



# Serum testosterone mirrors inflammation parameters in females hospitalized with COVID-19

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## Abstract

**Background** While low testosterone (T) was described as a predictor of unfavorable coronavirus-disease 19 (COVID-19) outcome in men, data concerning the role of T in women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are scant and limited to small cohorts. This study investigated the relationship between serum T values and outcomes of COVID-19 in a large female hospitalized cohort.

**Methods** One-hundred-sixty-eight adult women (median age 77, range 18–100 years; 154 in post-menopause) hospitalized for COVID-19 were assessed for PaO<sub>2</sub>/Fio<sub>2</sub> ratio, serum T and inflammatory parameters.

**Results** Median duration for hospital stay was 14.2 days (range 1–115) with overall mortality of 26% ( $n=44$ ). Subjects who died were significantly older ( $p<0.001$ ), had significantly more comorbidities ( $p=0.015$ ) and higher serum T ( $p=0.040$ ), white blood cells ( $p=0.007$ ), c-reactive protein (CRP;  $p<0.001$ ), interleukin-6 (IL-6;  $p<0.001$ ), procalcitonin (PCT;  $p<0.001$ ), lactate dehydrogenase (LDH;  $p=0.001$ ), D-dimer ( $p=0.035$ ), fibrinogen ( $p=0.038$ ) and lower serum free-triiodothyronine (FT<sub>3</sub>;  $p<0.001$ ) and luteinizing hormone (LH;  $p=0.024$ ) values. In post-menopausal women, significant associations were observed between T levels and serum CRP ( $\rho: 0.23$ ;  $p=0.002$ ), IL-6 ( $\rho: 0.41$ ;  $p<0.001$ ), LDH ( $\rho: 0.34$ ;  $p<0.001$ ), D-Dimer ( $\rho: 0.21$ ;  $p=0.008$ ), PCT ( $\rho: 0.26$ ;  $p=0.001$ ) and HDL cholesterol ( $\rho: -0.22$ ,  $p=0.008$ ). In multivariate regression analyses, serum T maintained the significant association with mortality after correction for age, coexistent comorbidities and serum LH and FT<sub>3</sub>, whereas it was lost after correction for inflammatory parameters.

**Conclusion** In females, high serum T levels might be a mirror of inflammatory phenotype and worse COVID-19 course.

**Keywords** Testosterone · COVID-19 · Female · Androgens · Inflammation

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused a devastating pandemic with more than 6 million deaths worldwide (<https://covid19.who.int>). The rapid emergence of SARS-Cov-2 variants has

raised concerns because of their higher transmissibility and their possible escape from vaccines and natural immunity resulting in new waves and growing reinfections [1]. Thus, the control of SARS-Cov-2 progression and death is still a major challenge.

The clinical heterogeneity of coronavirus-disease 19 (COVID-19) infection, ranging from entirely asymptomatic infection to the acute respiratory insufficiency (ARI) and death, is widely demonstrated [2, 3]. However, with the advent of vaccines and new variants, symptoms and clinical course of SARS-Cov-2 infection also become changeable with an even more variability in clinical manifestation [4]. Since new infection waves are highly expected, the identification of pathogenic mechanisms underlying the clinical heterogeneity is crucial to allow a better risk stratification. Several studies have revealed age, gender and pre-existing comorbidities, mainly chronic metabolic disease (diabetes,

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obesity, hypertension, cardiovascular, cerebrovascular and kidney disease), as major risk factors for the occurrence of acute respiratory distress syndrome (ARDS) and fatal outcome [5]. Epidemiological data on hospitalized COVID-19 patients highlighted a gender disparity with higher incidence, severity and mortality rate in males than in females [6]. However, the possible determinants of the gender issue of the COVID-19 pandemic are still argue of intense scientific debate. Previous data published by our group and other authors demonstrated the role of low circulating T levels as a marker of higher risk of severe outcomes among COVID-19 male patients [7–9], corroborating in SARS-Cov-2 infection the modulatory action of testosterone.

