Association of androgenetic alopecia with a more severe form of COVID-19 infection

Dunja Veskovic[1,2] · Tatjana Ros[1,2] · Tijana Icin[1,3] · Kristina Stepanovic[1,3] · Nebojsa Janjic[1,4] · Dusan Kuljancic[1,5] · Sonja Sedlarevic[1,3] · Dmitar Vlahovic[1,6]

Abstract

Background Individual susceptibility to develop acute respiratory distress syndrome is related to age and most frequent comorbidities. So far, it is known that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) primarily infects the type II pneumocytes in humans, with the help of transmembrane serine protease type 2 (TMPRSS2). Up to now, the only known transcriptional promoters of genes coding TMPRSS2 are androgenic. Theoretically, the elevated level of androgens or androgen receptors would lead to a higher expression of TMPRSS2 and a higher level of viremia as a consequence.

Aim The aim of our research was to indirectly investigate if the severity of SARS-CoV-2 infection is dependent on the expression of androgen receptors.

Methods This observational study analysed male patients hospitalized for SARS-CoV-2 infection with respect to the length of hospitalisation, the outcome of the disease, the type of necessary oxygen support and the presence of comorbidities and hairiness. In hairiness estimation, we used an adapted version of the Hamilton–Norwood scale and the presence of the Gabrin sign.

Results In total, 208 patients were enrolled in the study. There were statistically significant differences comparing the average age of patients with the different types of alopecia when groups were divided according to the presence of the Gabrin sign ($t = 4.958$, $p > 0.01$). The outcomes and the type of needed minimal oxygen support, compared with the type of alopecia in the case of Gabrin $+/-$ classification showed a statistically significant difference in the outcome of the disease ($p = 0.027$). There were no statistically significant differences in the distribution of comorbidities among alopecia groups, but hypertension was related to poor COVID-19 prognosis.

Conclusion Our findings suggest that the Gabrin sign and hypertension are related to a poor COVID-19 prognosis.

Keywords Androgenetic alopecia · Androgen receptors · Gabrin sign · SARS-CoV-2 · Transmembrane serine protease 2

✉ Dunja Veskovic
  dunja.veskovic@mf.uns.ac.rs

1 Medical Faculty, University of Novi Sad, Hajduk Veljkova 3 21000, Novi Sad, Serbia

2 Clinic for Dermatology, Clinical Centre of Vojvodina, Novi Sad, Serbia

3 Clinic for Endocrinology, Clinical Centre of Vojvodina, Novi Sad, Serbia

4 Clinic for Gastroenterology, Clinical Centre of Vojvodina, Novi Sad, Serbia

5 Clinic for Psychiatry, Clinical Centre of Vojvodina, Novi Sad, Serbia

6 Clinic for Neurology, Clinical Centre of Vojvodina, Novi Sad, Serbia

Introduction

From the beginning of the novel COVID-19 pandemic, caused by SARS-CoV-2, the whole academic community is pressured to find adequate parameters for grouping high-risk patients susceptible to rapid progression of the disease and the occurrence of complications, in order to provide them with adequate and timely therapy. Epidemiological analyses indicated that individual susceptibility to develop an acute respiratory distress syndrome (ARDS) resulting from the infection with SARS-CoV-2 virus is related to age and comorbidities such as hypertension (HT), diabetes mellitus (DM), cardiovascular diseases, chronic lung disease and cancer [1], and found disproportion based on the gender, i.e. 40% of patients were females and 60% were males [2, 3].

So far, it is known that SARS-CoV-2 in humans primarily infects the type II pneumocytes, by binding to their surface angiotensin-converting enzyme (ACE-2) receptors, which is enabled by proteolytic priming of viral spike proteins with the help of the transmembrane serine protease type 2 (TMPRSS2). [4] In vitro studies of the SARS-CoV-1 virus have shown that the inhibition of the serine proteases reduces the possibility of the virus binding to the ACE-2 receptor. Up to now, the only known transcriptional promoters of genes coding the TMPRSS2 are androgenic [5].

