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REVIEW ARTICLE

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Worse progression of COVID-19 in men: Is testosterone a key factor?

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Abstract

Background: The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) disease 2019 (COVID-19) seems to have a worse clinical course among infected men compared with women, thus highlighting concerns about gender predisposition to serious prognosis. Therefore, androgens, particularly testosterone (T), could be suspected as playing a critical role in driving this excess of risk. However, gonadal function in critically ill men is actually unknown, mainly because serum T concentration is not routinely measured in clinical practice, even more in this clinical context.

Objective: To overview on possible mechanisms by which serum T levels could affect the progression of COVID-19 in men.

Methods: Authors searched PubMed/MEDLINE, Web of Science, EMBASE, Cochrane Library, Google, and institutional websites for medical subject headings terms and free text words referred to "SARS-CoV-2," "COVID-19," "testosterone," "male hypogonadism," "gender" "immune system," "obesity," "thrombosis" until May 19th 2020.

Results: T, co-regulating the expression of angiotensin-converting enzyme 2 and transmembrane protease serine 2 in host cells, may facilitate SARS-CoV-2 internalization. Instead, low serum T levels may predispose to endothelial dysfunction, thrombosis and defective immune response, leading to both impaired viral clearance and systemic inflammation. Obesity, one of the leading causes of severe prognosis in infected patients, is strictly associated with functional hypogonadism, and may consistently strengthen the aforementioned alterations, ultimately predisposing to serious respiratory and systemic consequences.

Discussion and conclusion: T in comparison to estrogen may predispose men to a widespread COVID-19 infection. Low serum levels of T, which should be supposed to characterize the hormonal milieu in seriously ill individuals, may predispose men, especially elderly men, to poor prognosis or death. Further studies are needed to confirm these pathophysiological assumptions and to promptly identify adequate therapeutic strategies.

KEYWORDS

COVID-19, gender, male hypogonadism, obesity, testosterone, thrombosis

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel and highly transmissible infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Due to human-to-human transmission, the disease spreads consistently among countries,[3,4] leading the World Health Organization Director-General Tedros Adhanom Ghebreyesus to declare the state of pandemic in March 11th 2020 when 118,000 worldwide confirmed cases were detected in 114 different countries.[5] A wide range of clinical presentations has been reported among patients with COVID-19, mostly with mild to moderate symptoms (80%).[6] However, both severe and critical clinical course may occur especially in elderly patients with underlying cardiometabolic comorbidities, possibly contributing to a high case fatality rate in this cluster of patients.[7] Worldwide, more than 320,000 deaths have been detected among patients tested positive for SARS-CoV-2, of these, more than 90,000 in the United States; 35,000 in the United Kingdom; 32,000 in Italy; 28,000 in France and Spain (https://coronavirus.jhu.edu/map.html). Case fatality rate consistently differs across countries and different hypotheses have been formulated to explain this issue, including strategies for detecting cases and contacts, age, and comorbidity of affected patients, availability of hospital beds especially in intensive care units.[7-9] A clinical risk score to predict the occurrence of critical illness in hospitalized patients at admission has been recently proposed and validated.[10] Despite the calculator tool includes general, anamnestic, clinical, and laboratory parameters normally affecting the prognosis in patients with COVID-19, gender has not been considered among these variables. As matter of fact, men exhibit poor prognosis or die more frequently than women even regardless of age.[11] In fact, epidemiological data reported male sex among deceased patients as high as 73% in China,[12] 59% in South Korea,[13] and 70% in Italy,[7] thus highlighting that worldwide case fatality rates were almost three times higher in men than in women. In most of the cases, deaths are due to pulmonary distress, acute cardiovascular and renal injury, sepsis and multiorgan failure.[14-18] Emerging data suggest that thromboembolic events, such as venous thromboembolism and disseminated intravascular coagulation, are becoming a consistent cause of decease, mostly in critically ill patiens.[19,20] Finally, serious immune dysregulation with consequent systemic inflammation has been recognized in seriously ill COVID-19 patients.[21] Of note, life expectancy in men is currently shorter compared with that described for women and this difference might be attributable to a faster aging of men in comparison to women.[22] Several mechanisms are involved to explain this phenomenon, such as genetic, metabolism, hormonal balance, defense against oxidative stress, and immune system function.[23] Disease awareness and long-term adherence to specific treatments are usually lower in men than women and may also contribute to a different mortality rate between the two genders.[24,25] Despite some changes over time, tobacco exposure remains usually prerogative of male sex and this attitude may influence both the prevalence and outcomes especially for cardiovascular and respiratory diseases in this cluster of patients.[26] Apart from these general considerations which normally explain a slightly greater male susceptibility to aging-related outcomes, specific factors may influence a poor prognosis in COVID-19-infected men. Some hypotheses have been yet formulated for explaining gender difference in fatality rate, particularly emphasizing the role of testosterone (T).[27] Since serum T concentration is not routinely measured in patients with COVID-19, gonadal functional assessment in these men is still unknown. However, it could be speculated that COVID-19 patients with worse clinical course, being usually elderly with one or more underlying chronic diseases, are more likely to have hypogonadism.[28] On the other hand, angiotensin-converting enzyme 2 (ACE_2), which is essential for SARS-CoV-2 entry into host cells, is also expressed in spermatogonia, Leydig, and Sertoli cells.[29,30] Taken together, these results suggest that SARS-CoV-2 may infect testicles, potentially affecting T secretion also in younger patients. Considering that low serum T levels induce detrimental effects on cardiovascular system and predispose to impaired immune response, endothelial dysfunction and systemic inflammation, respectively,[28] herein, we will overview on possible putative mechanisms by which circulating T might affect the prognosis in men with COVID-19 (Table 1).

