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Research Article

Thyroid Dysfunction in Critically ill Patients with Covid-19 and Mortality: A Cross-Sectional Study

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Highlights

- Thyroid dysfunction was observed with high frequency among subjects with SARS-CoV-2 infection who were admitted to the intensive care unit.
- Thyrotoxicosis and isolated thyrotropinemia were the most prevalent, and the mortality rate was elevated in subjects with subclinical thyrotoxicosis.
- These findings represent a significant contribution to the field; as they furnish valuable information on the risk of thyroid dysfunction and mortality following COVID-19 infection, thus guiding treatment planning.

Abstract

Objective: The COVID-19 infection can affect the thyroid function. Our objective was to analyze relationship of the Thyroid dysfunction and in-hospital mortality in critically ill COVID-19 patients. Methods: A cross-sectional study was conducted of 51 consecutive subjects. The primary outcome was to determine the prevalence of thyroid dysfunction. Secondary outcomes included the prevalence of overt and subclinical thyroid dysfunction, and their association with in-hospital mortality. Results: Thyroid dysfunction was determinate in 30.8% of the subjects. Differences in serum TSH levels was observed between overweight vs obese subjects ($p< 0.05$). Overt thyroid dysfunction was observed in 5.8% of cases: all as hypothyroidism, with no hyperthyroidism identified ($p < 0.05$).

Subclinical thyroid dysfunction was observed in 25% of cases: 15.4% with hyperthyroidism and 9.6% with hypothyroidism ($p< 0.05$). The mortality rate was 34.6%, with a significant difference observed between subjects with euthyroidism vs subclinical hyperthyroidism ($p< 0.05$). Dysthyroidism was not associated with mortality OR 1.7 (0.52-5.96; $p = 0.36$). Subjects with subclinical thyroid dysfunction had a longer mean length of hospital stay. Conclusion: Thyroid dysfunction is common among subjects with COVID-19 admitted to the intensive care unit. The most prevalent thyroid alterations were subclinical hyperthyroidism and isolated thyrotropinemia. The mortality rate was higher in subjects with subclinical hyperthyroidism.

Keywords: COVID-19; thyroid dysfunction; hyperthyroidism; hypothyroidism; mortality

Introduction

The effects of SARS-CoV-2 and its new variants are not limited to the lungs, with various other organs and systems also affected, including the endocrine system [1-3]. Following the description of subacute thyroiditis associated with COVID19, there has been a notable increase in interest in the study of thyroid dysfunction [1,2,4]. In a case series documented by Brancatella et al. [5], subacute thyroiditis was observed in patients with this viral infection. Furthermore, Chen, et al. [6] also noted thyroid alterations, including transient cases of euthyroid sick syndrome. Additionally, the multi-organ tropism of SARS-CoV-2 has previously been shown for several major organs, found moderately to highly increased lymphocytic infiltration in the thyroid of the thyroid gland in autopsies of fatal cases [7]. Ashrafi, et al. [8], reported a prevalence of 26% for non-thyroidal illness syndrome and 10% for thyrotoxicosis in patients with COVID-19. A number of studies have documented alterations in thyroid profile in patients with COVID-19 infection [1,2,5,8].

However, the majority of these studies were conducted on non-critically ill patients, and only one evaluated the incidence of thyroid dysfunction in critically ill patients with COVD-19 [9]. In critically ill patients, the most frequent alterations observed are low concentrations of free triiodothyronine (fT3), normal concentrations of free thyroxine (fT4), or elevated rT3 in the presence of normal thyroid-stimulating hormone (TSH). Therefore, the objective of this study was to evaluate the prevalence of overt and subclinical thyroid dysfunction and their relationship with mortality in subjects with COVID-19 infection admitted to the ICU.

Subjects and Methods

Study Design

This was a cross-sectional study of consecutive subjects admitted to the ICU. The inclusion criteria were as follows: subjects of both sexes, aged between 18 and 60 years, with COVID-19 infection diagnosed by real-time reverse transcription-polymerase chain reaction (RT-PCR), and severe acute respiratory distress syndrome according to the Berlin definition. Subjects with a medical history of thyroid disease, use medications such as amiodarone, lithium, phosphodiesterase inhibitors, and dopaminergic agonists, and pregnant subjects were excluded. All patients received steroids as per the protocol for severe COVID-19 who develop sepsis or acute respiratory distress syndrome.

Outcomes

The primary outcome was to determine the prevalence of thyroid dysfunction. Secondary outcomes included the prevalence of overt and subclinical thyroid dysfunction, as well as their association with in-hospital mortality.