Androgenetic alopecia (AGA) is a chronic progressive disease that affects more than 50% of men older than 50 years of age [6] and is highly influenced by genetic factors, the number of androgen receptors at the hair follicle and their sensitivity to androgen hormones. When attached to androgen receptors at the level of dermal follicles of hair, androgen-dihydrotestosterone induces transforming growth factor beta (TGF-β), which results in the cyclical and continuous reduction of hair follicles and consequently leads to a distinctive form of hair thinning [7].

The most frequently used alopecia assessment scale is the Hamilton–Norwood scale. [8–10] In memory of Dr Frank Gabrin, who had suffered from androgenetic alopecia and bilateral testicular cancer for a long time before he died from COVID-19 infection, Wambier et al. published a paper introducing the so-called Gabrin sign [11]. The Gabrin sign refers to the lack or thinness of hair on the head vertex and belongs to at least the third stage of the Hamilton–Norwood scale [12]. The primary pathogenesis mechanism, as well as the role of androgens and androgenic receptors and its effect on the severity of COVID-19 disease, are still unknown to an extent, but more and more studies show promising explanations and results in this path [4, 11, 13, 14].

The aim of our research was to investigate the association between the severity of COVID-19 infection and different types of androgenic alopecia.

Material and methods

This observational, cross-sectional study was carried out in November 2020 at the Clinical Center of Vojvodina in Novi Sad, Serbia. We analysed hospitalised COVID-19-positive male patients needing oxygen support with respect to the length of hospitalisation, the outcome of COVID-19 infection as well as the type of applied oxygen support and the presence of comorbidities. In addition to that, we conducted a hairiness analysis of the subjects. The real-time reverse transcription-polymerase chain reaction (RT-qPCR) test was used to detect the presence of the SARS-CoV-2 virus, as well as the AMP COVID-19 Ag Respi-Strip test, a rapid immunochromatographic test for the detection of SARS-CoV-2 antigen. The
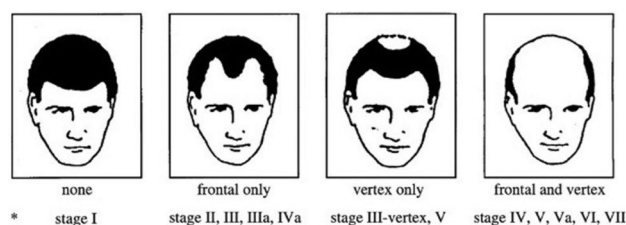

Fig. 1 The adapted Hamilton–Norwood scale [18]

outcome of the disease was defined as recovered or deceased. According to the type of the applied oxygen support, we differentiated three groups of subjects [15], those needing: (a) simple oxygen masks, (b) high-flow systems including high-flow nasal cannula (HFNC) or continuous positive airway pressure (CPAP), or (c) mechanical ventilation (MV). Of our interest were the three most common comorbidities in the general male population, frequently associated with the course of COVID 19, such as HT, DM, and prostate disease (PD), encompassing benign hyperplasia and prostate cancer that has not been treated with androgen deprivation therapy (ADT) [1, 16, 17]. For the purpose of hairiness analysis, we used an adapted version of the Hamilton–Norwood scale to classify subjects into four groups, ranging from one to four, by the type of alopecia, as it is shown in Fig. 1 [18].

In addition, we made the classification based on the presence of the Gabrin sign [19]. Namely, of the four groups of subjects, Gabrin negative group would include subjects with types 1 and 2, while the group with type 3 and 4 alopecia were considered Gabrin positive. Statistical analysis was performed by the Jamovi software, version 1.6.3 and R Core Team, version 3.6. We used statistical parameters such as absolute numbers and percentages, measures of central tendency, and dispersion (arithmetic mean, standard deviation).