2 | METHODS

Authors searched PubMed/MEDLINE, Web of Science, EMBASE, Cochrane Library, Google, and Institutional websites for medical subject headings terms and free text words referred to "SARS-CoV-2," "COVID-19," "testosterone," "male hypogonadism," "gender" "immune system," "obesity," "thrombosis" until May 19th 2020. The research focalized upon subgroup of infected patients which exhibited poor prognosis, including hospitalization and intensive care requirement or death. Only articles written in English were considered.

3 | RESULTS

3.1 | Testosterone and viral entry of SARS-CoV-2 into human cells

ACE_2, a carboxypeptidase involved in the cleavage of angiotensin I and angiotensin II, allows SARS-CoV-2 entry into host's cells, thus mediating both the transmissibility and severity of COVID-19 infection among humans.[31] ACE_2 is normally expressed at the level of lung,[32] oral mucosa,[33] intestine,[34] cardiovascular system,[35] brain,[36] pancreatic islets,[37] testicle,[29] kidney,[38] and immune cells.[39] Moreover, it plays an essential role in the regulation of pulmonary homeostasis, while protecting against pulmonary injury.[40] Indeed, low levels of ACE_2 have been described in severe acute and chronic pulmonary diseases.[41] Conversely, chronic diseases, such as hypertension and diabetes, and some medications may increase the level of ACE_2 expression in different tissues.[41,42] This last condition is believed to facilitate the internalization of SARS-CoV-2 into host cells in several systems, thus, contributing to worsen the prognosis in

TABLE 1 Summary of putative mechanisms leading to poor prognosis or death in men and their relationship with circulating levels of serum T (for details and abbreviations see the text)

Conditions predisposing to worse prognosis	Hypothesized mechanisms	Supposed serum T circulating levels
SARS-CoV-2 internalization in host's cells	Increased expression of $TMPRSS_2$	Normal
	Increased expression of ACE_2	Low
Baseline patients' characteristics	Aging	Low
	Cardiovascular diseases	Low
	Pulmonary diseases	Low
	Renal diseases	Normal/low
	Diabetes mellitus	Normal/low
	Obesity	Normal/low
Direct testicle involvement (primary hypogonadism)	SARS-CoV-2 infection	Low (high gonadotropins)
Thrombotic risk	Endothelial dysfunction	Low
	Thromboxane A_2-activated platelets	Normal
	Platelet activation	Low
	Won Willebrand Factor and P-selectin	Normal/low
	Decreased tissue plasminogen activator activity	Low
	Raised plasminogen activator inhibitor-1 activity	Low
Immune system dysfunction	Cytokines storm (IL-6, IL-1beta, TNF-alpha)	Low
	Decline in IL-10 levels and blunted T-reg response	Low
	Impaired B-cells activity	Normal

