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ORIGINAL ARTICLE

Androgenetic alopecia and COVID-19: Is there a clinical connection?

Moein Baghani[1] | Mohammad Reza Pourani[1] | Sayyed Mojtaba Nekooghadam[2,3] | Davood Ommi[2,4] | Alireza Fatemi[2,5] | Fahimeh Abdollahimajd[1,2] | Hamideh Moravvej[1]

[1]Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Clinical Research Development Unit of Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3]Internal Department of Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4]Functional Neurosurgery Research Center, Shahid Behehsti University of Medical Sciences, Tehran, Iran

[5]Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence
Fahimeh Abdollahimajd and Hamideh Moravvej, Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: fabdollahimajd@yahoo.com; fabdollahimajd@sbmu.ac.ir and hamidehmoravej@sbmu.ac.ir

Abstract

Background: During the coronavirus disease 2019 (COVID-19) outbreak, multiple studies showed higher rates of severe infection in adults and specifically in male patients, which may be related to differences in androgen receptor (AR) expression. Androgenetic alopecia (AGA) is one of the AR expression manifestations.

Aim: To explore AGA severity as a possible risk factor for COVID-19 severity in hospitalized patients.

Methods: A total of 164 subjects (116 men and 48 females) with confirmed COVID-19 in need of hospitalization were included in this study. An experienced dermatologist examined the correlation of clinical signs of COVID-19 severity with AGA types. For evaluation of the association between categorical variables and comparison of the mean age in three groups of COVID-19 patients, the Fisher's exact test and the analysis of variance were used.

Results: Our cross-sectional study included 116 male patients (70.7%) with a median age of 65.5 (age range: 22–97) years. Among them, 13.8% required intubation, 15.5% needed intensive care unit (ICU) care, and 70.7% required inward hospitalization. The Hamilton–Norwood Scale (HNS) was as follows: HNS I 14.7%, HNS II 12.1%, HNS III 20.7%, HNS IV 19.8%, HNS IV 29.8%, HNS V 17.2%, HNS VI 13.8%, and HNS VII 1.7%. Also, 29.3% of the patients were female, possessing a median age of 72 (age range: 23–98) years. In this group, 8.3% required intubation, 6.3% required ICU care, and 85.4% needed inpatient ward admission care. The Ludwig Scale (LS) was as follows: LS I 52.1%, LS II 35.4%, and LS III 12.5%.

Conclusion: The severity of AGA type did not correlate with the severity of COVID-19 among hospitalized patients. Our results were in contrast with other research that suggested AGA severity as a marker of unfavorable outcomes of COVID-19.

KEYWORDS
androgenetic alopecia, COVID-19, population at risk, risk factors, SARS-CoV-2 infection, treatment

Moein Baghani and Mohammad Reza Pourani contributed equally to this work and are considered as co-first authors

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic began following the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The pandemic has resulted in more than 75 million confirmed cases and over 1.6 million deaths worldwide.[1]

Multiple studies have mentioned the decreased severity of COVID-19 in children than adolescents and young adults. In adults, severe morbidity and mortality rates are significantly higher in male (58% and 2.8%, respectively) than female patients (42% and 1.7%, respectively).[2–4] Increased COVID-19 severity among men may be linked with androgen expression, in which there are significant differences among genders and between pre-puberty individuals and adults.

Cell entry of SARS-CoV-2 depends on the priming of a viral spike surface protein via transmembrane protease serine 2 (TMPRSS2), which has an association with androgen receptor (AR) expression.[5–7] Also, angiotensin-converting enzyme 2 (ACE2) is an attachment molecule for the viral spike surface protein. Furthermore, ACE2 activities are reduced by androgen decrements and are regulated by AR.[8,9] Therefore, a possible reason behind sex differences in COVID-19 burden could be androgen expression (Figure 1).[10]

One of the manifestations of the more significant expression of ARs in men is androgenetic alopecia (AGA), which has been labeled as the predominant cause of hair loss in both genders. Currently, AGA is believed to be mediated by factors related to androgens and gene expression.[11–14]

Therefore, we hypothesized higher grades of AGA to be correlated with more severe cases of COVID-19. To explore this hypothesis, we conducted this observational study of the prevalence of AGA among hospitalized COVID-19 patients.

