Prevalence of Hypothyroidism Among Patients With COVID-19, Tehran, Iran

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Abstract

Objective: Numerous comorbidities are involved in the severity of Corona Virus Disease 2019 (COVID-19). Hypothyroidism's impact on COVID-19 is yet to be understood properly. Cellular immunity and different cytokines, on the other hand, are thought to play a role in the development and progress of COVID-19 and thyroid disease, according to earlier research. The goal of this study was to find out how common (prevalent) hypothyroidism was among COVID-19 patients and its possible influence on the disease prognosis on hospitalized patients at a Tehran University Hospital.

Methods: Demographic information and other data related to our study, mainly comorbidities, were collected from 493 COVID-19 patients' medical records and analyzed.

Results: We identified that hypothyroidism was significantly prevalent in hospitalized COVID-19 patients than in the general population. Overall, in patients with hypothyroidism (n=65), n=21(32.3%) patients expired of whom 14 (66.7%) patients were females and 7 (33.3%) were males. In these patients, no statistically significant difference was observed between the expired and discharged groups (Adjusted Odds Ratio (OR_{adj}): 1.04 (95% Confidence Interval (CI): 0.59-1.83 p-value=0.87). As a result, hypothyroidism was not linked to an increased risk of death.

Conclusion: In this current study, we demonstrated that the prevalence of hypothyroidism was higher in hospitalized COVID-19 patients than in the normal population especially in females but without significant adverse effects on the risk of mortality from this disease.

1. Introduction

The name "COVID-19" was first created by the WHO on February 11th, 2020, in regards to the disease with similarity to SARS or "severe acute respiratory syndrome", which was later recognized as SARS-COV-2, a novel and incredibly contagious virus that resulted in a pandemic (1, 2). Unfortunately, both the severe and fatal rates of COVID-19 infection continue to rise rapidly. As a result, determining the predictors of severe COVID-19 infection is critical for early intervention therapy. Based on recent reports, the novel coronavirus can be identified through various but nonspecific symptoms including (fever, cough, dyspnea, loss of sense of smell, shortness of breath, and fatigue) (3). Decreased appetite, nausea, vomiting, diarrhea, and chest discomfort are common symptoms of COVID-19 that are not directly related to the respiratory system (4).

Despite the COVID-19's asymptomatic features (or moderate symptoms in most cases), immunologic problems such as macrophage activation syndrome (MAS) and cytokine storm may emerge in certain situations(5). In severely sick patients with COVID-19 pneumonia, abnormal and unmanaged cytokine production has been reported, and the resultant uncontrolled cytokine storm in COVID-19 patients is efficiently implicated in the worsening of symptoms and pathogenicity, and constitute a significant factor contributing to COVID-19 fatalities(6). Furthermore, severe COVID-19 infection was associated with an

increase in the number of highly pro-inflammatory CCR4+, CCR6+, Th17+, CD4 T cells, implying that T cell hyperactivation plays a role in the severe immunological damage seen in these subjects (7).

Endocrine metabolic problems may increase the likelihood of SARS-CoV-2 infection (8–10), and thyroid hormone may be a contributing factor for coronavirus infection through altering the interaction between coronaviruses and integrin αvβ3 in airway epithelial cells (11). Multiple investigations have discovered and presented evidence that the thyroid gland and the whole hypothalamic–pituitary–thyroid (HPT) axis may be key targets of SARS-CoV-2 damage. COVID-19-related thyroid diseases include thyrotoxicosis, hypothyroidism, and nonthyroidal sickness syndrome. Some signals of hormonal alterations (i.e. low T3 and TSH levels) and apparent thyrotoxicosis to be considered as indicators of negative COVID-19 outcome (i.e. extended length of hospital stay and more death) are already developing outside the COVID-19 context (12).