COVID-19,[41,42] even if this emergent issue remains still debated.[43] In animal model, ACE_2 expression in pulmonary and bronchial epithelium dramatically decreased with aging more in male rats than female.[44] Human ACE_2 locus gene is localized on X chromosome (Xp22), in an area where genes are reported to escape from X-inactivation and this finding may explain a greater expression of ACE_2 in women than men.[45] However, sex differences in ACE_2 expression/activity may be also attributable to hormonal factors, as observed in rat females in which estrogens enhanced the enzyme's expression.[46]

Transmembrane protease serine 2 ($TMPRSS_2$) is a human enzyme encoded by the $TMPRSS_2$ gene whose function is currently unknown in humans but there is evidence that it plays a crucial role in metastasizing prostate cancer.[47] $TMPRSS_2$ was found to be able to cleave hemagglutinin viral antigen, thus, resulting essential for viral infectivity during pandemic A H1N1 influenza and A H7N9 influenza.[48] Unfortunately, $TMPRSS_2$ also cleaves SARS-CoV-2 spike antigen at the level of S1/S2 and S2 sites and is crucial for allowing viral fusion with host cells membrane.[49] $TMPRSS_2$ gene expression is enhanced by androgens, including T and consequently its expression may be greater in men than in women triggering in the former a greater viral entry of SARS-CoV-2 into target host cells compared with the latter.[50] Given these findings, it should be hypothesized that the physiological difference in circulating androgen levels between genders could predispose men to a more extensive pulmonary or systemic exposure to SARS-CoV-2 once the infection has occurred. On the other hand, a lower ACE_2 tissue expression in men may predispose them to a wider lung and systemic damage in course of COVID-19 infection compared with women. In addition, lower levels of serum T, often observed in elderly patients and associated with chronic diseases, may concur to generate a poor baseline health status, particularly at the level of cardiovascular system, thus facilitating a worse clinical course of the infection in this cluster of patients.[51]

3.2 | Testosterone and cardiovascular system in COVID-19

Cardiovascular involvement in COVID-19 is typically observed in elderly patients and in those affected by chronic diseases, such as arterial hypertension, diabetes mellitus, established cardiovascular disease, chronic obstructive pulmonary disease, and active neoplasm, and in those with high levels of systemic inflammation.[18] Acute myocardial injury has been observed in several infected patients, particularly in those requiring intensive care due to a serious

clinical course.[52] Other patterns of myocardial damage are currently known to potentially affect the prognosis in infected patients, even including acute coronary events, left ventricle dysfunction, and cardiac arrhythmias.[53] The supposed mechanisms explaining these findings are likely attributable to a direct myocardial involvement, detrimental effects of systemic inflammation, raised myocardial demand-to-supply ratio, pro-thrombotic imbalance, and electrolytes disorders (mainly hypokalemia due to renin-angiotensin-aldosterone system interference by SARS-CoV-2), respectively.[53] Endothelium is essential to maintain cardiovascular homeostasis, considering that it secretes a wide range of substances normally involved in the regulation of vascular tone, cellular adhesion and antithrombosis, vessel's wall inflammation and smooth muscle cell proliferation.[54] Loss of physiological balance among these substances consequently leads to endothelial inflammation, predisposes to thrombosis and atherosclerosis, while facilitating the development of cardiovascular diseases (CVD).[55] Endothelial dysfunction has been particularly observed in elderly, smokers and in patients with arterial hypertension, dyslipidemia, and diabetes mellitus contributing to the onset and progression of CVD.[56] SARS-CoV-2 is able to infect endothelial cells, because of a marked ACE_2 expression also at this level. Endothelial inflammation and dysfunction and apoptosis are usually described in infected patients, thus, characterizing both macro- and microvascular damage in COVID-19.[57] Both the incidence and prevalence of CVD are more frequently reported in men than women, leading to concerns about possible detrimental cardiovascular effects of T.[58,59] In fact, CVD remain the main causes of mortality in men, even if low rather than normal or elevated levels of serum T are frequently observed in patients with underlying CVD.[60-64]

Elderly men, who often display hypogonadism, are more prone to the progression of atherosclerosis.[65] Indeed, normal levels of T are necessary for maintaining an optimal lipid metabolism and glucose control, as well as for reducing blood pressure, left ventricle mass, waist circumference, and circulating concentration of inflammatory cytokines.[65-68] In addition, T is a rapid-onset coronary vasodilator due to its ability to block calcium channel and promotes potassium channel opening.[69] Furthermore, T may improve systolic output and contribute to the amelioration of cardiorespiratory fitness with physical exercise.[69] Low levels of both total and free T are responsible for a relevant raise in all-cause mortality mostly due to cardiovascular events,[70-72] especially in elderly patients.[73] Considering these data, men with baseline low circulating levels of serum T are expected to have poor cardiovascular health status, which may contribute to increase cardiovascular risk also in COVID-19.

