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RAPID COMMUNICATION

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Association of hypothyroidism with outcomes in hospitalized adults with COVID-19: Results from the International SCCM Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) is associated with high rates of morbidity and mortality. Primary hypothyroidism is a common comorbid condition, but little is known about its association with COVID-19 severity and outcomes. This study aims to identify the frequency of hypothyroidism in hospitalized patients with COVID-19 as well as describe the differences in outcomes between patients with and without pre-existing hypothyroidism using an observational, multinational registry.

Methods: In an observational cohort study we enrolled patients 18 years or older, with laboratory-confirmed severe acute respiratory syndrome coronavirus-2 infection between March 2020 and February 2021. The primary outcomes were (1) the disease severity defined as per the World Health Organization Scale for Clinical Improvement, which is an ordinal outcome corresponding with the highest severity level recorded during a patient's index COVID-19 hospitalization, (2) in-hospital mortality and (3) hospital-free days. Secondary outcomes were the rate of intensive care unit (ICU) admission and ICU mortality.

Results: Among the 20,366 adult patients included in the study, pre-existing hypothyroidism was identified in 1616 (7.9%). The median age for the Hypothyroidism group was 70 (interquartile range: 59–80) years, and 65% were female and 67% were White. The most common comorbidities were hypertension (68%), diabetes (42%), dyslipidemia (37%) and obesity (28%). After adjusting for age, body mass index, sex, admission date in the quarter year since March 2020, race, smoking history and other comorbid conditions (coronary artery disease, hypertension, diabetes and dyslipidemia), pre-existing hypothyroidism was not associated with higher odds of severe disease using the World Health Organization disease severity index (odds ratio [OR]: 1.02; 95% confidence interval [CI]: 0.92, 1.13; $p = .69$), in-hospital mortality (OR: 1.03; 95% CI: 0.92, 1.15; $p = .58$) or differences in hospital-free days (estimated difference 0.01 days; 95% CI: −0.45, 0.47; $p = .97$). Pre-existing hypothyroidism was not associated with ICU admission or ICU mortality in unadjusted as well as in adjusted analysis.

Conclusions: In an international registry, hypothyroidism was identified in around 1 of every 12 adult hospitalized patients with COVID-19. Pre-existing hypothyroidism in hospitalized patients with COVID-19 was not associated with higher disease severity or increased risk of mortality or ICU admissions. However, more research on the possible effects of COVID-19 on the thyroid gland and its function is needed in the future.

KEYWORDS
COVID-19, COVID-19 disease severity, hypothyroidism, mortality

1 | INTRODUCTION

The World Health Organization (WHO) declared COVID-19 global pandemic in March 2020.[1] Even though Acute Respiratory Distress Syndrome is the most common severe complication that can lead to a fatal outcome, other common risk factors in the infection's progression were considered to be the pre-existing comorbidities, such as diabetes, obesity, coronary artery disease, psychiatric and neurological complications.[2–12] Given these multitude of complications, scientists and healthcare workers around the world have not formed a consensus over a uniform therapy for treating COVID-19.[11,13–16]

Thyroid hormones are highly involved in regulating innate and adaptive immune responses.[17–19] Additionally, thyroid hormone dysregulation is commonly described in critically ill patients admitted to the intensive care unit (ICU).[20] While the severe respiratory syndrome coronavirus 2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2) receptors to enter human cells,[21] which are also expressed on the thyroid gland,[22] integrins facilitate internalization of the SARS-CoV-2 and may also serve as alternative receptors.[23] The receptor for levothyroxine in tissues is located in close vicinity to the viral binding region or domain of the integrin αvβ3. Levothyroxine is known to regulate the internalization of αvβ3, and proteins bound to it, and also influence cytokine expression. Therefore, levothyroxine is proposed to potentially enhance SARS-CoV-2 uptake and facilitate cytokine storm.[24] Zhang et al.[20] studied thyroid functions in 71 patients with COVID-19 infection. This retrospective study found that 64% of the patients had thyroid dysfunction, and 56% of the COVID-19 patients had lower thyroid-stimulating hormone (TSH) levels than the control. Similarly, Chen et al.[25] described low TSH and total triiodothyronine (TT3) in COVID-19 patients and a positive correlation between TSH and TT3 serum levels and COVID-19 infection severity after retrospectively studying 50 COVID-19 patients. Also, there is suspicion that the destruction of thyroid tissue may be a complication of COVID-19, even in patients without pre-existing endocrinological conditions.[26] Even when it is known that the thyroid gland expresses angiotensin-converting enzyme 2 (ACE2) receptors,[27] the association between hypothyroidism and outcomes in patients with COVID-19 has been explored mainly in small single-centre retrospective studies.[28] It is therefore essential to understand the correlation between hypothyroidism and COVID-19.

