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Relationship of Hospitalized COVID-19 Patients and Thyroid Dysfunction

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ABSTRACT

Aims Although vaccines have been developed for COVID-19, the virus continues to present problems to the health sector. The current study assessed thyroid function in all hospitalized patients diagnosed with the virus to ascertain whether COVID-19 infection was linked to thyroid function abnormalities.

Instrument & Methods An observational cohort study was conducted on all COVID-19-positive patients hospitalized in the Al-Fourat Al-Awsat Hospital in Al-Kufa, Iraq, between September 2021 and April 2022. 208 potential patients were tested during this period, and 150 COVID-19 patients and 50 COVID-19-negative individuals were selected. A sample of blood was collected during hospitalization. A serum was used to determine the thyroid-stimulating hormone.

Findings Hypertension, shortness of breath, diabetes, liver dysfunction, and cardiac and pro-inflammatory diseases were the most frequent comorbidities in COVID-19 patients. The association between COVID-19 and Control groups indicated a significant difference in age, body mass index, gender, systolic- and diastolic blood pressure, fasting blood sugar, HbA1C, alanine aminotransferase, and aspartate aminotransferase. Also, the analysis indicated a significant ($p<0.001$) difference between COVID-19 patients and the control group in the level of TSH.

Conclusion Thyroid impairment is frequent in most individuals admitted to the hospital with a COVID-19 infection. Low thyroid-stimulating hormone level is a reliable indicator of poor prognosis in COVID-19-infected individuals.

Keywords Thyroid-Stimulating Hormone; Interlukin-6; Nuclear factor-κB; D-Dimer; COVID-19

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Introduction

SARS-COV-2 was first identified in China, sparking much speculation about its origins. It began in late 2019 and spread across the globe by 2020, sparking the beginning of the COVID-19 pandemic. Soon after it caught up in the world, various research and studies were conducted to better understand the novel virus. Once it was shown that the virus was involved in many body organs and systems beyond the lungs [1], connections between existing morbidities and infection were better understood.

Complications included venous thromboembolism, increased D-dimer, extended prothrombin time, and coagulopathy, primarily disseminated intravascular coagulation. Though superinfection with Staphylococcus aureus led to a fatal outcome [1], the incidents are not as significant as the major pulmonary embolism, which is the reason for suffocation and a drop in oxygen saturation in blood [2].

Cytokines are represented as the immune system's response to an invasion; cytokines are secreted from white blood cells (WBCs). They act on cells that secrete them (autocrine effect) or on cells surrounding them (paracrine effect) [3]. Among these cytokines is Interleukin-6 (IL-6), which was found to be downregulated by overexpression of TSH thyroid stimulating hormone [4]. Pointing to the inverse relation between TSH and IL-6.

Nuclear factor-κB (NF-κB) is thought to favorably control IL-6 transcription in a range of cells, which is the proposed mechanism [5]. Bound to the inhibitory-κB (IκB) protein, NF-κB stays in the cytoplasm quite. Following stimulation, IκB kinase (IKK)-β phosphorylates IκB, leading to IκB breakdown and NF-κB release. Initiating inflammation is one of the many transcriptional processes and cellular reactions that are triggered by free active NF-κB, which translocate to the nucleus and bind to sequence-specific DNA regions [6]. It verified the impact of TSH on this pathway when evaluated in adipose tissue [7]. The hyperresponsiveness of the immune system to COVID-19 infections caused a cytokine storm [8], which was characterized by an increase in D-Dimer as a result of pulmonary artery damage that was facilitated by ACE2 [9, 10].

Thyroid abnormalities are divided into two major categories: overproduction (hyperthyroidism) and low production (hypothyroidism). Most thyroid problems are primary, meaning a defect in the thyroid gland itself, while secondary are exogenous, referring to either the hypothalamus and/or pituitary gland [11]. It was found that COVID-19 may alter thyroid gland function.

The current study assessed thyroid function in all hospitalized patients who had been diagnosed with the virus to ascertain whether COVID-19 infection was linked to thyroid function abnormalities.

