoimmune skin disease presenting as a non-cicatricial alopecia with sudden onset of circumscribed areas of hair loss. Rarely, it can progress to involve the whole scalp (alopecia totalis) or body hairs (alopecia universalis). Genetic backgrounds can prone patients to triggering factors such as environmental factors and stressful life events. Great numbers of patients with AA suffer from enormous stress that can lead to disease exacerbation via a vicious circle [1-3]. The prevalence rate of the disease is about 0.1–0.2%,



Please cite this article as: Khalili M, Mohammadi S, Amiri R, Ahmaditabatabaei R, Aflatoonian M. Impact of demographic features and clinical factors on quality of life of patients with alopecia areata. Iran J Dermatol. 2023; 26(3): 127-133.

and each individual has a roughly 2% lifetime risk of AA. It has an entirely unpredictable course, from spontaneous improvement to chronic or recurrent disease [4-5]. Although there are several treatment modalities for AA, it can be recalcitrant to therapies and recur after cessation of treatment [1,5]. Therefore, due to the unclear prognosis of the disease and the importance of hair in the self-image of individuals, it can have a profound negative effect on patients' quality of life (QoL).

Patients with AA frequently have poor self-esteem and often feel distressed, annoyed, and embarrassed [6-8]. Some studies have reported a high prevalence of anxiety and depression among AA patients [7]. In addition, a few studies revealed a similar impact of AA on QoL compared to chronic skin diseases such as atopic dermatitis (AD) and psoriasis [4]. In this study, we evaluated the influence of demographic and clinical features on AA patients' QoL.

## METHODS

Exclusion criteria covered patients with other skin or systemic diseases affecting QoL. Firstly, demographic features of patients (age, sex, marital status, residential place, and educational and economic levels) were obtained. Then, clinical data (site, duration, age of onset, family history of AA, history of autoimmune disease, and history of previous treatments) were collected.

The severity of alopecia was evaluated based on the severity of alopecia tool (SALT) score [9]. Furthermore, the QoL of the patients was assessed by the dermatology life quality index (DLQI) for adults aged 17 or older and the child dermatology life quality index (CDLQI) for children aged 4 to 16 years old. Finlay developed English versions of the questionnaires; we used Persian versions of the questionnaires, the validity and reliability of which were confirmed previously (Cronbach'a alpha 0.88 for DLQI and 0.87 for CDLQI)] [10,11]. These questionnaires include ten questions about the effect of disease on different items, including feelings and symptoms, daily activities, leisure and sports activities, work and school, personal relationship, and treatment since one week ago. Each question is scored from 0 to 3, and the final score is calculated by summing of scores of the ten questions. The total score is between 0 and 30; the highest score represents the greatest effect of disease on QoL.

Finally, the impacts of demographic and clinical features of AA on patients' QoL were evaluated. The level of effects on the QoL of the patients was classified into five grades (G), including G1 (no effect, score 0-1), G2 (small effect, score 2-5), G3 (moderate effect, score 6-10), G4 (very large effect, score 11-20) and G5 (extremely large effect, score 21-30).

### Ethical considerations

This cross-sectional study was performed on AA patients at the dermatology clinic of Afzalipour Hospital, Kerman. The Kerman University of Medical Sciences Ethics Committee approved the proposal (IR.KMU.AH.REC.1398.134). Informed consent was obtained from all participants and parents of patients younger than 12.

### Statistical analysis

Data were analyzed by SPSS16 (software IBM, Armonk, NY, USA). Mean and standard deviation are reported for quantitative data; frequency and percentage are provided to describe qualitative data. Multivariate logistic regression was used to evaluate the correlation of clinical and demographic data with QoL items.

## RESULTS

One hundred and thirty-five patients with AA (86 adults and 49 pediatrics) were enrolled in the study. Just over half the patients were males (51.9%). The mean age of the patients was 22.15 ± 10.59 (range 4-44) years. The mean duration of AA was 12.91 ± 11.44 months (range one week to 48 months). The mean SALT score was 6.63 ± 6.34 (range 2-64). The mean DLQI and CDLQI scores were 7.55 ± 3.93 (range 1-19) and 6.65 ± 3.46 (range 2-15), respectively.

