The Clinical Characteristics and Outcomes of COVID-19 Patients with Pre-Existing Thyroid Dysfunction: A Nationwide Study

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ABSTRACT

To which extent the pre-existing hypothyroidism or hyperthyroidism has an impact on coronavirus infection 2019 (COVID-19) outcomes remains unclear. The objective of this study was to evaluate COVID-19 morbidity and mortality in patients with pre-existing thyroid dysfunction. A retrospective cohort of patients with a polymerase chain reaction (PCR)-confirmed COVID-19 infection (n = 14 966) from March 11 to May 30, 2020, was established using the database of the Turkish Ministry of Health. We compared the morbidity and mortality rates of COVID-19 patients with pre-existing hypothyroidism (n = 8813) and hyperthyroidism (n = 1822) to those patients with normal thyroid function (n = 4331). Univariate and multivariate regression analyses were performed to identify the factors associated with mortality. Mortality rates were higher in patients with hyperthyroidism (7.7 %) and hypothyroidism (4.4 %) than those with normal thyroid function (3.4 %) ($p < 0.001$ and $p = 0.008$, respectively). Pre-existing hyperthyroidism was significantly associated with an increased risk of mortality (OR 1.54; 95 % CI, 1.02–2.33; $p = 0.042$) along with advanced age, male gender, lymphopenia and chronic kidney disease ($p < 0.001$ for all). Although a potential trend was noted, the association between pre-existing hypothyroidism and mor-

tality was not significant (OR 1.36; 95 % CI, 0.99–1.86; p = 0.055). In conclusion, this study showed an association between pre-existing hyperthyroidism with higher COVID-19 mortality. A potential trend towards increased mortality was also observed for hypothyroidism. The risk was more pronounced in patients with hyperthyroidism.

Introduction

The coronavirus infection emerging in December 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11, 2020 and has led to a global death toll. It is still a growing public health concern worldwide. As of February 02, 2022, the total number of patients infected with COVID-19 in Turkey was reported to be 10.8 million, and the number of deaths recorded was 85 600 [1].

The clinical outcomes and severity of COVID-19 disease differ according to genetic variants of the virus [2]. Also, patients' age, gender, and co-morbidities are important risk factors for severe COVID-19 and mortality [3–5]. Consequently, risk stratification for COVID-19 is crucial for the optimization of treatment and follow-up strategies.

The association between pre-existing thyroid dysfunction and COVID-19 mortality is of interest because both hyperthyroidism and hypothyroidism are among the most common endocrine disorders [7]. Impaired thyroid function is associated with immune, metabolic, and cardiovascular complications [8]. Several nationwide studies have reported increased cardiac and all-cause mortality in patients with hypothyroidism when compared to people with normal thyroid function [9–11]. Also, several other studies reported increased morbidity and mortality in people with hyperthyroidism [12, 13]. According to Brandt's meta-analysis study, mortality is increased approximately 20 % in hyperthyroid patients [12]. In an observational Danish cohort study, Brandt et al. showed that hyperthyroid patients had higher risk of cardiovascular diseases, diabetes, and lung diseases [13].

The increased risk of mortality among those with hypo- and hyperthyroidism may result from adverse hemodynamic effects, endothelial dysfunction, coagulopathy, and increased proinflammatory cytokines [11, 14–16]. These alterations may have the potential to affect the course of COVID-19 through aggravating the cytokine storm, causing increased mortality. Thyroid hormone levels are also associated with the proper regulation of immune functions [17], as both hypothyroidism and hyperthyroidism affect the immune responses to infections [15, 18]. Finally, the SARS-CoV-2 virus uses the angiotensin-converting enzyme (ACE) 2 receptors to enter the cell [19], and thyroid dysfunction has been reported to influence the regulation of ACE2 level and its expressions in many tissues [20]. Therefore, pre-existing hyperthyroidism or hypothyroidism may theoretically affect the course of the COVID-19 disease, as well as associated mortality.

Several reports with conflicting results have been published so far about the relationship of thyroid dysfunction and adverse COVID-19 outcomes [21, 22]. This study was performed in a large national database to search for the rates of hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and mortality of patients with hyperthyroidism or hypothyroidism before the diagnosis of COVID-19 disease.

Patients and Methods

A retrospective cohort study was conducted using the Turkish Ministry of Health National electronic COVID-19 database. Patients were included if they had a positive SARS-CoV-2 reverse transcriptase polymerase-chain-reaction (RT-PCR) test, between March 11 and May 30, 2020 (n = 149 671). The study conforms to the ethical norms and standards in the Declaration of Helsinki. The Ministry of Health's Ethical Board Committee approved the study protocol (IRB number: 95741342020/27112019).