In this observational study, we are describing the frequency of hypothyroidism and the association of the effects of pre-existing hypothyroidism in COVID-19 using a Multicentre, International Society of Critical Care Medicine's Discovery Viral Infection and Respiratory Illness University Study (VIRUS): COVID-19 Registry.

2 | MATERIALS AND METHODS

2.1 | Study population

This study was performed as an ancillary project on data collected within the scope of the VIRUS: COVID-19 Global Registry.[29–31] The VIRUS: COVID-19 Registry is an international database of hospitalized patients with COVID-19. The study was approved by the Mayo Clinic International Review Board as exempt (IRB:20-002610).[29–31] The database collected hospitalization information of more than 20,000 patients with COVID-19 from March 2020 to February 2021. Study data were recorded and managed using the Research Electronic Data Capture System.[32] The study is registered on Clinicaltrials. gov: NCT04323787.

2.2 | Study inclusion/exclusion criteria

All patients 18 years or older, hospitalized due to COVID-19 (laboratory-confirmed SARS CoV2-related hospitalization) at participating institutions were included in this study. Patients with COVID-19-unrelated hospitalization, readmitted or without research authorization were not included in the study.

We included patients where we have responses (yes or no) for hypothyroidism as documented comorbidities in the VIRUS Registry case report form. We mainly focus on primary hypothyroidism as comorbidities, which accounts for over 95% of cases of hypothyroidism.[33,34] The clinical definition of primary hypothyroidism and associated International Classification of Diseases 9 and 10 (ICD 9 and ICD 10) codes were provided in VIRUS standard operating procedure to all participating sites and data abstractor before filling data in redcap for VIRUS Registry to identify a preadmission diagnosis of hypothyroidism in the electronic medical record. Comorbidities were a “check all that apply” response, and a “none” option was only recently added. As such, (i) for specific comorbidities, we were unable to separate a “no” and “unknown/missing” response, and (ii) at the patient level, we were unable to separate “none” from “did not complete” the section. Because comorbidities should frequently be present in adult patients hospitalized with COVID-19, as identified previously in our registry,[9] where 87% of included patients had at least one comorbid condition, we excluded hospitals with more than 70% of patients having “none” comorbidities were excluded. Hospitals below the threshold were considered noncompliant or not fully contributing. We took into consideration that the range of comorbidities in hospitalized patients is indeed around 90%, but also there are data showing that the percentage of the US adult population known to have two or more underlying medical conditions ranges is highly variable (38%–64% by state); therefore, we choose a value in between these two statistics.[35] Additionally, we used histograms to select natural cutoff values for comorbidities and oxygen support (Figures S1 and S2). The histograms reflected the distribution of the percentage of comorbidity data and percentage of oxygen support data that were captured at each site. The oxygenation method, which corresponds to the disease severity outcome, was similarly recorded. Because some level of supplemental support was common amongst hospitalized COVID-19 patients, we excluded hospitals with more than 50% of patients having “none” oxygenation support documented. The large majority of excluded patients were from sites in the United States. The average number of patients

excluded from sites in the United States was 923, and the median number excluded was 17.5.

2.3 | Outcome measures

The primary outcome of interest was disease severity, which is an ordinal outcome based on the Ordinal Scale for Clinical Improvement developed by WHO[36] that uses the highest severity level recorded during a patient's index COVID hospitalization. The severity levels pertinent to our population are (i) hospitalized but did not receive any oxygen support, (ii) oxygen by mask or nasal prongs, (iii) noninvasive ventilation or high-flow oxygen, (iv) intubation and mechanical ventilation, (v) ventilation and additional organ support (pressors, renal replacement therapy and/or extracorporeal membrane oxygenation) and (vi) death.

