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Thyroid Gland Dysfunction and COVID-19 Severity: Is There a Correlation?

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus pandemic to break out in 2019 has resulted in a serious health disaster all over the world. It has been suggested that thyroid gland dysfunction in coronavirus disease 2019 (COVID-19) patients can directly or indirectly affect COVID-19 severity and mortality rates. The aim of this study was to examine the possible effect of thyroid dysfunction on the severity and mortality in COVID-19 hospitalized patients.

Methods: This is a retrospective study that included 415 COVID-19 patients, who were admitted to the Ziv Medical Center between April 2020 and October 2021. Clinical and demographic data were collected from patient's electronic medical records.

Results: Patients with severe COVID-19 disease hospitalized in COVID-19 intensive care unit (ICU) department had significantly lower average level of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) levels compared with patients with mild or moderate disease in hospitalized patients in COVID-19 ward. Regarding hospitalization length, there was a statistically significant difference between the two groups with a mean of 14.6 days for COVID-19 ICU department and 8.6 days for the COVID-19 ward ($P < 0.001$). Similarly, the mortality rate also showed a significant difference, with 48.8% in COVID-19 ICU department compared to 10.4% in the COVID-19 ward ($P < 0.001$). However, it is worth noting that ethnicity, gender, body mass index (BMI), and chronic diseases did not exhibit any significant differences between the two groups. In a multivariate logistic regression model the risk of mortality was three times higher among patients with lowered T4 levels and six times higher among patients with lower TSH levels. Longer duration of hospitalization (odds ratio (OR) = 1.12) and older age (OR = 1.07) were also associated with higher mortality, while T3 was inversely associated (OR = 0.07).

Conclusions: It was suggested that lower thyroid hormones and TSH serum levels were associated with increased severity and mortality in COVID-19 hospitalized patients. Thyroid hormones and TSH levels may serve as additional tools for better evaluation of COVID-19 severity and mortality.

Keywords: Thyroid gland; T3; T4; TSH; COVID-19

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Introduction

The outbreak of the coronavirus pandemic caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) in December 2019 has become a huge healthcare problem worldwide, complex morbidity and long-term medical consequences.

The possible effects of coronavirus disease 2019 (COVID-19) infection may be attributed to the virus unique features [1]. Patients affected by SARS-CoV-2 infection (COVID-19) can show different clinical presentations from mild symptoms to severe hypoxic respiratory failure [2]. But COVID-19 acute and post long-term effects are yet to be clarified [3]. COVID-19 can cause both pulmonary and systemic inflammation, potentially determining multi-organ dysfunction [4]. In frail patients, acute respiratory distress syndrome, sepsis, acute cardiac injury, and heart failure are the most common critical complications during exacerbation of COVID-19 [5].

COVID-19 virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor for ingress into host pneumocytes. In addition, the viral ribonucleic acid (RNA) has also been detected in the plasma or serum of COVID-19 patients, suggestive of viremia [6], which implies that apart from pneumocytes, the virus is freely available to interact with ACE2 expressed in other tissues [7].

The thyroid gland tissue exhibits a high ACE2 expression, and there are multiple indications of a potential relationship between the thyroid gland and COVID-19, considering the presence of the receptor for COVID-19 entry (ACE-2). This suggests that the thyroid gland could be a possible target of COVID-19. However, it is important to note that existing data on thyroid involvement in coronaviruses are limited [8], and the precise impact on thyroid function still requires further

clarification [9].

The highly unpredictable nature of the current pandemic has made it difficult to detect the severity of the condition in time. It is crucial to establish a reliable diagnostic marker to follow the pattern of disease development and to halt the process from getting severe, even fatal [10]. Moreover, identifying sensitive and specific biomarkers would create an opportunity to promote stronger preventive and therapeutic strategies [11].

