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**Conflicts of interest:**

Dr. Cadegiani has nothing to disclose. Ms. Lim has nothing to disclose. Dr. Goren has nothing to disclose. Dr. McCoy has nothing to disclose. Dr. Situm has nothing to disclose. Dr. Kovacevic has nothing to disclose. Dr. Vano Galvan has nothing to disclose. Dr. Sinclair has nothing to disclose. Dr. Tosti has nothing to disclose. Dr. Wambier has nothing to disclose.

**To the Editor:** The mortality rate of COVID-19 has been observed to be higher in males than in females internationally.(1) In humans, the only known promoter of the TMPRSS2 gene is an androgen response element; (2, 3) therefore, androgens could potentially explain the sexual dimorphism observed in COVID-19 disease burden.(4)

Female hyperandrogenism is characterized by elevated androgen levels and is often a result of polycystic ovary syndrome (PCOS). It plays a role in the development of acne, hirsutism, and female pattern hair loss.(5) Thus, we hypothesized that women suffering from hyperandrogenism may face an elevated risk of severe COVID-19 symptoms.

A cross-sectional case-control analysis was conducted to measure incidence of clinical characteristics of COVID-19 in hyperandrogenic women. Subjects presented with symptoms of suspected COVID-19 infection to one of several outpatient clinics and were assigned to one of two groups: non-hyperandrogenic or hyperandrogenic, indicated by diagnosis of PCOS with 2 of 3 Rotterdam criteria satisfied, idiopathic hirsutism with at least 8 points in the Ferriman-Gallwey scale, or androgenetic alopecia confirmed by trichoscopy. Nasal swabs were collected for screening. Propensity scores were calculated to rule-out baseline characteristics, medications and supplements, and lifestyle factors as confounders (**Table 1)**. Of potential confounding variables, only age and BMI≥30 ($kg/m^2$) were significant. Confounding was addressed via matching implemented using a greedy algorithm with Euclidean distance in a 1:1 ratio. The Fisher exact test was used to compare the proportions of clinical symptoms between hyperandrogenic COVID-19 patients and their non-hyperandrogenic counterparts. Statistical significance was set at $p<0.05$.

A total of 233 SARS-CoV-2 positive women were identified. There were 177 subjects in the non-hyperandrogenic group and 56 subjects in the hyperandrogenic group. Following matching, 111 subjects were excluded, leaving 56 matched pairs included in the final analysis. The average age of the subjects was 34.8 ± 9.2 (mean ± standard deviation) years old and 23(20.5%) of the subjects had BMI ≥ 30 $kg/m^2$. Baseline characteristics of the study group are summarized in **Table 1**.

Frequency of symptoms observed is reported in **Table 2**. The most prevalent symptoms in both the hyperandrogenic and non-hyperandrogenic groups were anosmia, ageusia, and headache. Increased incidence of conjunctival hyperemia, upper back pain, hyporexia/anorexia, weakness, fatigue, dry cough, ageusia, anosmia, and low-grade fever, in the hyperandrogenic group were statistically significant ($p<0.05$). Incidence of breast pain, dry eyes, abdominal pain, vomiting, nausea, lower back pain, and arthralgia were indistinguishable between study groups ($p=1.00$) due to low frequency.

A marked gender difference in the SARS-CoV-2 pandemic suggests that men may be more susceptible to developing severe symptoms. Beyond the androgen sensitivity hypothesis, it has been proposed that males may be more affected by *ACE2* variants since they are hemizygous for the gene, and a recent study investigating *ACE2* gene regions found that the homozygous mutation rate of *ACE2* was much higher in males than in females.(6) Behavioral and social factors may also put males at higher risk for severe symptoms.

In this study, we observe that frequency of several common clinical symptoms of COVID-19 are significantly more pronounced in hyperandrogenic females than their non-hyperandrogenic counterparts. Limitations of this study include specificity of the population and relatively small sample size. Additionally, hyperandrogenism is often underdiagnosed, and its symptoms become more difficult to detect with age.(7) Underdiagnosis of hyperandrogenism in menopausal women may have affected our results. Further research surrounding COVID-19 presentation in hyperandrogenic women is warranted. Additional awareness of the cutaneous manifestations of hyperandrogenism in women could increase diagnoses in the dermatology clinic to improve identification of a potentially high-risk population for COVID-19.