Measurements and Biochemical Assays

Demographic variables were considered and disease severity markers such as the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II prognostic classification and thyroid function tests. The thyroid function tests were processed using the Elecsys assay from the Siemens® ADVIA Centaur XP Immunoassay System. The laboratory reference ranges for TSH and FT4 were 0.3 - 4.49 mU/L and 0.8 - 1.7 ng/dL, respectively. Blood samples were collected during the first week of admission to ICU in the morning.

Definitions

Thyroid dysfunction was defined as any deviation from the normal TSH reference range. The subjects were divided into the following subcategories: (a) isolated hyperthyrotropinemia or subclinical hypothyroidism (elevated TSH and FT4 values within the reference ranges), (b) subclinical hyperthyroidism (low TSH and FT4 values within the reference ranges), (c) overt hypothyroidism (elevated TSH and FT4 values below the reference ranges), and (d) overt hyperthyroidism (low TSH and FT4 values above the reference ranges).

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical data are expressed as numbers and percentages. Differences between groups were compared using the independent Student's t-test or analysis of variance for continuous variables and chi-squared test with Fisher's correction for categorical variables, as appropriate. A logistic regression analysis was performed to analyze the thyroid dysfunction associated with mortality in critically ill COVID-19 patients, we calculated adjusted hazard ratios (HRs) with a 95% CI of mortality by thyroid function classes, using the euthyroid group as the reference group. A value of $p < 0.05$ was considered statistically significant. The data were analyzed using the SPSS statistical package, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the population

A total of 58 subjects were eligible, 6 were excluded and 52 were finally analyzed, with a majority of women (59.6%) shown in Figure 1.

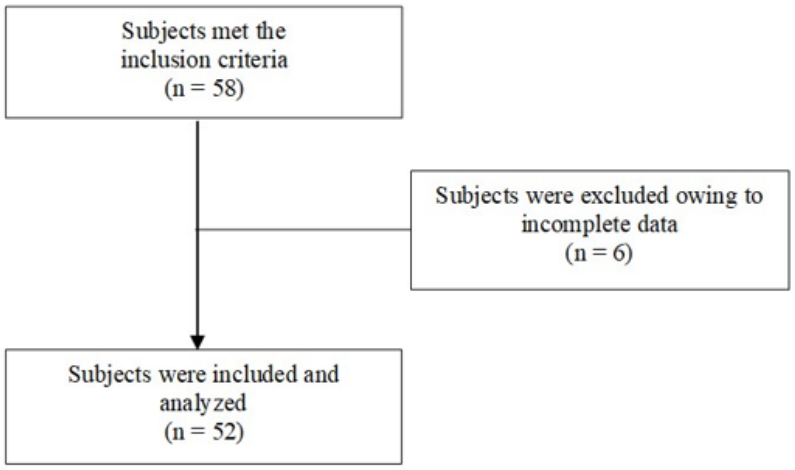

Figure 1: Participant flowchart.

The mean age of the participants was 46.65 ± 11 years, ranging from 18 to 60 years. The full complete demographic and clinical characteristics of the study population are shown in Table 1.

Table 1: Summary of demographic and clinical characteristics of the study population.

Characteristic	Total Population (n = 52)	Euthyroidism (n = 36)	Thyroid Dysfunction (n = 16)
Age (Mean ± SD)	46.6 ± 11.6	47.6 ± 11.2	44.3 ± 12.4
Sex women, n (%)	31 (59.6)	21 (58.3)	10 (62.5)
Diabetes mellitus, n (%)	10 (19.2)	8 (22.2)	2 (12.5)
Arterial hypertension, n (%)	11 (21.2)	10 (27.8)	1 (6.3)
Autoimmune diseases, n (%)	2 (3.8%)	1 (2.8)	1 (6.3)
Body mass index (kg/m2)	33.4 ± 6.9	33.2 ± 6.3	33.9 ± 8.2
PaO2FiO2 (mmHg)	97.2 ± 46.0	99.4 ± 48.1	92.3 ± 42.1
SOFA	12.1±4.6	12.4 ± 4.8	11.5 ± 4.2
APACHE	21.2±8.0	20.2 ± 8.0	23.5 ± 7.8

Primary Outcome

Thyroid dysfunction. Thyroid dysfunction was observed in 30.8% of the participants. Of these, 50% had TSH levels below the reference range, while the remaining 50% had elevated TSH levels. There were no significant differences in serum TSH levels between women and men, nor in serum FT4 levels. In the population, 67.3% had some degree of obesity, 35% were overweight and only 7.7% had a healthy BMI. Significant differences in serum TSH levels were observed between overweight and obese subjects (1.246 mIU/L, range 0.1 - 6.2 vs. 2.974 mIU/L, range 0.1 - 20.3 mIU/L; $p < 0.05$). A trend towards lower FT4 levels was observed in obese subjects compared to overweight subjects (1.354 ng/dL, range 0.9 - 1.8 vs. 1.126 ng/dL, range 0.3 - 2.0 ± 1.592; $p = 0.05$).