Studies performed following the former outbreak of SARS in 2003, suggested that a coronavirus infection can cause thyroid dysfunction in people not previously diagnosed with thyroid disorders [12]. One study has found that SARS patients had low triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) levels [12]. The first case report in May 2020 of subacute thyroiditis after COVID-19 provided the suggestion of a possible link [13]. Since then, thyroid dysfunction, especially thyrotoxicosis due to thyroiditis, has been described in several COVID-19 patient cohorts [14], and according to other multiple studies, COVID-19 has been implicated in causing euthyroid sick syndrome (ESS), which is also known as low T3 syndrome or non-thyroidal sickness syndrome. ESS is characterized by disruptions in the core components of the hypothalamic-pituitary-thyroid (HPT) axis and alterations in thyroid hormone metabolism within various target organs. In fact, ESS is considered the most prevalent pattern of thyroid dysfunction resulting from viral infections.

It is also possible that some new-onset or recurrent thyroid diagnosed dysfunctions might be an aftermath of COVID-19. Moreover, a pre-existing or new-onset thyroid hormone imbalance, such as the low T3 syndrome, could be associated with the disease severity in COVID-19 [15, 16].

The aim if this study was to compare thyroid hormone levels of COVID-19 hospitalized patients in relation to disease severity and mortality.

Materials and Methods

Participants

This is a retrospective study. A total of 458 COVID-19 adult patients were admitted to the Ziv Medical Center in Safed, Israel, between April 2020 and October 2021. Patients were included if they were positive for the COVID-19 polymerase chain reaction (PCR) test on admission and were hospitalized in one of the designated COVID-19 wards. Forty-three patients were excluded from the study due to previous thyroid gland dysfunction. Four hundred fifteen patients were included in the final analysis.

Measurements

COVID-19 disease severity was determined according to their hemodynamic and respiratory status upon admission (i.e., patients who were hospitalized in the standard COVID-19 ward were defined with mild to moderate COVID-19, while patients who were hospitalized in the intensive care unit (ICU) were defined with severe to critical COVID-19). Blood tests to determine levels of T3, T4, and TSH were taken from patients in the emergency room (ER) during the admission process.

Upon each patient's admission to the ER, blood tests, including complete hemogram, biochemical profile, and inflammatory markers like C-reactive protein (CRP), were conducted. Subsequently, these tests were repeated each morning during their hospitalization and even multiple times in the same day, based on their individual medical conditions.

Regarding the review of the literature, it was found that patients with COVID-19 did not exhibit specific values for complete hemogram, biochemical profile, and inflammatory markers. Consequently, we did not discuss these parameters in a specific manner.

Demographic characteristics (age, gender, body mass index (BMI) and ethnicity) and clinical data (levels of T3, T4 and TSH, chronic diseases, duration of hospitalization and mortality) were collected from patient's electronic medical records.

Determination of T3, T4 and TSH levels

The serum levels of T3, T4 and TSH were measured by the electro-chemiluminescence immunoassay (ECLIA) method for use on Cobas immunoassay analyzer, using the following Roche Diagnostics GmbH kits No. 11731360 for T3, 06437281 for T4, and 08429324 for TSH. For each kit, the normal expected values correspond to the 2.5th and 97.5th percentile (Table 1).

According to those kits, the normal serum levels were: T3: 1.3 - 3.1 nmol/L, T4: 12 - 22 pmol/L, and TSH: 0.27 - 4.20 μIU/mL. Levels below those ranges were defined as out of the normal range, while all patients with higher levels were excluded from the study due to previous thyroid gland dysfunction.

Definition of patient's severity of COVID-19

Patients hospitalized in the standard COVID-19 ward were defined as mild to moderate, while patients hospitalized in the ICU were defined as severe to critical.

