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Thyroid autoimmunity and SARS-CoV-2 infection: Report of a large Italian series

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ABSTRACT

Since the beginning of the pandemic, numerous risk factors have been associated with SARS-CoV-2 infection and COVID-19 outcomes, such as older age, male sex, and the presence of comorbidities, such as hypertension, obesity, and diabetes. Preliminary data also suggest epidemiological association between SARS-CoV-2 infection and systemic autoimmune disease. For this reason, we investigated if patients affected by autoimmune thyroid disorders (AITD) are at risk of developing SARS-CoV-2 infection or COVID-19 disease.

From April to September 2020, we have conducted a telephone survey that included 515 consecutive unselected patients with known thyroid disorders, of which 350 were affected by AITD. All 11 definitive diagnosis of COVID-19 (def-sympt-COVID-19) belonged to the AITD group, while the rest 14 cases highly suspected for COVID-19 (suspect-sympt-COVID-19) were equally detected in both group (7 in AITD and 7 in not-AITD). The overall prevalence of symptomatic COVID-19 (def-sympt-COVID-19 + suspect-sympt-COVID-19), recorded in the 350 AITD population was statistically significant higher compared to that reported in the Italian and Tuscan general population at the same time period of the present survey ($18/350 = 5.14\%$ vs $516/100000 = 0.51\%$ [$p < 0.001$; OR = 10.45, 95% CI 6.45–16.92] and vs $394/100000 = 0.39\%$ [$p < 0.001$; OR = 13.70, 95% CI 8.44–22.25], respectively).

Therefore, our results suggest a higher prevalence of SARS-CoV-2 infection and COVID-19 disease in patients with AITD.

1. Introduction

As of 31st January 2022, the COVID-19 pandemic caused by SARS-CoV-2 has spread around the world with nearly 300 million cases and >5 million confirmed deaths, based on the WHO databases [1].

SARS-CoV-2 infection can run asymptotically or provokes mild upper respiratory tract symptoms as dry cough, headache, fever, and loss of smell and taste, or it can induce an interstitial pneumonia that can result in ARDS (Acute Respiratory Distress Syndrome) with the need for

mechanical ventilation [2].

To date, the most effective weapon to fight SARS-CoV-2 infection is represented by primary prophylaxis with vaccines. In a short time, numerous sera have been released [3], including, for the first time, mRNA technology based vaccines (Pfizer-Biontech's BNT162b2 and Moderna's mRNA-1273) [4,5].

Since the beginning of the pandemic, numerous risk factors have been associated with severe COVID-19, need of hospitalization and/or intensive care unit admission and, consequently, increased mortality

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and their recognition helped to hasten more focused health interventions by the Public Health administrations. Among the frequent features associate with severe COVID-19 and death, there are older age, male sex, and the presence of comorbidities, such as hypertension, obesity, and diabetes [6].

Moreover, other researchers suggested epidemiological association between SARS-CoV-2 infection and several pre-existent diseases, including systemic autoimmune disease, showing higher incidence of the infection among people affected by this subset of diseases, especially connective tissue diseases, whose significant immune-system impairment may enhance susceptibility to infections [7–11]. These observations did not contemplate autoimmune thyroid diseases (AITD) and few data have been collected on the risk of infection in patients affected by these thyroid diseases.

For the reason, based on these preliminary observations, we investigated if patients affected by AITD are at risk of developing SARS-CoV-2 infection or COVID-19 disease.

2. Patients and methods

We have conducted an observational study that included 515 consecutive unselected patients with known thyroid disorders (from our institution list) by means of telephone survey from April to September 2020. Patients were divided in two groups: (a) patients with AITD (autoimmune thyroiditis, Graves’ disease, patients operated for different kind of thyroid diseases and presence of circulating AbTPO, or AbTg); (b) patients without autoimmune disorders (not-AITD): nodular or multinodular goiter, patients operated for different kind of thyroid diseases, all without cytological, histological, or humoral evidence of thyroid autoimmunity.

2.1. COVID-19 classification

On these bases, COVID-19 was classified as: (a) definite diagnosis of COVID-19 disease (def-sympt-COVID-19): presence of symptomatic COVID-19 infection always confirmed by positive oral/nasopharyngeal swabs at polymerase-chain-reaction testing; (b) highly suspected COVID-19 disease (suspect-sympt-COVID-19): presence of fever (temperature > 99 °F), and/or known contact with COVID-19 infected individual, plus four or more symptoms, such as: dry cough, sore throat, shortness of breath, dyspnea, sudden worsening of preexisting respiratory symptoms, anosmia, dysgeusia, nausea, vomiting, headache, diarrhea.

