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The incidence of alopecia areata in hospitalized patients with COVID-19

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Background: Alopecia areata (AA) is an autoimmune disorder characterized by hair loss caused by an inflammatory response that targets hair follicles. Based on a small number of previous studies, it was observed that the prevalence of AA has increased during the coronavirus disease 2019 (COVID-19) pandemic. However, there is a scarcity of data regarding this occurrence. Therefore, the present study aimed to determine the incidence of AA in COVID-19 patients with a previous history of hospitalization.

Methods: This cross-sectional descriptive study included 384 confirmed COVID-19 patients (positive polymerase chain reaction test) who were admitted to our institute hospital, between April 2020 and April 2021. The data was analyzed using SPSS software version 26, and a significance level of 0.05 was considered.

Results: The mean age of the patients was 44.66 ± 14.09 years, and 167 (43.5%) were men. Fifteen patients developed AA, which accounted for 3.9% (95% confidence interval [CI] = 2.2; 6.4%) of the total patients. The mean time interval between COVID-19 and AA development was 5.07 ± 1.59 weeks. Nail involvement was observed in 4 (26.7%) of these patients, while body hair involvement was observed in 6 (40%). Logistic regression analysis revealed a statistically significant correlation between AA and age (adjusted odds ratio [aOR] = 0.917, 95% CI = 0.860; 0.977, $P = 0.008$), methotrexate use (aOR = 21.184, 95% CI = 1.110; 404.136, $P = 0.042$), diabetes (aOR = 12.502, 95% CI = 1.154; 135.414, $P = 0.038$), Down syndrome (aOR = 54.004, 95% CI = 2.914; 1000.730, $P = 0.007$), and anxiety (aOR = 34.305, 95% CI = 1.372; 857.498, $P = 0.031$).

Conclusion: This study found that approximately 4% of patients, who were previously hospitalized with COVID-19, developed AA, which was associated with young age, methotrexate use, diabetes, Down syndrome, and anxiety.

Keywords: alopecia areata, anxiety, COVID-19, hospitalization, pandemic, virus

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), triggers immune system activation, which contributes to the development of the disease. Recent research has established a link between COVID-19 and various immune-related dermatological conditions [1-4].

Alopecia areata (AA) is an autoimmune disease characterized by non-scarring hair loss on the scalp, face, or body. This condition puts a significant psychological burden on those affected [5,6]. The prevalence of AA in the general population is between 0.1 to 0.2%, with no significant variations based on race/ethnicity or sex [7]. Alopecia areata typically occurs before the age of 40 in 70 to 80 % of cases; however, it can also manifest in the first and second decades of life. It is the leading cause of hair loss among otherwise healthy children [8].

The exact pathophysiology of AA is not fully understood; however, current hypotheses state that there is a loss of immunological control in hair follicles, leading to an abnormal immune response [9]. Viruses, including SARS-CoV-2, may play a significant role in the development, recurrence, or exacerbation of AA [10].

The relationship between COVID-19 and AA is still unknown. A study conducted in Turkey examined the prevalence of AA among patients attending an outpatient dermatology clinic during the COVID-19 pandemic. The prevalence of AA increased from 0.97% before the pandemic to 1.48% two months after its onset. However, due to the lack of relevant information and the potential influence of immune disorders and mental stress on AA, it is not possible to establish that the virus was solely responsible for the increase in AA case [7].

The primary objective of this study was to determine the incidence of AA in patients admitted for COVID-19.

METHODS

This is a cross-sectional descriptive study of patients with COVID-19 who were hospitalized at our institute Hospital from April 2020 to April 2021. The inclusion criteria were hospitalization due to COVID-19 and confirmation of COVID-19 through PCR testing. The exclusion criteria were an incomplete patient file and a refusal to participate in the study.

The study entailed reviewing the files of patients admitted with COVID-19. The patients were then reached via telephone. Initially, the patients were provided with explanations about AA and its various types. They were then asked about their experience with this disease. If the patient reported any manifestations of AA, they were requested to provide images of their condition before and after the treatment through social networks. If no treatment response was evident in the final image, the patient was recommended to seek treatment at the dermatology clinic of our institute Hospital.

The demographic information of patients, COVID-19 symptoms and severity, prescribed treatments, and the AA details including type, severity (based on SALT score [11]), and onset time, were all recorded.

