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Clinical and thyroid profile in patients with COVID-19 hospitalized in an intensive care unit

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Abstract. – OBJECTIVE: This study aimed to summarize the epidemiological and clinical features of thyroid function in COVID-19 patients in the intensive care unit (ICU) of Civil Fray Antonio Alcalde Hospital in Mexico.

PATIENTS AND METHODS: This is a cross-sectional study that included 63 ICU patients with COVID-19 from August 2021 to December 2021. Thyroid function was evaluated through the TSH, T4, T3, and FT3 measures. Comorbidities such as diabetes mellitus type 2 (T2DM), arterial hypertension (HT), body mass index (BMI), and biochemical biomarkers, including procalcitonin (PCT) and C reactive protein (CRP), were also analyzed.

RESULTS: A total of 63 patients with COVID-19 were hospitalized in the ICU; 42 (67%) were male, and 21 (33%) were female, with a mean age of 47 (range of 26-76 years). A total of 49 (78%) patients were non-vaccinated, 5 (8%) had an incomplete vaccination schedule, and 4 (6%) had completed the vaccination schedule. Regarding BMI, 10 (16%) were overweight, and 26 (40%) reported obesity. When assessing thyroid function, 8 (13%) patients were euthyroid, and 55 (87%) showed alterations on the thyroid hormonal axis, mainly a low concentration of TSH (0.56±0.79; *p*=0.0001) and FT3 (2.34±0.52; *p*=0.0006). In addition, increased PCT concentrations were associated with a higher risk to decease (1.22 *vs.* 8.21; *p*=0.0001) in this group of patients.

CONCLUSIONS: Based on our findings, it appears that COVID-19 patients with low TSH and FT3 levels, who have not been vaccinated against SARS-CoV-2, are overweight or obese, and exhibit high levels of PCT are more likely to experience a poor prognosis and even mortality.

Key Words:
COVID-19, Thyroid, SARS-CoV-2, Procalcitonin.

Introduction

The first cases of lethal Coronavirus disease 2019 (COVID-19) were patients with atypical pneumonia in China in 2019; however, it was not until January 9th, 2020, that the Control Disease Center of China informed the world of the discovery of a new virus responsible for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Up to January 7th, 2023, the World Health Organization (WHO) had reported 754,367,807 confirmed cases and 6,825,461 deaths due to COVID-19[1]. According to the International Committee on Taxonomy of Virus (ICTV), SARS-CoV-2 belongs to the *Nidovirales* order, *Coronaviridae* family, and has an approximate diameter of 125 nm and presents a single-stranded RNA (ssRNA), with 14 non-structural reading frames that encode for non-structural proteins used for assembly, and four structural proteins. The structural spicule (S) protein is formed of two regions: the receptor-binding domain (RBD) or S1 and the cellular membrane attach region (S2). The envelope (E) structural protein is responsible for the production, maturation, and release of the virions, while the membrane (M) protein, the most preserved and abundant in the virion, is crucial for the ensemble of viral particles to the nucleocapsid (N) protein[2,3]. The transmembrane S protein facilities the virus entrance into the host cell through the receptors of *angiotensin-converting enzyme* 2 (ACE2), which are highly expressed in the testes, ileum, adipose tissue, lungs, kidney, heart, and thyroid. Two other proteins involved in COVID-19 pathogenesis are the transmembrane protease serine-2 (TMPRSS2)

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and furin. TMPRSS2 plays an important role in the fusion of the virus with the host cell membrane and is highly expressed in the prostate, stomach, colon, pancreas, lung, small intestine, and salivary glands, while furin, a type-1 membrane-bound protease, is highly expressed in the liver, lung, thyroid, whole blood, and skin[4]. Ultimately, the entrance of SARS-CoV-2 to organs such as lungs, kidneys, and heart could aggravate pre-existing diseases or cause new ones[5]. In this sense, recent studies report a higher incidence of thyrotoxicosis in patients with COVID-19, with respect to the general population, suggesting direct damage to the thyroid gland or as a consequence of the elevated concentration of cytokines such as IL-6, among others[6,7]. In this study, we aimed to investigate the thyroid function of patients with COVID-19 hospitalized in an intensive care unit (ICU) during the first wave to better understand the multisystem effects of SARS-CoV-2 infection, due to one of the tissues recently affected by SARS-CoV-2 directly or by the RNA vaccines[8].

