

REVIEW



## SARS-COV-2-related immune-inflammatory thyroid disorders: facts and perspectives

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### ABSTRACT

**Introduction:** During the COVID-19 pandemic thyroid gland alteration/dysfunction has been emerged as a possible endocrine complication. The present review is focused on inflammatory and autoimmune thyroid complications triggered by SARS-CoV-2 infection by searching through databases like MEDLINE and Scopus up to April 2021.

**Areas covered:** Beside the occurrence of ‘non-thyroidal illness’ in severe clinical conditions, alterations of thyroid function and structure may occur during COVID-19 as a consequence of either direct or indirect effects of SARS-CoV-2 infection on the gland. On the one hand, SARS-CoV-2 uses ACE2 as a receptor to infect the host cells and ACE2 is highly expressed by follicular thyroid cells. On the other hand, COVID-19 is associated with a systemic inflammatory and immune response, involving Th1/Th17/Th2 lymphocytes and proinflammatory cytokines, which resembles the immune activation that occurs in immune-mediated thyroid diseases. COVID-19-related thyroid disorders include destructive thyroiditis and onset or relapse of autoimmune thyroid disorders, leading to a broad spectrum of thyroid dysfunction ranging from thyrotoxicosis to hypothyroidism, that may worsen COVID-19 clinical course and affect prognosis.

**Expert opinion:** Physicians should be aware of the possible occurrence of thyroid dysfunction during and after SARS-CoV-2 infection. Further longitudinal studies are warranted to evaluate potential long-term sequelae.

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COVID-19 – Sars-CoV-2 – cytokine storm – subacute thyroiditis – thyrotoxicosis – thyroid dysfunction – autoimmunity

## 1. Introduction

Coronavirus disease 2019 (COVID-19) epidemic started in December 2019 and spread worldwide with millions of people infected in the following years [1–3]. The causative agent is a novel RNA virus belonging to the Coronaviridae family, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. SARS-CoV-2 exhibits a marked respiratory tropism causing mainly interstitial pneumonia and acute respiratory distress syndrome (ARDS), defined as acute onset of hypoxemia with bilateral infiltrates, but is also able to induce a severe systemic inflammation, leading to multi-organ dysfunction and even death in subjects with high risk factors (i.e. old age, male gender, obesity, diabetes, and cardiovascular comorbidities) [1,2]. A part from the typical lung involvement, that can rapidly evolve toward respiratory failure and ARDS, patients with COVID-19 can experience several extra-pulmonary manifestations, including cardiovascular (heart failure, arrhythmias) and neuromuscular disorders, renal failure, coagulopathies (thrombosis, disseminated intravascular coagulation, anemia, and thrombocytopenia), and also

endocrinopathies [1,2,5]. Despite the whole spectrum of complications and long-term sequelae related to SARS-CoV-2 infection is far to be fully understood, thyroid gland involvement has been emerging as a quite common event in the course of COVID-19 [5]. More severe manifestations of COVID-19 are associated with an excessive immune and inflammatory response, characterized by elevated serum levels of several proinflammatory cytokines, the so-called ‘cytokine storm’ [1]. The cytokine response described in COVID-19 seems to resemble, at least in part, the immune activation that occurs in immune-mediated thyroid diseases [6]. Actually, alterations of thyroid function and structure may occur as a consequence of either direct or indirect effects of SARS-CoV-2 infection on the gland (Figure 1). Recent literature reports a not negligible frequency of subacute or painless thyroiditis in COVID-19 patients, as well as the onset of autoimmune hyperthyroidism or Graves’ disease. The possible development of chronic thyroid autoimmunity and persistent hypothyroidism in the long run has been also proposed as a consequence of either a preceding subacute thyroiditis or a viral triggering of autoimmunity in susceptible individuals.