The t-test and one-way univariate analysis (ANOVA) along with post hoc testing of differences based on Tukey's HSD were used after continual variables had shown normal distribution and homogeneity of variance. The differences between the category variables were examined by applying the χ^2 test, while Yates' continuity correction was applied on 2×2 test designs. Fisher's exact probability indicator was disclosed only in the case where the expected value in the contingency table cells was less than 5. Statistical significance was set at $p \leq 0.05$.

Results

In total, 208 male patients were enrolled in the study, with an average age of 65 (range 28–90 years old). The lethal outcome was registered in 23.8% of patients, with an average age of 77.

Table 1 Descriptive analysis of the subjects

Feature	N	%
The type of oxygen therapy:		
Oxygen mask	135	64.9
HFNC/CPAP	34	16.3
MV	39	18.8
Disease outcome:		
Recovered	154	76.2
Deceased	48	23.8
Most common comorbidities:		
Hypertension	112	55.4
Diabetes mellitus	55	27.2
Prostate disease	14	6.9
Chronic kidney disease	18	8,6
Chronic lung disease	11	5,2
Previous cancer	9	4,3
Previous pulmonary thromboembolism	3	1,4
The subtype of alopecia:		
1	11	5.3
2	61	29.3
3	57	27.4
4	79	38.0
Gabrin sign:		
Present	136	65.4
Absent	72	34.6

The average number of inpatient days was 14 ± 7 days. The rest of the descriptive analysis of the subjects is shown in Table 1.

The chi-square test showed no statistically significant difference in the outcomes ($p = 0.06$), nor in the type of oxygen therapy used ($p = 0.21$) in patients with various types of alopecia, ranging from types 1 to 4. However, when subjects were classified according to the existence of the Gabrin sign, a statistically significant difference in the outcome of treatment ($p = 0.027$) was seen, the mortality rate was higher among Gabrin positive patients, while there was no statistically significant difference in the type of oxygen support between Gabrin positive and negative patients (Table 2).

There was no statistically significant difference in the average length of hospitalisation between groups of type 1 to 4 alopecia (one-way variance analysis, $p = 0.233$), nor Gabrin sign $+/-$ groups (t-test, $p = 0.437$) (Fig. 2).

One-way analysis of variance served to test the differences regarding the average age of patients with different types of alopecia. Thus, the statistical significance of the entire model ($F = 14.8$, $p < 0.01$) was established while Tukey's post hoc testing (Tukey's HSD) determined statistically significant differences between all alopecia types except the type 3 and the type 4 ($p = 1.00$). A statistically significant difference in the average age was also present when subject groups were divided according to the presence of the Gabrin sign ($t = 4.958$, $p < 0.01$) (Fig. 3).

Table 2 The distribution of different types of oxygen therapy and disease outcome in different types of alopecia

	The type of alopecia				P
	Type 1 (N=11)	Type 2 (N=61)	Type 3 (N=57)	Type 4 (N=79)	
The type of oxygen therapy					
Oxygen mask	10	40	39	46	0.206
HFNC/CPAP	1	10	11	12	
IV	0	11	7	21	
Disease outcome					
Recovered	11	50	37	56	0.060
Deceased	0	10	17	21	
The presence of Gabrin sign					
	Gabrin − (N=72)		Gabrin + N=(136)		P
The type of oxygen therapy					
Oxygen mask	50		85		
HFNC/CPAP	11		23		0.567
MV	11		28		
Disease outcome					
Recovered	61		93		0.027
Deceased	10		38		

NIV noninvasive ventilation, *MVP* invasive ventilation

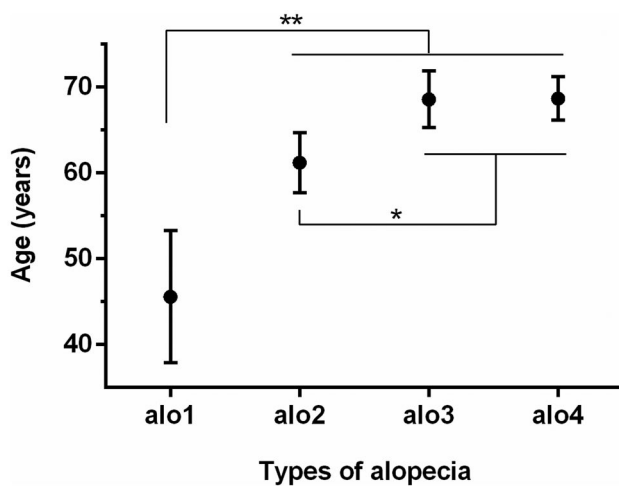*Statistically significant difference at the level of $P < 0.05$