Patients And Methods

Patients

A total of 63 patients hospitalized in the ICU of the Civil Fray Antonio Alcalde Hospital (Guadalajara, Mexico), who were diagnosed with COVID-19 by a positive polymerase chain reaction (PCR) test for SARS-CoV-2 in a sample obtained by nasopharyngeal swabbing, were included in this cross-sectional study. Patients were admitted between August 2021 and December 2021. Exclusion criteria were as follows: a) patients with thyroid dysfunction, b) those who used anti-thyroid drugs, c) those who received iodine-based contrast prior to sampling, and d) pregnant and breastfeeding women. The clinicopathological characteristics of the patients, such as age, sex, body mass index (BMI), associated comorbidities, and vaccination scheme, were obtained from the medical records. The protocol was considered in accordance with the Declaration of Helsinki and national research and approved by the ethics committee of the Civil Fray Antonio Alcalde Hospital with the office number HCG/CEI-2028/21. On behalf of the patients, family members provided their informed consent to participate in this study.

Determination of Body Mass Index (BMI)

Body weight (kg) and height (m) were measured in all patients at hospital admission, and BMI was determined using the formula BMI=weight (kg)/height $(m)^2$. According to BMI, participants were classified as normal weight (<18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese (≥30.0 kg/m^2), and morbidly obese (>40 kg/m^2)[9].

Thyroid Hormone Determinations

Thyroid hormone determination was performed using the paramagnetic particle chemiluminescent immunoassay technique with the UniCel DxI 800 analyzer© 2021 (Beckman Coulter, Inc., Brea, CA, USA). A sample of 3 mL of peripheral blood was taken in the ICU at admission for each patient. Within 2 hours, the sample was centrifuged at 1,600 g at room temperature for 10 minutes. Two mL of serum were collected and stored at -20°C prior to processing. The following reference values were provided by the manufacturer: thyroid stimulating hormone (TSH), low (<0.38 μIU/mL), normal (0.38-5.43 μIU/mL), high (>5.43 μIU/mL); triiodothyronine (T3), low (<0.87 ng/mL), normal (0.87-1.78 ng/mL), high (>1.78 ng/mL); free triiodothyronine (FT3), low (<2.5 pg/mL), normal (2.5-3.9 pg/mL), high (>3.9 pg/mL); and tetraiodothyronine (T4), low (<6.09-12.23 μg/dL), normal (6.09-12.23 μg/dL), high (>12.23 μg/dL). Patients with thyroid hormone alteration levels were classified as 1) Euthyroid patients with TSH, T3, FT3, and T4 in the normal range; 2) non-thyroidal illness (NTI), with TSH, FT3, and T3 low, but T4 being normal or low; 3) post-thyrotoxicosis, with normal or low TSH, high T4, and normal or high T3 and FT3; 4) subclinical hypothyroidism (SAT), with normal TSH, with low T3 and T4, and normal or low FT3; 5) primary hypothyroidism, with high TSH, normal or low T3, T4, and FT3; and 6) unclassifiable, patients with alterations to thyroid hormones levels but who cannot be included in any group. For C-reactive protein (CRP) determination, the normal reference value was <10.0 mg/L, while for abnormal procalcitonin (PCT), the values were either low (<0.5 μg/L) or high (<2 μg/L).

Statistical Analysis

Descriptive statistics are presented as means ± standard deviation, and categorical variables were compared using Student's *t*-test with the Statistical Analysis System (SAS) Institute Inc. (SAS Campus Drive, Cary, NC, USA). The statistical significance was set at $p<0.05$.