Hypothyroidism is a hormonal condition during which the thyroid gland produces insufficient thyroid hormone. Clinical symptoms of hypothyroidism are confirmed by a high sensitive TSH assay and a reduction in free thyroxine (fT4) (13). Hypothyroidism is one of the most prevalent disorders of the endocrine system. In iodine-deficient areas of the world, autoimmune thyroid disease (Hashimoto's thyroiditis) is the prevalent cause of hypothyroidism(14). Hashimoto's thyroiditis is thought to be caused by a mix of genetic predisposition and environmental influences (15). Hashimoto's thyroiditis patients' T lymphocytes react to processed thyroid antigens and peptides produced from these antigens. T cells that have been stimulated generate cytokines, which in turn induces a range of other immune cells. When stimulated by an antigen, Th1 CD4 + lymphocytes secrete interleukin-2 (IL-2), interferon-gamma, and tumor necrosis factor-beta. Th2 cells, on the other hand, release IL-4 and IL-5 when activated by antigens. Patients with Hashimoto's thyroiditis have both types of these T cells in their thyroid tissue, although Th1 cells predominate (16, 17).

Although the deleterious effect of many underlying diseases such as diabetes mellitus (DM), hypertension (HTN), obesity, age > 70 years, coronary artery disease (CAD), and heart failure on the severity and mortality of COVID-19 patients has been established in many studies (18), the definitive efficacy of hypothyroidism on the prognosis of COVID-19 positive patients is still unknown(19–21). In both COVID-19 disease and hypothyroidism, cellular immunity, T cells, and cytokine storm are involved in pathogenesis. Our descriptive study aimed to determine the prevalence of hypothyroidism in confirmed COVID-19 cases in the hospital and its possible influence on the clinical outcomes.

2. Materials And Methods

2.1. Study design and subjects

This retrospective cohort study was performed on 493 patients infected with COVID-19 who were admitted at Imam Khomeini Hospital Complex, a referral center in Tehran, Iran, from February 20th to

April 19th, 2020. All patients had PCR-confirmed COVID-19 or compatible clinical, laboratory, and imaging findings for COVID-19.

2.2. Eligibility criteria

The medical records of 493 patients were reviewed while the only relevant and useful data from them were collected for our study. COVID-19 patients were identified as having hypothyroidism as comorbidity when the reliable medical history in the medical record mentioned “hypothyroidism”.

2.3. *Measurements*

All information of this study was obtained using a structured questionnaire from electronic patient health records. Table 1 shows the variables in the questionnaire in collecting the data.

2.4. Ethical considerations

The research protocol was fully assessed and approved by the Ethics Committee, Deputy of Research, Tehran University of Medical Sciences (TUMS), Tehran, Iran (Ethics approval code: 99-1-101-47345).

2.5. Statistical analysis

Our data extraction and analysis were done with IBM SPSS Statistics software (version 25). We evaluated the proportion of COVID-19 patients, along with 95% confidence intervals (CIs), and stratified by demographics, comorbidities especially hypothyroidism. A *P*-value of less than 0.05 was considered statistically significant.

3. Results

Characteristics of included participants are provided in Table 1. Out of the n = 493 patients with COVID-19, (n = 332)67% were males, (n = 161)33% were females. The male to female ratio was 2:1 respectively. The total discharge rate was higher than the expired rate (68.6% vs 31.4%) In the 50–59-year-old age group, 92 (27.2%) patients, of the total discharged group, were released from the hospital which represents the age group with the highest discharge rate. Patients above the age of 70, on the other hand, made up the largest percentage of patients who perished (32.9%) out of the total case mortality rate. Fortunately, most patients (73.1%) were discharged from the hospital in less than 5 days. The most common underlying diseases in our patients were hypertension (36.7%), diabetes mellitus (27%), and coronary artery disease (26.9%). The total case fatality rate reported from our study was n = 155(31.4%). Out of this case fatality rate, n = 21(13.5%) patients had both hypothyroidism and COVID-19 while n = 134(86.5%) had COVID-19 without hypothyroidism. Case fatality rates for the stratified age groups and other comorbidities assessed in this study can be seen in Table 2. The male gender recorded most cases of death (57.4%) in the general cohort with hypertension recording the highest comorbid case fatality (41.9%).

