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Abnormal TSH Level as a Predictor of Severe Outcomes Among Patients Hospitalized With COVID-19

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Abstract

Objective: **To assess the association between thyroid dysfunction and mortality among patients hospitalized with COVID-19. Design: This is a retrospective multi-center study, which examined all patients admitted with Covid-19 diagnoses, and thyroid function results in absence of known thyroid disease.**

Results: **10,933 hospitalized COVID-19 positive patients were included in the study. These patients were without prior diagnosis or treatment of thyroid disease. Outcomes assessed were mortality, ICU admission, Ventilator use, length of stay, readmission and complications during hospital stay. Patients with low TSH and Low free T4 had odds of mortality of 10.07(95% CI [7.44−13.6]) compared to patients with Normal TSH and any free T4 levels. Patients with Low TSH and High free T4 also had odds of mortality of 1.38 (95% CI [1.19−1.59]) compared to patients with Normal TSH and Any free T4 level. Patients with Low TSH and Normal free T4 levels also had an Odds of mortality of 1.46 (95% CI [1.31−1.62]) compared to patients with Normal TSH and any free T4 level. Patients with Low TSH also had higher odds of ICU admission and Ventilator use when compared to patients with normal TSH.**

Conclusions: **This study shows that patients with low TSH, regardless of free T4 level, indicates poor prognosis for hospitalized patients with SARS-CoV-2 infection and offers further insights into possible prognostic value of TSH levels for severe COVID-19 outcomes.**

Keywords: COVID-19, TSH, Thyroid dysfunction, Mortality, Hospital outcomes, Critical care

1. Introduction

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic by WHO in March of 2020.[1] Globally, as of March 29, 2023 there have been 761,402,282 confirmed cases of COVID-19, including 6,887,000 deaths.[2] So far there have been a total of 6,074,793 admissions to hospitals in the USA.[3] According to the National hospital care survey (NHCS) In-hospital mortality from selected hospitals in the US due to COVID-19 have decreased from 20.7% in April of 2020 to 2.8% in November of 2022.[4] The CDC has determined multiple underlying medical conditions associated with higher risk for severe COVID-19.[5] Multiple laboratory features have been associated with severe COVID-19 including D-dimer, CRP (C - reactive protein), LDH (Lactate Dehydrogenase), Troponin, Ferritin, and absolute lymphocyte count.[6−11]

There is a complex association between thyroid hormones and different aspects of immune responses.[12] Interaction between thyroid gland and COVID-19 is complex and bidirectional.[13] Several studies have shown abnormal thyroid function tests among patients with COVID-19.[14-19] Recent meta-analysis showed increased mortality odds among COVID-19 patients with abnormally low TSH.[20]

We conducted a retrospective analysis to observe the association between levels of TSH and free T4 with outcomes in patients admitted with COVID-19. Patients with COVID-19 were further divided into categories based on their thyroid function tests and

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were assessed for mortality, ICU admission, ventilator use, readmission, in-hospital complications.

2. Subjects and methods

This is a retrospective multi-center study performed on all patients admitted to the hospital with positive COVID-19 polymerase chain reaction tests between March 1 2020 and December 31, 2021. Protocol was submitted to IRB and the research activity was determined to be exempt from Institutional Review Board oversight in accordance with institutional regulations and policy. Patients were included from nationwide HCA databases. Inclusion criteria for this study were adult patients admitted to hospitals with a positive COVID-19 test and whose TSH and free T4 levels were available during that admission. First available TSH and free T4 level during that hospitalization were used in the analysis. Diagnosis codes were used for exclusion of patients. Exclusion criteria included any patients with pre-existing history of hyper- or hypothyroidism, or documented use of thyroid supplementation or thyroid suppression medications (Supplement Figure 1) (Supplement Table 1 for diagnosis code of exclusion diagnosis). TSH values are in microIU/ml. Free T4 values are in ng/dl.