Ethical considerations

The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration and was approved by the local Ethical Committee at Ziv Medical Center (approval number: 0105-20-ZIV). All participants provided informed consent.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were presented as the mean (M) and 95% confidence interval (CI) since all variables did

Table 1. Levels and Normal Ranges of T3, T4, and TSH of Hospitalized COVID-19 Patients Stratified by Severity of COVID-19 and Patient Discharge Status

Variables (levels)	A. Severity of COVID-19		P[a]
	Mild/moderate (n = 374)	Severe/critical (n = 41)	
T3, nmol/L (M, (95% CI))	1.23 (1.18 - 1.29)	0.87 (0.79 - 0.95)	< 0.001
T4, pmol/L (M, (95% CI))	15.48 (15.09 - 15.86)	13.95 (12.71 - 15.20)	0.007
TSH, µIU/mL (M, (95% CI))	1.35 (1.17 - 1.53)	0.69 (0.39 - 0.99)	< 0.001

Variables (normal range)	B. Under Normal Range		P[b]
	Mild/moderate (%)	Severe/critical (%)	
T3 (1.3 - 3.1 nmol/L)	62.9	94.9	< 0.001
T4 (12 - 22 pmol/L)	14.3	25.6	0.068
TSH (0.27 - 4.20 µIU/mL)	10.4	48.8	< 0.001

Variables (levels)	C. Patient Discharge Status		P[a]
	Alive (n = 356)	Dead (n = 59)	
T3, nmol/L (M, (95% CI))	1.26 (1.20 - 1.32)	0.81 (0.75 - 0.87)	< 0.001
T4, pmol/L (M, (95% CI))	15.76 (15.39 - 16.13)	12.65 (11.53 - 13.77)	< 0.001
TSH, µIU/mL (M, (95% CI))	1.36 (1.17 - 155)	0.79 (0.54 - 1.05)	< 0.001

[a]P values were determined using the Mann-Whitney nonparametric test. [b]P values were determined using the Chi-square test. COVID-19: coronavirus disease 2019; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; M: mean; CI: confidence interval.

not show normal distribution shapes according to the Kolmogorov-Smirnov test of normality (Tables 1-3). Pearson's Chi-squared and the Fisher's exact test (depending on the sample size) were applied for testing the correlations between the study groups for the categorical variables.

Comparisons of continuous variables between the study groups were made using the Mann-Whitney nonparametric test (Tables 1-3). A multivariate logistic regression model was applied for testing the correlations between mortality and the study variables examined with adjustment to confounder (age

Table 2. Characteristics of Hospitalized COVID-19 Patients Stratified by Severity of COVID-19

Variables	All patients (n = 415)	Mild/moderate (n = 374)	Severe/critical (n = 41)	P
Age, years (M, (95% CI))	62.1 (60.5 - 63.7)	62.1 (60.4 - 63.9)	62.0 (58.0 - 66.1)	0.866
Gender (n, %)				
Male	230, 55.4	203, 54.3	27, 65.9	0.157
Female	185, 44.6	171, 45.7	14, 34.1	
BMI, kg/h^2 (M, (95% CI))[a]	29.6 (29.0 - 30.3)	29.6 (28.9 - 30.3)	29.9 (27.6 - 32.3)	0.745
Ethnicity (n, %)				
Jewish	173, 41.7	154, 41.2	19, 46.3	0.253
Druse	134, 32.3	125, 33.4	9, 22.0	
Muslim	94, 22.7	84, 22.5	10, 24.4	
Cristian	14, 3.3	11, 2.9	3, 7.3	
Duration of hospitalization, days (M, (95% CI))	9.2 (8.6 - 9.9)	8.6 (8.0 - 9.3)	14.6 (12.2 - 16.9)	< 0.001
Mortality (n, %)	59, 14.2	39, 10.4	20, 48.8	< 0.001
Hypertension (n, %)	193, 46.8	174, 46.9	19, 46.3	0.946
Diabetes (n, %)	147, 35.7	135, 36.4	12, 29.3	0.366
CVD (n, %)	101, 24.5	89, 24.0	12, 29.3	0.456
Chronic renal failure (n, %)	53, 12.9	51, 13.8	2, 4.9	0.140

[a]Missing data of 110 patients. ICU: intensive care unit; BMI: body mass index; CVD: cardiovascular disease; M: mean; CI: confidence interval.