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**Table 1. Characteristics of the study population**

| | | Total N=112 | Hyperandrogenic N=56 | Non-Hyperandrogenic N=56 |
|---|---|---|---|---|
| | | N (%) | | |
| Baseline Data | Average Age | 34.8 | 35.4 | 34.3 |
| | BMI >30 kg/m$^2$ | 23(20.5%) | 15(26.8%) | 8(14.3%) |
| | Hypertension | 11(9.8%) | 9(16.1%) | 2(3.6%) |
| | Myocardial Infarction | 0 | 0 | 0 |
| | Stroke | 0 | 0 | 0 |
| | Heart Failure | 0 | 0 | 0 |
| | Lipid Disorder | 20(17.8%) | 13(23.2%) | 7(12.5%) |
| | Diabetes | 6(5.4%) | 6(10.7%) | 0 |
| | Pre-Diabetes | 7(6.3%) | 6(10.7%) | 1(1.8%) |
| | Obesity | 23(20.5%) | 15(26.8%) | 8(14.3%) |
| | Asthma | 5(4.5%) | 3(5.4%) | 2(3.6%) |
| | COPD | 0 | 0 | 0 |
| | Cancer (current, excluding thyroid and prostate) | 0 | 0 | 0 |
| | Cancer (current, excluding thyroid and prostate) | 0 | 0 | 0 |
| | Chronic Renal Disease | 0 | 0 | 0 |
| | Liver Fibrosis/Cirrhosis | 0 | 0 | 0 |
| | Clinical Depression | 4(3.6%) | 2(3.6%) | 2(3.6%) |

| | | | | |
|---|---|---|---|---|
| | Anxiety | 16(14.3%) | 12(21.4%) | 4(7.1%) |
| | ADHD | 8(7.1%) | 6(10.7%) | 2(3.6%) |
| | Insomnia | 5(4.5%) | 4(7.1%) | 1(1.8%) |
| | Hypothyroidism | 26(23.2%) | 12(21.4%) | 14(25.0%) |
| | Autoimmune Disorder | 3 (2.7%) | 1(1.8%) | 2(3.6%) |
| | Menopause | 14(12.5%) | 7(12.5%) | 7(12.5%) |
| | Cancer (current, excluding thyroid and breast) | 0 | 0 | 0 |
| | Cancer (previous, excluding thyroid and breast) | 0 | 0 | 0 |
| | Endometriosis | 20(17.9%) | 11(19.6%) | 9(16.1%) |
| | Breast Cancer | 1(0.9%) | 1(1.8%) | 0 |
| | Other Diseases | 0 | 0 | 0 |
| Anti-Hypertensives | Beta-blockers | 0 | 0 | 0 |
| | ECAi | 1(0.9%) | 1(1.8%) | 0 |
| | Angiotensin II receptor blocker | 12(10.7%) | 10(17.9%) | 2(3.6%) |
| | Loop Diuretics | 1(0.9%) | 0 | 1(1.8%) |
| | Thiazide Diuretics | 2(1.8%) | 2(3.6%) | 0 |
| | Calcium Channel Blockers | 6(5.4%) | 5(8.9%) | 1(1.8%) |
| | K-sparing Diuretics | 1(0.9%) | 1(1.8%) | 0 |
| Lipid Reducing Agents | Statins | 17(15.2%) | 14(25.0%) | 3(5.4%) |
| | Others | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Anti-Coagulants | Aspirin | 0 | 0 | 0 |
| | Clopidogrel | 0 | 0 | 0 |
| | Xa Factor Inhibitors | 0 | 0 | 0 |
| Anti-Diabetics | Metformin | 20(17.9%) | 17(30.4%) | 3(5.4%) |
| | GLP1R Analogue | 7(6.3%) | 7(12.5%) | 0 |
| | SGLT2 Inhibitors | 11(9.8%) | 10(17.9%) | 1(1.8%) |
| | DPP4 Inhibitors | 1(0.9%) | 1(1.8%) | 0 |
| | Sylfonylureas | 0 | 0 | 0 |
| | Glitazone | 0 | 0 | 0 |
| | Acarbose | 1(0.9%) | 0 | 1(1.8%) |
| | Insulin | 0 | 0 | 0 |
| | Orlistat | 9(8.0%) | 9(16.1%) | 0 |
| Hypothyroidism | Levothyroxine | 26(23.2%) | 12(21.4%) | 14(25.0%) |
| | Liothyronine | 2(1.8%) | 0 | 2(3.6%) |
| | Progesterone | 0 | 0 | 0 |
| | Estradiol | 2(1.8%) | 1(1.8%) | 1(1.8%) |
| | Combined Therapy | 10(8.9%) | 5(8.9%) | 5(8.9%) |
| | Oral Contraceptives | 28(25.0%) | 17(30.4%) | 11(19.6%) |
| | Aromatase Inhibitors or SERMs | 1(0.9%) | 1(1.8%) | 0 |
| Central-Acting Drugs | Sedatives | 7(6.3%) | 5(8.9%) | 2(3.6%) |
| | SSRi | 16(14.3%) | 9(16.1%) | 7(12.5%) |
| | Other Antidepressants | 11(9.8%) | 8(14.3%) | 3(5.4%) |