### Article highlights

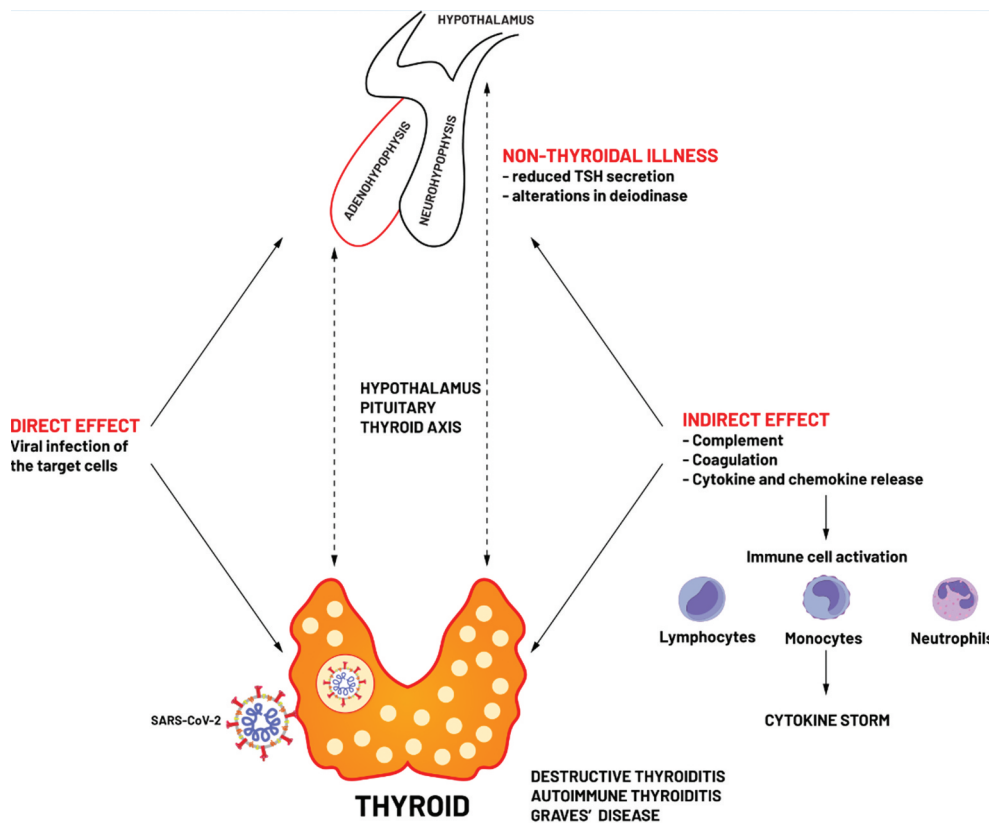
- SARS-CoV-2 infectious promotes the release of several pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, TNF $\alpha$ , and IFN- $\gamma$  being the key pathogenic ones), leading to immune response hyperactivity and uncontrolled systemic inflammatory response, the so-called 'cytokine storm'.
- Enhanced Th1/Th17 immune responses and cytokine pathways involved in SARS-CoV2 infectious resemble, at least in part, the immune activation that occurs in immune-mediated thyroid diseases.
- Thyroid function test alterations are quite common in the course of COVID-19 as a consequence of either non-thyroidal-illness or thyroidal gland involvement in the context of hypercytokinemia, as a consequence of hyperinflammatory response (subacute thyroiditis) or T-lymphocyte triggered autoimmunity (painless thyroiditis).
- Thyroid inflammation/damage may be also the consequence of a direct action of the SARS-CoV-2 virus on thyroid cells through ACE2 receptor.
- Excessive cytokine production and immune system dysregulation may favor the development/relapse of autoimmune disorders in genetically susceptible individuals. Future researches would investigate the intriguing connections and mutual relationships between SARS-CoV-2 and thyroid autoimmunity and the potential long-term increase of autoimmune thyroid disease after the COVID-19 outbreak.

The present review is focused on inflammatory and autoimmune thyroid complications triggered by SARS-CoV-2 infection, the related physio-pathological mechanisms and their possible long-term permanent sequelae.

## 2. Methods

The literature was searched by two authors independently (RMR and AC). Online databases including MEDLINE (via PubMed), Embase, ISI Web of Science, Google Scholar, and Scopus were systematically searched using multiple keywords combinations. The entree terms included 'thyroid', 'thyroiditis', 'destructive thyroiditis', 'hypothyroidism', 'hyperthyroidism', 'thyrotoxicosis', 'autoimmune thyroid disease', 'thyroid function', 'thyroid hormones' in combination with the terms 'coronavirus', 'SARS-CoV-2' and 'COVID-19'. This was complemented by a carefully hand-searching reference lists for additional studies to find additional studies and expand the search. Literature search was performed up to April 2021.

Primary studies and case series dealing with patients affected by COVID-19 and reporting thyroid involvement were included. Data concerning prevalence, geographical area, sex and age of patients, thyroid function test (TFTs) alteration and imaging, treatment and outcome of the related inflammatory and autoimmune thyroid disorders were extracted. We included in the present reviews, the articles matching the following inclusion criteria: English language and publication in peer-reviewed journals. We excluded articles for irrelevance to the topic in question, duplicates, and papers written in other languages apart from English. Systematic reviews and meta-analyses analyzing the prevalence of thyroid disorders in the course of COVID-19 with potential to be eligible were identified and included in the



**Figure 1.** Schematic representation of the potential mechanisms of hypothalamic-pituitary-thyroid axis injury by SARS-CoV-2 infection.

study, while narrative reviews, that do not represent an evidence-based information, and systematic reviews focusing on the general endocrine impact by COVID-19 were excluded, as well as recommendations by endocrine societies, editorials and opinions.