Table 3. Characteristics of Hospitalized COVID-19 Patients Stratified by Patient Mortality

Variables	Alive (n = 356)	Dead (n = 59)	P
Age, years (M, (95% CI))	60.2 (58.5 - 61.9)	73.6 (70.2 - 77.0)	< 0.001
Gender (n, %)			
Male	191, 53.7	39, 66.1	0.075
Female	165, 46.3	20, 33.9	
BMI, kg/h^2 (M, (95% CI))[a]	29.7 (28.9 - 30.4)	29.6 (27.9 - 31.3)	0.998
Ethnicity (n, %)			
Jewish	151, 42.4	22, 37.3	0.657
Druse	112, 31.5	22, 37.3	
Muslim	82, 23.0	12, 20.3	
Cristian	11, 3.1	3, 5.1	
Duration of hospitalization, days (M, (95% CI))	8.3 (7.6 - 8.9)	15.0 (12.9 - 17.1)	< 0.001
Hypertension (n, %)	158, 44.8	35, 59.3	0.038
Diabetes (n, %)	117, 33.1	30, 50.8	0.009
CVD (n, %)	73, 20.7	28, 47.5	< 0.001
Chronic renal failure (n, %)	41, 11.6	12, 20.3	0.065

[a]Missing data of 110 patients. ICU: intensive care unit; BMI: body mass index; CVD: cardiovascular disease; M: mean; CI: confidence interval.

and gender) providing odds ratio (OR) and 95% CI (Table 4).

All analyses were performed using SPSS software, version 28.0 (IBM) with a statistical significance threshold of $P < 0.05$.

Results

A total of 415 positive COVID-19 patients were included in the study. Three hundred seventy-four patients (90%) with mild to moderate COVID-19 patients were hospitalized in the COVID-19 ward, while 41 patients (10%) with severe to critical COVID-19 were admitted to the COVID-19 ICU. Table 2 shows the demographic characterization of the participants. Patients with severe to critical COVID-19 were hospitalized for a longer period compared to patients who were hospitalized with mild to moderate COVID-19 (14.6 days vs. 8.6 days, respectively, $P < 0.001$). The mortality rate among patients with severe to critical COVID-19 was almost five-fold compared to patients with mild to moderate COVID-19 (48.8% vs. 10.4%, $P < 0.001$). No statistical differences in age, gender, ethnicity, chronic diseases, and BMI were found between the two groups of severity.

Stratified by patient mortality, Table 3 shows that patient mortality is characterized by higher age (73.6 vs. 60.2 years, $P < 0.001$), hospitalized for a longer period (15.0 vs. 8.3 days, $P < 0.001$), and suffer more from chronic diseases (hypertension: 59.3% vs. 44.8%, $P < 0.05$, diabetes: 50.8% vs. 33.1%, $P < 0.01$ and cardiovascular disease (CVD): 47.5% vs. 20.7%, $P < 0.001$). No statistical differences in gender, ethnicity, BMI, and chronic renal failure were found between the two groups.

Stratified by COVID-19 disease severity, T3, T4, and TSH

Table 4. Multivariate Logistic Regression Models to Predict Mortality Among COVID-19 Patients With Adjustment for Age and Gender

Variables	Values	N	OR	95% CI	P
T3	nmol/L		0.07	0.01 - 0.42	0.004
T4	Normal range (12 - 22 pmol/L)	352	Ref.		
	Below of normal range	63	3.08	1.18 - 8.08	0.022
TSH	Normal range (0.27 - 4.20 µIU/mL)	356	Ref.		
	Below of normal range	59	6.08	2.54 - 14.54	< 0.001
Duration of hospital stay	Days		1.12	1.06 - 1.18	< 0.001
Age	Years		1.07	1.05 - 1.16	0.004
Gender	Female	185	Ref.		
	Male	230	1.74	0.73 - 4.13	0.211

COVID-19: coronavirus disease 2019; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; OR: odds ratio; CI: confidence interval; Ref.: reference.

