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Frequency of treated hypothyroidism and effect on disease complications in COVID-19 patients in Razi Hospital of Ahvaz

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Abstract

Introduction: COVID-19 infection (SARS-CoV-2) is associated with high morbidity and mortality rates, and worse outcomes have been reported for various morbidities. The impact of pre-existing hypothyroidism on COVID-19 outcomes is unclear.
Objectives: This study aimed to evaluate the frequency of treated hypothyroidism and its effect on disease complications in COVID-19 patients in Razi hospital of Ahvaz.
Patients and Methods: This cross-sectional study was conducted on patients with a laboratory and computed tomography (CT) confirmed COVID-19 diagnosis between August 2021 and December 2021 in Razi hospital in Ahvaz. The medical records of all patients were reviewed, and patient's characteristics and outcomes related to COVID-19, including severe disease, hospitalization in intensive care unit (ICU), need for mechanical or invasive ventilation, and all-cause mortality, was collected. The presence of hypothyroidism was identified based on the patient's medical history in the medical record.
Results: Of 850 patients with COVID-19 positive, 59 patients (6.9%) had pre-existing hypothyroidism and received thyroid hormone replacement therapy. Hypothyroidism was not associated with increased risk of ICU admission (odds ratio [OR]: 0.447; 95% CI: 0.216-0.925, $P=0.030$), severe disease (OR: 1.237; 95% CI: 0.688-2.223, $P=0.447$) mechanical ventilation (OR: 1.785; 95% CI: 0.894-3.562; $P=0.064$) and death (OR: 0.997; 95% CI: 0.478-2.080; $P=0.993$).
Conclusion: Our study showed that underlying hypothyroidism does not lead to worse outcomes and complications in patients with COVID-19. It suggests that hypothyroidism is not associated with a worse prognosis and should not be considered among the comorbidities that indicate a risk factor for COVID-19 severity and its complication.

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Introduction

COVID-19 is an acute respiratory tract infection caused by SARS-CoV-2 and has spread globally (1,2). Some epidemiologic evidence shows that involvement of some comorbidities such as chronic hypertension, cardiovascular disease, and diabetes are correlated with deterioration of COVID-19 infection outcomes (3,4). However, the correlation between thyroid dysfunction and outcomes in COVID-19 patients and the prognosis of the disease is still unknown (5,6). Coronavirus attacks human tissue cells via the cell receptor for angiotensin-converting enzyme-2 (ACE-2). The ACE-2 is the functional host receptor for SARS-CoV-2 and is highly expressed in numerous body cells, including the lungs and thyroid gland, which are connected with immune effects (7).

Key point

This study evaluated the frequency of treated hypothyroidism and its effect on disease complications in COVID-19 patients. Our study showed that underlying hypothyroidism does not lead to worse outcomes and complications in COVID-19 patients.

Although the exact incidence of thyroid dysfunction in COVID-19 patients is unknown, nevertheless, a study has shown that 15% of COVID-19 patients with mild to moderate disease, suffer from thyroid dysfunction (8). Furthermore, a study has reported that thyroid disease is related to the increased risk of COVID-19 (9). Even though numerous studies have been published on COVID-19, study results regarding the effects of thyroid dysfunction,

including hypothyroidism, on COVID-19 disease are contradictory. Such that some studies have reported that thyroid dysfunction is correlated with negative outcomes, including hospitalization and mortality, and exacerbation in COVID-19 patients (5,8-10), yet some other studies have found no correlation between thyroid dysfunction and negative outcomes, including mortality, hospitalization, need for mechanical ventilation or severe COVID-19 disease (6,11).

Owing to a low number of studies on thyroid disorders and COVID-19 and the contradictions in existing studies, there is a need for more research on this issue. Therefore, the present study was done with the aim of assessing the incidence of hypothyroidism in COVID-19 patients and its correlation with COVID-19's outcomes, including severe disease, intensive care unit (ICU) admission, and mortality.

Objectives

The main objective of this study is to evaluate the frequency of treated hypothyroidism and its potential effect on disease complications in COVID-19 patients admitted to Razi hospital of Ahvaz. The researchers aim to investigate whether patients with hypothyroidism experience different COVID-19 outcomes compared to those without this condition.