Table 1
List of the variables included in the data analysis

Demographics	Comorbidities
Gender	Coronary artery disease (CAD)
Age	Hypertension
Marital status	Diabetes mellitus (DM)
Duration of admission	Chronic pulmonary disease
	Cancer
	Chronic renal failure (CRF)
	Chronic liver disease
	Hypothyroid

Table 2
Demographic and comorbid findings of patients with COVID-19 based on two groups, a Referral Hospital, Tehran, 2020

Variables	Groups		OR (95% CI)	P-value
	Expired	Discharged		
	N (%)*	N (%)*		
Gender	89 (57.4%)	243 (71.9%)	0.52 (0.35–0.78)	0.002
Male	66 (42.6%)	95 (28.1%)	Referent	Referent
Female				
Age (years)	17 (11.0%)	50 (14.8%)	Referent	Referent
< 39	16 (10.3%)	61 (18.0%)	0.52 (0.29–0.94)	0.51
39–49	27 (17.4%)	92 (27.2%)	0.56 (0.35–0.91)	0.67
50–59	44 (28.4%)	80 (23.7%)	1.28 (0.83–1.97)	0.15
60–69	51 (32.9%)	55 (16.3%)	2.52 (1.62–3.93)	0.003
≥ 70				
Coronary artery disease (CAD)	49 (31.6%)	84 (24.9%)	1.39 (0.91–2.11)	0.12
Yes	106 (68.4%)	254 (75.1%)	Referent	Referent
No				
Hypertension	65 (41.9%)	116 (34.3%)	1.38 (0.93–2.04)	0.10
Yes	90 (58.1%)	222 (65.7%)	Referent	Referent
No				
Diabetes mellitus (DM)	44 (28.4%)	91 (26.9%)	1.05 (0.68–1.61)	0.82
Yes	111 (71.6%)	247 (73.1%)	Referent	Referent
No				
Chronic pulmonary disease	13 (8.4%)	27 (8.0%)	1.05 (0.52–2.10)	0.88
Yes	142 (91.6%)	311 (92.0%)	Referent	Referent
No				
Chronic liver disease	4 (2.6%)	8 (2.4%)	1.09 (0.32–3.68)	0.89
Yes	151 (97.4%)	330 (97.6%)	Referent	Referent
No				

Variables	Groups		OR (95% CI)	P-value
	Expired	Discharged		
	N (%)*	N (%)*		
Chronic renal failure (CRF)	11 (7.1%)	14 (4.1%)	1.76 (0.78–3.98)	0.17
Yes	144 (92.9%)	324 (95.9%)	Referent	Referent
No				
Cancer	24 (15.5%)	16 (4.7%)	3.68 (1.89–7.16)	< 0.001
Yes	131 (84.5%)	322 (95.3%)	Referent	Referent
No				
Hypothyroid	21 (13.5%)	44 (13.0%)	1.04 (0.59–1.83)	0.87
Yes	134 (86.5%)	294 (87.0%)	Referent	Referent
No				
Total	**155(31.4%)**	**338(68.6%)**		
	N = 493			

Among COVID-19 cases, n = 65(13.2%) patients including 39 (60%) females and 26 (40%) males had pre-existing hypothyroidism and were on replacement therapy. The prevalence of hypothyroidism among patients with COVID-19 was statistically significantly higher in women (P value < 0.001). Among the 65 COVID-19 patients with hypothyroidism, n = 21(32.3%) patients expired of whom 14 (66.7%) patients were females and 7 (33.3%) were males. There was no statistically significant difference between mortality of male and female patients with hypothyroidism (P-value = 0.44). Furthermore, out of the 65 hypothyroidism cases hospitalized, n = 44(67.7%) patients were released from the hospital, while n = 21(32.3%) patients died. As a result, hypothyroidism was not linked to an increased risk of death [Adjusted Odds Ratio (OR_{adj}): 1.04 (95% Confidence Interval (CI): 0.59–1.83; P-value = 0.87].