The mean DLQI scores for mild and moderate cases of AA were 7.4 and 12.5, respectively; the difference was insignificant. AA had mostly moderate and small effects on the QoL of adult and pediatric patients (44.2% and 36.7%), respectively. Table 1 demonstrates the demographic and clinical data of AA patients. Females had significantly higher DLQI scores than males (8.80 ± 0.64 vs. 6.36 ± 0.5, $P = 0.003$). Moreover, patients with a negative family history had significantly higher DLQI scores than patients with

**Table 1.** Demographic and clinical features of alopecia areata patients

| Variable | Number | Percentage |
|---|---|---|
| Sex | | |
| Male | 70 | 51.9 |
| Female | 65 | 48.1 |
| Age of onset | | |
| < 30 years | 100 | 75.2 |
| ≥ 30 years | 33 | 24.8 |
| Educational level | | |
| Under diploma | 88 | 65.7 |
| ≥ Diploma | 46 | 34.3 |
| Marital status | | |
| Married | 51 | 37.6 |
| Unmarried | 84 | 62.4 |
| Site | | |
| Scalp | 114 | 84.4 |
| Eyebrows | 14 | 10.4 |
| Beard | 32 | 23.7 |
| Income | | |
| < 30 million IRR | 69 | 51.5 |
| ≥ 30 million IRR | 65 | 48.5 |
| Living site | | |
| City | 83 | 61.7 |
| Rural | 52 | 38.3 |
| Positive family history of AA | | |
| Yes | 16 | 12 |
| No | 119 | 88 |
| History of other associated diseases | | |
| Yes | 50 | 36.8 |
| No | 85 | 63.2 |
| History of recurrence | | |
| Yes | 59 | 43.6 |
| No | 76 | 56.4 |
| Previous treatment | | |
| Yes | 79 | 57.9 |
| No | 56 | 42.1 |
| Disease duration | | |
| < 12 months | 71 | 51.9 |
| ≥ 12 months | 64 | 48.1 |
| Effect on QoL in adults | | |
| No effect | 1 | 1.2 |
| Small effect | 27 | 31.4 |
| Moderate effect | 38 | 44.2 |
| Very severe effect | 20 | 23.2 |
| Extremely large | 0 | 0 |
| Effect on QoL in pediatric | | |
| No effect | 23 | 46.9 |
| Small effect | 18 | 36.7 |
| Moderate effect | 8 | 16.4 |
| Very severe effect | 0 | 0 |
| Extremely large | 0 | 0 |

Abbreviations: AA, alopecia areata; QoL, quality of life

a positive family history (7.9 ± 0.45 vs. 5.18 ± 0.9, $P = 0.03$) (Table 2). Other demographic or clinical features did not correlate with DLQI or CDLQI scores (Tables 2 and 3).

## DISCUSSION

Studies emphasize the significant role of stress in precipitating AA. On the other hand, AA can lead to poor self-confidence and a sense of frustration in the patients. A few studies have evaluated AA's impact on patients' QoL, showing a mean DLQI score of 5.3–13.54 [4].

In the current study, the mean DLQI scores for mild and moderate cases of AA were 7.4 and 12.5, respectively; however, there was no significant association between the severity of AA and patients' QoL. This can be due to the low percentage of moderate cases of AA and the absence of severe cases in this study. Furthermore, it can be explained by the major concern of patients about the possibility of the spread of the lesions to the entire scalp or other body sites regardless of the severity of the alopecia. Other studies have shown conflicting results; some indicate that severe AA has a more negative impact on the QoL of the patients than mild cases [7,12,13], while others report significant QoL impairment in the patients regardless of the severity of AA [6,14].

Furthermore, our study showed significantly higher effects of QoL on personal relationships in moderate cases of AA than in mild cases. Abedini *et al.* demonstrated significantly higher effects of QoL on all the items of the DLQI questionnaire in severe cases compared to mild cases. This difference can be due to the high percentage of severe cases in the Abedini study [12].