Results

Demographic Characteristics of Patients with COVID-19 in ICU

A total of 63 patients with COVID-19 hospitalized in the ICU from August to November 2021 were included in this project. Demographic descriptions are shown in Table I. Of the 63 patients admitted to the ICU, 25 (39%) were discharged from the hospital with post-COVID-19 syndrome, including 20 (71%) males and 8 (29%) females. 30 (48%) patients died, including 20 (67%) males and 10 (33%) females, and 8 (13%) remained hospitalized at the time of analysis. Among the deceased patients, 13 had at least one comorbidity: 3 (23%) had arterial hypertension, 2 (15%) had diabetes mellitus type 2 and arterial hypertension, 1 (8%) had uncontrolled asthma and a history of anabolic consumption, 1 (8%) had controlled asthma, 1 (8%) dyslipidemia and morbid obesity, 1 (8%) had diabetes mellitus type 1, and 1 (8%) dyslipidemia and liver damage.

Body Mass Index (BMI)

Of the patients with normal weight, 14 (52%) were discharged with post-COVID-19 syndrome, 1 (4%) was transferred to the nephrology department for acute renal failure, 2 (7%) remained hospitalized, and 10 (37%) died. The average number of hospitalization days for patients with normo-weight who were discharged was 42 days, while it was 20 days for patients who died. The main cause of death was septic shock in 8 (80%) patients and cardio-respiratory failure in 2 (20%) patients. Among 13 overweight patients, 5 (39%) were discharged with post-COVID-19 syndrome, 6 (46%) died, and 2 (15%) were still hospitalized at the time that the analysis was completed. The main cause of death in overweight patients was septic shock and respiratory failure. As for obese patients, 6 (26%) were discharged with post-COVID-19 syndrome, 1 (4%) remained hospitalized, and 16 (70%) died. Among the latter, the causes of death were a septic shock in 11 (68%), pneumonia in 2 (13%), cardio-respiratory failure in 2 (13%), and cerebral infarction in 1 (6%). The average hospitalization days of these patients were 30 days, while it was 29 days for deceased patients. Of the 23 obese patients, 7 (30%) had morbid obesity with a BMI >40, two patients had bronchial asthma, four had diabetes mellitus type 2 and systemic arterial hypertension, and one had no comorbidities. Only one patient was discharged from the hospital with post-COVID-19 sequelae. Of the remaining 6 patients, 5 (72%) died of septic shock. The average days of hospitalization in patients with morbid obesity was 33 days.

Table I. Demographic description of patients with COVID-19 admitted to the ICU of the Civil Fray Antonio Alcalde Hospital.

Parameter	n (%)
Sex	
Male	42 (67)
Female	21 (33)
Age	47 years (26-76 years)
BMI	
Normo-weight (<18.5-24.9 Kg/m^2)	27 (43)
Overweight (25-29.9 Kg/m^2)	13 (21)
Obesity (≥30 Kg/m^2)	23 (36)
Vaccination	
Complete vaccination scheme	4 (6)
Incomplete scheme	5 (8)
Not specified data	5 (6)
Non-vaccinated	49 (78)
Hospitalization average days	11

BMI: Body Mass Index.

Vaccination

Of the 49 non-vaccinated patients, 18 (37%) were discharged with post-COVID-19 syndrome, 26 (53%) died, and 5 (10%) remained in the hospital or were referred to other specialized services. Of the 4 patients with a complete vaccination schedule, 1 (25%) died, and 3 (75%) were discharged without apparent sequelae; among 5 patients who had an incomplete vaccination schedule, 3 (60%) died, and 2 (40%) were discharged. In 5 patients, it was not possible to determine the vaccination status.

