Interplay between Male Testosterone Levels and the Risk for Subsequent Invasive Respiratory Assistance among COVID-19 Patients at Hospital Admission

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Abstract

Purpose: to evaluate the prognostic value of male serum total testosterone (TT) levels among COVID-19 patients requiring an invasive respiratory assistance at hospital admission.

Methods: 29 men with full haemato-chemical blood sample panel at hospital admission for COVID-19 related respiratory syndrome were retrospectively reviewed. Multivariable logistic regression model was implemented to test the predictive role of TT levels and subsequent risk for invasive oxygenation after adjusting for age, comorbidities and life-style related confounders.

Results: higher serum TT levels (ng/mL) were found independently associated with a lower odd of invasive oxygenation (Odds ratio [OR]: 0.43, 95%CI: 0.23-0.85; p=0.016). Significant negative correlation was found between TT and C-reactive protein, pH, Interleukine-6 and D-Dimer while positive correlation was established among TT levels and Monocytes ($x10^9$/L).

Conclusion: low testosterone levels may play a relevant role in the natural history of COVID-19 respiratory syndrome by making a patient with comorbidities and higher baseline levels of pro-inflammatory cytokines more susceptible to a potentially fatal clinical course at the moment of infection progression.

Full Text

A growing body of evidence has demonstrated higher age, male sex and medical comorbidity as risk factors for COVID-19 mortality [1]. In particular, male sex, and older age were found to be significant determinants for severe SARS-CoV-2 phenotype supporting the hypothesis that hormonal constitution may be an etiology for both COVID-19 susceptibility and acute respiratory distress syndrome (ARDS) development. Moreover, differences between male and female immune responses is well known establishing that genetics and sex hormones are important for the immunogenic sex-bias [2]. Higher serum total testosterone (TT) levels are associated with an immunosuppressive role on different components of the immune cell-mediated response [3]. Pozzilli et al [4] hypothesized a role for TT in the clinical course of the SARS-CoV-2 leading to multiorgan failure.

We aimed to evaluate whether serum TT levels among a cohort of twenty-nine COVID-19 men at the time of hospital admission were associated with severity of illness (i.e. requiring an invasive oxygenation strategy) and may allow for patient monitoring and predict disease outcome. This retrospective study received formal Institutional Review Board approval.

Patients' haemato-chemical and clinical characteristics are reported in Table 1. After adjusting for Age-adjusted Charlson Comorbidity Index (ACCI), history of hypertension, dyslipidemia and smoking status, higher serum TT levels (ng/mL) were found independently associated with a lower odd of invasive oxygenation (Odds ratio [OR]: 0.43, 95%CI: 0.23-0.85; p=0.016). In addition, linear regression was used to examine the correlation between serum TT and haemato-chemical variables of interest. A significant negative correlation was found between TT and C-reactive protein (CRP), pH, Interleukine-6 (IL-6) and D-

Dimer. Of note, a significant positive correlation was established among TT levels and Monocytes ($x10^9$/L) (Fig. 1A). Additionally, one-way ANOVA was used to test the differences between continuous TT and IL-6 values for the different respiratory assistance strategies confirming as thresholds of interest < 3.5-4 ng/mL for impaired T while identifying > 50 pg/mL for significantly elevated IL-6 (Fig. 1B). Locally weighted scatter-plot smoother (LOWESS) function was used to graphically depict the relationship concerning these two variables and the probability of their mutual interaction for the previously defined thresholds (Fig. 1C).

Male hypogonadism is typically of the aging male. Nevertheless, in our cohort, while age was not associated with need for O_2 assistance (p=0.082), TT levels were significantly lower in the ARDS group (p=0.003) and associated with worse clinical COVID-19 phenotype. Additionally, considering the observed inverse relationship between IL-6 and TT levels, we speculate that greater TT levels could serve as hormonal shield against the COVID-19 related cytokine syndrome. Similarly, low TT levels may allow the viral infection due to a loss of immunosuppressive effect of TT. Our results are in line with the recently reported experience by Rastrelli et al [5]. In addition, we were able to identify serum TT levels at hospital admission as a potential biomarker for the requirement for invasive respiratory assistance.

Certain limitations warrant mention. First, the retrospective design and limited sample size expose the current analysis to bias and the role of chance. However, given that testicular parenchyma was recently found as a potential target of SARS-CoV-2 infection [6], we might possibly postulate Leydig cells involvement with subsequent TT levels impairment in the etiopathogenesis of the more severe ARDS cases. Moreover, our data allowed us only to make implications on the clinical severity at hospital admission but not to better define the role of TT in later history of the disease. While promising, the interplay between TT levels and COVID-19 require additional study to determine the utility of TT in clinical practice.

Declarations

All patients gave informed consent and all diagnostic procedures reflected our routine clinical practice.