levels were significantly lower among patients with severe or critical disease, which were hospitalized in the COVID-19 ICU ward, compared to patients defined with mild or moderate disease and hospitalized in the standard COVID-19 ward ($P < 0.01$) (T3: 0.87 vs. 1.23 nmol/L, T4: 13.94 vs. 15.48 pmol/L, and TSH: 0.69 vs. 1.35 μIU/mL, respectively (Table 1A)). Further to the examination of the level's differences, when dichotomous values were defined - within/lower of the normal range, the proportion of patients with lower T3, T4, and TSH levels were common among patients with severe or critical disease, compared to patients defined with mild or moderate disease (T3: 94.9% vs. 62.9%, $P < 0.001$, T4: 25.6% vs. 14.3%, and TSH: 48.8% vs. 10.4%, $P < 0.001$ (Table 1B)). Significant lower T3, T4, and TSH levels were also characterized by the 59 (14.2%) patients who died during their hospitalization ($P < 0.001$) (Table 1C).

In Table 4, a multivariate logistic regression model was used to assess the correlation between mortality among COVID-19 patients and duration of hospital stay, T3 (continues), T4, and TSH (normal vs. out of normal range) with adjustment for age and gender. Most COVID-19 ICU patients (94.9%) were admitted with low T3 levels; therefore, we included it in the regression model as a continuous variable rather than a dichotomous variable, and we did not include the type of ward in the model (Table 4).

T4 and TSH out of the normal ranges were significantly associated with mortality (OR = 3.08, 95% CI: 1.18 - 8.08, $P < 0.05$ and OR = 6.08, 95% CI: 2.54 - 14.54, $P < 0.001$ respectively), as well as high duration of hospitalization (OR = 1.12, 95% CI: 1.06 - 1.18, $P < 0.001$) and older age of patient (OR = 1.07, 95% CI: 1.05 - 1.16, $P < 0.01$), while T3 was inversely associated with mortality (OR = 0.07, 95% CI: 0.01 - 0.42, $P < 0.01$). Patient's gender was not found to be a significant predictor of COVID-19 mortality (Table 4).

Discussion

The emergence of the SARS-CoV-2 virus in December 2019, which led to the coronavirus pandemic, has become a significant global healthcare issue with complex long-term medical implications.

Viral infections play a crucial role as environmental factors in the onset of various thyroid dysfunctions, including ESS, thyroiditis, clinical and subclinical hypothyroidism, central hypothyroidism, exacerbation of underlying autoimmune thyroid disease, as well as clinical and subclinical hyperthyroidism.

Recent studies have indicated that COVID-19 may have the potential to cause thyroid gland dysfunctions which could cause a more severe course of disease [17], especially in hospitalized ICU patients [18] and increase the mortality among affected individuals.

Multiple studies have suggested various mechanisms for COVID-19 infection. Yet, no clear evidence of the suspected mechanism and the possible resulting damage exists.

Vojdani et al have provided molecular evidence that COVID-19 antibodies react with the thyroid gland causing a thyroid hormones dysregulation [19].

Molecular analysis of thyroid surgical specimens demonstrated that thyroid follicular cells expressed ACE2 [20], and that cells expressing ACE2 are susceptible to COVID-19 damage once the patient is infected.

Autopsies of patients who died of COVID-19 observed disruption of thyroid follicles and parafollicular cells [21], which is a typical histopathological feature of thyroid injury.

One study showed that more than one-third of patients with COVID-19 infection can have abnormal thyroid function test (TFT), more so in those with severe illness. The most common thyroid function abnormality was a sick euthyroid syndrome, irrespective of thyroid autoantibody status [22].

Given the high mortality rate and the severity of COVID-19 disease, the concept of identifying a predictive factor for disease prognosis was brought forth. In our study we investigated the potential of thyroid hormone blood levels as a prognostic tool for assessing COVID-19 disease severity. The findings revealed a statistically significant association between lower levels of T3, T4, and TSH in the blood of hospitalized COVID-19 patients and increased disease severity as well as higher mortality rates.

In Table 2, we can observe a comparison of demographic information between the two groups. Notably, only the duration of hospitalization and mortality differed significantly between the groups. This suggests that patients admitted to the ICU were likely to be more ill and at a higher risk of deteriorating.