Thyroid Profile, C Reactive Protein, and Procalcitonin

Of the 63 patients, 8 (13%) were euthyroid, and 55 (87%) had abnormal values for at least one of the variables evaluated. We also observed that no euthyroid patients showed a significant increase in PCT levels (p=0.0001) relative to euthyroid patients (Table II). We also found that decreased levels of TSH and FT3, as well as increased levels of PCT, were significantly more frequent in decease patients and, therefore, could be a reliable prognostic marker (Table III). Finally, a comparison between euthyroid, NTI, post-thyrotoxicosis, SAT, primary hypothyroidism, and unclassified patients and regarding BMI, CRP, PCT, and glucose, we revealed that only the PCT had a significant difference in the NTI group (Table IV).

Table II. Comparison of BMI, C-reactive protein, procalcitonin and glucose between euthyroid and non-euthyroid patients with COVID-19.

	Euthyroid n=8	No euthyroid n=55	*p*-value
BMI	36.12±12.82	28.93±8.30	0.06
CRP	7.66±9.59	7.60±7.76	0.35
PCT	0.28±0.37	1.55 ±2.85	**0.0001**

Comparison of media values with *t*-Student tool. BMI=Body mass index, CRP=C-reactive protein, PCT=Procalcitonin.

Table III. Survived *vs.* deceased in COVID-19 patients regarding thyroid profile, BMI, C-reactive protein, and procalcitonin.

Variable	Survived	Deceased	*p*-value
TSH	0.89±1.65	0.56±0.79	**0.0001**
T4	6.99±3.33	5.47±3.28	0.94
T3	0.54 ±0.69	0.49±0.70	0.95
FT3	2.36±0.87	2.34±0.52	**0.0006**
BMI	28.80±9.32	30.99±9.04	0.87
CRP	7.77 ±8.82	7.43±6.96	0.20
PCT	1.22±1.78	8.21±36.2	**0.0001**

Comparation of media values with *t*-Student test. BMI=body mass index, CRP=C-reactive protein, FT3=free T3, PCT=procalcitonin, T4=Tetraiodothyronine, T3=Triiodothyronine, TSH=Thyroid stimulating hormone.

Table IV. Comparison of BMI, C- reactive protein, and procalcitonin between euthyroid and non-euthyroid patients with COVID-19.

	BMI	*p*-value	CRP	*p*-value	PCT	*p*-value
Euthyroid	36.12±82		7.66±9.59		0.28±0.37	
NTI	28.90±8.84	0.13	7.62±7.03	0.19	1.43±2.90	**0.0001**
Post-thyrotoxicosis	32.76±2.29	0.27	0.30±0.42	0.07	0.51±0.66	0.22
SAT	34.31±2.67	0.32	9.85±13.93	0.38	4.34±0.39	0.64
Primary hypothyroidism[a]	21.48		33.00		8.00	
Unclassified	26.97±5.11	0.09	4.36±4.33	0.14	0.69±0.75	0.09

[a]Statistical analysis was not applied since there was only one patient with this condition. BMI=body mass index, CRP=C-reactive protein, PCT=procalcitonin, NIT=non-thyroidal illness, SAT=subclinical hypothyroidism.

Discussion

In this study, we observed that males were more frequently hospitalized in the ICU and faced a higher risk of death compared to females. According to the China Center for Disease Control and Prevention, the male: female ratio of patients with COVID-19 is 2.7:1, and the case fatality rate (CFR) of 2.8% in males compared to 1.7% in females[10]. Moreover, epidemiological studies[11] in more than 38 countries worldwide have reported that the mean CFR in males is 1.7 times higher in males than in females. By contrast, in the European Union, the CFR is higher in women than in males, probably because of the high proportion of women with rheumatoid arthritis and their increased comorbidity and mortality documented there[12]. Other studies[13] have reported that the different affectation by COVID-19 in males and females may be due to numerous factors, including the adaptive immune response, which is innately greater and stronger in females than in males and allows for a better immune response to SARS-CoV-2 in females.