Conversely, data on the possible role of T in women with SARS-Cov-2 infection are scant and limited to small cohorts [10]. In this study, we aimed at evaluating the association between serum T values and inflammation markers in a large cohort of COVID-19 female subjects.

## Methods

This is a monocentric study of 168 consecutive female patients hospitalized for COVID-19 at the IRCCS Humanitas Research Hospital, Rozzano-Milan, Italy between November 1, 2020 and March 31, 2021. The inclusion criteria were: (1) laboratory pharyngeal-nose swab positivity of SARS-Cov-2 assessed by real-time reverse-transcriptase–polymerase-chain-reaction; (2) female sex; (3) older than 18 years; (4) completed hospital course at study end (discharged or dead). The first endpoint of the study was the association between serum T levels and inflammatory parameters at study entry. Secondary endpoint was to explore the associations between serum T levels and in-hospital mortality.

At study entry, before starting any treatment for COVID-19, enrolled patients were evaluated for arterial partial pressure oxygen (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio, measured by arterial blood gas analysis. ARI was defined as PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 300 mmHg on oxygen [11].

In 146 patients was also assessed the Body mass index (BMI), defined by the individual's weight in kilograms divided by the square of their height in meters. On the first morning after the admission blood samples were drawn for the determination of serum T (nmol/L), luteinizing hormone (LH, U/L), total white blood cells (WBC, n\*10<sup>3</sup>/ml), interleukin-6 (IL-6, pg/mL), C-reactive protein (CRP, mg/dL), procalcitonin (PCT, mg/dL), D-Dimer (ng/mL), fibrinogen (mg/dL), glycemia (mg/dL), 25-hydroxyvitamin D (25OHD, ng/mL), thyroid-stimulating hormone (TSH,  $\mu$ UI/mL), free-triiodothyronine (fT<sub>3</sub>, pmol/L), free-thyroxine (fT<sub>4</sub>, pmol/L), total cholesterol (TC, mg/dL), HDL cholesterol (HDL, mg/dL) and triglycerides (TG, mg/dL). Calculated low-density lipoprotein (cLDL, mg/dL) was obtained

using TC, TG and HDL according with Friedewald's formula [12]. Testosterone was measured using Access Testosterone assay (Beckman Coulter Inc, Fullerton, CA), a competitive immunoassay method that has analytical and clinical acceptable correlation with mass-spectrometry method [13]. Other parameters were measured using standardized methods routinely used for hospital clinical practice.

From the medical records we have also collected data about the following clinical conditions: hypertension, coronary artery diseases (CAD), past or active cancer, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) associated with stages 3–5 renal insufficiency as defined by estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m<sup>2</sup> (calculated by CKD-EPI).

The study was approved by the Ethics Committee of IRCCS Humanitas Research Hospital and the patients gave their consent to use the clinical and biochemical data for research purposes.

## Statistical analysis

Data were presented as median and absolute range, unless otherwise stated. Since most of variables were non-normally distributed as assessed by Kolmogorov–Smirnov test, non-parametric tests were used. The comparisons were performed by Mann–Whitney test. Spearman's correlation coefficient ( $\rho$ ) was calculated to determine association between continuous variables. Strength of  $r$  correlation was defined according to Evan's classification [14]. Multivariate logistic regression model was performed and the odds ratio (OR) with 95% confidence interval (95% C.I.) were calculated to evaluate determinants of mortality. All risk factors with a  $p$  value under 0.10 in univariate analyses were submitted to multivariable logistic regression analyses taking into account the minimal guidance criterion of ten events per variable [15].  $P$  value < 0.05 was considered as significant. Statistical analysis was performed using SPSS version 25.0.