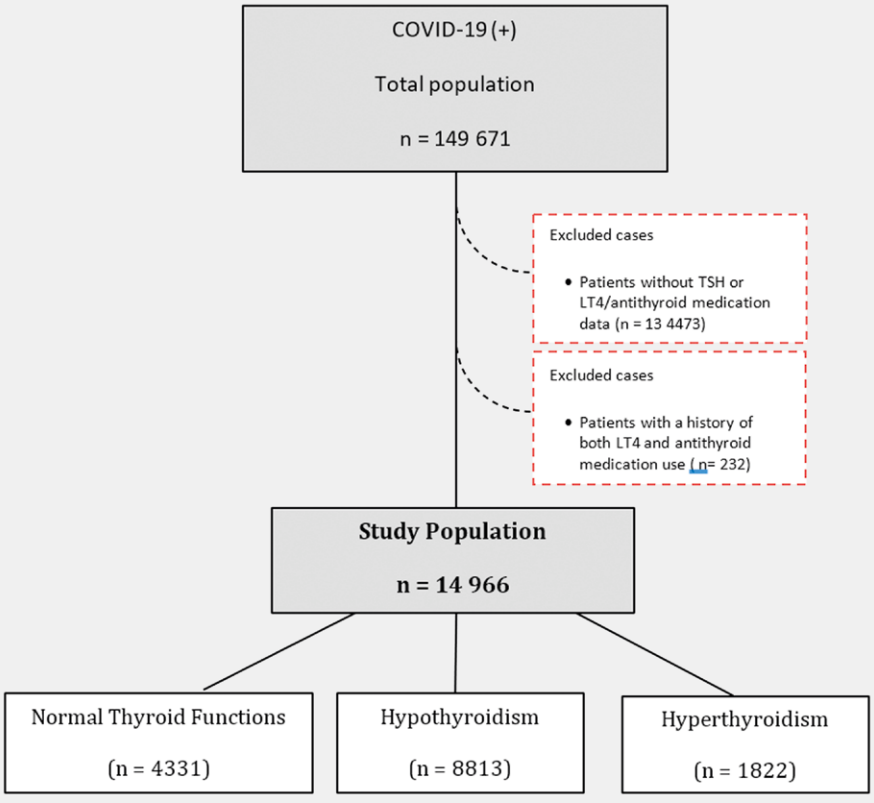
Patients without a TSH measurement within one year before the diagnosis of COVID-19 or without levothyroxine (LT4) and antithyroid medication data (n = 134 473), and patients who were prescribed both LT4 and antithyroid medication use in the screened period were excluded from the study (n = 232). The remaining subjects formed the study population (n = 14 966) in three groups of patients with normal thyroid function (n = 4331), hypothyroidism (n = 8813) and hyperthyroidism (n = 1822) (▶ **Fig. 1**).

Hypothyroidism was defined as receiving LT4 treatment or having a TSH level ≥ 4.5 mIU/l. Hyperthyroidism was defined as receiving antithyroid drugs or having TSH levels < 0.3 mIU/l. Normal thyroid function was defined as having a TSH level between 0.3 and 4.2 mIUml without receiving LT4 or antithyroid drugs. Antithyroid drug users and LT4 users were defined as patients who were taking these medications within 12 months before the diagnosis of COVID-19 disease.

Demographic and clinical characteristics including age, sex, smoking history, education, comorbid diseases, drug history, and body mass index (BMI) were reviewed. BMI was calculated as the ratio of weight to height squared (kg/m^2). Comorbid diseases were diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, heart failure, cerebrovascular disease, peripheral artery disease, chronic obstructive pulmonary disease (COPD), and asthma according to ICD-10 codes. Chronic kidney disease (CKD) was defined as the estimated glomerular filtration rate (e-GFR) below 60 ml/min/1.73 m^2 of body surface area [23].

Based on the available laboratory results TSH, plasma glucose, hemoglobin A1c (HbA1c), lipid profile, creatinine, liver function tests (AST and ALT), C-reactive protein (CRP), white blood cell count, lymphocyte count, fibrinogen, and D-dimer levels were recorded. Chest computed tomography (CT) results were evaluated for the presence of lung involvement.

The primary endpoint was all-cause mortality. The secondary endpoints were hospitalization and intensive care unit (ICU) admission or mechanical ventilation. Kaplan–Meier survival curves were plotted to visualize the differences between 30-day mortality rates



▶ **Fig. 1** Study inclusion flow chart (COVID-19, coronavirus infection 2019. TSH: Thyroid stimulating hormone; LT4, levothyroxine).

in hyperthyroidism and hypothyroidism groups compared to the euthyroid group.