### 3. The cytokine storm induced by Sars-CoV-2 infectious and its relationship with thyroid status

More severe COVID-19 is associated with an uncontrolled systemic immune and inflammatory response, involving also coagulation and complement systems that is characterized by a strong release of proinflammatory cytokines and results in a systemic hyperinflammatory state leading to multiorgan injury/failure and even death [1,7–9]. This overwhelming immune response is called ‘cytokine release syndrome’ or ‘cytokine storm’, a term that was first used to describe the impressive activation of the immune system that occurs in acute graft-versus-host disease [10]. The cytokine storm is the consequence of an excessive and dysregulated immune response against pathogens and is caused by a massive, rapid release of cytokines into the bloodstream from over-activated immune cells, leading to uncontrolled inflammatory responses [10]. The cytokine storm ultimately leads to extensive apoptosis of epithelial and endothelial cells, vascular leakage, and increased permeability and results in multiple-organ dysfunction [9,11]

A variety of cytokines, including the interleukin-1 (IL-1) family, IL-6, IL-8, IL-10, IL-17, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interferon (IFN)- $\gamma$ , and chemokines (CXCL8, CXCL9, CCL2, CCL3, CCL4, and CCL10 to mention a few) are involved in the development of a cytokine storm. Among these, IL-1 $\beta$  and IL-6, along with TNF- $\alpha$  and IFN- $\gamma$ , have been described as key pathogenic cytokines in COVID-19 related cytokine storm [9,12–14]. These cytokines are secreted mainly by dendritic cells and mononuclear macrophages that are activated by pattern recognition receptors (PRRs), such as toll-like receptor (TLR) and retinoic acid-inducible gene-1-like receptor (RLR). PRRs, expressed on the cell surface, recognize the pathogen-associated molecular pattern (PAMPs) derived from microorganisms, such as viral RNA, and damage-associated molecular patterns (DAMPs), such as DNA and protein oligomers resulting from tissue damage. Upon binding to their ligands, PRRs promote the inflammatory response against the triggering infection by activating several signaling pathways and subsequently transcription factors, including nuclear factor  $\kappa$ B, activation protein 1, interferon response factors three and seven, that induce the expression of genes encoding inflammatory cytokines, chemokines, and adhesion molecules. This sequence of events results in enhanced secretion of pro-inflammatory cytokines that drive acute-phase responses through activation of innate immunity [15,16]. These cytokines further promote the infiltration and recruitment of immune cells, namely, monocytes and T lymphocytes, from the bloodstream to the infected site in a positive feedback loop of inflammation. Meanwhile, IL-6 and IFN- $\gamma$  are key cytokines for T-cell mediated adaptive immunity, involving T helper lymphocytes (mainly, Th1/Th17 and Th2 subtype) and highly cytotoxic CD8+ T effector lymphocytes [17].

Enhanced Th1/Th17 immune responses and IL-17-related cytokine pathways are typically observed in the course of SARS-CoV-2 infectious [8,18,19] but are also well known to be associated with autoimmune disorders, including autoimmune thyroid diseases [20].

The cytokine responses described in COVID-19 resemble, at least in part, the immune activation that occurs in immune-mediated thyroid diseases [6,20,21]. Specifically, in patients with autoimmune thyroid diseases, a Th1/Th2 imbalance and hyperactivation of Th1 and Th17 response in peripheral lymphocytes have been described, and increased serum levels of the Th1/Th17-related cytokines, like IFN- $\gamma$ , IL-17, IL-21, IL-22, IL-23, and TNF- $\alpha$ , have been demonstrated [22–29]. A similar pattern of Th1 activation has been described in drug-induced autoimmune/inflammatory thyroid events occurring as a side effect of certain types of immunotherapy, especially those involving T-cells [30–33] whereas an increase in IL-6 was reported in the course of destructive thyroiditis and also in the development of autoimmune thyroiditis in the setting of viral infections [34,35]. Thus, it is conceivable the hypercytokinemia and the consequent hyperinflammatory status occurring in the course of SARS-CoV-2 infectious may trigger immune-mediated thyroid disorders and made them sustained.

Finally, excess circulating cytokines play an important role in the pathogenesis of non-thyroidal-illness (NTI), which is characterized by alterations in thyroid function parameters (low T3 syndrome) in response to severe systemic illness, including COVID-19, and represents an adaptive mechanism rather than a true thyroid dysfunction [36–38]. The most typical alteration is a decrease in serum T3 levels (low T3 syndrome) accompanied by low or inappropriately normal TSH; as the severity and/the duration of NIT increases, also T4 levels decrease. The underlying pathogenic mechanism is the reduced enzyme activity of 5'-monodeiodinase (D1 and D2) responsible for converting T4 into T3 in peripheral tissues, along with the increased activity of D3 deiodinase that catalyzes the inactivation of both T4 and T3 [36]. The NTI is commonly interpreted as a euthyroid sick syndrome, an adaptive compensatory and thus beneficial response that decreases metabolism and energy consumption during severe illness, either acute or chronic. Nonetheless, NTI and low T3 levels are strongly associated with poor outcome and mortality [36]. Cytokines such as IL-1 $\beta$ , IL-6, IFN- $\gamma$ , and TNF- $\alpha$  exert their actions at different levels: on the hypothalamus-pituitary thyroid axis (HPT) by lowering TSH secretion and on the peripheral metabolism of thyroid hormones via deiodinases by reducing the conversion of T4 to T3 and increasing inactivation of both T4 and T3 [13,39].