Interestingly, there were no significant differences between the two groups in terms of chronic illnesses, such as hypertension, diabetes, CVD, and chronic renal failure (CRF), as well as age, gender, and BMI. This suggests that these factors were not the main drivers of the differences observed in the duration of hospitalization and mortality between the two groups. This is an important observation, as the absence of significant differences in these factors suggests that the study might have been less biased concerning these variables. It can be considered a strength of the study, as it minimizes the potential impact of confounding variables on the outcomes. However, it is crucial to acknowledge that other variables, such as disease severity or treatment approaches, could still have influenced the results. These factors should be considered when interpreting the findings to obtain a comprehensive understanding of the study's implications.

Table 3 presents an analysis of the demographic characteristics in both the group of surviving patients and the group of deceased patients, with the aim of identifying any discernible differences between the two cohorts.

The mean age in the deceased patient's group (73.6) was clearly higher compared to the alive patient's group. A similar trend was observed for chronic diseases, as the deceased patient's group had a higher prevalence of hypertension (59.3%), diabetes (50.8%), and CVD (47.5%).

However, when examining Table 2, it becomes evident that these same factors did not show statistically significant differences between the ICU group and the standard ward group. This implies that there may be other factors contributing to the higher mortality rate, such as the increased number of hospitalization days observed in both the deceased patients

(15.0) and the ICU group patients. Additionally, we will later discuss the potential impact of thyroid hormone dysfunction on mortality, which will be detailed in Tables 1, 4.

Continuing with Table 3, no statistically significant differences were found between both groups regarding gender, ethnicity, BMI, and chronic renal failure. It is important to highlight that these factors also did not differ between the ICU and standard ward groups.

In summary, the deceased patient's group had a higher mean age and a greater prevalence of certain chronic diseases, but these factors did not significantly differ between the severe/critical patients group and mild/moderate patients groups. Other factors like prolonged hospitalization might be playing a role in the increased mortality rate.

In Table 1A, we have presented the average levels of each hormone in patients who were euthyroid. Notably, the mean average of each hormone in the severe/critical group was lower than in the mild/moderate ward group, with a particular emphasis on T3 and TSH. However, there was no significant difference in T4 levels between the two groups.

The outcomes of the study reveal that COVID-19 patients with severe or critical disease, who were hospitalized in the COVID-19 ICU ward, had significantly lower average levels of T3, T4, and TSH compared to those with mild or moderate disease hospitalized in the standard COVID-19 ward.

A recent study has demonstrated similar results, revealing that seriously ill patients tend to exhibit reduced levels of both serum T3 and T4. Moreover, low serum levels of total T4 are associated with a poor prognosis [15].

These findings suggest a potential association between COVID-19 disease severity and changes in thyroid function, which could even impact the mortality rate.

In Table 1B, we have presented the percentage of patients who had developed hypothyroidism according to the ward. Interestingly, we observed a higher percentage of patients with abnormal T3 levels in both groups, (62.9%) in the mild/moderate (regular ward) and (94.9%) in severe/critical (ICU). The same trend was observed for TSH, with a high percentage (48.8%) of patients in severe/critical group developing lower TSH levels, as compared to the mild/moderate group, where the percentage was only 10.4%.

Regarding T4, we observed a high percentage of dysregulation in the severe/critical group (25%), but this was not significantly different from the mild/moderate ward group ($P = 0.068$).

Overall, again these results suggest that low levels of T3 and TSH may be associated with a more severe disease course, The difference was particularly significant for T3 levels, with almost 95% of patients with severe or critical disease having lower T3 levels compared to only 62.9% of patients with mild or moderate disease.

These findings suggest a potential correlation between COVID-19 disease severity and thyroid hormone levels, which aligns with the conclusions of another study indicating a notable link between ESS and disease severity in COVID-19 patients [4].

However, as with Table 1A, this is an observational study, and further research is needed to establish causality between thyroid hormone levels and disease severity.

In Table 1C, we have presented the average levels of each hormone in the discharge home alive patients group and in the dead patients group. Interestingly, we observed that the average levels of each hormone were within the normal range in both groups. But patients with severe or critical disease, who were hospitalized in the COVID-19 ICU ward, had significantly lower levels of T3, T4, and TSH compared to patients with mild or moderate disease, who were hospitalized in the standard COVID-19 ward.

