Testosterone level and severity of COVID-19 infection in ambispective cohorts: the TESTOVID study.

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Background

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-SoV-2 virus, that has caused a global pandemic since early 2020. COVID-19 affects men more than women, and men have worse outcomes. SARS-CoV-2 virus enter pulmonary cells using the Angiotensin-converting enzyme and a protease called TMPRSS2, that is upregulated by androgen receptors. Lower risk of COVID-19 was reported in men with prostate cancer receiving androgen deprivation therapy (ADT) while low levels of testosterone were associated with a more severe disease and poor clinical outcomes in COVID-19 male patients. In the latter case, it is unclear whether low levels of testosterone are risk factors or consequences of COVID-19 disease. Here, we investigated testosterone and di-hydro-testosterone (DHT) levels impact on COVID-19 severity in ambispective cohorts of symptomatic SARS-CoV-2 infected patients.

Methods

In this study, we collected data from two cohorts of COVID-19 infected hospitalized patients: a multicentric retrospective cohort (R-cohort) from the FRENCH COVID database, and a monocentric prospective cohort (P-cohort) in , European Georges Pompidou Hospital , France.
The primary endpoint was to evaluate the relation between testosterone and DHT levels and the severity of the COVID-19 infection.
In each cohort, patients were divided in two groups: not severe cases and severe cases (defined as admission in intensive care unit [ICU]). We included at least two third of male patients in each cohort.
Hormone levels were tested less than 48 hours after patient's hospital admission. Clinical, radiological and biological data were collected.
The relation between hormone levels and the severity of the COVID-19 infection (ICU admission) was evaluated with univariate and multivariate logistic regression. In the retrospective cohort, the multivariate model was not performed due to lack of power.
The study was approved by the Institution ethic committee (IRB N°00011928).

Results

Among the 228 patients included, 117 were in the R-cohort and 111 in the P-cohort, respectively.
Patients clinical characteristics are presented in table 1 and 2.

Table 1 – Patient clinical characteristics

Variable	Retrospective cohort				Prospective cohort			
	Total n=117	Not severe n=59	Severe n=58	p	Total n=111	Not severe n=40	Severe n=71	p
Age, median (range)	60.5 (29-92)	60 (29-85)	61 (29-92)	0.16	64 (29-88)	60.5 (29-88)	68 (38-87)	0.16
Sex, n (%)				0.74				0.7
Male	89 (77)	46 (78)	43 (75)		78 (70)	29 (73)	49 (69)	
Female	27 (23)	13 (22)	14 (25)		33 (30)	11 (27)	22 (31)	
Obesity, n (%)	25 (22)	11 (19)	14 (25)	0.44	NA	NA	NA	-
BMI, kg/m² (range)	NA	NA	NA	-	27.5 (17.152.3)	26.7 (20.1-41.7)	28.4 (17.1-52.3)	0.25
Chronic pulmonary disease, n (%)								
Chronic bronchitis	15 (13)	5 (9)	10 (17)	0.16	11 (10)	4 (10)	7 (10)	1
Asthma	12 (10)	7 (12)	5 (9)	0.56	8 (7)	2 (5)	6 (8)	0.71
Diabetes, n (%)	30 (26)	18 (31)	12 (21)	0.22	29 (26)	7 (18)	22 (31)	0.12
Arterial hypertension, n (%)	45 (39)	19 (32)	26 (45)	0.16	50 (45)	16 (40)	34 (48)	0.42
Cancer, n (%)	8 (7)	4 (7)	4 (7)	1	12 (11)	5 (13)	7 (10)	0.67
Treatment, n (%)								
Corticosteroids	7 (6)	5 (8)	2 (3)	0.44	8 (7)	2 (5)	6 (8)	0.71
Sartan	15 (13)	8 (14)	7 (12)	0.81	21 (19)	9 (23)	12 (17)	0.47
ACE inhibitor	12 (10)	4 (7)	8 (14)	0.24	15 (14)	5 (13)	10 (14)	0.82
First symptoms to hospitalization, days, median (range)	7 (0-32)	7 (0-32)	7 (0-14)	0.27	8 (0-38)	9 (3-14)	7 (0-38)	0.57
COVID-19 specific treatment, n (%)								
Corticosteroids	21 (18)	6 (10)	15 (27)	0.02	109 (98)	40 (100)	69 (97)	0.54
Antiviral	25 (21)	9 (15)	16 (28)	0.10	0 (0)	0 (0)	0 (0)	-
Anti-IL6	3 (3)	1 (2)	2 (3)	0.62	26 (23)	19 (48)	7 (10)	< 0.001
Hydroxychloroquin	12 (10)	7 (12)	5 (9)	0.56	NA	NA	NA	NA
Thrombosis, n (%)	4 (17)	1 (9)	3 (3)	0.59	7 (6)	1 (2.5)	6 (8)	0.42
Hospit length, days, median (range)	9 (0-76)	6 (1-49)	13 (0-76)	< 0.001	12 (3-75)	8 (3-36)	17 (3-75)	< 0.001
Death, n (%)	15 (13)	1 (2)	14 (24)	< 0.001	23 (21)	1 (2.5)	22 (31)	< 0.001

