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The clinical outcomes of COVID-19 infection in patients with a history of thyroid cancer: A nationwide study

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Abstract

Background: There are scarce published data in differentiated thyroid cancer patients about new coronavirus disease 2019 (COVID-19) disease outcomes and mortality. Here, we evaluated COVID-19 infection outcomes and mortality in thyroid cancer patients with COVID-19 infection.

Design and methods: We included a cohort of patients with thyroid cancer with PCR-confirmed COVID-19 disease from 11 March to 30 May 2020 from the Turkish Ministry of Health database in our nationwide, retrospective study. We compared the mortality and morbidity of COVID patients with or without thyroid cancer. Univariate and multivariate analyses were used to assess the independent factors for mortality, length of hospital stay and intensive care unit (ICU) admission and mechanical ventilation. We also analysed the effect of radioiodine treatment on severity and death rate of COVID-19 disease.

Results: We evaluated 388 COVID-19 patients with thyroid cancer [median age: 54 years, interquartile range (IQR) 18 years, males: 23%] and age and gender-matched

388 COVID-19 patients without thyroid cancer. Patients with thyroid cancer had a similar mortality ratio compared with the non-cancer group. Among patients with thyroid cancer, age, presence of diabetes mellitus, asthma/COPD, heart failure, chronic kidney disease, prior coronary artery disease, RAS blocker usage and low lymphocyte count were associated with mortality. Radioactive iodine (RAI) treatment and cumulative radioactive iodine dosage did not negatively affect the severity and mortality of COVID-19 disease in our patient group.

Conclusions: Our study indicated that history of thyroid cancer did not have an increased risk of mortality or morbidity in COVID-19 disease. Besides, RAI therapy history and doses of radioactive iodine did not affect mortality or outcome.

KEYWORDS
COVID-19, mortality, radioactive iodine therapy, thyroid cancer

1 | INTRODUCTION

The new coronavirus disease 2019 (COVID-19) pandemic has caused serious social and health problems. So far, nearly 2 million people have died. There is a diverse clinical course of COVID-19. Many patients are asymptomatic but some develop acute respiratory failure, which leads to ICU admission and even death. Those who are diagnosed with diabetes mellitus, obesity, hypertension and the elderly are more likely to be affected by COVID-19.[1] Patients with cancer are considered a vulnerable subgroup of the population, and they have an increased risk of coronavirus disease 2019 (COVID-19) severity and mortality.[2] Patients with cancer are heterogeneous and divided into different groups, especially according to cancer type and stages. Cancer patients with metastatic disease or using systemic immunosuppressive therapies have a more severe clinical course and poor prognosis.[3] Patients with malignant tumours have impaired immune response to infections and increased thromboembolic and cardiac complications.[4] Both impaired immunity and thromboembolism may affect the course of COVID-19. Cancer types may affect morbidity and mortality in patients with COVID-19 differently.[2,3]

There are no sufficient data currently to evaluate the COVID-19 morbidity and mortality in patients with thyroid cancer. Generally, the prognosis in differentiated thyroid cancer is excellent. However, a small percentage of patients may have increased morbidity and mortality. It is unclear whether some thyroid cancer patients are more vulnerable to COVID-19 infection. Zhang et al reported low mortality rates of patients with thyroid cancer in COVID-19 but the number of thyroid cancer patients in this study was very low.[2] Thyroid cancer management has become a more personalized therapy approach. Thyroid cancer patients are diverse within themselves. They have different stages and prognostic factors, and some of them may receive radioactive iodine with different doses. Cancer type, stages and risk stratification may help optimizing initial therapy. Some patients receive ablation radioactive iodine (RAI) treatment, while others do not receive it. Also, few receive radioactive therapy for metastasis. In addition to these, RAI treatment may also affect the course. Also, thyroid hormones may affect immune cell function and inflammation.[5] ***Significantly increased*** thyroid hormone levels increase the pro-inflammatory cytokine release.[6] It is obscure whether thyroid suppression therapy may affect COVID-19 morbidity and mortality.

We aimed to evaluate whether the diagnosis of thyroid cancer and therapy modalities ***are*** associated with a higher risk of poor outcome in patients with COVID-19. In this study, among PCR-positive COVID-19 patients from the Turkish National Database between March 2019 and May 2020, we evaluated the differences in clinical characteristics, prognosis and mortality between COVID-19–infected thyroid cancer and without thyroid cancer patients. Also, it was investigated how specific factors related to thyroid cancer (RAI therapy, suppressed thyroid-stimulating hormone (TSH) level, tyrosine kinase inhibitors, etc) affect COVID-19 outcomes. We believe that the data in this study may help to understand the impact of thyroid cancer on the outcomes of COVID-19 disease and give recommendations to the physicians who follow these patients.