Baseline characteristics were obtained including Age, Sex, Race, history of Diabetes Mellitus (DM), Hypertension (HTN), Congestive heart failure (CHF), Chronic obstructive pulmonary disease (COPD), Asthma, End Stage renal disease (ESRD), Chronic kidney disease (CKD) (Please see Supplement Table 1 for the diagnosis code used). Outcomes obtained were Mortality, ICU admission, Ventilator use (Intubation), Readmission in 30 days of discharge, Complications during index hospital stay. Patients were recorded to have complications if they had at least one of Deep vein thrombosis (DVT), Pulmonary Embolism (PE), Atrial fibrillation (Afib), Stroke, Transient ischemic attack (TIA), Myocardial infarction (MI). To have complication recorded; diagnosis code must not be present on admission diagnosis (Supplement Table 1 for Diagnosis code used).

3. Statistical analysis

Logistic Regression model used to predict mortality, Readmission, Complication. ICU admission, Ventilation use. Odds ratio for outcomes calculated after keeping the variables constant. Variables used in the regression model were age, sex, race, DM, HTN, CHF, COPD, Asthma, ESRD and CKD. Linear Regression model used to predict the value of length of stay, after the variables were held constant. Variables used for linear regression model were Age, Race, DM, HTN, CHF, COPD, Asthma, ESRD, and CKD.

4. Results

Initially there were 17,922 encounters obtained and then after applying exclusion criteria, there were 10,933 unique patients in the final data set. A majority of patients were classified into Group D (Table 1) with TSH >0.36. 53.9% patients were male and 57.7% patients were White (Table 2). Out of the total sample size, 24.1% of patients died and 39.9% of patients went into ICU. 22.3% of patients were readmitted, 21.9% of patients had ventilator use, 5.2% had at least one complication during hospital stay (Supplement Table 2). Patients with Low TSH/Low free T4 had a mortality rate of 66.4%, ICU admission rate of 75.6% and ventilator rate of 65.4 % (Table 3). Mean age of the patient population was 62.06 years and mean length of stay was 12.21 days.

A Logistic regression model was used to predict mortality between abnormal thyroid level groups and normal thyroid level group after variables including age, sex, race, DM, HTN, CHF, COPD, Asthma, ESRD, CKD were held constant. Patients with Low TSH/Low free T4, Low TSH/High free T4, Low TSH/Normal free T4 (Group A,B,C) had higher odds of mortality when compared to patients with Normal TSH (Group D). Patients with highest odds of mortality were those with Low TSH/Low free T4 - OR of 10.07 (95% Confidence Interval [7.4–13.6] (Table 4). Similarly, there were higher odds of having ICU admission and ventilator use with abnormal TSH compared to normal TSH (Table 4), and higher odds of in-hospital complication in groups with Low TSH/Low free T4 and Low TSH/Normal free T4 when compared with patients of Normal TSH. Readmission was not clinically significant in patients with Low TSH/Low free T4 and Low TSH/Normal free T4 when compared to patients with Normal TSH. Other

Table 1. Patients were divided into four categories based on thyroid levels.

CATEGORIES (Based on Thyroid function tests)	TSH LEVEL (mIU/ml)	Free T4 LEVEL (ng/dl)
GROUP A (LowTSH/Low free T4)	<0.36	<0.76
GROUP B (LowTSH/High free T4)	<0.36	>1.46
GROUP C (Low TSH/Normal free T4)	<0.36	0.76–1.46
GROUP D (Normal TSH)	>0.36	Any T4 Level

Table 2. Demographics.

	N (No. of Patients)	N%
Female	5069	46.1%
Male	5924	53.9%
Race: Black	2065	18.8%
Race: White	6347	57.7%
Race: Other	2581	23.5%
DM (Diabetes Mellitus)	5086	46.3%
HTN (Hypertension)	7909	71.9%
Asthma	786	7.2%
COPD	1683	15.3%
ESRD	531	4.8%
CKD	2009	18.3%
Thyroid Group A[a]	1275	11.6%
Thyroid Group B[a]	217	2.0%
Thyroid Group C[a]	3238	29.5%
Thyroid Group D[a]	6263	57.0%

[a] See Table 1 for classification of groups according to thyroid function tests.

variables including DM, CHF, ESRD, and CKD were all associated with higher odds of mortality (Supplement Tables 3 and 4). Results from the linear regression model depicted significantly higher length of stay in the Low TSH/Low free T4 group of 9.89 days when compared to Normal TSH/Any free T4 group (Table 5). Other variables increasing length of stay were DM, HTN, CHF, COPD, ESRD, and CKD (Table 5).