Secondary Outcome

Overt and Subclinical Thyroid Dysfunction. According to the findings, 5.8% of the total population was diagnosed with overt thyroid dysfunction, with all cases classified as hypothyroidism ($p < 0.05$). Subclinical thyroid dysfunction was observed in 25% of subjects: 15.4% with hyperthyroidism and 9.6% with hypothyroidism ($p < 0.05$). Subjects with overt hypothyroidism had lower serum FT4 levels than those with subclinical hypothyroidism (0.333 ng/dL, range 0.3-0.3 vs. 1.440 ng/dL, range 1.1-1.7; $p < 0.001$).

Thyroid Dysfunction and Mortality

A total of 18 in-hospital deaths were recorded, resulting in a mortality rate of 34.6% among the closed cases (n = 52). The mean age of survivors was 44.7 years compared with 50.1 years for non-survivors ($p < 0.05$). The logistic regression analysis found no association between thyroid dysfunction and mortality OR 1.7 (0.52–5.96; $p = 0.36$). However, a difference in mortality rates was observed between subjects with euthyroidism and those with subclinical thyrotoxicosis ($p < 0.05$). Mortality rates by group are shown in Table 2.

Table 2: Comparison of hospital mortality stratified by groups.

Characteristic	Total Population (n = 52)	Euthyroidism (n = 36)	Thyroid Dysfunction (n = 16)
Age (Mean ± SD)	46.6 ± 11.6	47.6 ± 11.2	44.3 ± 12.4
Sex women, n (%)	31 (59.6)	21 (58.3)	10 (62.5)
Diabetes mellitus, n (%)	10 (19.2)	8 (22.2)	2 (12.5)
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PaO2FiO2 (mmHg)	97.2 ± 46.0	99.4 ± 48.1	92.3 ± 42.1
SOFA	12.1±4.6	12.4 ± 4.8	11.5 ± 4.2
APACHE	21.2±8.0	20.2 ± 8.0	23.5 ± 7.8

The mean length of hospital stay was longer in subjects with subclinical thyroid dysfunction (shown in Figure 2).