2 | METHODS

2.1 | Study design and participants

We used the Turkish Ministry of Health National Electronic Database to design a multi-centre, retrospective cohort study. Our study was conducted according to the Declaration of Helsinki. Ministry of Health Ethical Board approved our study (95741342020/27112019).

From 11 March to 30 May 2020, electronic data consisted of 149,671 COVID-19 patients with a positive SARS-CoV-2 polymerase chain reaction (PCR) test. The flow diagram of the study selection process is given in Figure 1. Our study group (total n = 776) included thyroid cancer patients (n = 388) (C 73) diagnosed with COVID-19 infection and as a control group gender and age-matched patients with COVID-19 without a cancer diagnosis (n = 388) (Table 1, Figure 1). We used 1:1 propensity score–matched (PMS) data for the non-cancer group.

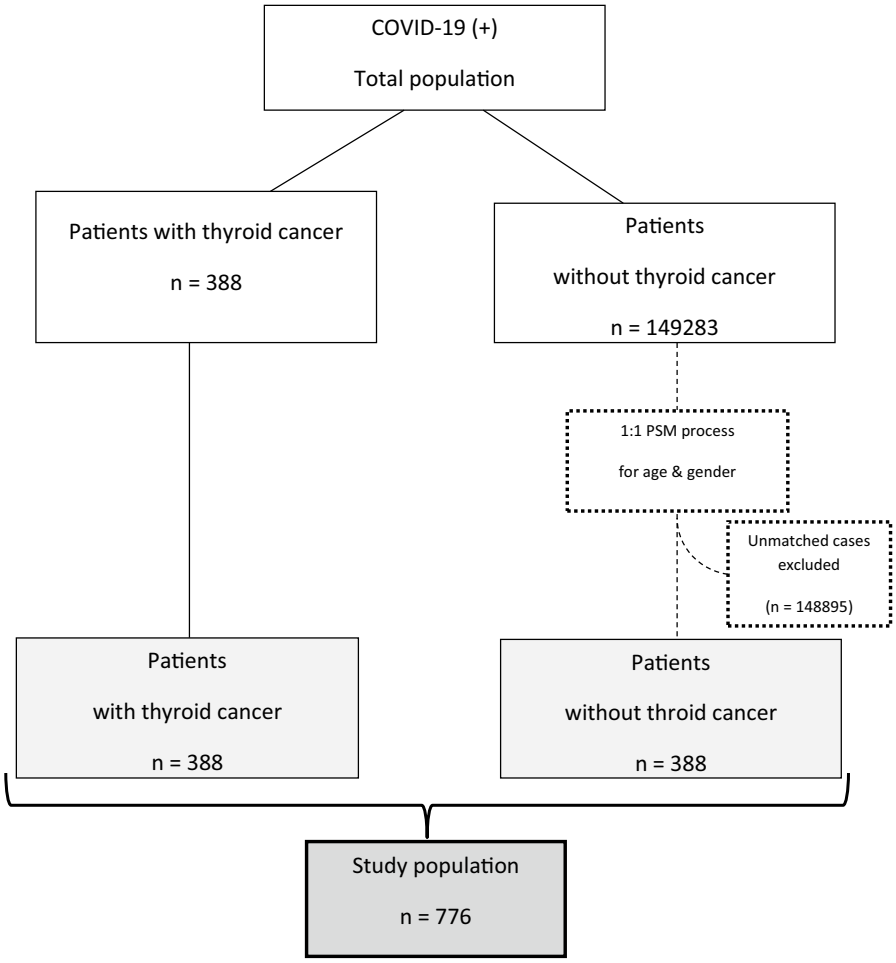

FIGURE 1 Consort diagram of the study

2.2 | Data collection

Data included age, gender, smoking history, education history and body mass index (BMI) as a demographic and patient's characteristics. Comorbid diseases and medication usage were also evaluated. In our data set, laboratory test results on fasting serum samples, including TSH, glucose, lipid profile (total cholesterol, HDL and LDL cholesterol, and triglycerides), creatinine, liver function tests (aspartate and alanine aminotransferase; AST and ALT), C-reactive protein (CRP), procalcitonin, lactate dehydrogenase, white blood cell count, lymphocyte count, fibrinogen, ferritin, D-dimer value and thyroglobulin levels. The history of RAI intake was also evaluated. Chest computerized tomography (CT) results were evaluated for the presence of COVID-19 pulmonary findings.