5. Discussion

Our study has shown a significant increase in mortality in COVID-19 patients with low TSH, regardless of T4 levels. Our study has the highest sample size in evaluating thyroid function tests in hospitalized patients with COVID-19. HCA Healthcare is one the nation's leading providers of health care services with hospitals across 20 states in the USA.[21] This study is unique, as it comprises data from nationwide HCA hospitals that yields substantial sample size. Our study has shown a significant increase in mortality in COVID-19 patients with Low TSH when compared to normal TSH. Mortality is even higher with Low TSH and Low free T4.

SARS-CoV-2 can have effects on the thyroid gland. ACE-2 receptor is expressed in thyroid follicular cells, making them a potential target for the viral entry.[22] The term "cytokine storm syndrome" is used to describe severe COVID-19 disease characterized by hyper-cytokinemia leading to multiorgan failure.[23,24] Angiotensin-converting enzyme 2 (ACE2) is involved in SARS-CoV-2 internalization into host cells. They are present in thyroid epithelial cells, the hypothalamus, and the pituitary gland. They play a role in the pathogenesis of thyroid disease during COVID-19 infection by

Table 3. Outcomes among different thyroid level groups.

Variable	Group A Low TSH/Low free T4 No. of patients = 217	Group B Low TSH/High free T4 No. of patients = 1275	Group C Low TSH/Normal free T4 No. of patients = 3238	Group D Normal TSH No. of patients = 6263
Mortality	144 (66.4%)	359 (28.2%)	831 (25.7%)	1317 (21.0%)
ICU admission	164 (75.6%)	583 (45.7%)	1373 (42.4%)	2267 (36.2%)
Ventilator	142 (65.4%)	281 (22.0%)	752 (23.2%)	1234 (19.7%)
Complication[a]	32 (14.7%)	55 (4.3%)	186 (5.7%)	295 (4.7%)
Readmission[b]	53 (24.4%)	255 (20.0%)	696 (21.5%)	1447 (23.1%)

[a] Complication: At least one of Deep vein thrombosis (DVT), Pulmonary Embolism (PE), Atrial fibrillation (A fib), Stroke, Transient ischemic attack (TIA), Myocardial infarction (MI).
[b] Readmission: Patient readmitted within 30 days of discharge with any diagnosis.

Table 4. Odds Ratio comparing abnormal TSH levels to normal TSH levels.

	Low TSH/Low T4 vs Normal TSH/Any T4		Low TSH/High T4 vs Normal TSH/Any T4		Low TSH/Normal T4 vs Normal TSH/Any T4	
	OR (CI)	p-Value	OR (CI)	p-Value	OR (CI)	p-Value
Mortality	10.07 (7.4–13.6)	<0.0001	1.38 (1.19–1.59)	<0.0001	1.46 (1.31–1.62)	<0.0001
ICU	5.53 (4.02–7.61)	<0.0001	1.50 (1.32–1.70)	<0.0001	1.37 (1.25–1.50)	<0.0001
Ventilator	7.76 (5.79–10.40)	<0.0001	1.18 (1.01–1.37)	0.0281	1.30 (1.17–1.44)	<0.0001
Complication[a]	3.57 (2.4–5.32)	<0.0001	0.88 (0.65–1.18)	0.411	1.30 (1.07–1.57)	0.0067
Readmission[b]	1.11 (0.81–1.53)	0.4888	0.83 (0.71–0.97)	0.0191	0.93 (0.84–1.03)	0.2046

OR= Odds Ratio, CI = (95% Confidence Interval). Odds ratio for comparison after variables including age, sex, race, DM, HTN, CHF, COPD, Asthma, ESRD, and CKD were held constant.
[a] Complication: Patient were recorded to have complication if they had at least one of Deep vein thrombosis (DVT), Pulmonary Embolism (PE), Atrial fibrillation (A fib), Stroke, Transient ischemic attack (TIA), Myocardial infarction (MI).
[b] Readmission: Patient readmitted within 30 days of discharge with any diagnosis.