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Table

Table 1. Clinical and haemato-chemical characteristics of COVID-19 patients at hospital admission

Variables	**None** O_2 **assistance**	**Invasive** O_2 **assistance** (Ventimask, CPAP, Intubation)	**p value***
Sample size, n (%)	9 (31.0)	20 (69.0)	_
Age, *years*	58 (23 – 90)	70 (35 - 86)	0.084
ACCI score, median (range)	3 (0 – 5)	3 (0 – 8)	0.315
Comorbidity, n (%)			
Hypertension	3 (33.3)	12 (60.0)	0.245
Diabetes	3 (33.3)	6 (30.0)	0.858
Dyslipidemia	3 (33.3)	3 (15.0)	0.339
History of Neoplasm	2 (22.2)	3 (15.0)	0.633
CVD	1 (11.1)	3 (15.0)	0.779
CKD	1 (11.1)	2 (10.0)	0.928
Lung disease	1 (11.1)	3 (15.0)	0.779
Smoking status	5 (55.5)	9 (45)	0.70
Complete Blood Count			
WBC, $x10^9/L$ Nr: 4.40-11.30	6.61 (3.90-17.26)	7.52 (3.06-23.61)	0.647
PLT, $x10^9/L$ Nr: 150.0-450.0	191.0 (167.0-633.0)	232.0 (142.0-547.0)	0.873
Lymphocytes, $x10^9/L$ Nr: 1.00-4.80	1.17 (0.67-2.39)	0.75 (0.27-4.16)	0.650
Lymphocytes CD4+, *n°/µL* Nr: 410.0-1590.0	384.0 (291.0-1349.0)	524.5 (97.0-1485.0)	0.775
Lymphocytes CD4+, *%* Nr: 31.0-60.0	45.3 (16.2-59.7)	36.0 (20.6-74.4)	0.461
Lymphocytes CD8+, *n°/µL* Nr: 190.0-1140.0	330.0 (224.0-1244.0)	221.0 (78.0-1117.0)	0.246

Lymphocytes CD8+, *%* Nr: 13.0-41.0	27.7 (16.6-69.5)	23.3 (12.2-46.7)	0.461
CD4+/CD8+, *ratio* Nr: 0.60-2.80	1.64 (0.23-3.61)	1.64 (0.71-5.57)	0.958
NK cells, *n°/µL* Nr: 90.0-590.0	160.0 (121.0-251.0)	82.0 (13.0-604.0)	0.360
NK cells, *%* Nr: 5.0-27.0	14.7 (6.6-18.3)	8.5 (1.7-40.2)	0.433
Lymphocytes B, *n°/µL* Nr: 90.0-660.0	113.0 (52.0-254.0)	137.0 (22.0-314.0)	0.512
Lymphocytes B, *%* Nr: 6.0-25.0	9.2 (5.4-13.3)	10.3 (2.9-36.2)	0.433
Monocytes, $x10^9/L$ Nr: 0.10-1.00	0.42 (0.28-1.63)	0.33 (0.07-1.33)	0.162
Monocytes, *%* Nr: 3.5-10.5	8.6 (2.2-24.4)	5.9 (1.9-10.2)	**0.028**
Blood chemistry			
Creatinine, *mg/dL* Nr: 0.70-1.20	0.95 (0.80-2.00)	0.90 (0.40-1.70)	0.421
Testosterone, *ng/mL* Nr: 2.80-8.00	5.40 (1.38-6.05)	2.54 (0.25-6.95)	**0.003**
IL-6, *pg/mL* Nr: 1.50-7.00	9.30 (0.60-41.70)	88.00 (6.80-195.40)	**0.001**
CRP, *mg/dL* Nr: 0.00-0.50	3.14 (13.00-24.50)	12.33 (0.31-46.91)	**0.006**
LDH, *U/L* Nr: 135.0-225.0	223.5 (141.0-424.0)	338.5 (143.0-951.0)	0.115
Lac, *mmol/L* Nr: 0.3-0.7	0.7 (0.6-1.4)	1.1 (0.6-3.4)	0.175
	137.0 (133.0-142.0)	135.0 (131.0-144.0)	0.229

Na^+, *mmol/L* Nr: 136.0-145.0			
K^+, *mmol/L* Nr: 3.40-5.50	3.97 (3.41-4.60)	3.80 (3.19-5.00)	0.671
D-Dimer, ng/mL Nr: < 500	484.5 (170-4473)	1146 (376-4486)	0.124
Vital signs			170
pH Nr: 7.35-7.45	7.44 (7.42-7.48)	7.49 (7.43-7.53)	**0.018**
pO_2, *mmHg* Nr: 83.0-108.0	101.0 (84.0-135.0)	67.5 (46.0-131.0)	**0.028**
PaO_2/FiO_2, *mmHg* Nr: 200-400	480.0 (400.0-576.0)	286.0 (172.0-566.0)	**0.006**
SO_2, *%* Nr: 94.0-98.0	98.0 (91.0-99.0)	95.5 (82.0-99.0)	0.459

Results are presented as n (%) or *median (range)*

***p-values according to Fisher's Exact test or Mann-Whitney U test when appropriate.

ACCI= Age-adjusted Charlson Comorbidity Index; **ICU**= Intensive Care Unit; **CPAP**= Continuous Positive Airway Pressure; **CVD**: cardiovascular disease; **CKD**: chronic kidney disease; **WBC**= White Blood Cells; **PLT**= Platelets; **NK**= Natural Killer; **IL-6**= Interleukin 6; **CRP**= C-Reactive Protein; **LDH**= Lactate Dehydrogenase; **Lac**= Lactate.