On the other hand, we showed that the impact of AA on the QoL of the patients was nearly comparable to the effects of other chronic skin diseases, such as acne (DLQI = 7.5) and contact dermatitis (DLQI = 7.3). However, QoL was better than other dermatologic diseases such as psoriasis (DLQI = 10.5), AD (DLQI = 10.5), and pemphigus vulgaris (DLQI = 12) [15,16]. Likewise, other studies revealed significantly better QoL in AA patients compared to psoriasis and vitiligo patients [7,17]. In contrast, Zhang *et al.* showed that AA patients had worse QoL than androgenetic alopecia (AGA) patients. The mean DLQI for AA and AGA patients

**Table 2.** Association between DLQI scores and adults alopecia areata patients' characteristics

| Variable | Symptom & feelings (Q1,2) | Daily activities (Q3,4) | Leisure (Q5,6) | Work and school (Q7) | Personal relationships (Q8,9) | Treatment (Q10) | Total score |
|---|---|---|---|---|---|---|---|
| Severity (SALT score) | | | | | | | |
| Mild < 25 | 1.89 ± 0.13 | 1.01 ± 0.11 | 0.86 ± 0.09 | 2.3 ± 0.05 | 0.73 ± 0.08 | 0.72 ± 0.07 | 7.44 ± 0.41 |
| Moderate (25-75) | 3.5 ± 1.5 | 2 ± 2 | 2.5 ± 1.5 | 2.5 ± 0.5 | 1 ± 0 | 1 ± 1 | 12.5 ± 6.5 |
| *P*-value | 0.075 | 0.2 | 0.473 | 0.607 | 0.004 | 0.593 | 0.570 |
| Sex | | | | | | | |
| Female | 2.33 ± 0.19 | 1.39 ± 0.19 | 1.14 ± 0.16 | 2.26 ± 0.09 | 1 ± 0.12 | 0.88 ± 0.11 | 8.80 ± 0.64 |
| Male | 1.54 ± 0.17 | 0.7 ± 0.11 | 0.68 ± 0.11 | 2.34 ± 0.07 | 0.5 ± 0.73 | 0.59 ± 0.09 | 6.36 ± 0.5 |
| *P*-value | 0.003 | 0.021 | 0.003 | 0.535 | 0.003 | 0.058 | 0.003 |
| Age of onset | | | | | | | |
| < 30 years | 1.94 ± 0.18 | 1.03 ± 0.15 | 0.94 ± 0.13 | 2.28 ± 0.07 | 0.62 ± 0.1 | 0.72 ± 0.1 | 7.44 ± 0.59 |
| ≥ 30 years | 1.9 ± 0.18 | 1.03 ± 0.16 | 0.84 ± 0.14 | 2.34 ± 0.08 | 0.93 ± 0.14 | 0.75 ± 0.1 | 7.75 ± 0.54 |
| *P*-value | 0.893 | 0.984 | 0.636 | 0.615 | 0.084 | 0.862 | 0.730 |
| Education level | | | | | | | |
| Under diploma | 2.37 ± 0.17 | 1.02 ± 0.16 | 1.07 ± 0.16 | 2.41 ± 0.07 | 0.77 ± 0.12 | 0.77 ± 0.1 | 8.45 ± 0.6 |
| Diploma or higher | 1.55 ± 0.19 | 1.04 ± 0.17 | 0.77 ± 0.12 | 2.22 ± 0.08 | 0.66 ± 0.12 | 0.71 ± 0.11 | 6.77 ± 0.58 |
| *P*-value | 0.002 | 0.932 | 0.139 | 0.110 | 0.139 | 0.679 | 0.051 |
| Marital status | | | | | | | |