2.3 | Definitions

Clinical definitions are given as follows. Smoking was defined as current smoking, higher education as receiving more than formal education (nine years and more). Body mass index (BMI) was calculated as the ratio of weight to the square of height (kg/m^2). Thyroid cancer was defined based on the International Classification of Disease (ICD-10) codes. Thyroid cancer patients were divided into two groups according to the administration of RAI therapy. We grouped RAI therapy, according to I-131 doses (30, 50, 75, 100, 125, 150 and 200 mCi). Comorbidities such as diabetes mellitus, coronary artery disease (CAD), heart failure, stroke, hypertension, peripheral artery disease, dyslipidaemia, chronic obstructive pulmonary disease (COPD) and asthma were defined based on ICD-10 codes. Chronic kidney disease (CKD) was determined as an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2.[7] Definition of CVD included CAD, stroke and peripheral artery disease. Data on drug use such as RAS, acetylsalicylic acid and statins were collected.

2.4 | Study outcomes

The primary endpoint was all-cause mortality. The secondary outcomes were the length of stay in the hospital and admitted to the intensive care unit (ICU) or mechanical ventilation need during hospitalization.

2.5 | Statistical analyses

All variables were assessed with descriptive statistics. The normality of data distribution was checked with the Kolmogorov-Smirnov test.

TABLE 1 Basic characteristics of patients with and without thyroid cancer hospitalized for COVID-19

	Non-cancer (n = 388)	Thyroid cancer (n = 388)	Available data (n) (Control/Thyroid cancer)	*p*
Age, years, median (IQR)	53 (19)	53 (19)	388/388	1.000
Gender, male, n (%)	93 (24)	93 (24)	388/388	1.000
Smoking (current smoker - n, %)	48 (18.2)	36 (14.4)	264/250	.25
Follow-up centre, n (%)				
Public hospitals	306 (78.9)	301 (77.6)		
University hospitals	40 (10.3)	31 (8.0)	388/388	.20
Private centres	42 (10.8)	56 (14.4)		
Follow-up period, days, median (range)	8 (1–37)	8 (1–49)	388/388	.214
Education (9 years and over - n,%)	13 (20)	18 (23.7)	65/76	.60
BMI, kg/m^2, median (IQR)	27.5 (7.5)	29.7 (10.8)	44/50	.31
Clinical severity				
Hospitalization	286 (73.7)	208 (53.6)	388 / 388	**<.001**
Hospital stays more than 8 days, n (%)	143 (50.0)	103 (49.5)	286/208	.916
ICU admission, n (%)	34 (11.9)	29 (13.9)	286/208	.50
Stay in ICU for more than 4 days, n (%)	16 (48.5)	16 (55.2)	33/29	.60
Intubation, n (%)	15 (5.2)	16 (7.7)	286/208	.27
Death, n (%)	16 (4.1)	15 (3.9)	388/388	.85
Chest CT on admission consistent with COVID-19, n (%)	143 (38.4)	102 (27.6)	372/369	**.002**
Laboratory values				
TSH mIU/l, median (IQR)	1.57 (2.63)	0.69 (3.40)	30 /127	**.048**
Thyroglobulin ng /ml	-------	0.20 (0.17)	----- / 31	NA
Glucose, mg/dL, median (IQR)	110 (39)	101 (55)	47/33	.61
eGFR, ml/min/1.73 m^2, median (IQR)	90.8 (33.6)	84 (22.7)	47/33	.42
AST, >ULN, n (%)	8 (9.9)	5 (10.0)	81/50	.98
ALT, >ULN, n (%)	10 (13.0)	8 (13.8)	77/58	.89
D-dimer >ULN, n (%)	21 (56.8)	11 (47.8)	37/23	.50
CRP, >ULN, n (%)	76 (61.8)	76 (71.0)	123/107	.14
Procalcitonin, >ULN, n (%)	0 (0)	2 (16.7)	15/12	.10
Lactate dehydrogenase, >ULN, n (%)	26 (37.7)	31 (40.8)	69/76	.70
Ferritin, >100 ng/ml, n (%)	29 (50.9)	32 (52.5)	57/61	.86
Lymphopenia, Lym# <1000, n (%)	41 (16.7)	37 (17.1)	246/216	.89
Comorbid conditions				
Hypertension, n (%)	203 (52.3)	246 (63.4)	388/388	**.02**
Type 2 diabetes mellitus	104 (27.4)	182 (47.4)	379/384	**<.001**
Dyslipidaemia, n (%)	85 (21.9)	125 (32.2)	388/388	**.01**
Obesity, n (%)	16 (36.4)	24 (48.0)	388/388	.25
Asthma/COPD, n (%)	116 (29.9)	133 (34.3)	388/388	.19
Heart failure, n (%)	21 (5.4)	21 (5.4)	388/388	1.00
Coronary artery disease (CAD), n (%)	72 (18.6)	111 (28.6)	388/388	**.001**
Peripheral artery disease, n (%)	11 (2.8)	15 (3.9)	388/388	.42
Cerebrovascular disease, n (%)	5 (1.3)	6 (1.5)	388/388	.76
Chronic kidney disease, n (%)	18 (11.9)	15 (9.9)	388/388	.57
Neck exploration, n (%)	-------	6 (1.5)	-----/388	NA