Other predefined outcomes of interest were in-hospital mortality and hospital-free days, ICU admission rate and ICU mortality. We calculated the hospital-free days subtracting hospital length of stay from 28. If patients died in the hospital, hospital-free days were 0. If hospital length of stay was longer than 28, then hospital-free days were 0.

2.4 | Statistical analysis and data reconfiguration

Patient demographics were summarized using median and interquartile range (IQR, i.e., 25th, 75th percentile) for continuous variables and frequency counts and percentages for categorical variables. These characteristics were presented separately for patients with hypothyroidism and those without. We evaluated the frequency of hypothyroidism and the association of outcomes with hypothyroidism. Unadjusted and multivariable mixed-effects proportional odds regression models assessed the association between hypothyroidism and ordinal disease severity during hospitalization. Models were fitted using a random intercept at the hospital level to account for the clustering of patients within locations. A proportional odds regression model analyses the relationship between pre-existing hypothyroidism and odds of the worse (higher level) outcome, that is, an odds ratio (OR) > 1 would suggest that pre-existing hypothyroidism is associated with worse outcomes than no pre-existing hypothyroidism. Unadjusted and multivariable-adjusted logistic regression models assessed the association between hypothyroidism and binary outcomes of interest. Models were fitted with generalized estimating equations (GEEs)[37] and an exchangeable working correlation to account for the clustering of patients within locations. Similarly, unadjusted and multivariable-adjusted linear regression models with GEE assessed the association between hypothyroidism and continuous outcomes. Adjustment variables included age,[38] body mass index (BMI),[38] gender,[38] race,[39] smoking history,[40] admission date in the quarter year since March 2020, and comorbidities (coronary artery disease,[41] hypertension,[41] diabetes[38] and dyslipidemia[42]). Multicollinearity of multivariable-adjusted models was assessed using variance inflation factors. Values of five or greater indicate collinearity; no multicollinearity was detected.

Despite hospital-level exclusions, there remained missing data. Data were missing for at least 10% of patients for disease severity (14%), ICU admission (11%), hospital mortality (10%), ICU mortality (15%), ICU-free days (15%), BMI (28%), admission date (36%) and smoking history (30%). Multiple imputation was used assuming data were missing at random, possibly related to other observed variables. Twenty imputed data sets were created, analyses run on each and results pooled across imputations to account for uncertainty in missingness. A sensitivity analysis was conducted for primary outcomes using only patients with complete data. Models for the sensitivity analysis were the same as the models used for the main analysis. In all analyses, two-tailed p values of .05 or less were considered statistically significant. Data management and statistical analysis were performed in SAS Studio 3.8 (SAS Institute Inc.).