| Unmarried | 2.02 ± 0.23 | 1.19 ± 0.21 | 0.97 ± 0.18 | 2.36 ± 0.08 | 0.36 ± 0.09 | 0.75 ± 0.12 | 7.66 ± 0.8 |
| Married | 1.86 ± 0.16 | 0.91 ± 0.12 | 0.85 ± 0.11 | 2.26 ± 0.08 | 1.02 ± 0.11 | 0.72 ± 0.09 | 7.48 ± 0.44 |
| *P*-value | 0.546 | 0.244 | 0.578 | 0.418 | 0.001 | 0.848 | 0.830 |
| Face involvement | | | | | | | |
| Yes | 2.2 ± 0.17 | 0.94 ± 0.17 | 0.72 ± 0.14 | 2.42 ± 0.07 | 0.81 ± 0.14 | 0.81 ± 0.12 | 1.21 ± 0.06 |
| No | 1.59 ± 0.21 | 1.10 ± 0.16 | 1.04+0.14 | 2.16 ± 0.09 | 0.7 ± 0.1 | 0.68 ± 0.09 | 1.25 ± 0.06 |
| *P*-value | 0.026 | 0.503 | 0.124 | 0.025 | 0.562 | 0.430 | 0.720 |
| Income | | | | | | | |
| < 30 million IRR | 2.19 ± 0.16 | 1.04 ± 0.14 | 1.07 ± 0.14 | 2.37 ± 0.09 | 0.82 ± 0.1 | 0.65 ± 0.09 | 8.19 ± 0.55 |
| ≥30 million IRR | 1.65 ± 0.21 | 1 ± 0.18 | 0.72 ± 0.14 | 2.22 ± 0.06 | 0.65 ± 0.1 | 0.79 ± 0.11 | 6.86 ± 0.63 |
| *P*-value | 0.05 | 0.837 | 0.083 | 0.206 | 0.333 | 0.380 | 0.119 |
| Living site | | | | | | | |
| City | 1.76 ± 0.18 | 1.11 ± 0.15 | 0.9 ± 0.12 | 2.29 ± 0.07 | 0.76 ± 0.11 | 0.76 ± 0.1 | 7.43 ± 0.57 |
| Rural | 2.22 ± 0.16 | 0.9 ± 0.16 | 0.9 ± 0.16 | 2.33 ± 0.08 | 0.7 ± 0.12 | 0.67 ± 0.11 | 7.77 ± 0.58 |
| *P*-value | 0.104 | 0.394 | 0.984 | 0.729 | 0.766 | 0.592 | 0.705 |
| Positive family history of AA | | | | | | | |
| Yes | 1.09 ± 0.34 | 0.27 ± 0.14 | 0.45 ± 0.15 | 2 ± 0.23 | 0.81 ± 0.29 | 0.54 ± 0.15 | 5.18 ± 0.9 |
| No | 2.05 ± 0.14 | 1.14 ± 0.12 | 0.97 ± 0.11 | 2.35 ± 0.05 | 0.73 ± 0.08 | 0.76 ± 0.08 | 7.9 ± 0.45 |
| *P*-value | 0.017 | 0.011 | 0.086 | 0.041 | 0.745 | 0.352 | 0.031 |
| History of recurrence | | | | | | | |
| Yes | 2.08 ± 0.19 | 1.19 ± 0.16 | 0.89 ± 0.15 | 2.25 ± 0.08 | 0.79 ± 0.1 | 0.93 ± 0.1 | 7.95 ± 0.61 |
| No | 1.73 ± 0.18 | 0.84 ± 0.15 | 0.92 ± 0.12 | 2.37 ± 0.08 | 0.68 ± 0.14 | 0.47 ± 0.09 | 7.05 ± 0.56 |
| *P*-value | 0.208 | 0.137 | 0.894 | 0.275 | 0.539 | 0.002 | 0.292 |
| Disease duration | | | | | | | |
| < 12 months | 2 ± 0.19 | 1.08 ± 0.17 | 0.94 ± 0.15 | 2.41 ± 0.08 | 0.81 ± 0.14 | 0.59 ± 0.11 | 7.86 ± 0.61 |
| ≥ 12 months | 1.87 ± 0.18 | 1 ± 0.15 | 0.87 ± 0.13 | 2.22 ± 0.07 | 0.69 ± 0.1 | 0.83 ± 0.09 | 7.32 ± 0.58 |
| *P*-value | 0.659 | 0.732 | 0.731 | 0.102 | 0.505 | 0.118 | 0.533 |

was 8.2 ± 7.6 and 5.51 ± 5.03, respectively [18].