Table 5. Linear Regression model to compare length of stay.

Comparison Variables	Estimate LOS difference (Days)	p-Value	CI
Low TSH/Low free T4 vs Normal TSH/Any free T4	9.89	<0.0001	7.97–11.81
Low TSH/High free T4 vs Normal TSH/Any free T4	−0.03	0.93	−0.89–0.82
Low TSH/Normal free T4 vs Normal TSH/Any free T4	0.60	0.04	0.005–1.21
DM vs No DM	2.09	<0.0001	1.53–2.66
HTN vs No HTN	2.81	<0.0001	2.12–3.50
CHF vs No CHF	2.68	<0.0001	1.85–3.51
COPD vs No COPD	0.86	0.026	0.10–1.63
ESRD vs No ESRD	5.31	<0.0001	4.04–6.58
CKD vs No CKD	1.61	<0.0001	0.88–2.35
Asthma vs No Asthma	0.08	0.86	−0.95–1.13

Linear regression model to compare length of stay differences between different variables. Besides the comparison variables, other variables including age, sex, race, DM, HTN, CHF, COPD, Asthma, ESRD, CKD, Thyroid level groups were held constant.

facilitating the entry of SARS-CoV-2 into the thyroid cells, hypothalamus, and the thyroid gland.[22,25] Also in one retrospective study it was found that in COVID-19 infection the TSH and FT3 are lower than in other patients with pneumonia or other illnesses.[14] In general, activation of the interleukin storm with the participation of IL-6 leads additionally to reduce TRH and TSH secretion by complex mechanisms and thyroid gland abnormalities. There is an interplay between the direct action of the SARS-CoV-2 virus and the interleukin storm in the pathogenesis of thyroid abnormalities in patients with COVID-19. Cytokines and inflammation affect the hypothalamus-pituitary-thyroid (HPT) axis and might be related to non-thyroidal illness syndrome.[25] The elevated cytokines and pro-inflammatory conditions during COVID-19 are likely responsible for the effects on the HPT axis.[25] One of the mechanisms proposed is that although the T3 is decreased in the circulation locally in the hypothalamus there is the activation of the enzyme deiodinase-2 which increases the conversion of T4 to T3 and T3 suppresses the secretion of TRH and subsequently the TSH secretion decreases.[25]

Non-thyroidal illness (NTI) is alterations in thyroid hormone tests in critical illness.[26] NTI are characterized by low plasma concentrations of active triiodothyronine (T3), low or normal plasma thyroxine (T4), and elevated reverse T3 (rT3) in the presence of low normal or normal TSH.[26,27] There are speculations that changes in thyroid function during critical illness might be protective.[28,29] J Vidart et al. did a systematic review and meta-analysis of NTI and mortality outcomes in critically ill patients.[30] NTI had an OR 2.21 (95% Confidence Interval (CI) [1.64–2.97]) for mortality but had high heterogeneity among the studies analyzed.[30] Pooled analysis on levels of TSH showed there was no difference in TSH levels between survivors and non-survivors.[30] Results are different in our study in which low TSH levels were significantly associated with higher mortality in COVID-19 patients. Low TSH with low free T4 had approximately 10 times higher odds of mortality in our population compared to normal TSH. Our study offers a new perspective regarding specific TSH levels in COVID-19 compared to previous NTI studies in critically ill patients.

Our study has multiple strengths. The sample size of 10,993 patients makes it the largest retrospective study on thyroid dysfunction and hospitalized COVID-19 patients. Rossetti et al. did a systematic review on available studies on COVID-19 hospitalized patients and thyroid dysfunction. They analyzed 27 studies with total patients' sample size of 4554 patients. For the studies reviewed, the number of patients evaluated ranged from 50 to 506.[26] By excluding patients with hypothyroidism, hyperthyroidism, and home thyroid medications (Levothyroxine, armor thyroid, Synthroid, Propylthiouracil and Methimazole), we tried to evaluate the effect of COVID-19 on thyroid function tests without prior existing thyroid issues. We also matched the major variables, which could have an impact on COVID-19 outcomes to observe the sole association of thyroid function tests to severe outcomes in COVID-19 patients. By using HCA nationwide databases, we utilized data from multiple centers/states and a variety of populations. Our sample population was divided into four groups of thyroid function tests, which helps to evaluate the impact of different thyroid levels on COVID-19 outcomes.