Patients and Methods

Study design

This descriptive, analytical, cross-sectional study was conducted on COVID-19 patients admitted to "Razi teaching hospital" in Ahvaz for a period of six months. Sampling was conducted by census, and the sample size included all COVID-19 patients admitted to Ahvaz Razi hospital, the center of COVID-19 patients in Ahvaz, from 23 August 2021 to 21 January 2022.

All COVID-19 patients with positive results on laboratory tests, imaging, and reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swab samples and with the age above 18 years were enrolled in the study. Exclusion criteria included ages under 18 years, incomplete data, and pregnancy in the previous six months.

First, essential characteristics of patients, including age, gender, comorbidities, smoking status, COVID-19 disease symptoms, and COVID-19 disease severity, were collected from patients' files and were registered in the sampling checklist.

Additionally, data on pulmonary involvement on computerized tomography (CT) scans, severity of the disease, and length of hospitalization were collected. Patient outcomes related to COVID-19 disease, including the need for ICU admission, mechanical ventilation, mortality, and length of hospitalization, were assessed and recorded. Patients' laboratory results and inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were evaluated and recorded.

The diagnosis of COVID-19 disease was based on symptoms such as fever, cough, and dyspnea. Afterward, the COVID-19 disease was confirmed by imaging data and nasopharyngeal swab sampling and detecting its nucleic acid in the respiratory tract by RT-PCR.

COVID-19 patients were classified based on disease severity into "severe" and "non-severe" COVID-19. Severe disease was defined as presence of any of the following criteria; respiratory distress with respiratory rate ≥ 30 per minute; arterial blood oxygen saturation ≥93% assessed by pulse oximetry; oxygenation index (partial arterial oxygen pressure/fraction of inspired oxygen [PaO2/Fio2]) ≤ 300 mm Hg; CT-scan of lungs showing acute exudative pulmonary lesions with > 50% progression in a short period of time; and need for mechanical ventilation and ICU admission (5,10). Patients who only had pneumonia without mentioned complications were classified as "non-severe" group (5). Diagnosis of hypothyroidism was based on patients' medical history in their medical files and self-report and hypothyroid patients who were under treatment before COVID-19 infection, were included in the study.

Statistical analysis

SPSS software version 22 (SPSS Inc., Chicago, IL, U.S.A) was used for statistical analysis. For quantitative variables, mean and median values were used to describe data centers, and standard deviation (SD) and interquartile range (IQR) values were used to describe data sparsity. For qualitative variables, numbers and percentages values were conducted for data description. The Kolmogorov-Smirnov test assessed data normality. The correlation between variables and univariate data analysis was assessed by independent *t* test and chi-square test (or Fisher's exact test). For multivariate data analysis and assessment of hypothyroidism's effect on patients' outcome, logistic regression and odds ratio (OR) estimates in 95% confidence interval (CI) were used. Significance level was defined as P value <0.05.

Results

In our study, from 850 files of COVID-19 patients, 59 cases (6.9%) had hypothyroidism. The comparison of basic characteristics comparison among hypothyroid and non-hypothyroid patient groups are shown in Table 1.

The comparison of severity and adverse outcomes of COVID-19 in both hypothyroid and non-hypothyroid groups is shown in Table 2. As it is shown, there was no correlation between the presence of hypothyroidism and COVID-19 occurrence ($P=0.532$). Overall, 45 patients (76.3%) in the hypothyroid group and 540 patients (68.3%) in the non-hypothyroid group required supplementary oxygen. Furthermore, the number of patients requiring ICU admission was significantly lower in the hypothyroid group than the non-hypothyroid group ($P=0.024$).