Statistical analysis

The data were analyzed using SPSS version 26. Descriptive statistics were used to describe the variables in terms of frequency and percentage. A 95% confidence interval was also provided for the incidence of AA. The Chi-square and Fisher's exact tests were used to compare qualitative variables between two or three groups. Logistic regression was utilized to determine factors related to AA. Independent variables with a *P*-value less than 0.2 in the univariate analysis were included in the multivariate model. Accordingly, the cOR (crude odds ratio), aOR (adjusted odds ratio), and 95% confidence interval of these indicators were reported. Since the incidence rate of AA was 3.9%, the interpretation areas of OR were as follows: less than 1 to 1.21 and 0.9 to 1 indicated a partial effect size, 1.22 to 1.85 and 0.55 to 0.89 indicated a low or small effect size, 1.86 to 2.99 and 0.34 to 0.54 indicated a medium effect size, and greater than or equal to 3 and less than or equal to 0.33 indicated a high or large effect size [12]. In all analyses, $P < 0.05$ was considered statistically significant.

Ethical issue

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

RESULTS

This study included 384 patients. Table 1 and Figure 1 show the demographic data, and the details related to COVID-19 are presented in Table 2.

Of 384 patients with COVID-19, 3 (0.8%) individuals had a family history of AA, while 15 (3.9%) patients with a 95% CI = 2.2 to 6.4% were diagnosed with AA. The average time interval from the onset of COVID-19 to the manifestation of AA in these patients was 5.07 ± 1.59 weeks. Out of the 15 patients with AA, 3 (20%) individuals had ophiasis, 5 (33.3%) patients had patchy alopecia, 5 (33.3%) patients had a multi-patchy type, and 2 (13.3%) patients presented with multi-patchy alopecia accompanied by ophiasis. Nail involvement was observed in 4 (26.7%) patients, while body hair involvement was present in 6 (40%) patients with AA. Based on the Severity of Alopecia Tool (SALT) score, alopecia was classified as S1 in 6 (40%) patients, S2 in 6 (40%) patients, and S3 in 3 (20%) patients. We used various parameters to assess the incidence of AA in patients with COVID-19, and the results are summarized in Table 3.

Table1. The demographic data of patients admitted due to COVID-19

Variables	Values
Age (years), mean (SD)	44.66 (14.09)
Sex, N (%)	
Male	167 (43.5)
Female	217 (56.5)
Level of education, N (%)	
Under diploma	153 (39.8)
Diploma	107 (27.9)
Associate's degree	59 (15.4)
Bachelor's degree	47 (12.2)
Master's degree	12 (3.1)
PhD	6 (1.6)
Occupation, N (%)	
Unemployed	123 (32.0)
Civil servant	113 (29.4)
Self-employed	148 (38.5)
Underlying conditions, N (%)	
Hypertension	79 (20.6)
Hyperlipidemia	58 (15.1)
Diabetes	39 (10.2)
Hypothyroidism	25 (6.5)
Ischemic heart disease	16 (4.2)
Asthma	11 (2.9)
Systemic lupus erythematosus	6 (1.6)
Rheumatoid arthritis	5 (1.3)
Iron deficiency anemia	4 (1.0)
Antiphospholipid syndrome	4 (1.0)
Down syndrome	4 (1.0)
Heart failure	4 (1.0)
Anxiety	3 (0.8)
Scleroderma	3 (0.8)
Inflammatory bowel disease	3 (0.8)
Hyperthyroidism	3 (0.8)
Pemphigus vulgaris	2 (0.5)
Sjogren syndrome	2 (0.5)
Vitiligo	2 (0.5)
Idiopathic thrombocytopenic purpura	2 (0.5)
Behcet's disease	1 (0.3)
Psoriasis	1 (0.3)
Pregnancy	1 (0.3)

Abbreviations: N, number; SD, standard deviation

Furthermore, the findings of the present study revealed no statistically significant association between the use of COVID-19 medications and the occurrence of AA (all *P*-values > 0.05, as determined by Fisher's exact test). To identify the factors associated with AA, each variable was initially entered into logistic regression as a single variable. Subsequently, variables with a *P*-value less than 0.2 were included in the multivariate model.