## Results

The study included 168 unselected adult women (median age 77; range 18–100 years; median BMI 26.3; range 15.6–48.6; 154 in post-menopause). Median duration for hospital stay was 14.2 days (range 1–115). Baseline characteristics of study population are summarized in Table 1. At time of hospitalization, ARI was diagnosed in 102 subjects (60%). During hospital stay, 44 subjects (26.0%) died. Subjects who died were significantly older ( $p < 0.001$ ) and had significantly more comorbidities ( $p = 0.015$ ) and higher serum T levels ( $p = 0.040$ ), WBC ( $p = 0.007$ ), CRP ( $p < 0.001$ ), IL-6 ( $p < 0.001$ ), PCT ( $p < 0.001$ ), LDH ( $p = 0.001$ ), D-dimer ( $p = 0.035$ ), fibrinogen ( $p = 0.038$ ) and lower serum FT<sub>3</sub>

**Table 1** Demographical and clinical features of 168 females with COVID-19 who were stratified according to the disease outcome

	Study population (n = 168)	Survival (n = 124)	Non-survival (n = 44)	p-value
Age (years)	77 (18–100)	74.5 (18–97)	83.5 (50–100)	<0.001
Menopause (%)	154 (91.7)	111 (89.5)	43 (97.7)	0.117
BMI (kg/m <sup>2</sup> )*	26.34 (15.6–48.6)	25.7 (15.6–46.6)	27.9 (16.6–48.6)	0.092
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHG)	280.9 (63–452)	295 (63–452)	229 (63–414)	<0.001
T (nmol/L)	1.11 (0.1–8.0)	1.02 (0.1–8.0)	1.30 (0.1–4)	0.040
LH (U/L)	15.6 (0.2–111.7)	19.0 (0.2–66.9)	5.95 (0.2–111.7)	0.024
TSH (uIU/mL)	0.915 (0.1–27.3)	0.9 (0.1–27.3)	0.9 (0.1–13.7)	0.400
ft3 (pmol/L)	3.45 (1.7–6.2)	3.6 (1.9–6.2)	2.9 (1.7–5.0)	<0.001
ft4 (pmol/L)	14.1 (5.1–24.1)	13.8 (5.1–17.0)	14.2 (7.9–24.1)	0.354
25-OH-D (ng/mL)	14.5 (1.0–105)	15.8 (2.0–68)	13.0 (1.0–105)	0.250
WBC (× 10 <sup>-3</sup> /mL)	7.025 (1.00–21.14)	6.66 (1.00–15.7)	9.03 (3.08–21.14)	0.007
CRP (mg/dL)	5.54 (0.1–30.8)	4.9 (0.1–22.5)	10.9 (0.2–30.8)	<0.001
Ferritin (mg/dL)	308.9 (15.7–4716)	308.9 (15.7–4716)	320.5 (26.2–3256.0)	0.691
IL-6 (pg/mL)	32.5 (0.9–3015)	25.5 (0.9–3015)	61.5 (4–362)	<0.001
PCT (mg/dL)	0.1 (0.1–19.1)	0.1 (0.1–14.5)	0.3 (0.1–19.1)	<0.001
LDH (U/L)	276 (103–963)	262.5 (103–963)	344 (195–839)	0.001
D-dimer (ng/mL)	384.5 (200–30,816)	364 (200–30,816)	618 (200–17,364)	0.035
Fibrinogen (mg/dL)	494 (210–976)	460.5 (210–955)	535 (241–976)	0.038
FBG (mg/dL)	114 (39–384)	111.5 (39–328)	117.0 (61–384)	0.117
TC (mg/dL)**	168 (74–321)	168.0 (74–321)	168.0 (82–307)	0.596
TG (mg/dL)**	128.5 (37–483)	128.5 (37–483)	134.0 (37–458)	0.423
HDL (mg/dL)**	40.0 (17–75)	40.0 (17–75)	38.0 (23–75)	0.533
cLDL (mg/dL)**	99.5 (28–227)	99.5 (28–227)	97.0 (40–205)	0.354
Duration (days)	14 (1–115)	14 (2–115)	13 (1–34)	0.300
Diabetes (%)	26 (15.5)	16 (12.9)	10 (22.7)	0.122
Hypertension (%)	98 (58.3)	67 (54.0)	31 (70.5)	0.058
CAD (%)	64 (38.1)	44 (35.5)	20 (45.5)	0.242
COPD (%)	15 (8.9)	9 (7.3)	6 (13.6)	0.202
CKD (%)	19 (11.4)	12 (9.7)	7 (16.3)	0.240
Cancer (%)	28 (16.7)	17 (13.7)	11 (25.0)	0.084
≥ 2 Comorbidities (%)	73 (43.5)	47 (37.9)	26 (59.1)	0.015
Anti-inflammatory drugs (%)	18 (10.7)	10 (8.1)	8 (18.2)	0.062