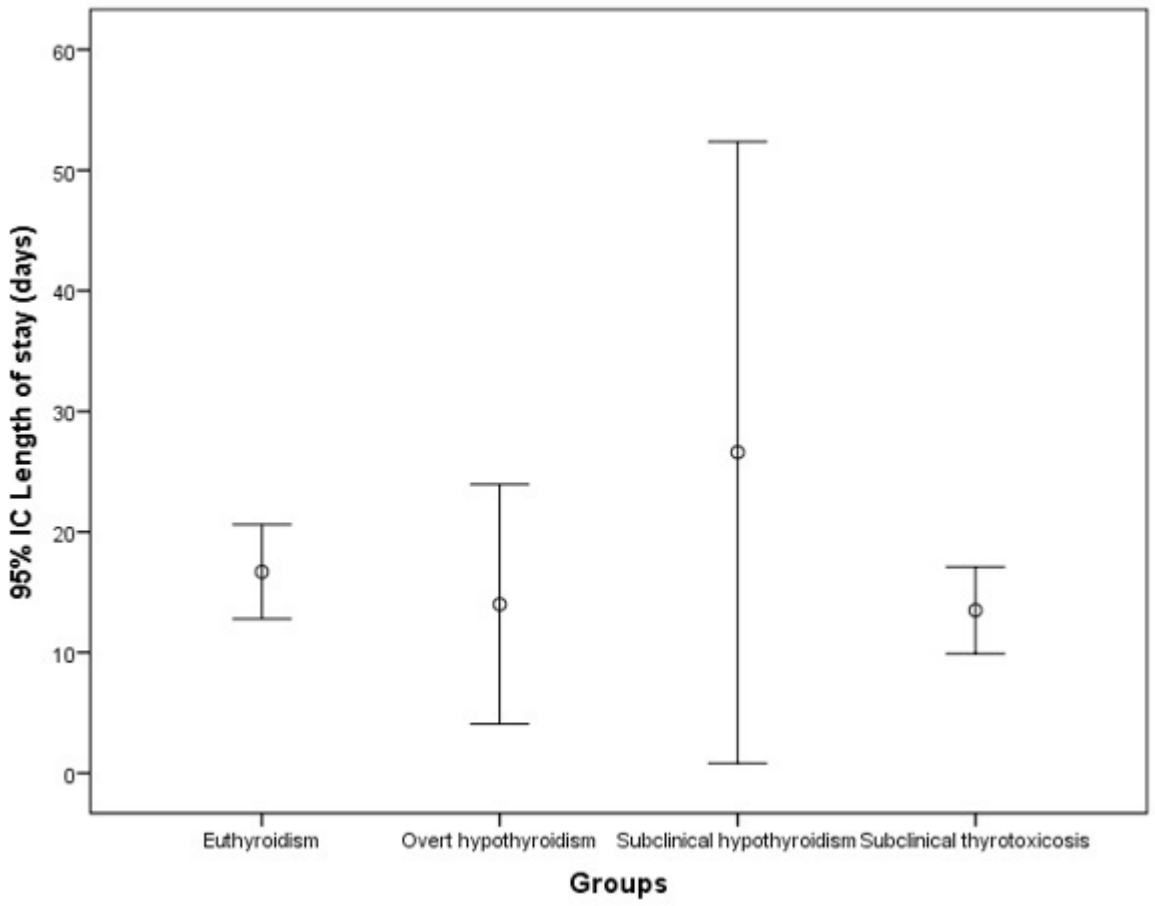

Figure 2: Comparison of hospital stay stratified by groups. Box plots of length of stay (days) for patients stratified by group. Data are expressed as median (IQR).

Discussion

In the present study, subclinical t hyperthyroidism was identified as the most prevalent thyroid alteration, occurring in 15.4%, followed by subclinical hypothyroidism in 9.6%. These findings are consistent with those published by Ashrafi, et al. [8], as well as those presented in the THYRCOV study [10], which was also conducted in patients with SARS-CoV-2 infection not admitted

to the ICU. In a study conducted by Hashemipour, et al. [11], it was observed that 8.1% of COVID-19 patients exhibited isolated elevated levels of free thyroxine. A systematic review by Malik, et al. [12] found hypothyroidism to be prevalent in patients with COVD-19. Hypothyroidism in these patients can be attributed to impaired hypothalamus-pituitary axis function or direct damage by destruction of thyroid tissue [13,14]. An alternative hypothesis suggests that alterations to the binding of thyroid hormones to their respective transporter proteins, as well as to the uptake of thyroid hormones, may be the cause [15].

Indeed, the cytokine storm characteristic of SARS-CoV-2 infection may have similarities to a thyroid storm with elevated inflammatory markers, leading to an alteration of the hypothalamic-pituitary-thyroid axis [16]. Several studies have shown that advanced age, male sex and obesity have been identified as risk factors for severe outcomes associated with SARS-CoV-2 infection. These risk factors are associated with an increased likelihood of admission to the intensive care unit (ICU), the need for mechanical ventilation, and an elevated risk of mortality [17,18]. In the present study, we found no associations between the age or sex of the subjects and the development of thyroid dysfunction. The 92.7% exhibited some degree of obesity or overweight. Serum TSH levels were found to be higher in subjects with obesity ($p < 0.05$), which is likely due to increased deiodinase activity and increased synthesis of cytokines [19]. In terms of mortality, we observed a rate of 36.5% in closed cases. The mortality rate was higher in the groups with subclinical thyroid dysfunction.

Our observations also indicated a longer hospital stay in those with subclinical hypothyroidism. These findings are consistent with those reported by Müge, et al. [20] who also suggested that thyroid dysfunction may have prognostic significance. At the same time, other authors reported that in critically ill patients with confirmed cases of COVID-19, low levels of fT4 were significantly associated with in-hospital mortality. Furthermore, they also agree on the complexity of determining the population that might be a candidate for hormone replacement therapy. The present study is subject to certain limitations: the cross-sectional design of the study precludes the capture of dynamic alterations in thyroid hormone levels and the sample size is small. Finally, due to resource limitations, the levels of FT3, total T4 and autoantibodies were not determined.

Conclusion

Thyroid dysfunction is common among subjects with COVID-19 admitted to the intensive care unit. The most prevalent thyroid alterations were subclinical hyperthyroidism and isolated thyrotropinemia. The mortality rate was higher in subjects with subclinical hyperthyroidism.

Acknowledgement

None

Statement of Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Hospital Juárez de México Ethics Review Board and was conducted according to the Declaration of Helsinki and Good Clinical Practice.

Consent to Participate Statement

The informed consent from patients was waived owing to the retrospective nature of the study.

Conflict of Interest Statement

The authors have no conflict of Interest to declare.

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Author Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by EPC and CGR. The first draft of the manuscript was written by EPC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available owing to patient privacy considerations, but are available upon reasonable request to the corresponding author.

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