(Continues)

TABLE 1 (Continued)

	Non-cancer (n = 388)	Thyroid cancer (n = 388)	Available data (n) (Control/Thyroid cancer)	*p*
RAI therapy, n (%)				
Low-dose RAI (30 to 50 mCi), n (%)	-------	10 (2.6)	----/388	NA
Medium-dose RAI (75 to 100 mCi), n (%)	-------	39 (10.2)	----/388	NA
High-dose RAI (>100 mCi), n (%)	-------	23 (5.9)	----/388	NA

Abbreviations: COVID-19: coronavirus disease 2019, CT: computed tomography, CAD: coronary artery disease, CKD: chronic kidney disease, HDL-chol: high-density lipoprotein-cholesterol, LDL-chol: low-density lipoprotein-cholesterol, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, CRP: C-reactive protein, TSH: thyroid-stimulating hormone, LDH: lactate dehydrogenase, ICU: intensive care unit, RAI: radioactive iodine.

Continuous variables were presented as a mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were expressed as absolute numbers and percentages. The chi-square test was used for assessing the difference between a categorical variable between two or more independent groups. Independent sample *t* test and Mann Whitney *U* test were used to compare means where appropriate.

Thyroid cancer patients for COVID-19 (n = 388) were matched using propensity score on a scale of 1:1 by age and gender of patients as a control group patients with COVID-19 infection without cancer.

Univariate analyses were used to investigate the set of variables associated with mortality, the length of stay in the hospital, ICU admission and mechanical ventilation need in thyroid cancer patients with COVID-19 infection. An odds ratio (OR) and its 95% confidence intervals (CI) were used for quantifying the effect. A multivariate model was used with variables that significant univariate association with the outcomes and mortality. A two-sided p-value ≤. 05 is statistically significant. Statistical analyses were performed using SPSS 25 (SPSS Inc).

3 | RESULTS

A total of 776 COVID-19 diagnosed patients with a diagnosis of thyroid cancer (n = 388) and propensity score–matched (PSM) patients without thyroid cancer according to age and gender (n = 388) were included. Clinical and socio-demographic characteristics of the study participants are shown in Table 1. The median and range of the follow-up period for patients with thyroid cancer was calculated as 8 (1-49) days and for non-cancer patients as 8 (1-37) days. There was no significant difference in BMI, smoking rates and the level of education between the two study groups. Comorbidities such as hypertension, type 2 diabetes, dyslipidaemia and coronary artery disease were more prevalent in patients with thyroid cancer (Table 1). Initial positive pulmonary manifestations of COVID-19 on chest CT and hospitalization rate were found less frequently in the thyroid cancer group.

The rate of hospitalization was significantly higher in the non-cancer group (63.7% to 53.6%; P < .001), while the rates of hospital stay, ICU admission, intubation and mortality were similar in both groups. There was no significant difference in the laboratory measurements other than the significantly lower rates of TSH levels in the thyroid cancer group (1.57 vs. 0.69mIU/L;P = .048).

We also give the data of the non-cancer patients before the PSM procedure in table S1. According to this table, the number (%) of deaths in the cancer group is 15 (3.9%) and non-cancer group is 4772 (3.2%) (P = .455).