2 | PATIENTS AND METHODS

The ethics committee of Shahid Beheshti University of Medical Sciences confirmed this cross-sectional investigation (IR.SBMU.SRC.REC.1400.007) aimed at analyzing the prevalence and types of AGA among 164 hospitalized COVID-19 patients and informed consent was obtained from all patients/family member. The patients were admitted to Hospital in need of inpatient care. An experienced dermatologist recorded the age and sex and evaluated alopecia among the admitted patients. The diagnosis of AGA was based on a clinical examination of the hair loss patterns of patients upon admission in the absence of other causes of non-scarring alopecia. Patients with chronic telogen effluvium, diffuse alopecia areata, and other types of alopecia and those using drugs that may cause alopecia were excluded from the study. Classification of the degree of hair loss for each patient was graded using the Hamilton–Norwood Scale (HNS) in men[15] and the Ludwig Scale (LS) in women.[16] The HNS grades patients with a scale from 1 (least severe) to 7 (most severe), while the LS for female pattern AGA ranges from type I to type III.

The degree of hair loss was categorized as mild AGA for HNS I & II and LS I, moderate AGA for HNS III and LS II, and severe AGA for LS III and HNS IV and above. We compared the prevalence and types of AGA among patients requiring intubation, intensive care, or ward admission based on the disease severity.

2.1 | Statistical analysis

The SPSS software version 24 was used for statistical analysis. The results were statistically described as mean ± standard deviation (SD) for continuous variables. Also, the frequency and percentage

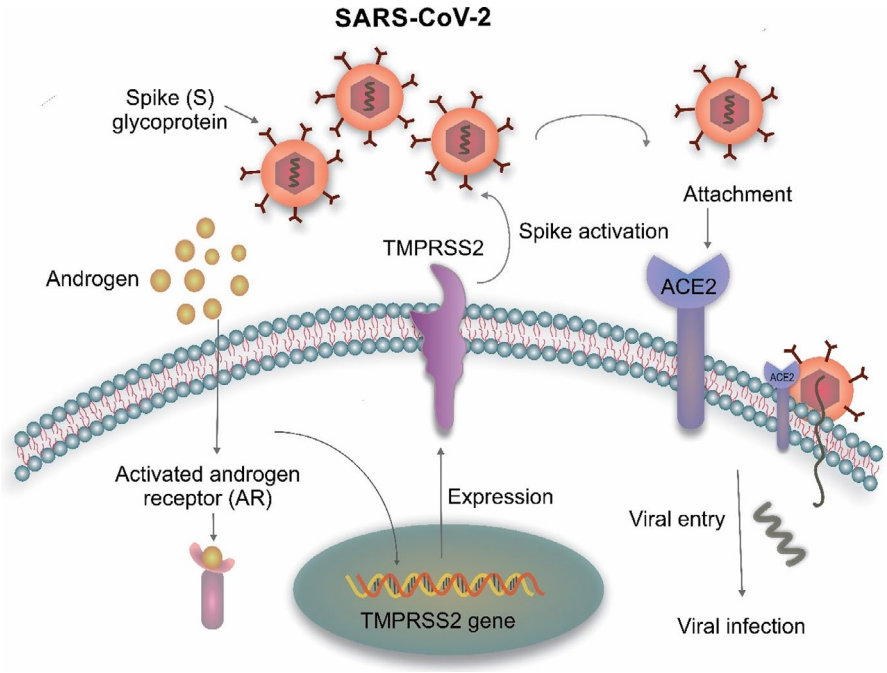

FIGURE 1 The androgenic receptor (AR)/angiotensin-converting enzyme 2 (ACE2)/ transmembrane protease serine 2 (TMPRSS2) pathway, which postulates the interaction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with androgenetic alopecia. The activated ARs promote the transcription of the TMPRSS2 gene. TMPRSS2 expression primes the spike of SARS-CoV-2, which is essential for viral cell entry. SARS-CoV-2 binds to membrane-bound ACE2 to enter the host cells. Activated ARs give rise to a low density of scalp hair

of categorical variables were reported. Fisher's exact test was performed to evaluate the association between categorical variables. Moreover, the normality of continuous variables was checked using the Kolmogorov–Smirnov test. Then, analysis of variance was used to compare the mean age in three groups of COVID-19 patients. The level of significance for statistical tests was 0.05.

3 | RESULTS

The demographic and clinical characteristics of all subjects are depicted in Table 1.

Of the 164 patients, there were 116 (70.7%) males and 48 (29.3%) females. Men had a significantly lower mean age (62.66 ± 15.69 years; range 29 to 97) compared with women (69.04 ± 12.65 years; range 23 to 89) ($p = 0.008$).

AGA was statistically more severe in male than female subjects ($p < 0.001$). However, no significant difference was found between COVID-19 severity in male and female patients ($p = 0.129$).

AGA severity was not correlated with COVID-19 severity in total and in the male subgroup ($p = 0.078$ and $p = 0.575$, respectively). On the other hand, the severity of AGA was associated with COVID-19 severity in female patients ($p = 0.018$); however, the number of female patients in multiple cells of analysis had an expected count of less than 5, which makes this result quite unreliable (Table 2).