Our study does have limitations. Being a retrospective study, we only included patients who had TSH and free T4 levels drawn. We could have missed patients who did not have thyroid levels drawn. In addition, we did not have T3 levels in our study, which could have caused further stratification of thyroid test groups. The TSH level >0.36 was considered normal in our study which could have

some patients with levels more than four microIU/ml. Another limitation is corticosteroid use was not evaluated. Steroids are used in treatment for severe COVID-19 infection and steroids can decrease TSH levels.[31] We need also to take into consideration that the TSH decreases also as a result of COVID -19 infection and to higher degree as per some studies than in other infections[26] irrespectively of the use of steroids.[26] Another limitation is that HCA database comprises data from multiple hospitals and different hospitals might be using different thyroid assays for measurement. Thyroid hormones modulate innate and adaptive immune responses. Thyroid hormone metabolism plays an important role in the host's defense against infection through the modulation of innate immune cell function.[32,33] Hyperthyroid state leads to a more activated immune system whereas hypothyroidism leads to a less activated immune system.[34] COVID-19 could have an impact on thyroid function and thyroid dysfunction could affect the prognosis of COVID-19. Our study adds to evidence of thyroid dysfunction associated with worse clinical outcomes in COVID-19 patients with a very high sample size. Further studies are needed to see the impact of thyroid hormone replacement therapy in severe COVID-19 and from the literature in non-thyroidal illness, there is no effect of thyroid hormone replacement in NTI because the process serves as an energy saver for the organism.[26]

6. Conclusion

In this large study of patients hospitalized with COVID-19 we found that patients with low TSH, regardless of T4 level, indicate poor prognosis including higher odds of mortality, ICU admission and ventilator use.

Disclaimer

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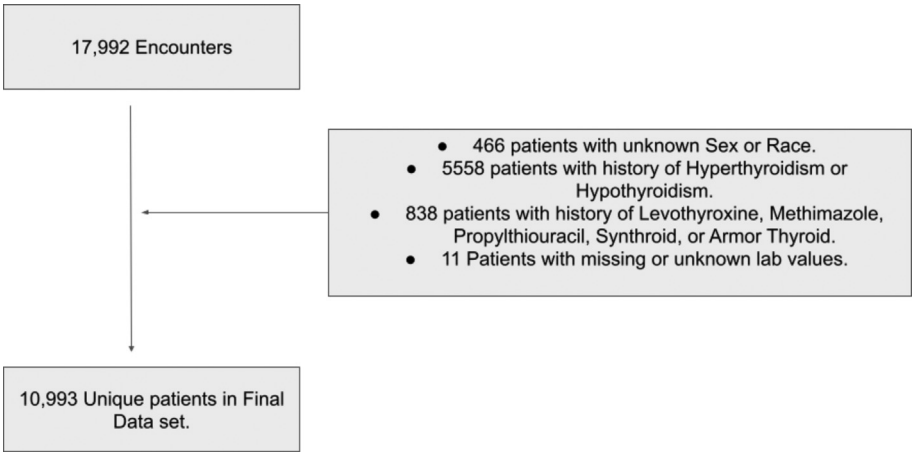
Ethical information

Protocol was submitted to IRB and this research activity was determined to be exempt from Institutional review board oversight in accordance with current regulations and institutional policy.

Conflicts of interest

All authors have no financial disclosures or conflicts of interest to report.

Supplementary material



Supplement Fig. 1. Patients included in the final data set.

Supplement Table 1. : Diagnosis code.