We analysed the effect of previous RAI therapy and RAI doses on the severity and mortality of COVID-19 in thyroid cancer patients (table 2). Patients without RAI treatment (non-RAI group) were older than the patients treated with RAI (54, vs. 49. 5 years; P = .041). TSH levels were significantly lower in the non-RAI group (0.81 vs. 0.34 mIU/L; P = .046). There was no significant difference in the comorbidity rates and the laboratory parameters between the RAI therapy group and the non-RAI group. Also, there was no difference in COVID-19 severity or mortality rates between the non-RAI and RAI groups (Table 2). Doses of RAI administered to patients were given in Table 1. COVID-19 mortality and outcomes are given in table 3.

The clinical and ***demographic*** properties of patients who survived and died for COVID-19 were compared in Table S2.

3.1 | Univariate associations with mortality in the thyroid cancer group

Significant variables associated with all-cause mortality were age, lymphopenia, diabetes mellitus, asthma/chronic obstructive pulmonary disease (COPD), heart failure, CKD and renin-angiotensin system (RAS) blocker usage in the thyroid cancer group (Table 4). RAI treatment or high-dose RAI treatment history was not found to be associated with a prolonged hospital stay, ICU admission, mechanical ventilation or mortality (Table 4).

In the whole group, multivariate analysis for predictors of hospitalization revealed three independent risk factors (Table 5). Age (OR, 1.03; 95% CI, 1.01–1.05; P = .001) and positive CT findings of COVID-19 (OR, 3.14; 95% CI, 2.08–4.76; P < .001) were independent factors associated with hospitalization. Thyroid cancer diagnosis is negatively associated with the hospitalization rate (OR, 0.38; 95% CI, 0.27–0.54; P <.001).

TABLE 2 Comparison of demographic and clinical characteristics of patients with thyroid cancer according to RAI therapy

	Thyroid cancer without RAI therapy (n = 316)	Thyroid cancer with RAI therapy (n = 72)	Available data	*p*
Age, years, median (IQR)	54 (18)	49.5 (18)	316/72	**.041**
Gender, male, n (%)	75 (23.7)	18 (25)	316/72	.820
Smoking (current smoker-n,%)	31 (15.4)	5 (10.2)	201/49	.351
Follow-up centre, n (%)				
Public hospitals	242 (76.6)	59 (81.9)	316/72	.602
University hospitals	26 (8.2)	5 (6.9)		
Private centres	28 (15.2)	8 (11.1)		
Education (9 years and over-n,%)	17 (29.7)	1 (6.7)	316/72	.084
BMI, kg/m^2, median (IQR)	29.45 (9.77)	32.36 (17.38)	42/8	.612
Clinical severity				
Hospitalization	166 (52.5)	42 (58.3)	316/72	.373
Hospital stay more than 8 days, n (%)	82 (49.4)	21 (50.0)	166/42	.944
ICU admission, n (%)	24 (14.5)	5 (11.9)	166/42	.670
Stay in ICU more than 4 days, n (%)	15 (62.5)	1 (20)	24/5	.082
Intubation, n (%)	13 (7.8)	3 (7.1)	**166/42**	.881
Death, n (%)	13 (4.1)	2 (2.8)	316/72	.596
Chest CT on admission consistent with COVID-19, n (%)	84 (27.9)	18 (26.5)	301/68	.811
Laboratory values				
TSH mIU/L, median (IQR)	0.81 (3.59)	0.34 (2.33)	94/33	**.036**
Thyroglobulin ng /mL, median (IQR)	0.20 (0.37)	0.12 (0.27)	21/10	.217
Glucose, mg/dL, median (IQR)	102.00 (55.00)	101.00 (28.00)	33/11	.521
Total cholesterol, mg/dL, median (IQR)	196.00 (65.00)	170.50 (31.50)	39/8	.395
Triglycerides, mg/dL, median (IQR)	138.50 (127.50)	107.00 (60.25)	39/9	.938
HDL cholesterol, mg/dL, median (IQR)	48.00 (19.70)	44.00 (11.75)	39/10	.455
LDL cholesterol, mg/dL, median (IQR)	115.20 (57.00)	107.40 (38.40)	39/9	.938
-GFR <60 mL/min/1.73 m^2	12 (9.8)	3 (10.3)	123/29	.924
AST, >ULN, n (%)	4 (10.8)	1 (7.7)	37/13	.747
ALT, >ULN, n (%)	4 (9.3)	4 (26.7)	43/15	.093
D-dimer >ULN, n (%)	9 (47.4)	2 (50.0)	19/4	.924
CRP, >ULN, n (%)	58 (69.0)	18 (78.3)	84/23	.388
Procalcitonin, >ULN, n (%)	2 (18.2)	0	11/1	.640
Lactate dehydrogenase, >ULN, n (%)	24 (41.4)	7 (38.9)	58/18	.851
Ferritin, >100 ng/mL, n (%)	24 (48.0)	8 (72.7)	50/11	.137
Fibrinogen, >ULN, n(%)	2 (33.3)	2 (66.7)	6/3	.343
Lymphopenia, Lym# <1000, n (%)	27 (15.9)	10 (21.7)	170/46	.350
Comorbid conditions				
Hypertension, n (%)	205 (64.9)	41 (56.9)	316/72	.208
Dyslipidaemia, n (%)	106 (33.5)	19 (26.4)	316/72	.241
Obesity, n (%)	19 (45.2)	5 (62.5)	42 / 8	.370
Asthma/COPD, n (%)	113 (35.8)	20 (27.8)	316 /72	.198
Heart failure, n (%)	19 (6.0)	2 (2.8)	316 / 72	.274
Coronary artery disease, n (%)	93 (29.4)	18 (25.0)	316 / 72	.453
Peripheral artery disease, n (%)	11 (3.5)	4 (5.6)	316 / 72	.410
Stroke, n (%)	6 (1.9)	0	316 / 72	.239
Chronic kidney disease, n (%)	12 (9.8)	3 (10.3)	123 / 29	.924
Neck exploration, n (%)	2 (0.6)	4 (5.6)	316 / 72	**.002**