Instrument and Methods

An observational cohort study was conducted on all COVID-19-positive patients hospitalized in the Al-Fourat Al-Awsat Hospital in Al-Kufa, Iraq, between September 2021 and April 2022. 208 potential patients were tested during this period, and 8 were excluded because of known hypothyroidism. In the end, 150 COVID-19 patients and 50 COVID-19-negative individuals were selected and entered the study as COVID-19 and control groups, respectively.

Clinical, demographic, and diagnostic values (age, sex, hypertension, diabetic history, liver dysfunction, and respiratory rate) were extracted from patient records at admission. Body mass index was assessed as weight (kg) divided by height squared (m^2).

A blood sample was collected during hospitalization. Serum was used to determine thyroid-stimulating hormone (TSH). TSH was assayed on an automated integrated clinical chemistry and immunoassay analyzer (Biomeurex; Germany) using the commercially (Ref: 30403) available assay kit (VIDAS®; France). The normal ranges of TSH were 0.465-4.680 μIU/ml.

A COVID-19 diagnosis was constructed using the LightCycler-96 real-time reverse transcriptase polymerase chain reaction RT-PCR (Roche; Germany) confirmation of infection from a nasopharyngeal swab.

The SPSS 25 software was used for all analyses. Chi-square and student t-tests were used to assess the distinctions between the groups. Found non-parametric, Spearman's correlation coefficient (r) was employed to investigate the relationships between TSH, D-Dimer, and IL-6. The discriminatory potential of D-Dimer, IL-6, and TSH as disease severity biomarkers were assessed utilizing receiver operating characteristics and area under the curve analysis.

Findings

The mean age in the COVID-19 group was 48.42±9.50 years, and in the control, group was 37.72±12.88 years ($p<0.001$). Females were the majority of the population in the COVID-19 group (60%), while males were prevalent in the control group (62%; $p<0.01$; Table 1)

The TSH level of the COVID-19 group (2.80±0.71μIU/MI) was significantly ($p<0.001$) higher than the control group (0.55±0.39μIU/MI). TSH (AUC=0.96; 95%CI: 0.93-0.99; $p<0.001$), IL-6 (AUC=0.96; 95%CI: 0.91-1.00; $p<0.001$), and d-dimer (AUC=0.72; 95%CI: 0.63-0.82; $p<0.001$) were good prognosticator for disease negative outcome (Figure 1).

TSH had negative significant correlations with IL-6 ($r=-0.97$; $p<0.001$) and d-dimer ($r=-0.66$; $p<0.001$; Figure 2).

Table 1. Comparing the Mean±SD (student T-test) or frequency (Chi-square test) of characteristics between the COVID-19 (n=150) and control (n=50) groups

Parameters	COVID-19	Control	p-Value
Age (year)	48.42±9.501	38.72±12.88	<0.001*
BMI	24.63±3.76	21.01±1.49	<0.001*
Fasting blood sugar (mg/dl)	210.40±384.87	128.70±27.08	<0.001*
HbA1C (%)	5.54±0.53	4.72±0.49	<0.001*
Respiratory rate (>24 breaths per min)	105 (70)	N/A	N/A
D-dimer (µg/L)			
<1000	136 (90.7)	N/A	N/A
≥1000	24 (9.3)		
Systolic blood pressure (mmHg)			
<120	57 (38.0)	36 (72.0)	0.001**
≥120	93 (62.0)	14 (28.0)	
Diastolic blood pressure (mmHg)			
<80	38 (25.3)	30 (60.0)	0.001**
≥80	112 (74.7)	20 (40.0)	
ALT (U/L)			
>50	95 (63.3)	12 (24.0)	<0.001**
≤50	55 (36.7)	38 (76.0)	
ASL (U/L)			
>40	90 (60.0)	18 (36.0)	<0.01**
≤40	60 (40.0)	32 (64.0)	