Figures

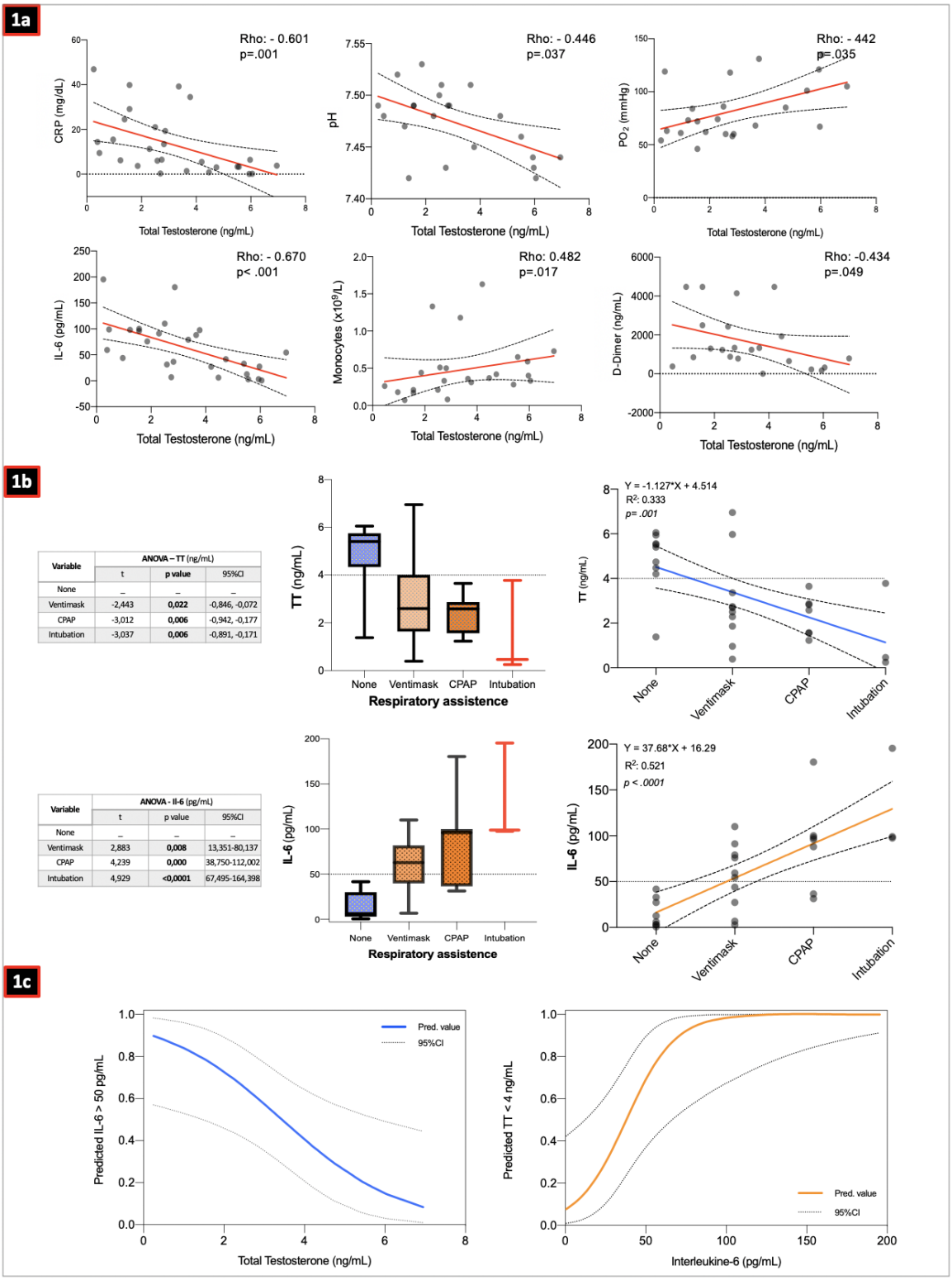

Figure 1

(A) Scatter plots and Spearman's rank correlation test of Total Testosterone (ng/mL) with haemato-chemical and vital signs among the COVID-19 cohort population. CRP= C-Reactive Protein (mg/dL); IL-6= interleukine-6 (pg/mL) (B) Box plots and one-way ANOVA testing the differences between continuous Total Testosterone (TT) and Interleukine-6 (IL-6) values for the different respiratory assistance strategies.

(C) Locally weighted scatter-plot smoother (LOWESS) function depicting the predicted probability of reciprocal interaction between Total Testosterone (TT) and Interleukine-6 (IL-6).