*BMI* body mass index, *CAD* coronary artery disease, *cLDL* calculated low-density lipoprotein cholesterol, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *CKD* chronic kidney disease, *FBG* fasting blood glucose, *ft3* free-triiodothyronine, *ft4* free-thyroxine, *HDL* high-density lipoprotein cholesterol, *IL-6* interleukin-6, *LDH* lactate dehydrogenase, *LH* luteinizing hormone, *25-OH-D* 25-hydroxyvitamin D, *PCT* procalcitonin, *PaO<sub>2</sub>/FiO<sub>2</sub>* (arterial partial pressure oxygen/fraction of inspired oxygen ratio), *TC* total cholesterol, *TG* triglycerides, *T* testosterone, *TSH* thyroid stimulating hormone, *WBC* white blood cell

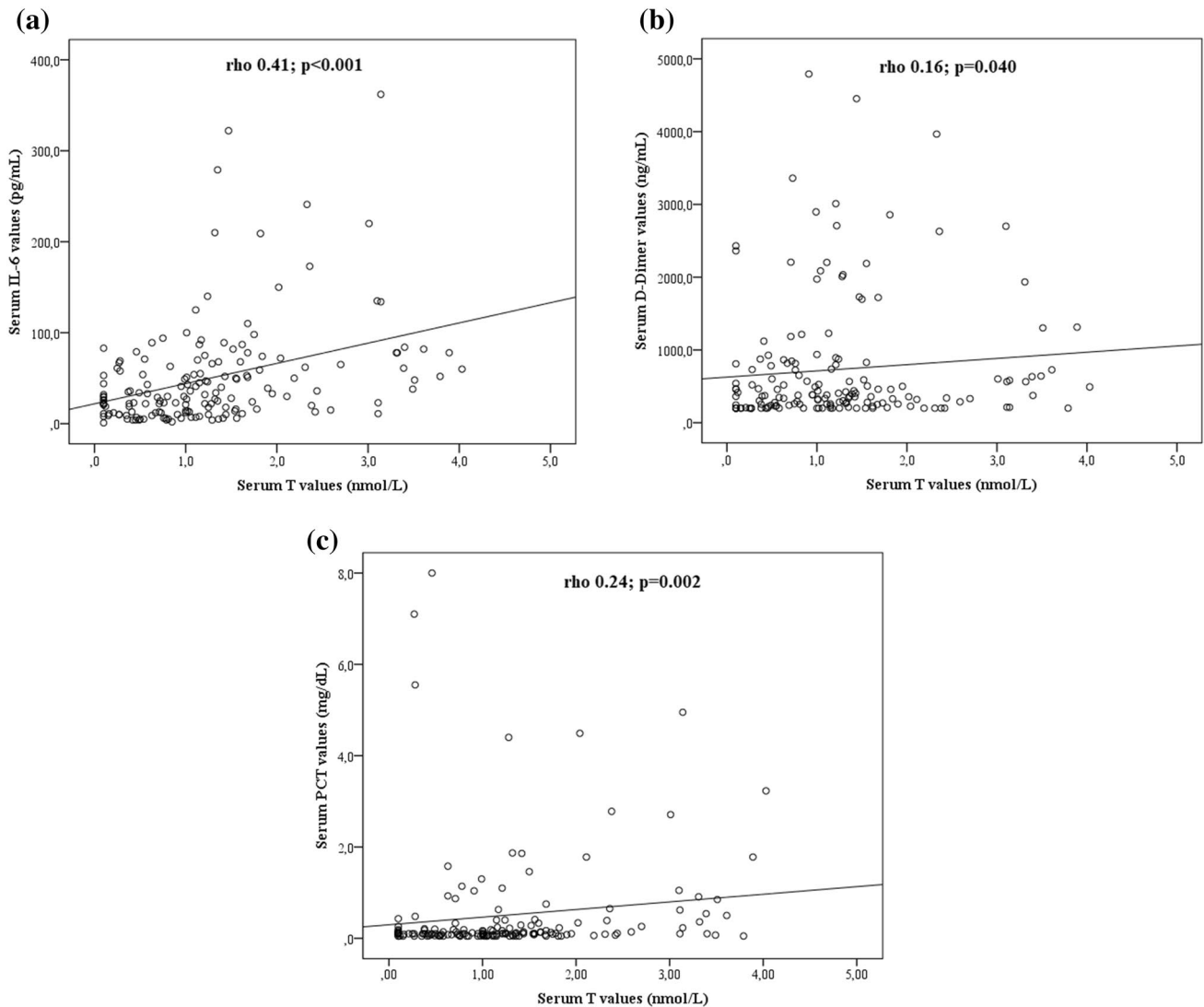
Categorical data were presented as *n* (%), whereas continuous data were presented as median and range. Comparisons were performed using Mann–Whitney's test.\*evaluated in 149 subjects; \*\*evaluated in 163 subjects