Abbreviations: COVID-19: coronavirus disease 2019, CT: computed tomography, CAD: coronary artery disease, CKD: chronic kidney disease, HDL-chol: high-density lipoprotein-cholesterol, LDL-chol: low-density lipoprotein-cholesterol, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, CRP: C-reactive protein, TSH: thyroid-stimulating hormone, LDH: lactate dehydrogenase, ICU: intensive care unit, RAI: radioactive iodine.

TABLE 3 COVID-19 outcomes and mortality, according to RAI doses

	Low dose 30-50 mci (n = 10)	Medium dose 75-100 mci (n = 39)	High dose >100 mci (n = 23)	*p*
Death	0	1 (2.6)	1 (4.3)	.778
Hospitalization	6 (60)	25 (64.1)	11 (47.8)	.452
ICU admission	0	4 (16.0)	1 (9.1)	.524
Intubation	0	2 (8.0)	1 (9.1)	.759

TABLE 4 Univariate associations of patients with thyroid cancer (dependent variable: mortality)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR, 95% CI	*p*
Age, years	1.102 (1.052–1.154)	**<.001**	1.04 (0.97–1.12)	0.232
Gender (male)	1.619 (0.539–4.864)	.390	2.46 (0.51–11.94)	0.262
CT findings of COVID-19	2.386 (0.842–6.758)	.102	3.14 (0.70–14.12)	0.136
Lymphopenia (Lym# <1000/micL), n (%)	10.208 (2.815–37.013)	**<.001**	6.93 (1.55–31.02)	**0.011**
CRP	1.021 (0.187–5.566)	.981		
Diabetes	6.433 (1.406–29.424)	**.016**	7.26 (0.78–67.50)	0.082
Hypertension	3.906 (0.869–17.563)	.076		
Dyslipidaemia	1.891 (0.670–5.337)	.229		
Asthma/COPD	3.012 (1.049–8.653)	**.041**		
Heart failure	4.931 (1.277–19.036)	**.021**	0.67 (0.50–8.96)	0.764
Chronic kidney disease	16.242 (3.220–81.931)	**<.001**		
Prior CAD	2.996 (1.059–8.471)	**.039**	1.27 (0.28–5.76)	0.759
RAS blocker ± combinations	3.217 (1.078–9.602)	**.036**	0.39 (0.08–1.82)	0.230
Statins	2.245 (0.689–7.315)	.18		
Acetylsalicylic acid	2.127 (0.737–6.141)	.163		
RAI therapy	0.67 (0.15–3.02)	.60		
RAI ≤100 Mci	0.46 (0.03–7.67)	.59		
RAI >100 or neck dissection	2.00 (0.12–33.38)	.63		
TSH mIU/L	1.00 (0.99–1.00)	.70		

Note: Abbreviations: COVID-19: coronavirus disease 2019, CT: computed tomography, CAD: coronary artery disease, CKD: chronic kidney disease, BMI: body mass index, CRP: C-reactive protein, TSH: thyroid-stimulating hormone, ICU: intensive care unit, RAI: radioactive iodine.