*Students t-test; **Chi-square test; #N/A: Not Applicable

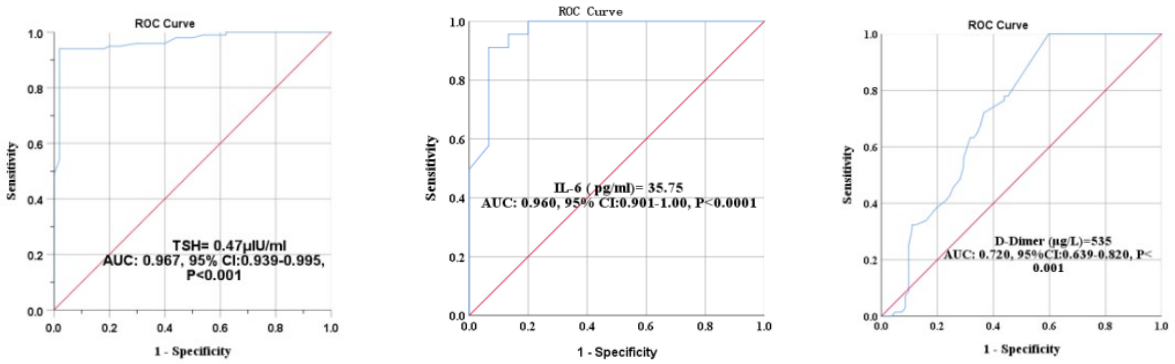

Figure 1. Receiver operating characteristic (ROC) curve showing the predictive power of TSH (a), IL-6 (b), and D-Dimer (c) to predict progression to severity of COVID-19

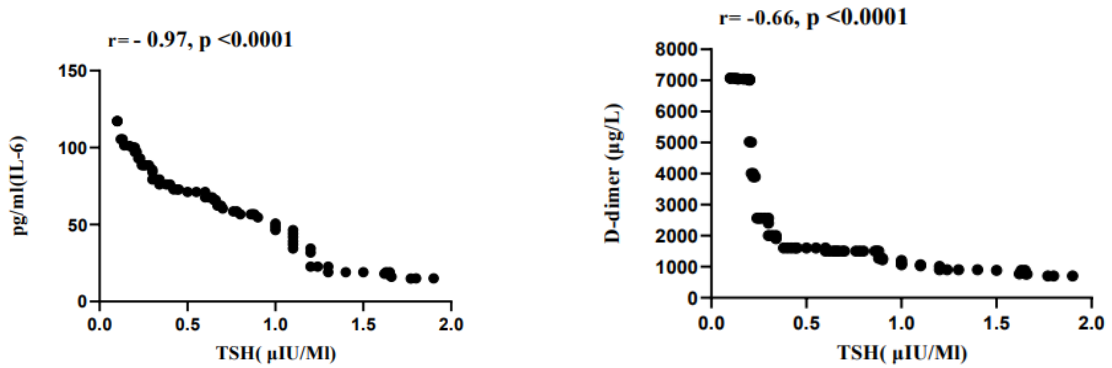

Figure 2. Spearman correlation plot between (a) thyroid-stimulating hormone (TSH) and interleukin (IL)-6; and (b) thyroid-stimulating hormone (TSH) and D-Dimer

Discussion

COVID-19 infection has been found to affect many organs besides the lungs, such as the heart, kidneys, liver, brain, and thyroid gland [12, 13]. The majority of recent research found abnormal thyroid function in COVID-19 patients described as ill euthyroid syndrome [14-24] or thyrotoxicosis in conjunction with destructive thyroiditis [16, 17]. Similar to other viruses, SARS-COV-2 can directly damage thyroid tissue and cause subacute thyroiditis. According to certain theories, SARS-COV-2 may engage with and enter thyroid gland surface ACE-2 receptors to cause destructive thyroiditis [23].

TSH levels are down in COVID-19 patients in the majority of research, including ours, that look at thyroid function in the virus. Nevertheless, there is disagreement about how to interpret this result. According to the current study, patients with COVID-19 had TSH levels that were statistically considerably lower than those of the non-COVID-19 control groups ($p<0.001$). The study found that about sixty patients were indicated with thyroid dysfunction based on their TSH levels. TSH levels were less than 0.4μIU/Ml in COVID-19 patients, a difference not observed in those hospitalized without COVID-19. Most of the non-COVID-19 were euthyroid, according to the reference range for TSH (0.4-4.5μIU/Ml). These results suggested that COVID-19 patients might have biochemical thyrotoxicosis or subclinical thyrotoxicosis [25]. Our results are comparable with numerous studies. According to research by Khoo *et al.* [19], 5.6% of the participants exhibited subclinical thyrotoxicosis. Subclinical thyrotoxicosis was also reported by others to affect 9.4% of COVID-19 patients [17, 20]. According to Campi *et al.*, around 10.4% of COVID-19 patients had temporary TSH levels below the cutoff upon admission. However, these results were accompanied by a normal concentration of thyroid hormone such as free T4, which was not carried out in our study. The same study indicated that most patients who had a temporary low TSH level during hospitalization can return to normal range in only survivors before discharge [23].