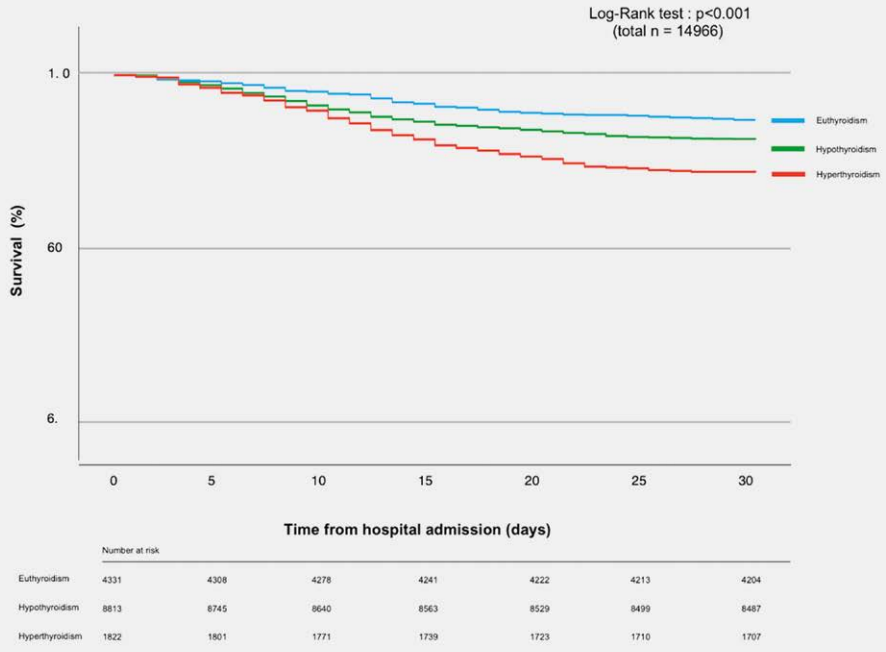
Statistical analyses

All data were statistically analyzed using SPSS Statistics for Windows 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Continuous data were displayed as mean (standard deviation-SD) or median (interquartile range-IQR) as was appropriate. Categorical variables were summarized as count (n) of all patients and percentage (%) in a subset of the evaluated group. The Kolmogorov–Smirnov test was used to test the normality of distributions. The differences between groups were compared using the Chi-square test for the categorical variables, and the Student's *t*-test or the Mann–Whitney U-test for the scale variables as appropriate. Univariate analysis was performed to evaluate the potential variables associated with mortality in euthyroid, hypothyroid, and hyperthyroid groups, and the results were presented as the odds ratio (OR) and 95 % confidence interval (CI). Variables with significant univariate association with outcomes were included in a multivariate model. The Hosmer and Lemeshow test and the likelihood ratio test were used to assess final model fitting. Kaplan–Meier survival curves were plotted to visualize the differences in the 30-day mortality rates. In addition, we created age- and sex-matched euthyroid, hypothyroid and hyperthyroid groups using the propensity score matching (PSM) method. Statistical significance was defined as the two-sided p value ≤ 0.05.

Results

The demographic characteristics, laboratory results, COVID-19 outcomes, and mortality rate in patients with normal thyroid function (n = 4331), hypothyroidism (n = 8813) and hyperthyroidism (n = 1822) are shown in ▶ **Table 1S**. Age, gender, smoking habits, education, and BMI were significantly different across the three groups ($p < 0.05$). There were also significant differences in TSH, glucose, lipids, e-GFR, D-dimer, lactate dehydrogenase, ferritin and lymphocyte count ($p < 0.05$ for all), and comorbidities (hypertension, type 2 diabetes, dyslipidemia, obesity, CKD, asthma, heart failure, coronary heart disease, and cerebrovascular disease) ($p < 0.001$ for all). Finally, the proportion of subjects who were hospitalized due to COVID-19, admitted to the ICU and/or mechanically ventilated or died differed significantly in the three groups ($p < 0.001$ for all).

When compared to the group with normal thyroid function, hyperthyroidism group was significantly older ($p < 0.001$), less educated ($p < 0.001$), and had higher blood glucose ($p = 0.007$), lower HDL-cholesterol ($p < 0.008$), lower e-GFR ($p < 0.001$). This group also had higher proportion of patients with a raised level of



▶ **Fig. 2** 30-Day mortality in patients with and without thyroid dysfunction.