| | | | | |
|---|---|---|---|---|
| | Benzodiazepenes | 0 | 0 | 0 |
| | Atypical Antipsychotics | 4(3.6%) | 2(3.6%) | 2(3.6%) |
| | CNS stimulants | 8(7.1%) | 5(8.9%) | 3(5.4%) |
| Hair | Finasteride | 4(3.6%) | 4(7.1%) | 0 |
| | Oral Minoxidil | 7(6.3%) | 5(8.9%) | 2(3.6%) |
| | Other Drugs | 0 | 0 | 0 |
| Supplements | Omega-3 | 2(1.8%) | 1(1.8%) | 1(1.8%) |
| | Vitamin D | 9(8.0%) | 7(12.5%) | 2(3.6%) |
| | Zinc | 7(6.3%) | 4(7.1%) | 3(5.4%) |
| | Biotin | 12(10.7%) | 6(10.7%) | 6(10.7%) |
| | Vitamin C | 7(6.3%) | 6(10.7%) | 1(1.8%) |
| Vaccines | BCG | 112(100%) | 56(100%) | 56(100%) |
| | Influenza A (in 2020) | 11(9.8%) | 7(12.5%) | 4(7.1%) |
| | Pneumococcal (in 2020) | 11(9.8%) | 7(12.5%) | 4(7.1%) |
| Lifestyle | Current Smoking | 1(0.9%) | 0 | 1(1.8%) |
| | | | | |

**Table 2. Clinical symptoms of the study population**

| Symptoms | Hyperandrogenic (N=56) | Non-Hyperandrogenic (N=56) | p |
|---|---|---|---|
| Fever (>37.8) | 9(16.1%) | 4(7.1%) | 0.237 |
| Low Grade Fever ("Feverish") | 20(35.7%) | 8(14.3%) | 0.015 |
| Shortness of Breath | 3(5.4%) | 1(1.8%) | 0.618 |
| Anosmia | 48(85.7%) | 35(62.5%) | 0.009 |
| Ageusia | 45(80.4%) | 30(53.6%) | 0.005 |
| Dry Cough | 27(48.2%) | 15(26.8%) | 0.031 |
| Sore Throat | 15(26.8%) | 6(10.7%) | 0.051 |
| Dizziness | 13(23.2%) | 7(12.5%) | 0.217 |
| Fatigue | 28(50%) | 13(23.2%) | 0.006 |
| Weakness | 22(39.3%) | 9(16.1%) | 0.011 |
| Myalgia | 24(42.9%) | 20(35.7%) | 0.562 |
| Arthralgia | 4(7.1%) | 5(8.9%) | 1.000 |
| Hyporexia/Anorexia | 25(44.6%) | 7(12.5%) | 0.000 |
| Thoracic Pain | 20(35.7%) | 14(25.0%) | 0.304 |
| Upper Back Pain | 10(17.9%) | 2(3.6%) | 0.029 |
| Lower Back Pain | 3(5.4%) | 4(7.1%) | 1.000 |
| Diarrhea | 18(32.1%) | 11(19.6%) | 0.195 |
| Nauseas | 5(8.9%) | 4(7.1%) | 1.000 |
| Vomiting | 1(1.8%) | 1(1.8%) | 1.000 |
| Abdominal Pain | 6(10.7%) | 5(8.9%) | 1.000 |
| Jaundice | 0 | 0 | -- |
| Conjunctival Hyperemia | 10(17.9%) | 1(1.8%) | 0.008 |
| Pre-Orbital Pain | 8(14.3%) | 3(5.4%) | 0.203 |

| | | | |
|---|---|---|---|
| Dry Eyes | 1(1.8%) | 0 | -- |
| Dry Mouth | 1(1.8%) | 0 | 1.000 |
| Runny Nose | 22(39.3%) | 16(28.6%) | 0.318 |
| Headache | 32(57.1%) | 24(42.9%) | 0.186 |
| Breast Pain | 0 | 1(1.8%) | 1.000 |
| Skin Lesions | 0 | 0 | -- |
| 100% Asymptomatic | 2(3.6%) | 9(16.1%) | 0.053 |