The results of non-adjusted and adjusted logistic regression for the anticipation of hypothyroidism effect on

Table 1. Comparison of basic characteristics between hypothyroid and non-hypothyroid groups

Variable	Hypothyroid (59 cases)	Non-hypothyroid (792 cases)	*P* value*
Age (mean ± SD)	52.47±13.07	55.30±15.68	0.177***
Gender			<0.0001*
Female, no. (%)	41 (69.5)	351 (44.4)	
Male, no. (%)	18 (30.5)	440 (55.6)	
Clinical symptoms, no. (%)			
Fever	26 (44.1)	360 (45.5)	0.893*
Dyspnea	39 (66.1)	524 (66.3)	0.972**
Cough	35 (59.3)	475 (60.1)	0.912**
Myalgia	30 (50.8)	422 (55.9)	0.498*
Diarrhea	11 (18.6)	58 (7.3)	0.005*
Abdominal pain	4 (6.8)	33 (4.2)	0.317*
Nausea and vomiting	16 (27.1)	157 (19.8)	0.182*
Headache	12 (20.3)	167 (21.1)	0.888**
New CVA	1 (1.7)	7 (0.9)	0.439*
New ACS	3 (5.1)	18 (2.3)	0.174*
New HF	0 (0)	10 (1.3)	0.385**
Hemoptysis	2 (3.4)	10 (1.3)	0.200*
Loss of appetite	20 (33.9)	232 (29.3)	0.462*
Anosmia	3 (5.1)	11 (1.4)	0.067*
Sore throat	3 (5.1)	11 (1.4)	0.725*
Comorbidities, no. (%)			
DM	35 (59.3)	364 (46.0)	0.058**
IHD	8 (13.6)	153 (19.3)	0.388*
CKD	1 (7.1)	40 (5.1)	0.353*
Cancer	4 (6.8)	24 (3.0)	0.123*
HTN	24 (40.7)	318 (40.2)	0.523*
Lung disease	4 (6.8)	44 (5.6)	0.568*
HF	5 (8.5)	30 (3.8)	0.088*
ESRD	1 (1.7)	25 (3.2)	0.528**
CVA	4 (6.8)	20 (2.5)	0.078*
Liver disease	1 (1.7)	5 (0.6)	0.351*
Smoking	2 (3.4)	18 (2.3)	0.644*
Inflammatory biomarkers			
ESR, mm/H, mean ± SD	44.05±29.35	48.29±28.89	0.300***
CRP, g/L, mean ± SD	36.17±26.43	46.15±44.54	0.179***

DM: Diabetes mellitus, IHD: Ischemic heart disease, CKD: Chronic kidney disease, HTN: Hypertension, HF: Heart failure, ESRD: End-stage renal disease, CVA: Cerebrovascular Accident, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein.
* Fisher's exact test; ** Chi-square test; *** Independent *t* test.

Table 2. Comparison of severity and outcomes of COVID-19 between hypothyroid and non-hypothyroid groups

Variable	Hypothyroid (59 cases)	Non-Hypothyroid (792 cases)	*P* value*
COVID-19 severity			0.532*
Severe	17 (28.8%)	195 (24.7%)	
Non-severe	42 (71.2%)	596 (75.3%)	
Hospitalization duration			0.463**
Mean ± SD	7.20 ± 3.23	6.81 ± 4.03	
Median (IQR)	7 (5-9)	6 (4-9)	
Need for ICU admission, no (%)	9 (15.3)	227 (28.7)	0.024*
Need for ventilation, no. (%)			
Mechanical ventilation	18 (30.5)	340 (43.0)	0.075*
Non-invasive ventilation	11 (18.6)	90 (11.4)	0.098*
Invasive ventilation	7 (11.9)	103 (13.0)	0.798*
Death, no. (%)	9 (15.3)	121 (15.3)	1.000*

* Fisher's exact test; ** Independent *t* test.

Table 3. Logistic regression for prognostication of hypothyroidism's effect on COVID-19 disease

Disease outcomes	Non-adjusted analysis		Adjusted analysis*	
	OR (95% CI)	*P* value	OR_{adj} (95% CI)	*P* value
Severe disease	1.237 (0.688-2.223)	0.477	1.414 (0.771-2.595)	0.263
ICU admission	0.447 (0.216-0.925)	0.030	0.507 (0.242-1.063)	0.072
Mechanical ventilation	0.582 (0.329-1.032)	0.064	0.557 (0.312-0.995)	0.048
Non-invasive ventilation	1.785 (0.894-3.562)	0.096	2.060 (1.012-4.191)	0.046
Invasive ventilation	0.899 (0.398-2.033)	0.798	0.973 (0.432-0.249)	0.984
Death	0.997 (0.478-2.080)	0.993	1.095 (0.513-2.335)	0.814

* Adjusted for age, gender, comorbidities (DM, HTN, lung disease, smoking).
OR_{adj}: Adjusted Odds Ratio; CI: Confidence Interval.