Additionally, it has been suggested that the biallelic expression of some genes that escape X-chromosome inactivation may be associated with this difference in COVID-19 presentation between sexes. The endosomal Toll-Like receptor 7 gene (*TLR7*) has its locus at Xp22.2 and plays a key role in the recognition of viral antigens and strongly and effectively activates the immune response[14,15]. For instance, four young males with severe complications of COVID-19 had gene variants in *TLR7*, which generated a negative impact

on the production of both type I and II IFN[15,16]. Other X-chromosome non-inactivated genes overexpressed in women with COVID-19 are *FOXP3, XIST,* and *TLR8*, which are all associated with the production of interleukins[17]. It should be noted that one of the main genes associated with a worse prognosis and evolution of COVID-19 is the always-active *ACE* gene located in Xp22. This gene enables women to present a greater amount of ACE2 receptors, mainly in type 2 pneumocytes, which in turn favor the digestion of angiotensin II and provide greater protection against pulmonary edema[17]. Finally, estrogens have been shown to have a greater protective effect against SARS-CoV-2 in murine models in which ovariectomized females are at a greater risk of developing severe disease and death from COVID-19[18]. This result may be related to the crucial role estrogens in the regulation of monocyte, macrophage, and antigen presentation, not to mention their interaction with different TLRs[19]. Otherwise, some Y-linked genes, such as *SRY* and *SOX9* have a higher expression in males and may contribute to a low inflammatory response to the SARS-CoV-2 infection.

In our sample, the average age of patients was 47 years. According to the WHO, as of February 2022, the most vulnerable age group for COVID-19 is 25-64 years (67.76%), followed by the groups of 15-24 years (12.5%), 65+ (9%), 5-14 years (8.02%) and <5 years group (2.72%). However, variations in age groups between countries have been reported. According to lethality, in Mexico, the National Institute of Statistic and Geography (Instituto Nacional de Estadística y Geografía- INEGI) reports that a total of 200,270 people died from COVID-19 in 2020 and 238,772 in 2021; among the latter, 145,115 (61%) were males and 93,652 (39%) were females[20]. In the present work, we observed that 48% of our population with COVID-19 died, which represents a high mortality rate compared to that reported worldwide, which is estimated to be 2.10% to 3.4%[21,22]. Some of the risk factors associated with a worse prognosis and mortality in our patients with COVID-19 were age >35 years (mean 47 years), male sex, and secondary outcomes like the acute respiratory distress syndrome (ARDS) with a SpO_2 <95% and dyspnea, liver failure, acute cardiac and renal failure and septic shock. Moreover, it has been suggested that two other factors are directly involved in the evolution of non-severe to severe COVID-19, namely coagulation alterations (increased Activated partial thromboplastin-APTT and D-dimer) and dyslipidemias (decreased high-density lipoprotein cholesterol- HDL-c)[22].

Our results confirm that obesity is one of the main risk factors for severity and death in patients with COVID-19. We observed that most of the hospitalized patients were overweight or obese, which increased the probability of death with respect to those with normal weight; in the group of morbidly obese patients, 6 of the 7 patients died. In this regard, a small study[23] of 23 patients with COVID-19 has been published in which only 3 patients had a normal weight; 7 were overweight, and 13 were obese. Of these patients, 85% required mechanical ventilation, and 62% died, thus demonstrating that obesity is strongly associated with a poor prognosis for COVID-19. This higher risk of death in patients with obesity may be due to concomitant chronic degenerative diseases, such as hypertension, T2DM, renal disease, dyslipidemia, and a higher risk of thromboembolic diseases[24,25]. Regarding thyroid function in patients with COVID-19, we observed that 87% of the patients in this study had some alterations in levels of the hypothalamic-pituitary-thyroid axis hormones TSH, T3, FT3, or T4. In this sense, thyrotoxicosis was found in 5.4-20% of patients with COVID-19 in some populations, suggesting a higher incidence in these patients with respect to the general population. Two hypotheses attempt to explain this intriguing association: a) indirect immunological involvement of the gland generated by the elevated circulating concentration of several cytokines such as IL-6, IL-7, and TNF-α and b) by direct thyroid damage by SARS-CoV-2 through tissue-localized ACE receptors, transmembrane serine protease 2 (TMPRRSS) and fucine[6,7]. Other studies[7,27] have shown that thyroid dysfunction entails a poor prognosis and longer hospital stay for patients with COVID-19, as is longer hospital stays[26]. Furthermore, a high serum CRP concentration in euthyroid patients was correlated with thyrotoxicosis or subclinical thyrotoxicosis by SARS-CoV-2. Christensen et al[28] reported the outcomes of subacute thyroiditis in (mostly female) patients with COVID-19 whose ages ranged from 18 to 65 years. Among them, subacute thyroiditis was diagnosed 5-49 days after the onset of COVID-19 symptoms and included, as the main clinical feature, neck (13/17; 82%), tachycardia (8/17; 47%), anxiety, heat intolerance, agitation, insomnia, weight loss, fever, asthenia, tremor, hyperreflexia, and goiter. The authors also observed that the CRP concentration