DVT	I82
PE	I26
Atrial fibrillation	I48
Stroke	I63
TIA	G45
Myocardial infarction	I21
DM	E08, E09, E10, E11, E13
HTN	I10, I11, I12, I13, I15, I16
CHF	I502, I503, I504
COPD	J41, J42, J43, J44
Asthma	J45
ESRD	N186
CKD	N18
Hypothyroidism (Exclusion Criteria)	E03.9
Hyperthyroidism (Exclusion Criteria)	E05

Supplement Table 2. Outcomes.

Variable	No. of Patients (N)	N%
Mortality	2651	24.1%
ICU admission	4387	39.9%
Readmission	2451	22.3%
Ventilator use	2409	21.9%
Complication*	568	5.2%
DVT	131	1.2%
PE	66	0.6%
MI (Myocardial Infarction)	95	0.9%
TIA	5	0.0%
Stroke	98	0.9%

*Patient were recorded to have complication if they had at least one of Deep vein thrombosis (DVT), Pulmonary Embolism (PE), Atrial fibrillation (A fib), Stroke, Transient ischemic attack (TIA), Myocardial infarction (MI).

Supplement Table 3. Odds ratio for comparison between variables.

	DM vs No DM		HTN vs No HTN		CHF vs No CHF	
	OR (CI)	p-Value	OR (CI)	p-Value	OR (CI)	p-Value
Mortality	1.19 (1.08−1.32	0.0003	1.08 (0.95−1.23)	0.192	1.37 (1.20−1.56)	<0.0001
ICU	1.43 (1.31−1.55)	<0.0001	1.34 (1.21−1.49)	<0.0001	1.68 (1.49−1.90)	<0.0001
Ventilator	1.38 (1.25−1.52)	<0.0001	1.46 (1.28−1.66)	<0.0001	1.49 (1.30−1.70)	<0.0001
Complication[δ]	1.16 (0.97−1.39)	0.09	1.37 (1.08−1.75)	0.0099	1.25 (0.99−1.59)	0.0578
Readmission[#]	0.96 (0.87−1.06)	0.5052	1.06 (0.94−1.19)	0.3404	1.13 (0.99−1.29)	0.0680

OR= Odds Ratio, CI = Confidence Interval. Besides the variables being compared, other variables including age, sex, race, DM, HTN, CHF, COPD, Asthma, ESRD, CKD, Thyroid level groups were held constant.
[δ]Complication: Patient were recorded to have complication if they had at least one of Deep vein thrombosis (DVT), Pulmonary Embolism (PE), Atrial fibrillation (Afib), Stroke, Transient ischemic attack (TIA), Myocardial infarction (MI).
[#]Readmission: Patient readmitted within 30 days of discharge with any diagnosis.

Supplement Table 4. Odds ratio for comparison between variables.

	COPD vs No COPD		ESRD vs No ESRD		CKD vs No CKD	
	OR (CI)	p-Value	OR (CI)	p-Value	OR (CI)	p-Value
Mortality	1.05 (0.93−1.19)	0.3771	1.75 (1.43−2.14)	<0.0001	1.73 (1.54−1.94)	<0.0001
ICU	1.11 (0.99−1.25)	0.998	1.72 (1.43−2.07)	<0.0001	1.49 (1.43−2.07)	<0.0001
Ventilator	0.98 (0.86−1.12)	0.8568	2.00 (1.65−2.42)	<0.0001	1.59 (1.41−1.79)	<0.0001
Complication[δ]	0.76 (0.59−0.98)	0.03	1.59 (1.14−2.21)	0.0058	1.14 (0.92−1.42)	0.2134
Readmission[#]	1.15 (1.02−1.31)	0.0202	1.37 (1.2−1.69)	0.0020	1.35 (1.2−1.52)	<0.0001

OR= Odds Ratio, CI = Confidence Interval. Besides the variables being compared, other variables including age, sex, race, DM, HTN, CHF, COPD, Asthma, ESRD, CKD, Thyroid level groups were held constant.
[δ]Complication: Patient were recorded to have complication if they had at least one of Deep vein thrombosis (DVT), Pulmonary Embolism (PE), Atrial fibrillation (Afib), Stroke, Transient ischemic attack (TIA), Myocardial infarction (MI).
[#]Readmission: Patient readmitted within 30 days of discharge with any diagnosis.

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