In the present study, AA had a mostly moderate and small influence on the QoL of adult and pediatric patients (44.2% and 36.7%), respectively. Liu *et al.* demonstrated small effects of AA on most adults and children (28.1% and 38.5%, respectively) [8]. Similarly, Abedini *et al.* revealed either no or a small effect of AA in most cases (70.9 %). This could be due to different study designs, AA severities, and cultural values [12].

The current study demonstrated a significantly higher negative impact of AA on QoL in female adults

**Table 3.** Association between CDLQI scores and pediatric alopecia areata patients' characteristics

| Variables | Symptom and feelings (Q1,2) | Daily activities (Q3,4) | Leisure (Q5,6) | Work and school (Q7) | Personal relationships (Q8,9) | Treatment (Q10) | Total score |
|---|---|---|---|---|---|---|---|
| Severity (SALT score) | | | | | | | |
| Mild < 25 | 1.73 ± 0.17 | 1.04 ± 0.15 | 0.55 ± 0.14 | 2.43 ± 0.07 | 0.18 ± 0.07 | 0.48 ± 0.1 | 6.65 ± 0.49 |
| Sex | | | | | | | |
| Female | 1.92 ± 0.27 | 1.07 ± 0.2 | 0.64 ± 0.18 | 2.5 ± 0.09 | 0.25 ± 0.12 | 0.64 ± 0.14 | 7.17 ± 0.72 |
| Male | 1.47 ± 0.19 | 1 ± 0.22 | 0.42 ± 0.22 | 2.35 ± 0.1 | 0.1 ± 0.06 | 0.28 ± 0.12 | 5.95 ± 0.62 |
| *P*-value | 0.209 | 0.818 | 0.464 | 0.312 | 0.341 | 0.08 | 0.223 |
| Face involvement | | | | | | | |
| Yes | 3.25 ± 0.47 | 2.5 ± 0.28 | 1.5 ± 0.95 | 2.5 ± 0.28 | 0.50 ± 0.28 | 0.50 ± 0.28 | 1.5 ± 0.28 |
| No | 1.6 ± 0.17 | 0.91 ± 0.14 | 0.46 ± 0.12 | 2.43 ± 0.07 | 0.15 ± 0.07 | 0.48 ± 0.1 | 1.13 ± 0.05 |
| *P*-value | 0.009 | 0.003 | 0.361 | 0.798 | 0.224 | 0.976 | 0.295 |
| Economic status | | | | | | | |
| < 30 million IRR | 1.85 ± 0.28 | 1.10 ± 0.22 | 0.57 ± 0.18 | 2.51 ± 0.09 | 0.25 ± 0.12 | 0.67 ± 0.14 | 7.21 ± 0.72 |
| ≥30 million IRR | 1.57 ± 0.17 | 0.95 ± 0.18 | 0.52 ± 0.22 | 2.33 ± 0.1 | 0.09 ± 0.06 | 0.23 ± 0.11 | 5.9 ± 0.61 |
| *P*-value | 0.43 | 0.61 | 0.87 | 0.2 | 0.29 | 0.03 | 0.19 |
| Living site | | | | | | | |
| City | 1.64 ± 0.2 | 0.82 ± 0.17 | 0.64 ± 0.23 | 2.32 ± 0.08 | 0.22 ± 0.12 | 0.32 ± 0.11 | 6.25 ± 0.6 |
| Rural | 1.85 ± 0.31 | 1.33 ± 0.25 | 0.42 ± 0.13 | 2.6 ± 0.11 | 0.14 ± 0.07 | 0.71 ± 0.17 | 7.19 ± 0.82 |
| *P*-value | 0.554 | 0.095 | 0.464 | 0.057 | 0.614 | 0.055 | 0.352 |
| Positive family history of AA | | | | | | | |
| Yes | 2 ± 0.63 | 1.2 ± 0.48 | 0.6 ± 0.24 | 2.8 ± 0.2 | 0 ± 0 | 1 ± 0 | 7.6 ± 1.5 |
| No | 1.7 ± 0.18 | 1.02 ± 0.16 | 0.54 ± 0.15 | 2.39 ± 0.07 | 0.20 ± 0.08 | 0.43 ± 0.1 | 6.54 ± 0.52 |
| *P*-value | 0.618 | 0.727 | 0.910 | 0.088 | 0.411 | 0.09 | 0.524 |
| History of recurrence | | | | | | | |
| Yes | 1.81 ± 0.35 | 1.27 ± 0.35 | 0.09 ± 0.09 | 2.45 ± 0.15 | 0.3 ± 0.15 | 0.72 ± 0.19 | 7 ± 0.86 |
| No | 1.71 ± 0.2 | 0.97 ± 0.16 | 0.68 ± 0.17 | 2.43 ± 0.08 | 0.15 ± 0.08 | 0.42 ± 0.11 | 6.55 ± 0.59 |
| *P*-value | 0.803 | 0.416 | 0.083 | 0.89 | 0.45 | 0.21 | 0.71 |
| Disease duration | | | | | | | |
| < 12 months | 1.85 ± 0.2 | 1.05 ± 017 | 0.73 ± 0.19 | 2.5 ± 0.08 | 0.18 ± 0.1 | 0.52 ± 0.13 | 7.08 ± 0.62 |
| ≥ 12 months | 1.46 ± 0.33 | 1 ± 0.29 | 0.13 ± 0.13 | 2.28 ± 0.12 | 0.2 ± 0.1 | 0.4 ± 0.13 | 5.66 ± 0.73 |
| *P*-value | 0.319 | 0.86 | 0.05 | 0.18 | 0.91 | 0.49 | 0.18 |