Furthermore, when dichotomous values were defined within or lower than the normal range, the proportion of patients with lower T3, T4, and TSH levels was significantly higher among patients with severe or critical diseases. This indicates that low T3, T4, and TSH levels may be associated with the severity of COVID-19 disease. However further research would be needed to establish the causality between thyroid hormone levels and mortality risk.

In relation to the pattern of thyroid hormone dysfunction, other studies have reported similar findings, consistent with what we have presented in Table 1. The prevailing hormonal abnormalities observed in ESS consist of low plasma T3, low or normal plasma T4, or high plasma reverse (rT3) concentrations, accompanied by a normal or slightly low TSH concentration [23].

In Table 4, a multivariate logistic regression model was used to predict mortality among COVID-19 patients with adjustment for age and gender.

The results indicate that T4 and TSH levels below the normal range are significantly associated with mortality, with ORs of 3.08 and 6.08, respectively. This suggests that thyroid dysfunction may play a role in the severity of COVID-19 and its associated mortality. The duration of hospitalization and older age were also significant predictors of mortality.

Interestingly, the analysis found that lower T3 levels were inversely associated with mortality, with an OR of 0.07. This finding contradicts the previous results showing that patients with severe or critical disease had lower T3 levels compared to those with mild or moderate disease. It is possible that the relationship between T3 and mortality is complex and affected by other factors not included in the model.

Regarding the treatment approach, management of ESS includes treating the underlying illness, in this case treating COVID-19. There is no need for thyroid hormone replacement in patients with ESS [24]. But according to the American Association of Clinical Endocrinology, they recommended the continuation of regular levothyroxine treatment for patients with recently diagnosed hypothyroidism after COVID-19 infection [25]. Therefore, each patient in our study received thyroid replacement therapy based on their individual condition.

Moreover, patients in the ICU group received steroid therapy (hydrocortisone), with the dosage tailored to their individual conditions, and they also received invasive ventilatory support. On the other hand, patients in the standard ward received only oxygen supplementation and hydrocortisone as per their individual requirements.

Immunization status was not reviewed since the data were not available for all included patients. The possibility of thyroid dysfunction lingering further than the acute phase of COVID-19 is not discussed since many patients have been lost to follow-up.

Conclusions

It has been observed that previously healthy people who are hospitalized for COVID-19 may develop thyroid dysfunction during hospitalization. Additionally, lower thyroid hormones and TSH serum levels have been found to be strongly associated with severity and mortality in COVID-19 hospitalized patients, and they may serve as additional tools for better evaluation of COVID-19 severity and mortality. These findings suggest that the possibility of utilizing thyroid hormone supplementation in hospitalized COVID-19 patients should be considered.

Indeed, it is important to note that this study is observational and only shows an association between thyroid dysfunction and COVID-19 severity and mortality. Further research is needed to confirm these findings and establish the causal relationship between the two.

Moreover, while the possibility of utilizing thyroid hormone supplementation in hospitalized COVID-19 patients is suggested, further research is also required to determine the efficacy and safety of such supplementation in this specific population. Therefore, caution should be exercised before implementing any interventions based solely on the findings of this study.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

All participants provided informed consent.