range was 4.5-176 mg/L (mean 41 mg/L), with 27% of patients exhibiting CRP measurements above 100 mg/L. Jakovac et al[29], reported that the S protein of SARS-CoV-2 is sparse across the thyroid tissue and, although it is located mainly in the cytoplasm of follicular cells, it was also found in the epithelioid cells of destroyed follicles, while the N protein was sparser in the perinuclear area of the thyrocytes[7,27]. The vast majority of thyrocytes were immunopositive for caspase-3, pointing to apoptosis as an underlying mechanism for thyroid pathology due to SARS-CoV-2 infection[29]. Even though subacute thyroiditis often causes thyrotoxicosis and is commonly associated with SARS-CoV-2, SAT has also been reported after the application of the SARS-CoV-2 vaccine[30]. The observation that SAT and Graves's disease can develop post-vaccination with mRNA or adenovirus-vector type vaccines was attributed to the higher immunogenicity of both, vaccines relative to those with inactivated SARS-CoV-2 and the subsequent production of stimulatory anti-TSH receptor antibodies[31]. Yet, the latter vaccines contain several proteins of SARS-CoV-2 partially homologous to human thyroid peroxidase and can therefore induce an autoimmune thyroid disease[31].

Limitations

We should consider two main limitations in this study. First, our patients were infected by the initial SARS-CoV-2 strain, which had the ability to affect different tissues, including the thyroid gland. The remarkable SARS-CoV-2 strain variation and the massive vaccination of the global population make our study hardly reproducible and prevent its clinical application in the current SARS-CoV-2 setting. However, these results can be relevant for future emergent viral infections. Second, the death of most patients prevented us to assess the evolution of their thyroid disorders. Thus, it remains to be elucidated if the thyroid affection by SARS-CoV-2 induces permanent or transitory damage.

Conclusions

In conclusion, this study provides evidence of the higher mortality during the first wave of COVID-19 in our population, an outcome mainly associated with obesity, insufficient application of SARS-CoV-2 immunization, and thyroid abnormalities. In addition, we observed that procalcitonin determination is a valuable biomarker in assessing the prognosis of COVID-19 patients.

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Ethics Approval

Ethics Committee of the Civil Fray Antonio Alcalde Hospital approved the protocol with the office number HCG/CEI-2028/21.

Informed Consent

The protocol was performed in accordance with the Declaration of Helsinki, and the participants or their families provided written informed consent.

Authors' Contributions

MGNM, MVOD, VZDE, and LUE designed, analyzed, and wrote the article. VZDE and SAR collected and performed the studies. All authors contributed to and approved the final version of the paper.

Data Availability

All data associated with this paper are available from the corresponding author upon reasonable request.

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Conflict of Interest

All authors declare no conflicts of interest that could be perceived as prejudicing the impartiality of the research report.

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