In the univariate analysis, significant relationships were observed between younger age, history of ICU hospitalization, history of intubation, longer hospital stay, longer symptom duration, longer time interval from symptom onset to hospitalization, family history of AA, types of symptoms, use of methotrexate for underlying diseases, diabetes, asthma, Down syndrome, inflammatory bowel disease (IBD), vitiligo, and anxiety in COVID-19 patients with AA. After adjusting for potentially influential factors, age was found to decrease the likelihood of developing AA by 8% per year (adjusted odds ratio [aOR] = 0.917, 95% confidence interval [CI] = 0.860-0.977, *P* = 0.008). The use of methotrexate for underlying diseases such as scleroderma and rheumatoid arthritis (RA) increased the likelihood of developing alopecia areata by almost 21 times (aOR = 21.184, 95% CI = 1.110- 404.136, *P* = 0.042). Diabetic patients with COVID-19 had a nearly 13-fold increased risk of developing AA than those without diabetes (aOR = 12.502, 95% CI = 1.154-135.414, *P* = 0.038). Having Down syndrome increased the likelihood of AA by approximately 54 times in COVID-19 patients (aOR = 54.004, 95% CI = 2.914-1000.730, *P* = 0.007). COVID-19 patients with anxiety (or anxiety disorders) had almost 34 times higher odds of developing AA

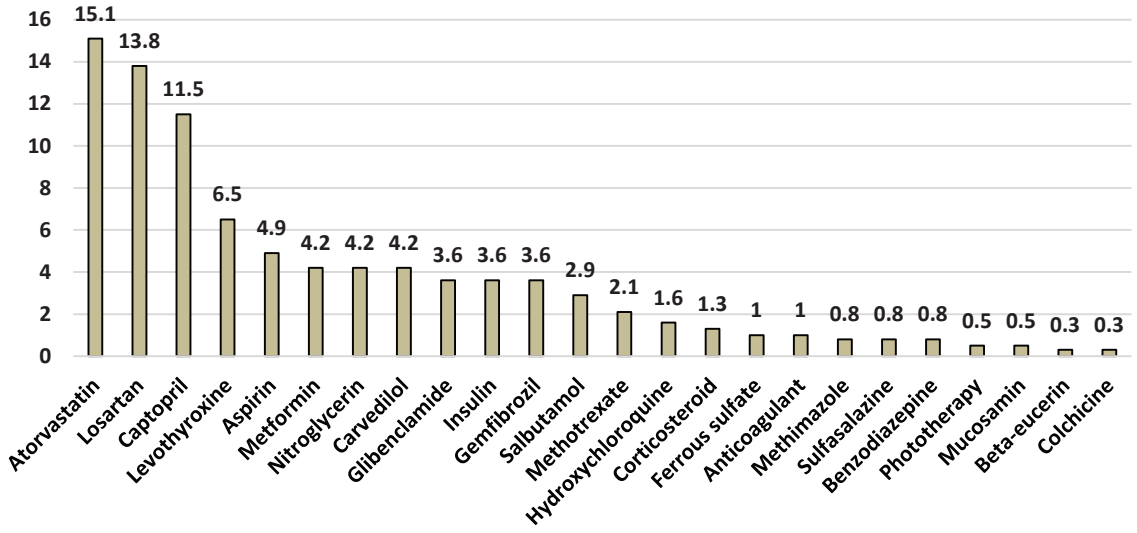

Figure 1. Medications used for underlying diseases.

Table2. Details related to COVID-19

Variables	Values
Length of hospital stay (days), mean (SD)	6.18 (4.03)
COVID-19 symptoms, N (%)	
Pulmonary	353 (91.9)
Gastrointestinal	16 (4.2)
Pulmonary and gastrointestinal	15 (3.9)
Symptom duration (days), mean (SD)	3.86 (2.94)
COVID-19 severity, N (%)	
Mild	79 (20.6)
Moderate	118 (30.7)
Severe	187 (48.7)
Symptom onset to hospital admission interval (days), mean (SD)	1.89 (1.15)
ICU admission, N (%)	
No	356 (92.7)
Yes	28 (7.3)
Intubation, N (%)	
No	374 (97.4)
Yes	10 (2.6)
Medications for COVID-19, N (%)	
Corticosteroids	367 (95.6)
Remdesivir	301 (78.4)
Interferon	64 (16.7)
Hydroxychloroquine	12 (3.1)

Abbreviations: COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; N: number; SD: standard deviation

than those without anxiety (aOR = 34.305, 95% CI = 372.1-857.498, $P = 0.031$).

DISCUSSION

This study aimed to assess the incidence rate of AA in patients hospitalized due to COVID-19. The findings of this study indicated that this incidence rate was approximately 4%. Factors associated with an increased risk of AA development in these patients included younger age, history of hospitalization in the intensive care unit (ICU), history of intubation, longer duration of hospitalization, longer duration of symptoms, longer time interval between symptom onset and hospitalization, family history of AA, types of symptoms, use of methotrexate for underlying diseases, diabetes, asthma, Down syndrome, IBD, vitiligo, and anxiety.