Abbreviations: AA, alopecia areata; QoL, quality of life; SALT, severity of alopecia tool

than in male adults. A reasonable explanation for this is the importance of hair in women's attractiveness and feminine features. The main factors AA influenced in both genders were feelings, daily and leisure activities, and personal relationships. Like the current study, Abedini *et al.* in Iran showed that females had worse QoL than males. The most impaired factors in their studies were feelings and leisure activities [12]. Other studies demonstrated paradoxical results; some showed that males had worse QoL [19]; others showed worse QoL in female patients or no significant difference between the genders [7,13,20,21].

The current study demonstrated no difference between QoL and disease duration, compatible with Al-Mutairi *et al.* [13], while other studies showed worse QoL with longer disease duration [12,22].

Results of the current study demonstrated no difference between QoL and patients' education levels, compatible with most other studies [7,12,13,18]. However, lower educational levels had a significantly higher impact on items related to feelings in the DLQI. Higher knowledge of patients with a good level of education about the disease, its aggravating factors, and its relatively good prognosis in most cases can explain this difference.

The current study revealed a more negative influence of AA on personal relationships in married couples than unmarried patients, although there was no difference between QoL based on marital status. These results are compatible with some other studies [7,13,18], though Masmoudi *et al.* demonstrated worse QoL in single patients [20].

In this study, patients with a positive family history of AA had significantly better QoL than patients with

a negative family history, especially in feelings, daily activities, and work items. This can be due to the experience of spontaneous improvement of hair loss by other family members. In addition, patients with a history of recurrent AA experienced significantly greater negative effects of treatment on QoL. This can be due to less acceptance of treatments because of the recurrent course of the disease.

The current study showed no significant difference between the influence of either "age of onset" or "face involvement" variables on the QoL of the patients, agreeing with the Abedini study [12]; however, some studies showed significantly worse QoL in patients under 30 years old [7,18,21,23,24].

## CONCLUSION

This study demonstrated no link between AA severity (based on the SALT score) and DLQI score. In addition, females and patients with a negative family history of AA experienced a significantly greater negative impact of AA on the DLQI score than males and patients with a positive family history. However, other demographic or clinical features did not correlate with QoL.

### Authors contributions

M.K. and M.A. contributed to the study's conception and design. All of the authors performed material preparation and data collection. The acquisition, analysis, and interpretation of data for the work were performed by M.A. M.K., R.Am., R.Ah., and S.M. M.A. and M.K. wrote the first draft of the manuscript. All authors revised the manuscript and approved the final version.

### Acknowledgments

None

### Funding source

None

**Conflict of interest:** None declared.

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