Higher ages overall and in the male subgroup were related to the severe form of AGA ($p = 0.003$ and $p < 0.001$, respectively). However, the severity of COVID-19 was not correlated with higher age ($p = 0.397$). It seems that in our study, older patients experienced more severe forms of AGA but similar clinical severity of COVID-19 in comparison with younger patients (Table 3).

The severity of COVID-19 was not correlated with age. Overall, AGA severity was associated with the age of our study population ($p = 0.003$). In addition, higher grades of AGA severity were seen in older male ($p < 0.001$), but this was not replicated among female patients ($p = 0.238$).

4 | DISCUSSION

In this cross-sectional study, we investigated the potential association between AGA and COVID-19 severity. Although there might be a relation between COVID-19 severity and androgen levels,[17] we found no significant relationship between AGA and COVID-19 severity. Müller Ramos et al.[18] associated hair amounts and severity of COVID-19 in 1474 confirmed cases via a patient-filled questionnaire. However, hair amounts were categorized as only these three options of a head full of hair, mild alopecia, and baldness, without delineating the type of alopecia. Meanwhile, our research was designed to evaluate AGA-related parameters specifically.

Lee et al. analyzed 1941 admitted patients tested for SARS-CoV-2 infection by extracting data from the UK Biobank. Among them, 16.83%, 18.15%, and 20.05% of patients with mild, moderate, and severe AGA tested positive for COVID-19, respectively.[19] They reported that hospitalized patients with severe AGA were significantly more likely to test positive for COVID-19 than patients without AGA. On the contrary, mild-to-moderate AGA did not correlate with a considerably higher percentage of COVID-19 affliction. Lee et al. described severe AGA as a potential sign of higher risk of adverse COVID-19 outcomes.[19] In contrast, our study did not depict significantly different proportions of undesirable COVID-19 consequences among patients with mild, moderate, or severe AGA.

The prevalence of AGA was comparable to what has been previously found in the normal population. Fatemi et al.[20] studied Iranian women in Isfahan city with AGA and reported LS 1: 41.7%, LS 2: 48.7%, and LS 3: 4.9%. We found a similar distribution of AGA among inpatient COVID-19-positive women, where mild and moderate AGA were more prevalent than the severe form of AGA. Salman et al.[21] examined the Turkish population and established the following distribution of AGA severity among men: HNS 1: 6%, HNS 2: 13%, HNS 3: 45%, HNS 4: 4%, HNS 5: 5%, HNS 6: 8%, and HNS 7: 19%. In our study, we categorized AGA severity in male patients hospitalized due to COVID-19 (HNS 1: 14.7%, HNS 2: 12.1%, HNS 3: 20.7%, HNS 4: 19.8%, HNS 5: 17.2%, HNS 6: 13.8%, and HNS 7: 1.7%). Salman et al. delineated a higher frequency of HNS 7, while HNS 4–6 were more prevalent in our study. Compared with our work, Wambier et al.[22] reported a higher prevalence of AGA but a similar rate of need for hospital care between genders. Their sample consisted of 175 hospitalized COVID-19 patients in Spain, including 122 (69.7%) men (median age 62.5 years) and 53 (30.2%) women (median age 71 years), which is comparable to the median ages of 65 and 72 in men and women of our study, respectively. Their results were categorized into three groups: mild (HNS I & II), moderate (HNS III), and severe (HNS IV to VII). They detected 17 mild, 20 moderate, and 59 severe cases of AGA among men, compared with 7 mild, 7 moderate, and 8 severe cases of AGA in women. Since Wambier et al. lacked a control group, they compared their results in Madrid with a group of age-matched Australians, representing one of their study limitations.[22]

Wambier et al., in another pilot prospective observational study, investigated 44 admitted COVID-19-positive male patients with AGA. The most unfavorable outcomes occurred in the group with HNS >II.[23] Our results did not reveal an association between the severity of AGA in male patients and adverse COVID-19 consequences. Our data contrast with other studies suggesting critical outcomes in COVID-19 patients with higher grades of AGA (Gabrin sign).[22,23] In conclusion, the association of AGA severity and COVID-19-related adverse complications should be further evaluated in future studies.

This study has certain limitations, such as the limited sample size and lack of a control group. As far as we know, there is no research on the prevalence of AGA types in Iranian men for allowing a more precise comparison of HNS types' frequencies. We had only a few women with severe COVID-19, resulting in analysis with lower validity in that group.