COVID-19 disease outcomes are shown in Table 3. Logistic regression results showed that presence of hypothyroidism did not affect severe COVID-19 disease, the need for mechanical ventilation, non-invasive ventilation, invasive ventilation, and mortality of COVID-19 patients; however, hypothyroidism caused a decrease in ICU admission (OR: 0.447; 95% CI: 0.216-0.925; $P=0.030$).

Discussion

The results of our study showed that the incidence of hypothyroidism in COVID-19 patients was 6.9%. Furthermore, the female-to-male ratio of the hypothyroid group was higher than that of the non-hypothyroid group. Our study showed that in COVID-19 patients, those with hypothyroidism were less likely to need ICU admission. Nonetheless, duration of hospitalization, occurrence of severe COVID-19, need for mechanical ventilation, non-invasive ventilation, and too-invasive ventilation, and mortality rate were similar between both hypothyroid and non-hypothyroid groups, and the difference was insignificant. These results show that hypothyroidism isn't correlated with worsening of outcomes in COVID-19 patients.

Evaluation of studies on this topic mostly show that a well-treated and well-controlled hypothyroidism has no relation with increasing the risk of infection (6,12). Additionally, COVID-19 patients who are hypothyroid and do not take levothyroxine are more likely to die, stay in the hospital more than 12 hours, require ICU admission, need mechanical ventilation, and require dialysis in 30 days following infection compared to those who take levothyroxine; however, hypothyroidism was not linked to COVID-19 infection outcomes such as hospitalization, ICU admission, and mortality (12). Therefore, overall, the treatment of thyroid disorders in COVID-19 patients is of significant importance.

In previous epidemiologic studies in Iran on the general population, overt hypothyroidism was observed in 2% (13). Therefore, it seems that the hypothyroidism rate is higher in COVID-19 patients in comparison with general population. This study needs a control group and/or normal cases without COVID-19 infection, as well as information on the incidence of hypothyroidism in Ahvaz, which makes a definite conclusion impossible.

The interaction between the thyroid gland and COVID-19 is complex and bidirectional. COVID-19 infection is associated with triggering of Graves' disease and sub-acute thyroiditis, and possibly hypothyroidism. Until more is understood regarding the impact of coronavirus on the thyroid gland, it seems advisable to monitor patients with COVID-19 for new thyroid disease or progression of preexisting thyroid disease (14).

Results from some other studies including Zhang et al (11), Lang et al (15) and Lui et al (8) showed that presence of thyroid disorder had no correlation with severe COVID-19 disease. Likewise, Muller et al (16) and Gong et al (17) showed in their studies that there is no relation between thyroid dysfunction and negative outcomes of COVID-19 including ICU admission and mortality.

Moreover, a study in United States achieved by van Gerwen et al (6) evaluated 3703 hospitalized patients with COVID-19 infection, of which 251 patients (6.77%) were suffering from hypothyroidism before infection. This study showed that in these patients, no relation between hypothyroidism and COVID-19 infection was seen. Among COVID-19 patients with and without hypothyroidism, no significant correlation between COVID's adverse outcomes, hospitalization risk, need for mechanical ventilation, or mortality rate was found. Likewise, Pereira et al (18) in their study in Brazil showed that from 7762 COVID-19 patients, 526 cases (6.77%) had hypothyroidism. Additionally, the number of women among hypothyroid patients was higher than that among patients without hypothyroidism. Presence of comorbidities, COVID-19 disease symptoms, inflammatory biomarkers and the mortality rate was not significantly different between the two groups. However, the need for mechanical ventilation and hospitalization duration was significantly lower in hypothyroid patients than non-hypothyroid patients. These results are consistent with our study.