3.3 | Testosterone and thromboembolic risk in COVID-19

A severe alveolar epithelial and endothelial damage in seriously ill COIVD-19 patients has been reported. As a result, tissue factor and plasminogen activator inhibitor-1 accumulate in lung, leading to both fibrin deposition and hypofibrinolytic state, thus predisposing to thrombosis.[74] Some of the cases of severe COVID-19 may be complicated by disseminated intravascular coagulation, which is a pro-thrombotic condition, predisposing to a high risk of venous, and arterial thromboembolism.[75,76] Patients with poor prognosis usually display higher levels of fibrinogen and D-dimers, longer prothrombin and partial activated thrombin time, and are more prone to develop thrombocytopenia and disseminated intravascular coagulation.[77] Thrombocytopenia is frequently observed in infected patients and should be considered as a clinical biomarker of poor prognosis.[78] To avoid harmful clinical outcomes, recent recommendations advice to administer thromboprophylaxis or full therapeutic intensity anticoagulation, if such an indication is needed in COVID-19 inpatients.[75]

Endothelial dysfunction, which is described in seriously ill patients, promotes the release of pro-thrombotic factors, including von Willebrand factor and P-selectin and could predispose to thrombosis and thromboembolism in this clinical setting.[79] Additionally, systemic inflammation may occur particularly in predisposed patients leading to a progressive "thromboinflammatory" syndrome with consequent disseminated microvasculature involvement, multiorgan failure, or death.[80] So far, the published cases of inpatients with COVID-19 complicated by intravascular thrombosis have shown a higher frequency in men, especially among non-survivor patients.[19,20] Despite these thrombotic events may be elicited by an exaggerated host immune response, a wide range of other predisposing factor may be involved, such as a prolonged immobilization due to hospitalization, endothelial dysfunction, and cardiometabolic risk factors.[77] In this clinical scenario, sexual hormones may also play a role in the regulation of hemostasis and thrombosis homeostasis. Indeed, T has been shown to increase the expression of thromboxane A_2 receptors at the level of platelets, thus, enhancing platelet activation and aggregation in humans.[81] On the other hand, serum T levels were found to be negatively associated with platelet activation and reactivity as suggested by the results of a recently published ex vivo study.[82] T enhances both the synthesis and secretion of endothelial nitric oxide,[83] which is a potent inhibitor of platelet activation.[84] In addition, megakaryocytes and platelets contain both estrogen and androgen receptors, consequently their activities are also directly influenced by sexual hormones.[85] This finding may explain gender differences in platelet activation and thrombotic diseases. In women, platelet function is enhanced by estrogen, thus fluctuating according to the ovarian cycle, and being more efficient in premenopausal than climacteric state as for protecting against an excessive bleeding during menstrual phase.[86,87] Thus, it could be speculated that T may protect men in comparison to women against and excessive platelet activation, but when a status of hypogonadism occurs, such as in elderly and comorbid patients, this effect declines. Exactly, hypogonadal men exhibit higher value of the mean platelet volume which is a biomarker of platelet activation, and is an independent risk factor for CVD.[88] Glueck et al found that serum T concentrations positively correlated with tissue plasminogen activator activity and were inversely associated with plasminogen activator inhibitor-1 activity and fibrinogen,[89] thus suggesting a direct anti-thrombotic role of this androgen on coagulation and fibrinolysis.[90] T is critically involved in

maintaining platelet and coagulative homeostasis. Therefore, hypogonadism may contribute to increase the risk of new onset thrombotic events in COVID-19 and this concern should be taking into account especially in elderly and comorbid men.