The mechanism and pathophysiology of AA involved the loss of immunity in hair follicles during the anagen phase. Viral infections lead to the accumulation of reactive oxygen species, causing oxidative stress and increasing the expression of major histocompatibility complex (MHC) class I ligands on the hair root sheath. This is associated with increased activity of T cells. T cells release interferon-gamma and TNF-α around the hair follicle, eventually leading to hair loss due to autoimmunity [13,14]. The relationship between other viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and hepatitis B vaccination with alopecia areata was reported. Other potential mechanisms connecting COVID-19 and alopecia areata include molecular similarities, super-antigens, and epitopes [15]. On the other hand, SARS-CoV-2 might contribute to the pathogenesis of alopecia areata by activating an interferon-dependent inflammatory response as well as other inflammatory cascades, including interleukin 6 (IL-6). Increased levels of IL-6 were reported in both COVID-19 and

Table 3. Rate of alopecia areata (AA) in patients with COVID-19 according to patients' demographic information, COVID-19-related data, and AA-related data

Variables	Alopecia areata		*P*-value
	No	Yes	
Age, N (%)			
<60 years (n=320)	307 (95.9)	13 (4.1)	1.000*
≥60 years (n=64)	62 (96.9)	2 (3.1)	
Sex, N (%)			
Male (n=167)	161 (96.4)	6 (3.6)	0.781**
Female (n=217)	208 (95.9)	9 (4.1)	
University education, N (%)			
No (n=260)	250 (96.2)	10 (3.8)	1.000*
Yes (n=124)	119 (96.0)	5 (4.0)	
Occupation, N (%)			
Unemployed (n=123)	117 (95.1)	6 (4.9)	0.574*
Employed (n=261)	252 (96.6)	9 (3.4)	
Hospital length of stay, N (%)			
<1 week (n=222)	220 (99.1)	2 (0.9)	<0.001**
≥1 week (n=162)	149 (92.0)	13 (8.0)	
COVID-19 severity, N (%)			
Mild (n=79)	79 (100.0)	0 (0.0)	<0.001*
Moderate (n=118)	118 (100.0)	0 (0.0)	
Severe (n=187)	172 (92.0)	15 (8.0)	
ICU admission, N (%)			
No (n=356)	349 (98.0)	7 (2.0)	<0.001*
Yes (n=28)	20 (71.4)	8 (28.6)	
Intubation, N (%)			
No (n=374)	361 (96.5)	13 (3.5)	0.054*
Yes (n=10)	8 (80.0)	2 (20.0)	
Family history of alopecia areata, N (%)			
No (n=381)	368 (96.6)	13 (3.4)	0.004*
Yes (n=3)	1 (33.3)	2 (66.7)	
Symptom onset to hospital admission interval, N (%)			
<3 days (n=381)	263 (98.5)	4 (1.5)	0.001*
≥3 days (n=3)	106 (90.6)	11 (9.4)	
COVID-19 symptoms, N (%)			
Pulmonary (n=353)	343 (97.2)	10 (2.8)	<0.001*
GI (n=16)	16 (100.0)	0 (0.0)	
Pulmonary & GI (n=15)	10 (66.7)	5 (33.3)	
COVID-19 symptom duration, N (%)			
<1 week (n=309)	302 (97.7)	7 (2.3)	0.003*
≥1 week (n=75)	67 (89.3)	8 (10.7)	
Underlying diseases, N (%)			
No (n=381)	190 (98.4)	3 (1.6)	0.017**
Yes (n=3)	179 (93.7)	12 (6.3)	

*Based on the Fisher Exact test
**Based on the Chi-square test

AA [16,17]. Among the inflammatory cytokines, IL-6 specifically inhibits the proliferation of follicular keratinocytes and hair follicle stem cells, thereby inhibiting the transformation from the telogen to anagen phase [18].

In the present study, a significant relationship was found between younger age and the occurrence of AA in COVID-19 patients who were hospitalized. Each one-year increase in age was associated with an 8% decrease in the likelihood of developing AA in these patients. It is important to note that the adjusted odds ratio (aOR) for age was 0.917, implying- a partial effect size. This finding was consistent with those of previous studies. Although AA can occur

at any age, it predominantly affects individuals in the first decades of life. More than 80% of patients with AA experience symptoms before the age of 40, and 40% of patients have their first symptoms before the age of 20. Furthermore, it appears that a younger age at disease onset increases the likelihood of developing more extensive forms of AA, such as totalis and universalis [19]. In a retrospective study involving 1641 patients with AA, the mean age was 29.86 years [20]. In the present study, the mean age of the patients was 44.66 years, with one-sixth of the patients being over 60 years old.