On the other hand, another study has shown that a history of thyroid disease is correlated with 2.48 times increase in risk of severe COVID-19 (9). According to Zhang et al, patients with thyroid dysfunction were significantly more likely to suffer from severe and critical

COVID-19 than those without. Moreover, patients with thyroid dysfunction had a higher mortality rate and longer hospitalization duration. As a result, thyroid dysfunction has been associated with an unfavorable COVID-19 disease prognosis (10). A meta-analysis by Damara et al (19), evaluated 21 reports on 31 339 COVID-19 patients; they reported that hypothyroidism and unspecified thyroid disorder, increase negative outcomes including severe disease, ICU admission and mortality in COVID-19 patients.

Although in some studies, a positive correlation between thyroid dysfunction and severity of COVID-19 clinical symptoms has been reported (5,8,20,21). Even though up to this date, WHO has not had any recommendations regarding evaluation of thyroid function tests in COVID-19 patients (22). Furthermore, there are no evidence regarding prescription of thyroid hormone in order to improve the prognosis in COVID-19 patients.

Although connection and interaction between thyroid hormones and immune response has been thoroughly studies, but the exact mechanism in the context of COVID-19 infection is still unknown. Like other viral infections, in COVID-19 disease, the immune response has a great role in disease outcomes (23,24). Previous studies show that thyroid hormones have an important role in adjusting innate and acquired immune response on cellular levels (25,26). On the other hand, the outcomes of COVID-19 disease are widely various and can be affected by different background disorders and diseases (25). Thus, definite conclusion on the matter of correlation between hypothyroidism and negative outcomes among COVID-19 patients is difficult due to the heterogeneity in existing studies results. Furthermore, difference in sample size and characteristics of evaluated patients, presence of other background diseases, different methods of diagnosis and identification of thyroid disorder are of the reasons of the diversity of results.

In conclusion, our study's data show that the presence of hypothyroidism does not result in worsening of outcomes and adverse events in COVID-19 patients. In addition, the correlation between hypothyroidism and less need for ICU admission which was reported in our study, was not reported in other studies on this topic; this was somehow unexpected. Although in the study by Pereira et al (18), a significant relation between hypothyroidism and need for mechanical ventilation and mortality was reported. Possibly, these results are due to the lower number of hypothyroid patients as compared with non-hypothyroid patients and to the difference in characteristics among the observed patients.

Conclusion

The results of our study showed that a presence of hypothyroidism does not result in worsening of outcomes and adverse events in COVID-19 patients including severe COVID-19 disease, need for ICU admission, need for mechanical and invasive ventilation and patient's mortality. These results showed that hypothyroidism has no correlation with a poor prognosis of COVID-19 patients and should not be considered as a risk factor comorbidity for severe COVID-19 infection and its outcomes. Yet, more prospective studies on the subject of potential effect of COVID-19 on thyroid gland and its function is recommended.

Limitations of the study

COVID-19 patients had pre-existing hypothyroidism in the study, limiting the sample size to a relatively small number. A larger sample size could provide more robust and generalizable results. A single-center study was conducted at Razi hospital in Ahvaz, which may not fully represent the characteristics and outcomes of the broader population.

Authors' contribution

Conceptualization: Leila Moradi
Data curation: Ferdos Zaman.
Formal analysis: Ferdos Zaman.
Funding acquisition: Leila Moradi.
Investigation: Mona Hoseini, Fatemeh Amiri.
Methodology: Leila Moradi, Ferdos Zaman.
Project administration: Leila Moradi.
Resources: Mona Hoseini, Fatemeh Amiri.
Supervision: Mona Hoseini.
Validation: Ferdos Zaman, Mona Hoseini.
Visualization: Leila Moradi.
Writing–original draft: Leila Moradi, Mona Hoseini.
Writing–review and editing: Mona Hoseini, Fatemeh Amiri, Leila Moradi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapour University of Medical Sciences approved this study (Ethical code #IR.AJUMS.REC.1400.360). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from the M.D thesis of Mona Hosseini at this university (Thesis #D-0006). Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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