3.4 | Testosterone and immune system dysfunction in COVID-19

Both innate and adaptive systems are essential for promptly contrasting virus replication, facilitating virus clearance, stimulating tissue repair, and developing persistent defense.[91] Seriously ill COVID-19 patients exhibit an exaggerate neutrophil and alveolar macrophage response and a marked peripheral lymphocyte dysfunction.[92,93] Both number and function of B and T cell are impaired,[94,95] and a hypercoagulability state has also been observed. The greater the magnitude of these hematological and biochemical alterations, then, the greater the severity of the prognosis.[77,96] SARS-CoV-2 may infect T cells through receptor-dependent, spike protein-mediated membrane fusion but it is still unclear whether the virus replicates in lymphocytes and the infection leads to apoptosis of T cells.[97] However, $CD8^+$ T cells, B cells, and Natural Killer cells are remarkably reduced in SARS-CoV-2-infected patients.[98] Specifically, $CD8^+$ T cells tend to be an independent predictor for COVID-19 severity and treatment efficacy.[98] Immunological dysfunction may not allow an easy control of viral infection, thus, fostering viral dissemination with a consequent systemic spread of the disease.[92] In addition, a secondary hemophagocytic lympho-histiocytosis with hyperinflammatory syndrome, characterized by a fulminant and lethal hypercytokinemia and multiorgan failure, has been recognized as a harmful prognostic factor.[99] Several and specific interleukins (ILs), including IL-2, IL-6, and tumor necrosis factor (TNF)–alpha, and chemokines are markedly up-regulated in patients displaying a serious pulmonary involvement or requiring intensive care with a poor long-term prognosis.[100,101] Despite the fact that the so-called "immunocompetence handicap hypothesis" in men still remains debated,[102] differences in circulating sexual hormones levels may condition a gender-related response to infections.[103] In fact, T exhibits modulating effects on the immune system that may potentially predispose men to different clinical course and prognosis in case of infectious diseases.[104] According to Foo et al, T exerts immunosuppressive effects.[104] In animal models, T suppresses the production of IL-6, IL-1beta, and TNF-alpha, and enhances the production of IL-10.[105] Moreover, T suppresses T-helper (h) 17 cells and enhances regulatory T cells (T-reg) differentiation, thus attenuating inflammatory immune response.[106] T facilitates both the production and secretion of higher T-h 1 to T-h 2 cytokine ratio by stimulated T cells and reduces B-cell proliferation and humoral response.[107] On the other hand, T insufficiency may exactly revert these immunological features, consequently predisposing to systemic inflammation with possible concerns for elderly and comorbid patients.[108] Women compared with men generate a more robust antibody response against viral (influenza) vaccine.[109] T in comparison to estradiol seems to reduce both eosinophil and neutrophil recruitment, also impairing T-h 2 $CD4^+$ activation and IgE production.[110] Dendritic cell presentation is enhanced in women and this phenomenon should be attributable to genetic (X-linked) and hormonal (estrogens) mechanisms which are able to stimulate more Toll-like receptor-7 and -9 expression and interferon-alpha secretion.[111,112] Due to these findings, men exhibit a baseline immunologic condition, which could predispose them to poor prognosis in COVID-19. To date, neither vaccine nor specific treatment received approval for COVID-19, whereas promising results have been obtained in critically ill patients treated with convalescent plasma.[113] Since the growing evidences from bedside led to positive results, several clinical trials have been started and are currently ongoing to methodologically test both the safety and effectiveness of convalescent and hyperimmune plasma in this clinical setting.[114-116] These therapeutic aspects emphasized the concept that a blunted antibody response (particularly IgG) may precipitate a severe clinical course in COVID-19 patients. In a recently published observational study, 331 inpatients tested positive for SARS-CoV-2 infection were enrolled (127 men and 204 women) displaying that men were more prone to develop poor prognosis compared to women, also recovering less frequently from the infection (55.6% vs. 63%).[117] Interestingly, authors found some significant differences in humoral response between genders. Particularly in seriously ill patients' subgroup, a delayed peak of antibody response with a lower generation of effective IgG was found in men compared to women, thus confirming that a blunted antibody response in men was associated with worse prognosis.[117] These findings are actually attributable to sexual hormones influence on B-cells proliferation, survival, and activity which are enhanced by estrogen and impaired by T, respectively.[118] Indeed, estrogen alfa- and beta-receptors are both expressed on B-cell membrane, where estrogens upregulate the expression of several genes involved in B-cells activation and survival, such as CD22, SHP-1, and Bcl-2.[119] Contrariwise, T exerts opposite effect on B cells, thus impairing immunoglobulin generation and antibody response such as in case of viral infection.[120,121] In addition, the lysophosphatidylserine receptor (GPR174), codified by the homonymous X-linked gene, is widely expressed on lymphocyte cell membranes, including T-reg and B cells, and its activity seems to be enhanced in women and reduced in men.[122] Specifically, GPR174 is known to regulate macrophage polarization and proinflammatory cytokine secretion, predisposing to a marked immune response normally observed in Gram-negative induced septic shock.[123] Indeed, GPR174-deficient mice were more resistant to the development of septic shock, and were more prone to control cytokine storm particularly due to IL-6 and TNF-alpha.[123] In addition, GPR174 has been recognized to modulates B-cell migration in response to the chemokine CCL21 in mice.[124] B-cell migration in response to CCL21 is more effective in female than male B cells, and is furtherly impaired in absence of T. Thus, these data confirmed that T may negatively influence the baseline antibody