3 | RESULTS

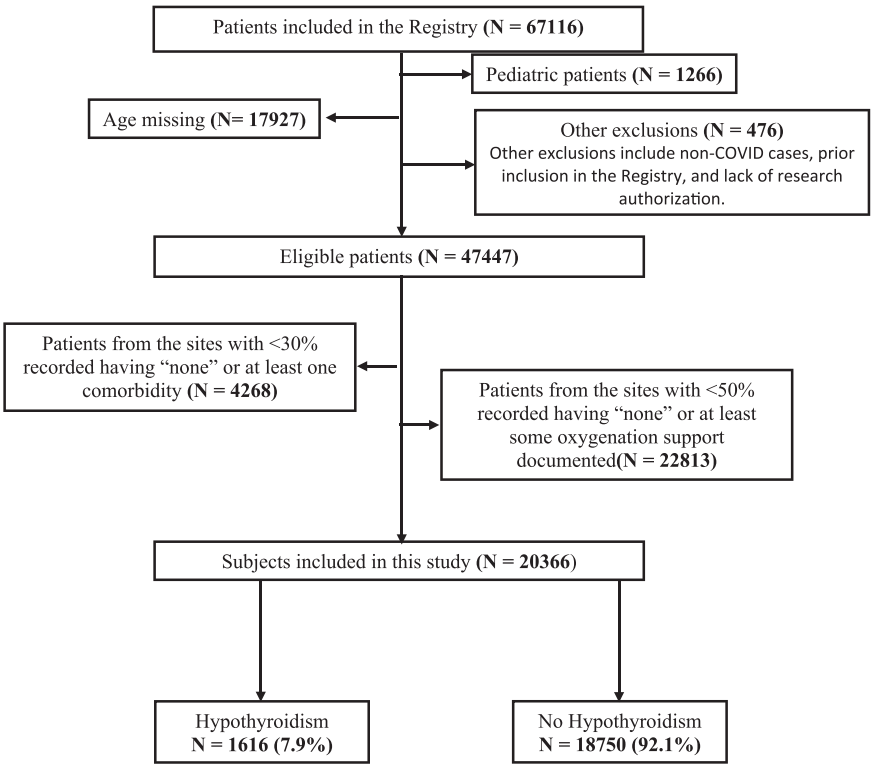
After following the eligibility criteria, we included 20,366 adult patients with laboratory SARS CoV2 |infection (Figure 1, flowchart). There were 1616 (7.9%) patients with pre-existing hypothyroidism and 18,750 (92.1%) without it. Patients with hypothyroidism had a median age of 70 years, IQR (59.0, 80.0) and 65% were female. Most of the patients were White (67%), followed by Black (17%). The most common comorbidities in the Hypothyroid group were hypertension (68%), diabetes (42%) and dyslipidemia (37%) (Table 1).

Among the included patients, 17,539 patients had an available severity score index. The univariate analysis showed that hypothyroidism was associated with higher odds of severe disease (OR: 1.18; 95% confidence interval [CI]: 1.07, 1.30; $p < .001$) (Tables 2 and 3), but after adjusting for age, BMI, sex, admission date in the quarter year since March 2020, race, smoking history and comorbid conditions (coronary artery disease, hypertension, diabetes, and dyslipidemia), hypothyroidism was not associated with increased odds of severe COVID-19 (adjusted odds ratio [aOR]: 1.02; 95% CI: 0.93, 1.13; $p = 0.65$) (Table 3). Patients in the Hypothyroidism group did not have an increased odds of in-hospital mortality (OR: 1.03; 95% CI: 0.92, 1.15; $p = .64$) or longer length of stay (estimated difference in hospital-free days: 0.00 days; 95% CI: −0.46; 0.46; $p = .99$) (Table 3). Pre-existing hypothyroidism was not associated with ICU admission or ICU mortality in unadjusted as well as in adjusted analysis (Table 3). The sensitivity analysis using complete case data yielded similar estimates and conclusions to the main analysis results (Table S1).

4 | DISCUSSION

Due to the impact of COVID-19 on healthcare and individual's health, it is important to evaluate how common comorbid conditions are associated with outcomes in hospitalized patients. Using the large

FIGURE 1 Study flowchart



international VIRUS: COVID-19 Registry of hospitalized patients with COVID-19, we identified that almost 1 out of 12 hospitalized adult patients with COVID-19 had pre-existing hypothyroidism. We focused on hypothyroidism instead of on thyroid dysfunction in general due to the lack of data for the latter. Our study found that pre-existing hypothyroidism does not correlate with disease severity; it is also not associated with increased risk of hospital mortality, length of stay or ICU needs.

These findings are consistent with previously reported observational studies. In a small cohort from New York City, van Gerwen et al.[28] compared 251 patients with hypothyroidism against 3452 without it and found that hypothyroidism was not associated with increased risk of mechanical ventilation (aOR: 1.17; 95% CI: 0.81, 1.69) or death (aOR: 1.07; 95% CI: 0.75, 1.54). A large study from Denmark evaluated 16,502 patients with COVID-19 and identified that 572 (3.5%) of them were using levothyroxine. After propensity score weighting the use of levothyroxine was not associated with increased risk of death, ICU admission or need for mechanical ventilation.[27] Similarly, Daraei et al.'s[43] single-center study of 390 patients, presented no statistically significant mortality difference between the general population and patients with hypothyroidism.