D-dimer (p = 0.009), CRP (p = 0.038), LDH (p < 0.001), and ferritin (p = 0.044) and comorbidities including hypertension, CKD, asthma, heart failure, and coronary heart disease were significantly higher in patients with hyperthyroidism (p < 0.001 for all). The rates of ICU admission (p = 0.011) and mortality (p < 0.001) were significantly higher in the group with hyperthyroidism when compared with the euthyroid group (3.4 %) (p < 0.001) (▶ **Table 1S**).

Patients with hypothyroidism were significantly older, predominantly female, less smoker, less educated and had higher BMI when compared to patients with normal thyroid function (p < 0.05 for all). This group had higher levels of blood glucose, total cholesterol, triglycerides, and LDL-cholesterol, and lower e-GFR; higher proportion of patients with an elevated LDH and ferritin level, and lymphopenia (p < 0.05 for all). The prevalence of hypertension, type 2 diabetes, dyslipidemia, obesity, asthma (p < 0.001 for all), CKD (p = 0.018), and cerebrovascular disease (p = 0.025) were also significantly higher in patients with hypothyroidism compared with the euthyroid group. The rate of hospitalization and ICU admission or mechanical ventilation were significantly lower (p < 0.001 and p = 0.035, respectively) in the hypothyroidism group, whereas the rate of mortality was significantly higher (p = 0.008) than the euthyroid group (▶ **Table 1S**).

Multivariable logistic regression analysis showed advanced age (OR 1.08; 95 % CI, 1.06–1.09; p < 0.001), male gender (OR 2.22; 95 % CI 1.66–2.94; p < 0.001), lymphopenia (OR 2.86; 95 % CI, 2.17–3.78; p < 0.001), CKD (OR 1.75; 95 % CI, 1.3–2.37; p < 0.001), and pre-existing hyperthyroidism (OR 1.54; 95 % CI, 1.02–2.33; p = 0.042) were independently associated with an increased mortality risk (▶ **Fig. 1S**).

▶ **Figure 2** shows the Kaplan–Meier survival curves for patients with COVID-19 according to pre-existing hypothyroidism, hyperthyroidism, and euthyroidism. Reduced survival in patients with pre-existing hyperthyroidism is shown in ▶ **Fig. 2**.

Using the propensity score matching (PSM) approach we created two sets of age and gender-matched groups as hypothyroid vs. euthyroid patients, and hyperthyroid versus euthyroid patients. The median levels of total cholesterol, LDL-cholesterol and triglycerides were higher, but e-GFR was lower in the hypothyroid group compared with the euthyroid group. Furthermore, in this group, the proportion of patients with raised LDH levels was higher, whereas the frequencies of a raised ferritin level and lymphopenia were lower. In addition, this group had a lower frequency of cerebrovascular disease, but a higher frequency of cancer as compared to the euthyroid group. While the lower hospitalization rate persisted, the ICU admission rate was not significantly different from euthyroid group. The mortality rate remained higher in the hypothyroid group, but the association was marginally nonsignificant (Supplementary **Table 2S**).

In the case of hyperthyroidism PSM study, the group was less educated, pulmonary involvement, type 2 diabetes, and dyslipidemia rates were lower, but the frequency of hypertension was higher than the euthyroid group. Although the hospitalization rate was lower, the mortality rates were higher than the euthyroid group (Supplementary **Table 3S**). Logistic regression analysis showed that both hypothyroidism and hyperthyroidism were significant associates of mortality due to COVID-19 (data not shown).

Additional analyses were performed in hyperthyroidism and hypothyroidism groups stratified into categories of normal and abnormal TSH levels. Hyperthyroid patients who were prescribed antithyroid drugs were subgrouped according to normal-range TSH level ≤ 0.3 mIU/l vs. TSH > 0.3 mIU/l. As shown in Supplementary **Table 4S**, patients with suppressed TSH levels had significantly

higher mortality. Hypothyroid patients who were prescribed LT4 replacement was subgrouped according to TSH levels TSH ≥ 4.5 mIU/l versus TSH < 4.5 mIU/l. As shown in Supplementary **Table 5 S**, hypothyroid patients with high TSH level had significantly higher mortality but the difference was marginally not significant. Nevertheless, the number of patients with available TSH measurement was low.

Discussion

The results of the present study showed that patients with pre-existing thyroid dysfunctions had significantly higher rates of COVID-19 related mortality. Hyperthyroidism was independently associated with COVID-19 related mortality along with older age, male gender, lymphopenia, and CKD.