( $p < 0.001$ ) and LH ( $p = 0.024$ ) as compared to subjects who did not die, without significant differences in BMI, menopause status, serum TSH, ft4, 25(OH)D, ferritin, FBG, TC, HDL, Tg and cLDL values (Table 1).

In post-menopausal women (154 cases), serum T was significantly correlated with serum CRP ( $\rho = 0.23$ ;  $p = 0.002$ ), IL-6 ( $\rho = 0.41$ ;  $p < 0.001$ ), LDH ( $\rho = 0.34$ ;  $p < 0.001$ ), D-Dimer ( $\rho = 0.21$ ;  $p = 0.008$ ), PCT ( $\rho = 0.26$ ;  $p = 0.001$ ) and HDL ( $\rho = -0.22$ ;  $p = 0.008$ ). After exclusion

of outliers, the associations between T and IL-6, D-Dimer and PCT were maintained (Fig. 1a–c). No outliers of CRP, LDH and HDL were detected. In pre-menopausal women (14 cases), serum T did not result to be significantly correlated with any biochemical parameter (data not shown).

In multivariate regression analyses including all covariates significantly associated with mortality in univariate analysis (Table 1), serum T maintained the significant association with mortality after correction for age, coexistent



**Fig. 1** Correlations between serum testosterone (T) and interleukin-6 (IL-6; **a**), D-Dimer (**b**) and procalcitonin (PCT; **c**) after exclusion of outliers. The analyses were performed by the non-parametric Spearman's test

comorbidities and serum LH and FT3, whereas it was lost after correction for inflammatory parameters and use of anti-inflammatory drugs (Table 2).

## Discussion

This study reports an association between serum T levels and inflammatory parameters in COVID-19 female patients and, for the first time, the evidence of higher serum T levels in females deceased for SARS-Cov-2 infection, suggesting a possible predictive role of T on clinical outcome.