response in male and T deficiency may accentuate the gender dimorphism in B cells efficiency.[124] Very interestingly, gonadotropins may play a role in immune system regulation. Luteinizing hormone-releasing hormone (LHRH) is secreted by hypothalamus (but also mammary gland, gonadal, placenta, spleen, thymus), and normally regulates pulses of pituitary gonadotropins release finally controlling gonadal steroidogenesis and gametogenesis.[125] However, LHRH receptors have been found on lymphocytes membrane and are involved in normal thymocyte maturation. High circulating levels of LHRH, as observed in neonatally castrated animals, lead to a relevant increase in $CD4^+$ T cells.[126] On the other hand, a LHRH antagonist-induced tertiary hypogonadism seemed to significantly reduce both the number and activity of circulating B cells and $CD8^+$ T cells thus blunting humoral immune response against circulating antigens.[127] Placental gonadotropins are also involved in immune response regulation, and should be considered a relevant determinant in immunotolerance during pregnancy.[128] Particularly, human chorionic gonadotropin (hCG) demonstrated to attract and activate T-reg at the level of trophoblast in early stages of pregnancy, therefore orchestrating a phenomenon which is thought to be essential for immune tolerance toward embryo.[129] Moreover, hCG positively regulates the generation of IL-10 secreting B cells,[130] which normally regulate immune tolerance during infectious diseases.[131] In addition, alpha-fetoprotein demonstrated to drive B cells to apoptosis, acting as another defensive mechanism against an exaggerate humoral response.[130] Luteinizing hormone in mice and hCG in humans seem to enhance T-reg activity, and impair $CD4^+$ T-cell differentiation in sense of T-h 1.[132] Given these considerations, it should be noted that gonadotropins may play a role in modulating immune response, also beyond the effect of sexual steroids. Since male hypogonadism may affect the prognosis in COVID-19 infected patients, it should not be excluded that a different etiology of this clinical condition may differentiate the prognosis, too. Nevertheless, no studies assessing the gonadal status of affected men have been currently carried out; hence, this issue remains unclear. Interestingly, Iglesias et al analyzed the prevalence of hypogonadism among 150 geriatric inpatients (aged ≥ 65 years) hospitalized for acute illness, considering serum T levels < 200 ng/dL as a cutoff point.[133] Hypogonadism was found in 80 (53%) patients; of these, 43.7% were hypergonadotropic, 40% were normogonadotropic, and 15% were hypogonadotropic.[133] The leading causes of hospitalization among hypogonadal men were congestive heart failure and respiratory tract infection, and 12 out of 13 patients who died during hospitalization had hypogonadism.[133] Similar results were observed also in a cohort of male hemodialysis patients, with a median levels of serum T of 11.7 nmol/L, in whom hypogonadism was found to be associated with a higher risk of hospitalization for infective diseases (HR 2.12) and all-cause mortality (HR 2.26) regardless of gonadotropins levels.[134] Men with human immunodeficiency virus usually display a wide range of endocrine imbalances, including hypogonadism which furtherly aggravate health status in these individuals.[135] Despite the leading cause of hypogonadism is actually attributable to a primary (hypergonadotropic) hypogonadism, some of them displayed a hypothalamic or tertiary form.[136] Even in this case, the role of serum T and gonadotropins on infective risk burden is not well understood.