Hypothyroidism manifestations and health implications are broad; therefore, it is not surprising that there are conflicting data regarding the impact of thyroid disease on the prognosis of COVID-19. A single-center small study in France identified 43 patients with hypothyroidism among 433 patients hospitalized with COVID-19; their univariate analysis showed that patients with hypothyroidism had a higher risk of developing severe forms of COVID-19.[44] Similarly, Bakshi et al.[45] published a preliminary report where they presented the increased association of COVID 19 infection and hypothyroidism in a small sample size of 24 patients with Hypothyroidism. Furthermore, Gong et al.[46] observed that low FT4 and TSH levels were linked to mortality, and low TSH levels were an independent risk factor for death in patients with COVID-19. A recently published meta-analysis by Llamas et al.[47] concluded that serum T3 concentrations in patients with severe COVID-19 are considerably lower than in nonseverely sick patients and predict all-cause death in patients with severe COVID-19. Moreover, a meta-analysis published in July 2020 that included 8 studies and 2169 patients showed that pre-existing thyroid disease was associated with higher odds of having severe COVID-19.[48] However, our results refute the hypothesis that pre-existing hypothyroidism may correlate with disease severity and increase the risk of mortality with COVID-19 when adjusted for relevant confounding factors.

Our study has several strengths. First, we included 20,366 adult patients from 28 countries and 306 different sites, including academic, community and private hospitals, which, to our knowledge, is one of the largest international studies evaluating the presence of hypothyroidism in COVID-19; thus, increasing the external validation of our findings. Second, we were able to perform multivariable analyses adjusting for several known confounders and effect modifiers. Third, we were able to explore patient-important outcomes such as mortality, hospital-free days and ICU admission. Reporting on these outcomes will help clinicians to provide accurate and meaningful information to patients with hypothyroidism if they get infected with SARS CoV-2. Fourth, due to the large number of patients enrolled in

TABLE 1 Patient demographics and distribution between hypothyroidism and no hypothyroidism (n = 20,366)

Characteristics	Hypothyroidism, N = 1616 (7.9%)	No hypothyroidism, N = 18,750 (92.1%)	p value
Age, median (Q1, Q3), N = 20,366	70.0 (59.0, 80.0)	62.0 (49.0, 73.0)	<.001
Gender, n (%), N = 20,340			<.001
Female	1048 (65%)	7809 (42%)	
Male	568 (35%)	10,915 (58%)	
Race, n (%), N = 20,026			<.001
White	1075 (67%)	8657 (47%)	
Black or African American	278 (17%)	4757 (26%)	
Mixed race	38 (2%)	588 (3%)	
Other	155 (10%)	960 (5%)	
South Asian	38 (2%)	1381 (7%)	
Unknown	28 (2%)	312 (2%)	
BMI, median (Q1, Q3), N = 14,560	30.0 (24.8, 36.3)	29.0 (25.1, 34.4)	.003
Smoking history, n (%), N = 14,188			<.001
Current	40 (3%)	733 (6%)	
Former	350 (28%)	2723 (21%)	
None	801 (65%)	8903 (69%)	
Unknown	41 (3%)	597 (5%)	
Coronary artery disease, n (%), N = 20,366	520 (32%)	3516 (19%)	<.001
Hypertension, n (%), N = 20,366	1105 (68%)	8800 (47%)	<.001
Obesity, n (%), N = 20,366	459 (28%)	3199 (17%)	<.001
Diabetes (DM), n (%), N = 20,366	680 (42%)	5572 (30%)	<.001
Dyslipidemia, n (%), N = 20,366	594 (37%)	3566 (19%)	<.001
Other comorbidities, n (%), N = 20,366	718 (44%)	5139 (27%)	<.001

Abbreviations: BMI, body mass index; DM, diabetes mellitus.

the registry, we were able to protect our findings against nonrandom missingness by excluding "noncompliant" sites but still having a significant amount of patients for analyses.