Fig. 3 The distribution of patients with different types of alopecia in relation to their age Legend: *statistically significant difference at the level of $p < 0.05$, **statistically significant difference at the level of $p < 0.001$

There were no statistically significant differences in the distribution of comorbidities among different AGA groups ($p = 0.23$ for HT, $p = 0.8$ for DM). Also, no statistically significant difference in the average length of hospitalisation in relation to HT ($p = 0.25$), DM ($p = 0.44$), or PD ($p = 0.45$) was noticed. A statistically significant difference was found between the outcome and the presence of HT ($\chi^2 = 6.03$, $p = 0.014$): 30% of patients (34/112) with HT died, compared to 15.6% (14/90) of patients without HT. There were no statistically significant differences in outcomes related to DM ($p = 0.14$) nor PD ($p = 0.28$). The distribution of the most frequent comorbidities among different types of alopecia is shown in Table 3.
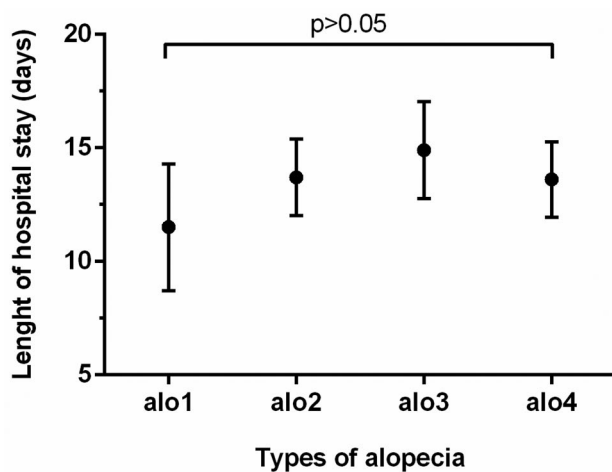

Fig. 2 The distribution of patients with different types of alopecia compared to the number of days of hospitalisation

Table 3 Distribution of most frequent comorbidities among different types of alopecia

Type of alopecia	HT N (%)	DM N (%)
1	3 (26.7)	2 (3.63)
2	33 (29.4)	17 (30.9)
3	29 (25.8)	17 (30.9)
4	47 (41.96)	19 (34.5)
	112 (100%)	55 (100%)

HT arterial hypertension, *DM* diabetes mellitus

Discussion

From the first detected case up to June 2021, more than 154 million people in the world have been infected with the SARS-CoV-2 virus [20], and the results of intense research point to the role of androgens in the pathogenesis and the course of COVID-19.

Androgen activity is conditioned by the existence of the receptors coded by the copy of the gene on the X chromosome, which correlate with different levels of androgen sensitivity depending on the phenotype variants of the gene. Modifications to this gene increase the risk for androgen-related diseases such as androgenetic alopecia and prostate cancer, as well as other diseases that interact with interleukin-6 (IL-6). [25]

Studies from Italy and Germany have shown that lower serum levels of testosterone were significantly associated with elevated levels of the pro-inflammatory cytokines as well chemokines and can be detected in most patients treated in intensive care units, with poorer prognosis and higher mortality [21–23], meaning that circulating androgens may not be crucial for promoting expression of TMPRSS2.

In this observational, cross-sectional study, we were investigating the association between the severity of the COVID-19 disease among male patients and the presence of androgenic alopecia as an indicator of androgen receptor expression and sensitivity because the decrease in scalp hair is one of the most common clinical manifestations of androgen receptor hyperactivation.