For COVID-19 patients, identifying potential factors that contribute to the early onset of serious illness and/or death is critical to effective management. It was found that suppression of TSH levels is associated with patients' poor outcomes and mortality [21]. Zhang and his colleagues indicated that thyroid dysfunction might result in fatal outcomes in COVID-19 patients [21]. Contrary to our findings, which were based only on routine measurements of TSH levels, these anomalies can include euthyroid illness syndrome, clear thyrotoxicosis, severe hypothyroidism, and subclinical thyrotoxicosis. Consequently, the current investigation did not indicate that thyroiditis or thyroid toxicosis was caused by COVID-19.

Regarding the outcomes of our investigation into the TSH, IL-6, and D-dimer area under the receiver operating characteristic curve (AUC) as predictors of COVID-19 severity. Numerous investigations have examined the predictive power of TSH serum levels in COVID-19 patients, however with inconsistent findings when considering TSH level alone. According to a recent study by Clausen *et al.*, the area under the curve (AUC) for TSH levels was 0.54, whereas IL-6 had an AUC of 0.78. Our findings, however, indicate that TSH serum levels (AUC 0.97) and IL-6 (AUC 0.96) have good predictive power for poor outcomes in patients with severe COVID-19 [26]. Apart from TSH and IL-6, a multitude of global studies have elucidated many pathophysiological mechanisms and identified a possibly pro-coagulant condition linked to extended prothrombin, elevated fibrinogen, and elevated D-dimer levels [27, 28]. Research has revealed that upon hospital admission and over the course of their stay, COVID-19 patients often have a high titer of d-dimer blood levels. In fact, an increase in D-dimer concentrations of three to four times has been linked to the emergence of more severe acute respiratory distress syndrome, augmented probability of intensive care unit (ICU) admission, and a bad prognosis [29-32]. D-dimer can thus be utilized to identify individuals with greater fatality rates and forecast the severity of the illness in severe COVID-19 patients with acute respiratory failure [33-35]. Similar to our findings, other research also looked at how well d-dimer serum levels describe the COVID-19 prediction. The AUC of the ROC curve for serum levels of D-dimer was found to be 0.807 by Poudel *et al.* [36]. Furthermore, our findings show that the d-dimer serum level at admission (AUC 0.72) is a good predictor of patient survival in cases of significant COVID-19. The bulk of published data classifying d-dimer serum levels with an AUC<0.7 as having poor discriminating capacity is consistent with these reported findings [37-39].

An increase in IL-6, which is commonly seen in patients with severe COVID-19 disease, has been related to changes in TSH levels during infection [17, 23]. The results of the present investigation demonstrated a substantial ($p<0.001$) association between the thyroid stimulating hormone, D-dimer, and IL-6 plasma levels (TSH). The present study's results were in line with previous research [20, 21, 40-43], which exhibited a variety of cytokines that were connected to thyroid autoimmune disorders. Specifically, IL-6 cytokine was found to have a notable impact on changes in the axis of the hypothalamus, pituitary, and thyroid observed in COVID-19 hospitalized patients, and this cytokine was found to be negatively correlated with TSH. Since the pituitary expresses the ACE2 virion binding receptor, this is probably explained by the direct cytopathic action of SARS-CoV-2 on thyrotropes [44]. This is confirmed by the fact that once individuals recovered from COVID-19 infection, their TSH levels returned to normal [19].

Conclusion

Thyroid impairment is frequent in most individuals admitted to the hospital with a COVID-19 infection. Low thyroid-stimulating hormone level is a reliable indicator of poor prognosis in COVID-19-infected individuals.

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Ethical Permissions: The study was approved by the University of Kufa's Human Research Ethics Committee (Approved ID: MEC/5.8.2021).

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