BMI: Body Mass Index; ACE inhibitor: angiotensin converting inhibitor; IL6: interleukin 6

Table 2 – Patient biological characteristics

Variable	Retrospective cohort				Prospective cohort			
	Total n=117	Not severe n=59	Severe n=58	p	Total n=111	Not severe n=40	Severe n=71	p
Admission to biology, days, median (range)	0 (0-11)	0 (0-4)	1 (0-11)	0.16	1 (0-16)	1 (0-2)	1 (0-16)	-
Testosterone, nmol/L, median (range)	**2.66 (0.13-27)**	**4.04 (0.13-25)**	**1.77 (0.13-27)**	**0.03**	**1.4 (0.13-13.75)**	**2.7 (0.13-13.75)**	**0.84 (0.13-10.15)**	**0.001**
DHT, nmol/L (range)	**0.31 (0-4.3)**	**0.38 (0-4.3)**	**0.22 (0-3.1)**	**0.03**	**0.16 (0-1.3)**	**0.31 (0-1.1)**	**0.14 (0-1.3)**	**0.04**
LH, UI/L (range)	6.6 (0.1-49)	6.8 (0.8-49)	6.35 (0.1-37)	0.12	7.1 (0-71.3)	9 (0-46)	5.6 (0-71.3)	0.06
FSH, UI/L (range)	5.4 (0.7-83)	6.4 (1-83)	4.95 (0.7-64)	0.06	5.5 (0.6-80)	5.5 (1.6-51)	5.55 (0.6-80)	0.64
Other, median (range)								
Haemoglobin, g/dL	13.2 (8.4-17.3)	13.8 (11-17.3)	12.65 (8.4-16)	< 0.001	13 (8.5-16.9)	13.5 (8.5-16.9)	12.9 (9.8-16.3)	**0.03**
Leukocytes, /mm3	6 500 (6-33 030)	5 600 (6-11 900)	7 050 (1830-33 030)	0.01	8400 (4.5-54800)	7500 (9.1-18500)	9500 (4.5-54800)	**0.003**
CRP, mg/L	67.6 (5-312)	57.5 (5-258)	100 (5-312)	0.08	103 (6-427)	97.5 (7.2-272)	107 (6-427)	0.36
PCT, ng/mL	NA	NA	NA	-	0.16 (0.02-228)	0.1 (0.02-2.07)	0.26 (0.03-228)	**0.008**

DHT: Di-Hydro-Testosterone, LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone; CRP: C Reactive Protein; PCT: Procalcitonin.