4 | DISCUSSION

The results of the present study show that the risk of mortality in COVID-19–infected patients with thyroid cancer is similar to non-cancer patients. Our findings show that the presence of thyroid cancer does not increase the clinical severity of COVID-19 disease and even lower the hospitalization rates due to COVID-19 infection. We also observed that RAI treatment and RAI dose did not have any effect on the risk of hospitalization and mortality. We did not find any association between TSH levels and mortality or morbidity.

Cancers may induce general immunosuppression and negatively affect local defensive systems. A compromised immune system may occur due to cancer itself or the treatment agents. So, patients with cancer generally are more susceptible to viral infections. Additionally, the presence of malignancy might complicate cytokine release, pro-coagulant state and endothelial disease in patients. All may be responsible for more severe COVID-19 disease. The severity and mortality of SARS-CoV-2 infection are reported to be increased in especially haematological and lung cancers, compared to the non-cancer population.[8–10] Active therapy in patients with cancer is reported to be an increased risk of respiratory viral infections and sepsis.[10] But cancer consists of different diseases with different tumour pathology, stages and courses. The early-stage disease may have a different effect on severity or death due to COVID-19 infection. All cancer types may have different infection risks and the effect on the COVID-19 course. The risk of COVID-19 infection and severity must be evaluated individually.

TABLE 5 A multivariate analysis of risk factors associated with hospital admission in the whole group of COVID-19 patients

	Multivariate	
	OR (95% CI)	p
Age	1.03 (1.01–1.05)	.001
Gender (male)	1.27 (0.84–1.91)	.252
Pulmonary CT findings of COVID-19	3.14 (2.08–4.76)	<.001
Hypertension	1.20 (0.79–1.82)	.387
Dyslipidaemia	1.01 (0.65–1.56)	.973
Asthma/COPD	1.47 (0.99–2.17)	.051
Type 2 diabetes mellitus	0.72 (0.48–1.08)	.111
CVD	1.14 (0.72–1.80)	.577
Thyroid cancer	0.38 (0.27–0.54)	<.001

Abbreviations: COVID-19: coronavirus disease 2019, CT: computed tomography, CAD: coronary artery disease, CKD: chronic kidney disease, BMI: body mass index, CRP: C-reactive protein, TSH: thyroid-stimulating hormone, ICU: intensive care unit, RAI: radioactive iodine.

COVID-19 in patients with thoracic malignancies study (TERAVOLT) and COVID-19 and Cancer Consortium (CCC19) (only 30 patients were head and neck cancers) studies show the high mortality and poor prognosis associated with COVID-19 infection in patients with cancer.[11,12] Progressive cancers, chemotherapy usage and steroid therapy were reported to be associated with the higher mortality risk of COVID-19 infection. Lee et al[13] show different SARS-CoV-2 infection and prognosis risks in patients with different tumour types and report increased SARS-CoV-2 severity in haematological cancer patients. However, only 4 endocrine cancers were included in the study. Robilotti et al[14] found major surgery, chemotherapy within 30 days, and metastasis did not increase risk in a retrospective tertiary centre study.

Thyroid cancer is the most common form of endocrine cancers, and its incidence rate is increasing.[15] There are still limited data for thyroid cancers in the COVID-19 era. Patients with completed treatment for thyroid cancer are not considered at a higher risk of COVID-19 infection, and they are unlikely to be immunocompromised in theory.[16,17] Our study results are compatible with these views. Recently, a study reported a weak significant association between recent diagnosis of thyroid cancer and COVID-19 infection risk. In this study, 50 thyroid cancer patients (20 were recently diagnosed) were included.[18] Besides, they reported synergistic effects between COVID-19 and cancer on death.[18]