Aging is related with immune senescence and should also be considered as a risk factor for poor prognosis in case of infectious diseases.[137] Moreover, age-related comorbidities significantly contribute to impair immune system efficiency.[138] From a pathophysiological point of view, age-related mitochondrial dysfunction is responsible for a low energy production that impairs $CD8^+$ T-cell activation and proliferation.[139] Of note, these cells are essentially involved in cell-mediated immune responses which assume a critical role against viral infections and may expose elderly patients to poor prognosis in this clinical condition.[139] Aging also affects innate immune response, as suggested by a decline in the efficiency of dendritic cells, macrophages, and neutrophils.[140-142] In conclusion, immune response against viral infections may be impaired by aging, particularly in men and a consequent weak immune response should be double-sided in SARS-CoV-2 infection. In fact, normal levels of serum T generally predispose men to a dampened immune response,[143] leading to systemic viral spreading with potentially harmful clinical consequences on one side, but protecting them against cytokine dysregulation (the so-called cytokine storm) on the other side. Differently, male hypogonadism could furtherly impair immune response against viral infection but it is thought to favor rather than contrast harmful cytokine dysregulation in course of COVID-19.

3.5 | Focus on male obesity

Obesity is a common underlying comorbidity in COVID-19 inpatients, and its prevalence has been reported as high as 42% in this cluster of patients.[144] Despite first reports did not mention the overweight/obesity syndrome as an important risk factor for respiratory complications and poor prognosis in patients with COVID-19,[15,17,145] further findings confirmed that those individuals with elevated body mass index are more likely to require intensive care and are at greater risk of death.[146-149] Particularly, body mass index > 35 kg/m^2 has been usually observed in patients requiring invasive mechanical ventilation[150] and should be considered as a risk factor for admission to acute (OR 1.8) and critical (OR 3.6) care also in younger patients (aged < 60 years).[151] Pathophysiological mechanisms possibly related with poor prognosis in this cluster of patients are not completely understood but may be attributable to a greater inflammatory background, as similarly observed in insulin-resistant and diabetic patients.[152] However, considering that ACE_2 is also expressed on adipose cells, a larger extension of adipose tissue in obese patients may reliably increase the number of available receptors leading to a much greater systemic response to SARS-CoV-2.[153] Obese patients are also at greater risk of vitamin D deficiency/insufficiency and sedentary lifestyle, which are considered as predisposing factors for worse prognosis in response to acute and chronic diseases, including COVID-19.[154] Abdominal obesity usually leads to a low cardiorespiratory reserve

and systemic inflammatory dysfunction which predispose to a worse prognosis in COVID-19.[155] Moreover, obesity is typically associated with a decreased pulmonary ventilation or obstructive sleep apnea which both predispose to a baseline low levels of blood oxygenation and consequently to worse clinical course in case of acute infectious respiratory diseases.[156] Visceral obesity is also a risk factor for both the development and progression of congestive heart failure especially in elderly patients.[157] Since abdominal obesity is more frequently observed in men in comparison to women due to hormonal background,[158] it could be expected that "belly fat" predisposes men to poor prognosis in COVID-19. To support this hypothesis, it should be considered that visceral obesity per se fosters higher level of prothrombotic circulating factors, thus, predisposing to thrombosis.[159] Moreover, obesity and male hypogonadism are both associated with one other.[160] The so-called "male obesity-related secondary hypogonadism" is frequently found in obese men and is characterized by a complex and multifactorial pathogenesis,[161] which includes adipose tissue dysfunction, T-to-estrogen shunt, impaired release of hypothalamic gonadotropin-releasing hormone, insulin resistance and obstructive sleep apnea.[162] Of note, adipose tissue dysfunction and male hypogonadism, even if subclinical, are associated with higher circulating levels of cytokine (IL-6, IL-1, and TNF-alpha), endothelial dysfunction,[163] and amplified thrombosis risk, possibly prompting to detrimental clinical consequences in case of SARS-CoV-2 infection.[108] High levels of prostaglandin E_2 have been found in visceral adipose tissue collected from obese men, contributing to both detrimental (inflammation and fibrosis) and adaptive mechanism of compensation (adaptive thermogenesis and lipolysis).[164] Of these, prostaglandin E_2 induces the expression of aromatase gene,[165] and T-to-estrogen shunt usually observed in obese men adipose tissue is attributable to this phenomenon.[166] In male mice visceral adipose tissue, an increased aromatase activity locally raises estrogen levels which seem to reduce local inflammation, ameliorate insulin sensitivity hence contrasting the development of systemic diseases.[166] Body mass index positively correlates with circulating levels of estrogen and negatively correlate with circulating T also in humans.[167] Aromatase gene expression is enhanced in men adipose tissue, and is positively related with body weight and levels of systemic inflammation, therefore confirming same results observed in animal models.[168] However, aromatase has been detected in a wide range of other tissues, and its expression is differently modulated in each of these districts. Consequently, the magnitude of an enhanced aromatase activity at the level of adipose tissue (as observed in visceral obesity) on the systemic T-to-estrogen shunt remains questionable. Nonetheless, despite same controversial, low T-to-estrogen ratio seems to increase cardiovascular risk, as observed in elderly and in patients with underlying CVD.[169,170] In an observational study, elderly men with high levels of circulating estrogen (top quintile: >34 pg/mL) compared to those with low levels of circulating estrogen (lower quintile: <14 pg/mL) displayed a twofold risk of stroke (relative hazard 2.2, $P < .0001$).[171] Indeed, high levels of estrogen irrespective to serum T concentration are believed to prime a thrombophilia state in men leading to thrombosis, particularly in predisposed patients.[172,173] In conclusion, male obesity should be considered a relevant risk factor for poor prognosis in COVID-19. It may affect baseline respiratory function, thus increasing the risk of mechanical ventilation requirement once the infection occurred; increase the number of baseline comorbidities, consequently predisposing to poor prognosis or death as certificated by epidemiological studies; fosters hormonal imbalance (decline in circulating serum T and increase in serum estrogen concentration) which are involved in the fine regulation of immune system and coagulative homeostasis in case of infection, and predispose men to poor effective immune response, cytokine dysregulation; endothelial dysfunction and thrombosis.