Table 3 – Factors associated with the severity of COVID-19 infection

Table 3a. Prospective cohort analysis

Variable	Univariate analysis		Multivariate analysis	
	OR (IC)	p	OR (IC)	p
Testosterone, nmol/L	**0.76 (0.65-0.89)**	**0.001**	**0.8 (0.65-0.98)**	**0.035**
DHT, nmol/L	**0.16 (0.03-0.82)**	**0.03**	0.38 (0.04-3.46)	0.39
LH, UI/L	0.97 (0.94-1)	0.08	-	-
FSH, UI/L	0.99 (0.98-1.02)	0.65	-	-
Haemoglobin, g/dL	0.74 (0.56-0.98)	**0.03**	-	-
Leukocytes, /mm3	1 (1-1)	**0.02**	1 (1-1)	0.5
CRP, mg/L	1 (0.99-1.01)	0.38	-	-
Creatinin, µmol/L	1.01 (1-1.02)	**0.03**	1.01 (0.99-1.03)	0.15
Albumin, g/L	0.71 (0.61-0.82)	**< 0.001**	0.74 (0.61-0.89)	**0.002**
IL6 treatment	8.27 (3-22.4)	**< 0.001**	-	-
Antibiotic treatment	10.8 (3.8-30.68)	**< 0.001**	-	-
Initial oxygen flow, L/min	1.28 (1.11-1.46)	**0.001**	1.37 (1.1-1.71)	**0.005**
First symptoms				
Fever	-	-	0.23 (0.07-0.77)	**0.02**
Cough	-	-	2.99 (0.92-9.74)	0.07

SIGNIFICANCE	OR
<1	Lower risk of being admitted to ICU
>1	Higher risk of being admitted to ICU

DHT: Di-hydro-testosterone; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone; CRP: C Reactive Protein; IL6: Interleukin 6

Table 3b. Exploratory analysis in the retrospective cohort

Variable	Retrospective cohort	
	OR (IC)	p
Testosterone, nmol/L	**0.91 (0.23-0.99)**	**0.047**
DHT, nmol/L	**0.43 (0.18-1)**	**0.052**
LH, UI/L	0.96 (0.92-1)	0.14
FSH, UI/L	0.98 (0.95-1)	0.07

Testosterone and DHT levels were significantly lower in severe-cases in both R-and P-cohorts.

Global testosterone levels were lower than healthy subjects (laboratory norm: 3.8 to 34 nmol/L).
We investigated prognosis clinical and biological factors that were associated with the severity of the illness (table 3). Both hormones were significantly associated with admission in ICU therefore with worse outcome.

In a subgroup analysis in the R-cohort, we found out that 11 patients were first admitted to the hospital not in critical care, and had a secondarily clinical deterioration that led to ICU admission. Their testosterone level trend to be lower than non-severe cases but, higher than severe-cases, (table 4).

Table 4 – Secondarily patients admitted to ICU

Variable	R-cohort			
	Not severe n=59	Secondarily severe n=11	Severe n=47	p
Testosterone (nmol/L), median, range	4.04 (0.13-25)	2.99 (0.13-8.9)	1.74 (0.19-26.5)	0.11
DHT, nmol/L, median, range	0.38 (0-4.3)	0.17 (0-0.83)	0.24 (0-3.06)	0.1
LH, UI/L, median, range	6.8 (0.8-49)	8.1 (0.1-37.2)	6.3 (0.7-29)	0.07
FSH, UI/L, median, range	6.4 (1-83)	7.8 (1.4-64.4)	4.7 (0.7-44.5)	0.13
Death, n, %	1 (1.7)	2 (18)	12 (25.5)	< 0.001

DHT: Di-Hydro-Testosterone; LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone

Testosterone has been found to have a suppressive effect on multiple cytokines such as IL6. There is evidence in literature that androgen may also play a role in SAR-SoV-2 cell entry and susceptibility, through expression of ACE and TMPRSS2. Since TMPRSS2 depend on androgen receptor and prostate tissue, Italian and Brazilian research teams investigated the role of ADT in protection and treatment for COVID-19, and showed interesting results. Proxalutamide, a androgen receptor inhibitor, has shown to significantly decrease 30-days hospitalization rate in men with non-severe COVID-19 infection versus placebo (2.2% vs 26%, p < 0.001)[1].

Conclusions

This study shows that low testosterone level is a negative prognosis factor in patients infected by COVID-19.
Taken together, testosterone could represent an interesting treatment pathway, either for prevention of the virus cell entry with androgen receptor inhibitors or in curative intent to lower the immune response with exogenous testosterone administration. Further studies are warranted to evaluate the impact of the hormone regulation in SARS-CoV-2.

Fundings and conflict of interest

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1. Proxalutamide Reduces the Rate of Hospitalization for COVID-19 Male Outpatients: A Randomized Double-Blinded Placebo-Controlled Trial, John McCoy and al., Frontiers in Medicine, July 2021