RAI is an important component of treatment in selected patients with differentiated thyroid cancers. In general, RAI treatment is used for remnant ablation, or as an adjuvant, and for metastatic thyroid cancers.[19] Different RAI dosages are used according to the patient's situation. RAI therapy affects immune functions. Especially in high doses, RAI may cause bone marrow suppression and may deplete T and B cells.[19,20] Bone marrow suppression is defined as a high risk for COVID-19 infection.[21] Although high-dose radioiodine administration may cause bone marrow suppression, clinical immunosuppression is limited in therapy with conventional radioactive doses.[20,21] High-dose RAI may also cause lung fibrosis. RAI may cause cytokine release as an acute effect that may contribute to harmful cytokine storm in COVID-19 patients. Salivary dysfunction may also increase the infection risk.[22] RAI damages cells and may cause release of auto-antigens into the circulation and immunoreactivity. Due to the adverse effects of RAI treatment mentioned above, we hypothesized that the history of previous RAI ablation could be associated with the more severe outcomes of COVID-19 infection.

However, as we did not have the data about the time of the RAI treatment, it is not possible to comment on the potential association of recent RAI therapy to COVID-19 clinical outcomes. Also, TSH suppression therapy and the levothyroxine dose were not found to be associated with an increased risk of COVID-19 severity and mortality.[23] Besides, we did not find any effect of TSH levels on COVID-19 morbidity and mortality. We could not find a unique effect of comorbidities on COVID-19 mortality in thyroid cancer patients.

Although the prevalence of comorbidity is higher in thyroid cancer patients, we do not know the real reason for the low hospitalization ratio. Thyroid cancer patients may not have accepted recommendations for hospitalization. Most of the thyroid cancers may be ***differentiated*** and early-stage cancers. Thyroidectomy and RAI treatment may affect immune and inflammatory responses to infections in these patients.

A significant lung metastasis, systemic tyrosine kinase inhibitors or immunotherapy may affect the immune system negatively in a small number of patients. In our study, we could not detect any COVID-19 case receiving tyrosine kinase inhibitors.

There are several limitations of the present study. First, due to the retrospective observation, we could not establish a causal effect relationship between the diagnosis of thyroid cancer and clinical outcomes. Second, we have insufficient clinical information about cancer staging, metastasis, remission or recurrence in these patients. Also, as a limitation, short follow-up in thyroid cancer has generally excellent prognosis and likely not increase mortality. Recently, Sud et al published a modelling study from the UK, which predicts almost 8 excess deaths over the next 10 years in thyroid cancer, due to a 6-month delay diagnosis and therapy because of COVID-19 pandemic.[24] Another limitation of the study is that due to the lack of special coding for the subgroups of thyroid cancers, it is possible that some cases of thyroid cancer may be anaplastic or medullary cancer. On the other hand, the ***prevalence*** of these two thyroid cancer types are low, and we do not anticipate them to change the overall results of the study.

On the other hand, the most important strength of the study is that the results reflect the population-based national data with adequate follow-up (30 days). To our knowledge, this is the first large-scale study related to COVID-19 in patients with history of thyroid cancer. Besides, this is the first study in the literature about the effect of RAI therapy on COVID-19 infection. PMS provides confidence in the strength of the observed results of our study. Strength was the standard management of all thyroid cancer patients in our

national database. But still, there may be some residual confounding factors that we could not evaluate.

In conclusion, these data showed that the history of differentiated thyroid cancer or RAI therapy does not indicate a poor prognosis of COVID-19. Thyroid cancer patients should be evaluated for COVID-19 similar to other patients and should not stop taking thyroid hormone drugs. Also, it should be considered that having a history of RAI therapy does not worsen the COVID-19 in patients with thyroid cancer. Future studies examining the effect of histological subtypes of differentiated thyroid cancers on the course of COVID-19 are needed. Specific studies in patients who have recently been diagnosed with thyroid cancer or received RAI treatment will be helpful. The effects of the COVID-19 pandemic period on thyroid cancer recurrence and prognosis should be additionally investigated.

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AUTHOR CONTRIBUTIONS

MS, AS, CH, ID, IT were involved in the design of the study. NA, OC, and MC were responsible for the data download and verification. ID and CH cleaned the data. ID, IT, CH, MS, AS analyzed the data. MS, AS, ID prepared the figures and tables. MS drafted the manuscript. All authors were involved in the interpretation, critically reviewed the first draft, and approved the final version.

CONFLICT OF INTEREST

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The database was established by the Ministry of Health, Turkey, for the management of hospitalization and follow-up of patients COVID-19. The data are available to researchers who meet the criteria for access (requests are evaluated by the General Directorate of Health Information Systems). The authors are not permitted to share these data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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