Thyroid hormones affect all cells in the body and play a significant role in hemostasis and immunity. All-cause mortality and unfavorable cardiovascular effects have been reported higher in patients with hyperthyroidism and hypothyroidism [8, 12]. Thyroid dysfunction may influence cytokine release and immune response to infection [14]; while uncontrolled hypothyroidism increases the susceptibility to infection [10]. These hemodynamic and pathological consequences of thyroid dysfunction may potentially increase the risk of mortality in COVID-19 patients.

The increased COVID-19 mortality in patients with hyperthyroidism in the current study is not consistent with a recent meta-analysis that reported poorer COVID-19 outcomes in patients with unspecified thyroid diseases and hypothyrodism but not in patients with hyperthyrodism [21]. Nevertheless meta-analyses included retrospective studies from heterogeneous populations, with low sample size.

The analytical approaches of different author groups might vary as even the meta-analyses and systemic reviews have drawn divergent conclusions from the literature. In this context, our results differ from the findings by Brix et al., who reported similar mortality events in a single group of hypothyroidism and hyperthyroidism compared with the euthyroid groups [24]. The primary explanation of the observed difference from our findings may be that we incorporated TSH results into patient classification in the current study. The study by Brix et al. identified the subjects with thyroid dysfunction using the prescription records. Which method can provide more reproducible results remains unclear. However, we performed additional analyses taking into account the prescription records and the measured TSH levels which showed higher mortality in both types of thyroid dysfunction, although the overall mortality in the hypothyroidism group was marginally not significant. As with other diseases, the different genetic backgrounds of populations may be the cause of different results between the studies.

A recent study conducted in the New York City metropolitan area suggested that hypothyroidism was not associated with increased risk COVID-19 severity and mortality [25]. Laboratory parameters including the TSH level were not available to that New York-based study and hypothyroidism diagnosis was made using the ICD codes. Using a similar approach, our study provides the first population-based evidence of an increased mortality trend among patients with pre-existing hypothyroidism diagnosis.

Even with a prescription of antithyroid or LT4 drug therapy, euthyroidism may not always be achieved. We have observed that patients with hyperthyroidism diagnosis were at significantly higher risk of mortality when the TSH level was still suppressed despite treatment. This finding suggests that hyperthyroidism increases the mortality risk primarily due to cardiac complications but antithyroid drug therapy normalizes this risk if biochemical euthyroidism is achieved [26]. Moreover, early and effective control of hyperthyroidism increases improves the survival [27]. Mortality risks may also be normalized when euthyroidism with LT4 is achieved. It should be emphasized that both hyperthyroidism and hypothyroidism may increase mortality through under-or over-treatment.

This study has several limitations. Large registries allow evaluation of a large population with commonalities; however, the analytical methods in such works do not replace clinical decision making. As the main limitation, we were unable to collect free T4 and T3 levels data and differentiate abnormal TSH results potentially related to a non-thyroidal illness syndrome. Inconsistent coding of potential causes in the same individual on different occasions also prevented us from collecting more robust information on the etiology of hypothyroidism and hyperthyroidism. Moreover, the number of hyperthyroid subjects on antithyroid drugs were low in the subanalysis, limiting the clinical meaningfulness of the observed association between hyperthyroidism and COVID-19 outcomes. Besides, given the retrospective study design, the complete duration of drug therapy and medication adherence were not available. Finally, although the overall sample was large, the missing values for important contributors of COVID-19 outcomes or low event rates may have negatively affected the level of contrast in statistical analyses.

Our study does, however, offer a fresh contribution in that it provides a large database, a nationwide set of patients with standardized COVID-19 management, and follow-up data. This includes laboratory results, clinical follow-up data, and prescription information.

In conclusion, this study showed increased COVID-19 mortality in patients with pre-existing hyperthyroidism, along with a trend towards increased mortality among hypothyroid patients. The number of hyperthyroidism cases has increased during the COVID-19 pandemic [28], which may be related to subacute thyroiditis or Graves' disease due to vaccine or COVID infection. The current findings emphasize the importance of a close follow-up of individuals with thyroid dysfunction and the maintenance of euthyroid status to prevent from the adverse outcomes of a COVID infection.

Data availability

The database used in this study was established by the Ministry of Health of the Republic of Turkey for the management and evaluation of follow-up, treatment, hospitalization, and intensive care unit admission of COVID-19 patients. The requests of researchers who met the criteria to data access were evaluated by the General Directorate of Health Information Systems.

Conflict of Interest

The authors declare that they have no conflict of interest.

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