These results confirm in a large cohort what previously reported by a study performed in a smaller sample by Di Stasi et al. [10], who found in a cohort of 17 female patients with SARS-Cov-2 pneumonia a significant and positive

association between T levels and inflammatory markers, including PCT, CRP and fibrinogen as well as higher T levels as predictor of a worse hospital course in terms of hospitalization length. The authors hypothesized that the high T level found in COVID-19 female patients was mostly produced by the adrenal gland because of an adrenal cortex hyperactivity in response to the stressful condition induced by SARS-Cov-2 infection, arguing that T was a mirror, rather than a pathogenetic factor, of the inflammatory status reported in these patients. The adrenal origin of T was supported by the strong association with cortisol level and by the surprising evidence of relative low LH level for the menopausal patients' cohort. The authors suggested an inhibitory effect of high T levels of adrenal source on the physiological post-menopausal LH increase [10]. Interestingly in this concern, our results are consistent with the data

**Table 2** Multivariate logistic regression analyses evaluating the determinants of mortality in women hospitalized for COVID-19

Covariates	Odds ratio	95% CI	p-values
Serum T	<b>1.43</b>	0.99–2.05	0.06
Age	<b>1.09</b>	1.04–1.14	<0.001
BMI <sup>§</sup>	1.07	0.99–1.14	0.08
PaO <sub>2</sub> /FiO <sub>2</sub>	0.99	0.98–1.00	0.043
Serum T	<b>1.46</b>	1.05–2.05	0.027
Age	<b>1.07</b>	1.03–1.12	0.001
Serum LH	1.00	0.98–1.02	0.978
Serum fT3	<b>0.26</b>	0.13–0.52	<0.001
Serum T	1.16	0.75–1.79	0.497
Age	<b>1.09</b>	1.04–1.13	<0.001
WBC tertiles	1.52	0.92–2.51	0.101
Serum CRP	<b>1.14</b>	1.06–1.21	<0.001
Serum T	1.27	0.86–1.86	0.231
Age	<b>1.09</b>	1.04–1.13	<0.001
Serum IL-6	1.00	0.99–1.00	0.520
Serum PCT	1.20	0.94–1.53	0.144
Serum T	1.24	0.86–1.77	0.250
Age	<b>1.07</b>	1.03–1.11	0.001
Serum LDH tertiles	<b>1.77</b>	1.06–2.95	0.028
Serum D-Dimer tertiles	1.40	0.85–2.32	0.186
Serum T	1.35	0.95–1.90	0.09
Age	<b>1.09</b>	1.05–1.13	<0.001
Serum fibrinogen tertiles	1.61	0.99–2.61	0.54
Use of anti-inflammatory drugs	2.70	0.88–8.26	0.08
Serum T	<b>1.42</b>	1.02–1.97	0.04
Age	<b>1.08</b>	1.04–1.12	<0.001
≥ 2 comorbidities	1.51	0.71–3.21	0.290

*BMI* body mass index, *CRP* C-reactive protein, *fT3* free-triiodothyronine, *IL-6* interleukin-6, *LDH* lactate dehydrogenase, *LH* luteinizing hormone, *PCT* procalcitonin, PaO<sub>2</sub>/FiO<sub>2</sub> (arterial partial pressure oxygen/fraction of inspired oxygen ratio), *T* testosterone, *WBC* white blood cell

The variables included in the analyses were those which resulted associated with mortality in univariate analysis

The multivariate analyses were performed taking into account the minimal guidance criterion of ten events per variable. The values in bold refer to statistically significant associations

<sup>§</sup>Available for 149 subjects

from Di Stasi et al. [10], since a positive correlation was observed between serum T levels and main inflammatory parameters. Moreover, in our cohort of postmenopausal women, low LH level were found, endorsing the hypothesis of the negative feedback exerted by high T levels on pituitary. The evidence of lower LH levels in postmenopausal women with an unfavorable outcome confirms in these patients a greater inflammatory status of adrenal origin and consistent greater negative feedback. Conversely, we found no correlation between serum T levels and hospital in stay duration. Significantly higher serum T levels were found in