4. Discussion

We found that the commonness of hypothyroidism among COVID-19 patients was 13.2% of which 60% of the patients were females and 40% were males. In comparison with the Iranian general population, this was higher (13.4% Vs 2.3%) (22). Therefore, our study supports the available research data that hypothyroidism is more common in Iranian women than men. Also, we found that the general case mortality rate was higher in males than females (57.4% vs 42.6%). This also conforms with the hypotheses that COVID-19 mortality is higher in the male gender (23). Fortunately, among the 493 COVID-19 patients, 338(68.6%) were discharged out of which 294(87.0%) did not have a past medical history of hypothyroidism, and 44(13.0%) patients had a past medical history of hypothyroidism. Approximately

32.3% of patients with pre-existing hypothyroidism expired (66.7% women and 33.3% men). As shown in Table 2, there was no statistically significant difference between expired and discharged groups in patients with hypothyroidism (32.3% vs 67.7%) (p = 0.87). Our findings and hypothesis align with van Gerwen M et al retrospective cohort study on 3,703 patients with COVID-19 in the United States. They reported 6.8% had hypothyroidism and 68.1% of the patients with hypothyroidism needed hospitalization, nonetheless, hypothyroidism was not linked with an increased risk of COVID-19 hospitalization or other worse possibilities such as death compared to the non-hypothyroid cases (24).

In pathogenic COVID-19 infections, various factors determine illness severity, including initial viral titers in the airways, as well as the infected person's age and concomitant diseases(25). Current evidence suggests that people with comorbidities such as diabetes, obesity, heart failure, and kidney failure experience more severe illness than others but there is insufficient evidence for the effects of hypothyroidism on COVID-19 prognosis. According to the pathophysiology, some may hypothesize that prognosis of COVID-19 patients with a history of hypothyroidism, especially Hashimoto's thyroiditis will get worse than the normal population. Our findings do not support this hypothesis and in addition, this hypothesis seems to be in contrast with the findings of Chen M et al. which stipulates that, individuals with COVID-19 had considerably lower TSH and serum total triiodothyronine (TT3) levels than healthy controls and non-COVID-19 pneumonia cases. Furthermore, the severity of the condition was positively linked with the degree of the declines in TSH and TT3 levels. The total thyroxine (TT4) level of COVID-19 patients, on the other hand, was not statistically different from that of the control group. Also, low TSH, T3, and thyrotoxicosis seem to be predictors of poor prognosis in COVID-19 patients, according to Chen T. et al (26). Although alterations in serum TSH and TT3 concentrations could be crucial symptoms of COVID-19's fate, hypothyroidism which is dependent on low fT4 levels may not be implicated directly in the poor prognosis of COVID-19 as compared to thyrotoxicosis (27). Moreover, a comparable study conducted in Iran on 390 COVID-19 admitted patients reported n = 21(5.4%) hypothyroid instances with approximately 90% of the participants being above the age of 50. In terms of hypothyroidism's impact on COVID-19 death rates, n = 60 (15.3%) of total patients and n = 4 (19%) of hypothyroid patients died, with no statistically significant difference between the two sets(19). Thyroid disease (TD) is not known to be related to an increased risk of viral infections in general, nor is there an increased chance of developing more severe COVID-19 disease, according to the British Thyroid Association and the Society for Endocrinology (BTA/SFE) in their joint paper.

COVID-19 elicits a two-phase immune response; in the initial (asymptomatic, pre-incubation) phase the adaptive immune response plays a critical role in its attempt to kill infected epithelial cells and thereby preventing viral replication. Phase two indicates that adaptive immunity fails to remove the virus, and as a result, COVID-19 spreads (28). Moreover, angiotensin-converting enzyme 2 (ACE2), the functional receptor for SARS-CoV-2, plays a role in the pathogenesis of COVID-19 (29, 30). Accumulating evidence demonstrates that ACE2 expression is present in many endocrine organs, including the pancreas and thyroid gland. As a consequence, the thyroid gland could be a point for a targeted COVID-19 attack (31). Patients with this disease fall into two categories: those who get minor symptoms and recover, and those who acquire severe symptoms and die (32). In normal circumstances, innate immunity's NK cells and

adaptive immunity's CD8 positive cytolytic T cells work together to eliminate virus-infected cells. When lymphocyte cytolytic activity is impaired, it leads to prolonged interactions between innate and adaptive immune cells, resulting in a cytokine storm, ARDS, and multi-organ failure. This critical condition is one of the significant causes of fatality in COVID-19 patients (33).