In the present study, the incidence rate of AA in patients with a history of hospitalization for COVID-19 was about 4%. Nguyen and Tosti conducted a systematic review of 41 studies and 1826 patients. They reported that the incidence of AA was found to be 7.8% [21]. Most of the studies included in this systematic review and meta-analysis were case reports or case series, which might explain the difference in the rate of AA between this study and the present study. Nguyen and Tosti assessed patients with COVID-19 and different types of alopecia, and among those with different types of alopecia, 7.8% had AA, which could explain the higher percentage of AA in their study. Nguyen and Tosti also conducted another cross-sectional study, in which they assessed patients with AA and COVID-19, as well as patients with AA who received the vaccine. Among the 59 patients with a positive COVID-19 test, 25 individuals (42.4%) experienced AA symptoms on average 50.6 days after SARS-CoV-2 infection. Of these, only 15 (25.4%) patients were diagnosed with new AA, while the others experienced a relapse of the disease [22]. This study differed from ours in that it included all patients with COVID-19, while we focused specifically on hospitalized patients with COVID-19.

Kim *et al.* reported a low incidence of new cases of AA, only 0.2%, among 7958 COVID-19 patients from South Korea with no history of AA [23]. This study also included a control group of 218,779 individuals who were not affected by COVID-19. There was no significant difference between the incidence of new cases of AA among COVID-19 patients and the control group. Therefore, there appears to be no relationship between COVID-19 and AA. In the present study, due to the lack of a control group, it was not possible to make this comparison. Thus, it remains unclear how much of the incidence of AA in these patients was caused by COVID-19 on its own. Additionally, it is important to consider that the prevalence of AA might be influenced by racial differences [24], which might also contribute to the discrepancy between their findings and ours.

Consumption of methotrexate was found to be associated with an increased risk of developing AA in hospitalized COVID-19 patients. The chance of developing AA in these patients was nearly 21 times higher than those who did not take methotrexate. This finding contradicted the results of previous studies. Methotrexate could be administered alone or in combination with corticosteroids to treat AA [25]. It has shown promise as a safe treatment for severe cases [26] and treatment-resistant AA [27]. Therefore, it was expected that the use of methotrexate would decrease the risk of developing AA. However, it should be noted that among the patients assessed in this study, those with scleroderma and RA used methotrexate, implying a potential association between methotrexate use and AA in these diseases. The exact dosage of methotrexate administered to these patients is unknown. Previous studies reported an increased risk of AA in patients with RA, scleroderma, and autoimmune diseases in general [28-30]. Another finding of the present study was an increased likelihood of developing AA in patients with diabetes and Down syndrome, even after adjusting for other factors. This finding was also supported by previous studies [29,31-33].

There was a significant correlation between anxiety in patients with COVID-19 and a history of hospitalization with AA. A Previous study in this field indicated the presence of anxiety in patients with AA [34]. Stressful life events play a crucial role in the onset and progression of AA [35,36], although the exact role of anxiety in the development of AA remains unclear [37,38]. Cakirca *et al.* attempted to establish a link between anxiety, depression, and oxidative stress in the incidence of AA but were ultimately unable to find any such relationship [39]. The COVID-19 pandemic introduced several stressors, such as travel restrictions, social quarantine, prohibition of gatherings, and limitations on public transportation. The rise in unemployment and deaths resulting from the pandemic further contributed to people's stress levels [40]. All these factors could increase the risk of developing AA during the COVID-19 pandemic [41].

CONCLUSION

The findings of the present study indicated that COVID-19 was associated with the occurrence of alopecia areata. Approximately 4% of patients who were hospitalized due to COVID-19 developed alopecia areata. Factors such as younger age, consumption of methotrexate, presence of diabetes, Down syndrome, and anxiety could influence the development of AA in hospitalized COVID-19 patients. It is recommended that physicians regularly examine the hair condition of these patients, especially in the 4-8-week period following hospitalization, so that if alopecia areata occurs, the necessary actions can be taken promptly.

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Authors' contributions

Z.T. and F.A. contributed to the conception of the work. M. R., A. B., H. R., and A. F. contributed to the acquisition, analysis, and interpretation of data for the work. M. R. and A. B. drafted the manuscript. Z. T. and F. A. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

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