TABLE 1 The demographic and clinical characteristics of COVID-19-positive inpatients

	Males	Females	*p*-value
Age (Mean ± SD)	62.66 ± 15.69	69.04 ± 12.65	0.008
COVID-19 Severity			
Ward admitted	82 (70.7%)	41 (85.4%)	0.129
ICU admitted	18 (15.5%)	3 (6.3%)	
Intubated	16 (13.8%)	4 (8.3%)	
AGA Severity			
Mild	31 (26.7%)	25 (52.1%)	<000.1
Moderate	24 (20.7%)	17 (35.4%)	
Severe	61 (52.6%)	6 (12.5%)	

Abbreviations: AGA, Androgenetic alopecia; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

TABLE 2 COVID-19 severity association with other factors

	COVID-19 patients				
		Disease Severity			
Variables	Total (%)	Intubated (%)	ICU admitted (%)	Ward admitted (%)	*p*-value
Sex					0.129
Male	116 (70.7%)	16 (13.8%)	18 (15.5%)	82 (70.7%)	
Female	48 (29.3%)	4 (8.3%)	3 (6.3%)	41 (85.4%)	
AGA Severity					0.078
Mild		8 (40%)	5 (23.8%)	43 (35%)	
Moderate		1 (5%)	4 (19%)	36 (29.3%)	
Severe		11 (55%)	12 (57.1%)	44 (35.8%)	
Male AGA Severity					0.575
HNS I	17 (14.7%)	4 (23.52%)	3 (17.64%)	10 (58.82%)	
HNS II	14 (12.1%)	1 (7.14%)	2 (14.28%)	11 (78.57%)	
HNS III	24 (20.7%)	1 (4.16%)	3 (12.5%)	20 (83.33%)	
HNS IV	23 (19.8%)	6 (26.08%)	3 (13.04%)	14 (60.86%)	
HNS V	20 (17.2%)	3 (15%)	4 (20%)	13 (65%)	
HNS VI	16 (13.8%)	1 (6.25%)	3 (18.75%)	12 (75%)	
HNS VII	2 (1.7%)	0 (0%)	0 (0%)	2 (100%)	
Female AGA Severity					0.018[a]
LS I	25 (52.1%)	3 (12%)	0 (0%)	22 (88%)	
LS II	17 (35.4%)	0 (0%)	1 (5.88%)	16 (94.11%)	
LS III	6 (12.5%)	1 (16.66%)	2 (33.33%)	3 (50%)	

Abbreviations: AGA, Androgenetic alopecia; COVID-19, coronavirus disease 2019; HNS, Hamilton–Norwood Scale; ICU, intensive care unit; LS, Ludwig Scale.

[a]Pearson Chi-squared test; six cells (66.7%) had expected counts of less than 5. The minimum expected count was 0.38.

5 | CONCLUSION

Although there has been much debate on the subject, regarding the higher prevalence of AGA in older age and higher comorbidity of COVID-19 in that age group, we found that AGA's types are not correlated with the severity of COVID-19. In addition, our data challenged the Gabrin sign as an indicator of COVID-19 severity. Regarding the possibility of ethnic variations and different levels of AR expression, research on other manifestations of higher AR expression may lead to the discovery of alternative associations with COVID-19 severity.[24] Further research with a larger scale and broader ethnic diversity is also recommended, facilitating the analysis of the relation of

TABLE 3 Assessment of AGA and COVID-19 severity in relation to age

	Age					
	Total	*p*-value	Males	*p*-value	Females	*p*-value
COVID-19 Severity						
Ward admitted	65.69 ± 14.06	0.397	64.43 ± 14.37	0.217	68.22 ± 13.20	0.530
ICU admitted	61.10 ± 17.30		58.89 ± 17.72		74.33 ± 4.04	
Intubated	60.95 ± 18.43		57.81 ± 18.86		73.50 ± 10.47	
AGA Severity						
Mild	59.16 ± 15.95	0.003	52.84 ± 13.73	<0.001	67.00 ± 4.59	0.238
Moderate	65.20 ± 13.27		62.21 ± 14.91		69.41 ± 9.39	
Severe	68.60 ± 14.26		67.82 ± 14.67		76.50 ± 4.59	

Abbreviations: Androgenetic alopecia, AGA; coronavirus disease 2019, COVID-19.

AGA severity and unfavorable COVID-19 outcomes among different groups.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The ethics committee of Shahid Beheshti University of Medical Sciences confirmed this cross-sectional investigation (IR.SBMU.SRC.REC.1400.007) and informed consent was obtained from all patients/family member.

AUTHOR CONTRIBUTIONS

HM and FA contributed to the conception of the work. SMN, DO, and AF were involved in the diagnosis and management of the patients. MB contributed to the acquisition of data. MB, MRP, and FA contributed to the analysis, and interpretation of data for the work. MB and MRP drafted the manuscript. FA and HM critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Mohammad Reza Pourani https://orcid.org/0000-0003-3222-7528

Fahimeh Abdollahimajd https://orcid.org/0000-0002-9463-0665

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