Acute respiratory injury in patients with severe COVID-19 is portrayed by inflammation and tissue damage in the lung tissue, which has been linked to T-helper type 17 (Th17) cell responses, as IL-17 can cause alveolar epithelial cell apoptosis and the advancement of pulmonary fibrosis, affecting the normal alveolar structure, alveolar-capillary gas exchange, and alveolar-capillary gas exchange (34). Increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor (GCSF), interferon-inducible protein 10, monocyte chemoattractant protein 1 (MCP 1), macrophage inflammatory protein 1, and tumor necrosis factor (TNF) are associated with COVID-19 disease severity, according to Puja Mehta et al(33). The causes of excessive production of these cytokines are thought to induce a dysregulated innate immune response to COVID-19 infection (35). IL-17 is involved in the pathogenesis of both COVID-19 and HT. Based on the results of previous studies, there is a significant increase in serum IL-17 levels in HT patients suggesting a potential role of this cytokine in disease pathogenesis (36).

Interestingly, there are notable reports that are in contrast to our findings. A study discovered that COVID-19 patients with hypothyroidism had a greater in-hospital death rate than COVID-19 patients with euthyroidism. Hypothyroidism, like thyrotoxicosis, but to a lesser level, may have a detrimental impact on COVID-19 results. They added that the degree of COVID-19 appears to be the most important factor of the kind of thyroid injury that occurs. As a result, there's a chance primary hypothyroidism might develop during or after COVID-19(12). Wang W et al also performed a study on eighty-four COVID-19 hospitalized patients which reported common thyroid function abnormalities in patients with COVID-19, especially in severe cases. Within the course of the disease, thyroid dysfunction appeared to vary continuously and recovered steadily and spontaneously. Thyroid malfunction was also found to be linked to viral nucleic acid cleanup time, implying that virus infection and replication seem to be implicated for aberrant thyroid hormones (37). Furthermore, Alice Horisberger et al study showed that the frequency or severity of COVID-19 increased in patients with autoimmune diseases (38). Hariyanto Ti et al also confirmed that the severity of the COVID-19 infection is increased among patients with thyroid disease. Their hypotheses highlighted the critical role played by thyroid hormones in controlling innate immune responses. As a consequence, dysregulation of the innate immune response, as demonstrated by greater neutrophil counts, increased CD14 + monocyte and macrophage counts, reduced NK cell counts, and elevated complement levels were found to be substantially related to severe COVID-19 infections. In addition, individuals with thyroid dysfunction had higher levels of pro-inflammatory cytokines notably TNF- and IL-6 (39).

A limitation of our study is that we did not have access to the patient’s thyroid tests since this is a retrospective study and we used data gathered from electronic medical records which did not make those tests public. Hence, the results could be strongly influenced by differences in the definition of thyroid malfunction, the timing of the dysfunction, and whether or not the problem was treated. Furthermore,

when thyroid hormone or anti-thyroid medicines were administered in patients with thyroid dysfunction, thyroid hormone levels could be normal. Nonetheless, there is no direct evidence to indicate a link between COVID-19 severity and thyroid hormone level due to a paucity of reliable data on thyroid hormone levels. Further studies should address the influence of thyroid dysfunction treatment on the prognosis of COVID-19.

5. Conclusions

In the current study, we found that the prevalence of hypothyroidism in COVID-19 patients was higher than the normal population especially in women though the general case-mortality rate in males is higher than the females. Consequently, women with hypothyroidism and COVID-19 seem to have a higher mortality rate than men (66.7% vs 33.3%) but there was no statistically significant difference, hence, hypothyroidism seems not to affect patients' outcomes.

Declarations

Author Contributions Statement

1. The conception and design of the study: Fatemeh Esfahanian
2. Analysis, interpretation of data, and revising: SeyedAhmad SeyedAlinaghi
3. Drafting the article and final approval of the version to be submitted: Nazanin Janfaza
4. Rewriting and editing of text for submission: Marcarious M. Tantuoyir

Conflict of Interest

The authors confirm that there is no conflict of interest.

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