Wambier et al. pointed to a higher prevalence of androgenetic alopecia in 175 hospitalised COVID-19 positive patients, both genders, in comparison to the general population of the same age [11]. Cadegiani et al. performed a case–control analysis of 112 female patients in order to measure the incidence of clinical characteristics of COVID-19 in hyperandrogenic women and showed that women without hyperandrogenic manifestations usually had fewer and less severe symptoms of the COVID-19 infection. [13] Subramanian et al. were searching for the link between the incidence of the COVID-19 disease and androgen excess in females that was clinically presented as polycystic ovary

syndrome (PCOS) and found that women with PCOS have a 51% higher risk of COVID-19 compared to women without PCOS [14]. The expression of androgen receptors is far less present in the prepubertal period, which is a possible reason why children with COVID-19 have mild clinical manifestations [24, 25]

Population-based studies show that the usual onset of AGA is at 30 years of age, the prevalence, as well as grade of alopecia, increases with age [26] and that some form of AGA is present in more than 50% of patients over 50 years of age [6]. Age as a risk factor for developing severe clinical manifestations of AGA has been highlighted in a number of studies [27, 28].

Avial et al. conducted a population-based cross-sectional study on Caucasian men 30 to 40 years of age, based on questionnaires and photograph evaluation, and concluded that severe AGA (Norwood type VI or VII) had an overall prevalence of 15.33% [29].

In a series of patients, Goren et al. observed 41 Caucasian males, with an average age of 58 years, admitted to the hospitals with a diagnosis of bilateral SARS-CoV-2 pneumonia and found that 39% of them had severe AGA (Hamilton–Norwood scale 4 to 7) [31].

In our research, the average age of subjects was 65 years, 94.7% of subjects had type 2, 3, or 4 of AGA, and more than 65% of patients type 3 or type 4 (severe AGA), which is in the line with the average age of our patients. There was a statistically significant difference in the patient's age with regard to the type of alopecia meaning that patients with the positive Gabrin sign, i.e. severe AGA were significantly older, in concordance with the literature data.

Our study showed no statistically significant difference in the outcome of treatment between all four types of alopecia, but by looking at the Gabrin sign classification of subjects, we found a statistically significant number of patients with mortality outcomes in the Gabrin positive group.

Comorbidities were evenly distributed within all AGA types in our study, but looking at the whole study population, only HT was significantly more frequently associated with the lethal outcome of COVID-19. Whether this finding is a consequence of HT being present in 55.4% of our patients and more than twice as frequent as other diseases, remains unclear. There still are controversies considering the role of HT itself in COVID-19 severity [30]

Some authors observed that even though cancer patients have an increased risk of SARS-CoV-2 infections compared with non-cancer patients, patients treated for prostate cancer with ADT, such as dutasteride or proxalutamid, have demonstrated a reduced risk of SARS-CoV-2 infection compared to the patients treated for prostate cancer with some other types of therapy. This phenomenon can be explained by the fact that androgens promote androgen receptor transcription, so the patients taking ADT therapy have fewer free receptors

to promote TMPRSS2 transcription and to allow the virus binding to the type II pneumocytes [4, 32–34]. Our study did not confirm this observation, most probably due to a relatively small number of patients with PD.

Some studies found a statistically significant association of early AGA with metabolic syndrome consisting of central obesity, HT, hyperlipoproteinemia, and high-fasting blood sugar [35, 36]. Although we did not evaluate all the constituents of metabolic syndrome, in our study HT and DM were frequently associated with AGA, especially among Gabrin-positive patients, with 68% having HT and 64% DM.

Our findings suggest that the Gabrin sign as an indirect indicator of activity and the expression of androgen receptors, and HT as comorbidity, are related to a poor COVID-19 prognosis. Further research on a larger number of subjects and homogeneous sampling is necessary to rule out interactions of each of the analysed features in our study and bring stronger conclusions.

Declarations

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