This group comprises a significant number of patients characterized by manifestations highly suggestive of COVID-19 disease not confirmed by COVID-19 oral/nasopharyngeal swabs at polymerase-chain-reaction testing (because they were not submitted to the test, often due to limited availability of virological tests).

2.2. Statistical analysis

Statistical analysis of the results was carried out using the Odds Ratio (OR) by Java-Stat 2-way Contingency Table Analysis. STATA, and StatView were also used to evaluate other variables (data are expressed as mean ± 2SD).

Table 1
Demographic data and COVID-19 prevalence in Italian patients with AITD vs not-AITD.

	N° of patients	Gender	Mean Age	COVID-19 Definite	P* RR value 95% CI	COVID-19 Highly suspected	P* RR value 95% CI	COVID-19 Definite + Highly suspected	P* RR value 95% CI
AITD vs	350	54 M/ 296 F	57.9	11	0.021	7	ns	18	ns
not-AITD	165	43 M/ 122 F	61.7	0	1.487 1.004–1.487	7		7	

* Mantel-Haenszel; AITD: autoimmune thyroid diseases.

3. Results

Of 515 interviewed patients, 350 were affected with AITD, of which 30 had also a diagnosis of thyroid cancer with thyroid antibodies positivity (AbTg and/or AbTPO). 165 patients had no AITD nor thyroid antibodies positivity, included 36 patients with thyroid cancer. The mean age was 58.91 years old and there was a female gender predominance in all subgroups of patients (Table 1).

3.1. Prevalence of Covid-19

Overall, COVID-19 was recorded in 25 (def-sympt-COVID-19+ suspect-sympt-COVID-19) out of 515 patients (4.8%). Of these 11 had a definitive diagnosis of COVID-19 (def-sympt-COVID-19), while the rest 14 reported a clinical history highly suspected for COVID-19 (suspect-sympt-COVID-19). All 11 confirmed case (mean age 52.09, 9/11 [81.8%] were female) belonged to the AITD group, while 7 suspect-sympt-Covid-19 cases were detected in each group (AITD and not-AITD). Among the 11 confirmed cases, 4 have been hospitalized because of development of COVID-related pneumonia (Tables 2, 3). The overall prevalence of symptomatic COVID-19 (Table 2), (def-sympt-COVID-19+ suspect-sympt-COVID-19), recorded in the 350 AITD population was statistically significant higher compared to that reported in the Italian and Tuscan general population at the same time period of the present survey (18/350 = 5.14% vs 516/100000 = 0.51% [p < 0.001; OR = 10.45, 95% CI 6.45–16.92] and vs 394/100000 = 0.39% [p < 0.001; OR = 13.70, 95% CI 8.44–22.25] respectively); data from the Italian Superior Institute of Health (ISS) [12]. These results were confirmed also when only the 11 definite cases have been considered (11/350 = 3.14% vs 516/100000 = 0.51% [p < 0.001; OR = 6.25, 95% CI 3.41–11.47] and vs 394/100000 = 0.39% [p < 0.001; OR = 8.20, 95% CI 4.46–15.076]).

Noteworthy, the prevalence of COVID-19 confirmed cases (def-sympt-COVID-19) was statistically higher in the AITD group compared to not-AITD group (11/350 = 3.14% vs 0/165 = 0% [p < 0.021; Relative Risk (RR) = 1.487, 95% CI 1.004–1.487]) (Table 1).

4. Discussion

Heterogeneous data have been collected about the potential impact of pre-existing thyroid diseases on COVID-19 development and prognosis.

For example, in the early phase of the pandemic, exploratory cohort-based retrospective analysis have reported that patients treated for hypothyroidism or hyperthyroidism seem to be not at increased risk of SARS-CoV-2 infection, hospitalization, mechanical ventilation nor death and that therapy for thyroid disease, when controlling for relevant confounding, does not affect the prognosis of SARS-CoV-2 infection [13,14]. Nonetheless, none of these aforementioned researches have addressed the underlying etiologies of hypothyroidism and hyperthyroidism conditions, which in turn can have a different impact on the risk and the course of the infection. In fact, other studies have suggested that thyroid autoimmunity increased the risk of COVID-19 infection [15], and that, hypothyroidism was associated with a more severe COVID-19 disease instead [16].