The study's results should be considered in the context of its limitations. First, the retrospective, observational study design leaves the possibility of unmeasured confounders that could impact our results. Second, we are aware that missing may not be missing at random; however, we are reporting how missingness was strictly handled following the recommendations from the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.[49] Third, we did not have baseline data for thyroid lab panel and preadmission use of thyroid medication, especially levothyroxine for correlation with outcomes; therefore, we could not differentiate between patients with restored euthyroid state, patients still having a hormonal deficit and patients with over-replacement. However, interpretation of thyroid function tests with outcomes could be complex as both critical illness[50] and many medications are known to affect thyroid function tests.[51–53] Fourth, we did not include various prognostic markers in the final analysis such as C-reactive protein, estimated glomerular filtration rate and so forth for adjustment due to lack of data.

To our knowledge, this is the first multinational study exploring COVID-19 outcomes with pre-existing hypothyroidism.

TABLE 2 Comparison of the outcomes between hypothyroidism and no hypothyroidism (n = 20,366)

Outcome	Hypothyroidism (N = 1616)	No hypothyroidism (N = 18,750)	p value
Disease severity as per WHO Ordinal Scale for Clinical Improvement, n (%), N = 17,539			<.001
No oxygen therapy	300 (20)	3941 (25)	
Oxygen by mask or nasal prongs	438 (30)	4413 (27)	
Oxygen by noninvasive ventilation or high-flow oxygen	207 (14)	2177 (14)	
Hospitalized, and require intubation and oxygen by mechanical ventilation	81 (6)	1228 (8)	
Mechanical ventilation and required additional organ support (pressors, RRT and/or ECMO)	97 (7)	1132 (7)	
Death	344 (23%)	3181 (20%)	
Hospital mortality, n (%), N = 18,179	345 (22)	3191 (19)	<.001
Admitted to ICU, n (%), N = 18,013	690 (46)	8224 (50)	.510
Hospital-free days, median (Q1, Q3), N = 18,475	19.0 (0, 23.0)	19.0 (0, 24.0)	.008
ICU mortality, n (%), N = 8203	241 (36)	2388 (32)	.065

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RRT, renal replacement therapy; WHO, World Health Organization.

TABLE 3 Unadjusted and adjusted outcomes

Outcome	Unadjusted		Adjusted[a]	
	Estimate[b] (95% CI)	p value	Estimate[b] (95% CI)	p value
Disease severity[c]	1.18 (1.07, 1.30)	<.001	1.02 (0.93, 1.13)	.648
Admitted to ICU	0.97 (0.88, 1.07)	.510	0.97 (0.88, 1.05)	.421
Hospital mortality	1.23 (1.09, 1.39)	<.001	1.03 (0.92, 1.15)	.639
Hospital-free days	−0.88 (−1.53, −0.23)	.008	0.00 (−0.46, 0.46)	.986
ICU mortality	1.12 (0.99, 1.26)	.065	0.99 (0.88, 1.11)	.843

Abbreviations: BMI, body mass index; CI, confidence interval; ICU, intensive care unit; WHO, World Health Organization.

[a]Adjustment variables were age, BMI, sex, time since pandemic, race, smoking history, and comorbidities (coronary artery disease, hypertension, diabetes obesity, dyslipidemia, and others).

[b]Estimates are odds ratios for disease severity, ICU admission, hospital mortality and ICU mortality. Estimate for hospital-free days is the estimated difference in days alive and out of the hospital in the 28 days from admission; patients who die have zero hospital-free days.

[c]Disease severity as per WHO Ordinal Scale for Clinical Improvement.

5 | CONCLUSION

Our results showed that hypothyroidism is commonly identified in hospitalized adult patients with COVID-19. There is no association between pre-existing hypothyroidism and COVID-19 severity and in-hospital mortality. The effects of thyroid disturbances beyond hypothyroidism on COVID-19 outcomes are yet to be evaluated, and the role of thyroid hormone in the disease needs to be studied further

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CONFLICT OF INTERESTS

Allan J. Walkey received royalties from UpToDate. Ognjen Gajic and Rahul Kashyap received royalties from Ambient Clinical Analytics Inc.

DATA AVAILABILITY STATEMENT

The data sets generated during and or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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