4 | PERSPECTIVE HYPOTHESIS AND CONCLUSIONS

Gender difference in prognosis and fatality rate is a relevant clinical issue in COVID-19 pandemic. Further investigations are needed to analyze this biological phenomenon for providing appropriate diagnostic and therapeutic tools. A different biological and clinical background, which generally predisposes men to a lower life expectancy than women, could potentially condition these clinical outcomes in case of SARS-CoV-2 infection, especially among elderly. Despite gender difference in adverse events and life-threatening outcomes was long believed to be paradigmatically ascribable to a higher serum T concentration in men than in women, normal levels of serum T are essential for sustaining men's health. Contrariwise, low levels of serum T, which may be associated with aging and obesity and other chronic diseases, lead to systemic inflammation, endothelial dysfunction and increased platelet activity, predisposing to thrombosis and thromboembolism and promoting atherosclerosis and CVD. In men with obstructive sleep apnea syndrome or in those affected by chronic obstructive pulmonary disease or other background pulmonary disease, a higher prevalence of hypogonadism has been found.[174] In these clinical settings, men with lower level of T are more prone to develop pulmonary and systemic inflammation and worse respiratory and general parameters. Moreover, T predisposes men to less effective immune response against infectious agents and male hypogonadism may trigger a detrimental cytokine dysfunction, including high circulating levels of IL-6, TNF-alpha, and IL-1beta, responsible for poor prognosis in COVID-19.[101] Additionally, androgens enhance $TMPRSS_2$ expression, thus, leading to a baseline predisposition to a wider SARS-CoV-2 spread into man body than that occurring in women. This mechanism could explain a greater male susceptibility to a more serious clinical course in COVID-19. Of note, SARS-CoV-2 could infect testicle, potentially affecting T secretion also in young men and directly inducing (primary hypogonadism) or aggravating a preexistent condition of hypogonadism in already predisposed men. The magnitude of this phenomenon as well as the importance of gonadotropins' levels, which varies among the different forms of hypogonadisms in affected patients (primary versus secondary or tertiary hypogonadism or mixed

forms), remains still debated and the potential implications on the prognosis in the course of SARS-CoV-2 infection require further investigation for both diagnostic and therapeutic purposes.

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

VAG conceived the review. All researchers performed database search, drafted the manuscript, read, provided feedback, and approved the final manuscript.

ETHICS APPROVAL

The present review was conducted in accordance with the principles of the Declaration of Helsinki. Discussed data extracted from published papers.

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