Author Contributions

Nidal El Khatib: conceptualization and design of the study, data collection, writing and editing; supervision or project administration. Adi Sharabi-Nov: statistical analysis, writing and editing. Raed Farhat: data collection, writing and editing. Or Sror-Turkel: data collection. Yaniv Avraham: conceptualization and design of the study, writing and editing, supervision or project administration. Shlomo Merchavy: conceptualization and design of the study, writing and editing, supervision or project administration.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. Seyed Hosseini E, Riahi Kashani N, Nikzad H, Azadbakht J, Hassani Bafrani H, Haddad Kashani H. The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. Virology. 2020;551:1-9. doi pubmed pmc
2. Tang X, Du RH, Wang R, Cao TZ, Guan LL, Yang CQ, Zhu Q, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. Chest. 2020;158(1):195-205. doi pubmed pmc
3. Meyer PT, Hellwig S, Blazhenets G, Hosp JA. Molecular imaging findings on acute and long-term effects of COVID-19 on the brain: a systematic review. J Nucl Med. 2022;63(7):971-980. doi pubmed pmc
4. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2021;22(4):803-815. doi pubmed pmc
5. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1295. doi pubmed
6. Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. Transfus Med Rev. 2020;34(2):75-80. doi pubmed pmc
7. Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. J Endocrinol Invest. 2020;43(7):1027-1031. doi pubmed pmc
8. Zhang Y, Lin F, Tu W, Zhang J, Choudhry AA, Ahmed O, Cheng J, et al. Thyroid dysfunction may be associated with poor outcomes in patients with COVID-19. Mol Cell Endocrinol. 2021;521:111097. doi pubmed pmc
9. Trimboli P, Camponovo C, Scappaticcio L, Bellastella G, Piccardo A, Rotondi M. Thyroid sequelae of COVID-19: a systematic review of reviews. Rev Endocr Metab Disord. 2021;22(2):485-491. doi pubmed pmc
10. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58(7):1021-1028. doi pubmed
11. Jafrin S, Aziz MA, Islam MS. Elevated levels of pleiotropic interleukin-6 (IL-6) and interleukin-10 (IL-10) are critically involved with the severity and mortality of COVID-19: an updated longitudinal meta-analysis and systematic review on 147 studies. Biomark Insights. 2022;17:11772719221106600. doi pubmed pmc
12. Wang W, Ye YX, Yao H, Sun LQ, Wang AS, et al. Evaluation and observation of serum thyroid hormone and parathyroid hormone in patients with severe acute respiratory syndrome. J Chin Anti-tuberculous Assoc. 2003;25:232-234 (In Chinese).

13. Kakodkar P, Kaka N, Baig MN. A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). Cureus. 2020;12(4):e7560. doi pubmed pmc
14. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY, Law CY, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. J Clin Endocrinol Metab. 2021;106(2):e926-e935. doi pubmed pmc
15. Zou R, Wu C, Zhang S, Wang G, Zhang Q, Yu B, Wu Y, et al. Euthyroid sick syndrome in patients with COVID-19. Front Endocrinol (Lausanne). 2020;11:566439. doi pubmed pmc
16. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid. 2014;24(10):1456-1465. doi pubmed pmc
17. Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. Thyroid. 2021;31(1):8-11. doi pubmed
18. Brix TH, Hegedus L, Hallas J, Lund LC. Risk and course of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism. Lancet Diabetes Endocrinol. 2021;9(4):197-199. doi pubmed pmc
19. Vojdani A, Vojdani E, Kharrazian D. Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. Front Immunol. 2020;11:617089. doi pubmed pmc
20. Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST, Villani L, et al. Detection of SARS-COV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. J Endocrinol Invest. 2021;44(5):1085-1090. doi pubmed pmc
21. Wei L, Sun S, Xu CH, Zhang J, Xu Y, Zhu H, Peh SC, et al. Pathology of the thyroid in severe acute respiratory syndrome. Hum Pathol. 2007;38(1):95-102. doi pubmed pmc
22. Patel D, Naik D, Kamalanathan S, Tamilarasu K, Sahoo J, Roy A, Merugu C, et al. Thyroid Function Abnormalities and Outcomes in Hospitalized Patients with COVID-19 Infection: A Cross-Sectional Study. Horm Metab Res. 2023;55(3):169-175. doi pubmed
23. Chopra IJ. Clinical review 86: Euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab. 1997;82(2):329-334. doi pubmed
24. Inaba H, Aizawa T. Coronavirus disease 2019 and the thyroid - progress and perspectives. Front Endocrinol (Lausanne). 2021;12:708333. doi pubmed pmc
25. Pramono LA. COVID-19 and thyroid diseases: how the pandemic situation affects thyroid disease patients. J ASEAN Fed Endocr Soc. 2020;35(2):155-157. doi pubmed pmc