Table 2
Prevalence of COVID-19 in Italian patients with AITD compared to general, and regional population.

	Pts n°	COVID-19 Definite	P* OR value 95% CI	COVID-19 Highly suspected	P* OR value 95% CI	COVID-19 Definite + Highly suspected	P* OR value 95% CI
AITD vs	350	11	0.000	7	0.000	18	0.000
Italian general population	100000	516	6.25 3.41–11.47	516	3.93 1.85–8.35	516	10.45 6.45–16.92
AITD vs	350	11	0.000	7	0.000	18	0.000
Tuscan general population	100000	394	8.20 4.46–15.076	394	5.15 2.42–10.97	394	13.70 8.44–22.25

* Mantel-Haenszel; AITD: autoimmune thyroid diseases.

Table 3
Patients with AITD and COVID-19 infection, clinical data.

Patient	Gender	Age	Nasopharyngeal Swab -COVID	Symptoms	Hospitalization	Comorbidities
1	F	45	+	yes	no	no
2	F	50	+	yes	yes Pneumonia	Obesity
3	F	52	+	yes	yes Pneumonia	no
4	F	81	+	yes	yes Pneumonia	Papillary Thyroid Cancer, Metabolic syndrome
5	F	88	+	no	no	no
6	F	67	+	yes	yes Pneumonia	Arterial hypertension
7	F	57	+	no	no	Anti-phospholipid Ab syndrome
8	F	24	+	yes	no	no
9	F	57	+	yes	no	SLE
10	M	50	+	yes	no	Vitiligo
11	M	22	+	yes	no	no

AITD: autoimmune thyroid diseases.

On the other hand, there are more and more evidences that COVID-19 itself may acutely disrupt the thyroid function. The range of thyroid disorders associated with SARS-CoV-2 infection is rather broad non-thyroidal illness syndrome (NTIS), thyrotoxicosis and subacute thyroiditis (SAT) [17–19], and in part, they could be explained by the direct virus replication within thyroid follicular cells through the angiotensin-converting enzyme 2 (ACE2) receptor [20–22]. However, preliminary prospective studies suggested that when altered, the thyroid dysfunction recovers to baseline during the follow-up without specific therapy and the meaning of such thyroid perturbations could be rather their relationship with more severe disease and worse prognosis during acute presentation with COVID-19 [23].

In particular, it appeared that low T3 syndrome (low FT3, normal or low TSH, normal FT4) is a marker of inflammation in COVID-19 infection, it can be associated with the severity of the disease, with cytokine storm, and with treatments, such as corticosteroids [24–26].

Our findings suggest a higher prevalence of SARS-CoV-2 infection and COVID-19 disease in patients with AITD. To date, in the literature there is only one other study which evaluate the prevalence of SARS-CoV-2 infection in a smaller sample of AITD patients and through a similar methodology (retrospective telephone survey) and it suggests that this subset of patients carries similar risk of COVID-19 compared to the general population [27]. However, differently from this paper, our study has considered a wider sample and it has been conducted only during the first peak of the pandemic, with no vaccinated patients enrolled, which may justify the discordant susceptibility to COVID-19 of the examined populations.

Understanding the impact of SARS-CoV-2 infection in AITD patients may be clinically relevant since hypothyroidism (the thyroid dysfunction most frequently associated with AITD) has been demonstrated to be associated with an increased death rate in the general population [28].

Therefore, we aim to shed a light on the incidence and risk of developing SARS-CoV-2 infection or COVID-19 disease in patients with thyroid autoimmune disease.

This survey presents some limitations, such as: 1) the time of the survey study; it has been conducted in the first phase of the pandemic

spread, during which there were several issues in the management of the disease, such as the lack of virological tests to assess the presence of the virus. Therefore, the number of asymptomatic, or with mild symptoms patients could be higher; 2) since the modality of collecting data was based on a telephone survey, the possibility of a recall bias should be considered.

Despite the above-mentioned limitations, our strengths are: 1) data obtained from a broader AITD population of different areas of Italy; 2) the study has been conducted during the first phase of the pandemic wave, during which no vaccine protection was available, and the only types of protection that could aid in preventing the infection were the use of masks and social distancing.

However, larger prospective studies are needed to compare and evaluate the different impact of the various SARS-CoV-2 variants as well as the effect of anti SARS-CoV-2 vaccines in this subset of population with autoimmune thyroid disorders [29].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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