women who died as compared to survivors even after correction for age, comorbidities and serum LH and fT3 values. However, such an association was lost after correction for inflammatory parameters and use of anti-inflammatory drugs, suggesting that increase of testosterone values does not represent an independent predictor of clinical outcome of SARS-CoV-2 infection in women, but it is likely to reflect a functional dysregulation linked to disrupted inflammation mechanisms. Noteworthy, high T levels have been investigated as one of the factors responsible for the higher risk of COVID-19 infection in women with PCOS [16–18]. Androgen excess is a crucial feature of PCOS and women with PCOS and hyperandrogenism have a worse metabolic profile than women with PCOS and normal androgen level [19, 20]. Moreover, hyperandrogenism is a primary driver of increased risk of diabetes and fatty liver disease in PCOS women [21, 22]. In addition to the higher susceptibility to SARS-Cov-2 infection, PCOS women with hyperandrogenic phenotype are more likely to develop clinical symptoms of COVID-19 compared to their non-hyperandrogenic counterparts [23]. Although potential mechanisms underpinning these observations are not fully understood, high T levels in this clinical setting could reflect the result of a chronic metabolic dysfunction, which ultimately influences outcome in SARS-Cov-2 infection. Several studies stated that T controls the expression of transmembrane serine protease 2 (TMPRSS2) involved in the proteolytic processing of the SARS-Cov-2 spike protein [24, 25]. Thus, high T levels in female patients could influence COVID-19 severity both directly, facilitating viral penetration into cells of various tissues, and indirectly, promoting the inflammatory status.

Overall, the clinical scenario depicted in women is remarkably different from the one occurring in men. Mortality from COVID-19 is higher in men with lower testosterone levels, worse metabolic control, and presence of relevant comorbidities [26]. Testosterone has a dimorphic role in inflammation [27], reducing the inflammatory response in men [28] and promoting the inflammatory status in women [18]; however, in men low testosterone is also associated with worse metabolic control [29], therefore providing further reasons for increased disease severity.

Finally, our results confirm the contribution to mortality from dysregulation of thyroid function during acute COVID-19 illness, consistent with what previously described [30, 31].

This study has some limitations. Due to the lack of a control group, we cannot confirm the causative relationship of T as a determinant of increased mortality in the study cohort. Serum T was measured in a single blood sample at admission not allowing to estimate the duration of exposure to high T values during hospital stay. Moreover, lack of serum sex-hormone binding globulin (SHBG) assay, we did not provide information on the true peripheral T status

in the enrolled women. Furthermore, the lack of information on adrenal function did not allow to draw conclusion on the origin of serum T levels.

Notwithstanding these limitations, our study points out an opposite role of T in female patients with COVID-19 infection than one observed in males suggesting a different action of this hormone in inflammation response depending on gender.

## Conclusion

This study cohort adds consistent evidence to previous reports about the role of T as a mirror of higher inflammatory phenotype in female with SARS-Cov-2 infection and provides first evidence on possible predictive role of T on COVID-19 clinical outcome. Further studies are needed to clarify the pathophysiology of the gender differences observed and to establish the clinical relevance of high T levels in COVID-19 female patients.

**Author contributions** Conceptualization: AGL, GM. Data curation: MFB, SJ. Data analysis: WV, GM. Funding acquisition: not applicable. Supervision: AGL, GM. Original draft writing: MFB, WV. Review and editing: AP, EL, AB, NB, ACB, GM, AGL. All authors have read and approved the final version of the manuscript.

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**Data availability statement** The data used for this manuscript will be made available upon reasonable request to the corresponding author.

## Declarations

**Conflict of interest** Walter Vena received a project grant from IBSA. All other authors declare they do not have any conflict of interest that is relevant to the subject matter or materials included in this work.

**Ethical approval** All the procedures performed in the study were in accordance with the ethical standards of the Ethics Committee of IRCCS Humanitas Research Hospital, Rozzano-Milan, Italy, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all the individual participants included in the study.

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