### 4. Destructive thyrotoxicosis in COVID-19 patients

Destructive thyrotoxicosis represents a relatively uncommon cause of thyrotoxicosis, resulting from the release of pre-formed thyroid hormone secondary to the destruction of the thyroid follicles [40]. Common etiologies include painful subacute thyroiditis (SAT) linked to microbial infection and painless destructive thyroiditis, such as both post-partum and sporadic forms and those induced by drugs (lithium,

amiodarone, interferons, immune-checkpoint inhibitors and so on) [40].

SAT is a self-limiting inflammatory disorder of the thyroid gland that is thought to be induced by viruses. Genetic factors, including human leukocyte antigen (HLA) haplotype, seem to play an important role in the onset of SAT, conferring susceptibility to develop the disease, that affects mostly women [40,41]. The acute onset of SAT is often preceded by an upper respiratory tract infection caused by viruses, such as influenza, adenovirus, coxsackie, or less frequently Epstein-Barr and cytomegalovirus, and may occur during viral outbreaks, so that it can ensue as a viral or post-viral manifestation [41,42]. The clinical course of SAT usually shows three consecutive phases which unfold over a period of about 6 months. At the onset and during the first weeks, inflammatory destruction of the thyroid leads to transient thyrotoxicosis as preformed thyroid hormones are released from the damaged gland. Within few weeks, as thyroid hormone stores are depleted, many patients undergo a hypothyroid phase, which may last up for three or more months and is generally followed by euthyroidism restoration. Transient thyrotoxicosis, when severe, may require symptomatic therapy with beta-blockers, while anti-thyroid drugs are contraindicated because there is no excess thyroid hormone production by the gland. Thyroid hormone replacement therapy may be started in patients who are symptomatic with the hypothyroid phase or if this phase is prolonged; levothyroxine treatment should be continued for approximately 6–9 months and then withdrawn to determine whether thyroid function has normalized [43]. Since the disorder is self-limiting, its diagnosis is not infrequently underestimated. However, the disease should be not overlooked since the associated thyrotoxicosis may worsen the clinical course of concomitant disorders, and long-term sequelae, such as autoimmune hypothyroidism, are reported [21]. Although chronic hypothyroidism is most closely associated with preexisting Hashimoto's thyroiditis and high serum levels of thyroid antibodies, all types of thyroiditis may progress to permanent hypothyroidism, as a consequence of severe and extensive inflammatory damage of the gland. This outcome is more likely observed in patients in whom a more severe hypothyroid phase develops. This is the case, for instance, of destructive thyroiditis occurring in the course of anticancer immunotherapies [31].

During the recent SARS-CoV-2 pandemic, SAT has been emerged as a possible endocrine complication triggered by COVID-19. As summarized in Table 1, an increasing number of isolated cases of SAT associated with SARS-CoV-2 infection have been reported, occurring either simultaneously with COVID-19 [44–48] or after the resolution of distinctive symptoms of COVID-19 [49–59]. Following the first case reports, a retrospective study of 287 patients hospitalized for COVID-19 reported a 20.2% frequency of thyrotoxicosis related to destructive thyroiditis, as supported by its self-limiting clinical course in the absence of TSH-receptor autoantibodies (TRAb) and by the correlation with increased levels of serum IL-6 (Table 2) [60]. Such an incidence was higher than expected in the general population, providing evidence of an increased risk of SAT during/after SARS-CoV-2 infectious [61]. Similarly, Muller and coworkers [61] found an

increased prevalence of thyrotoxicosis due to SAT in a cohort of 85 COVID-19 patients admitted to the high intensity of care units (HICUs) compared to that reported in 78 patients admitted to the same HICUs in 2019, thus SARS-CoV-2 negative, as a control group (15% vs 0.5%,  $P = 0.002$ ). Either autoimmune or non-autoimmune preexisting thyroid disorders did not represent a risk factor for the development of SARS-CoV-2 related SAT [61]. On the contrary, a low prevalence of SAT-related thyrotoxicosis was reported in two studies from the UK including hospitalized patients with various degrees of severity of COVID-19. In the study by Liu et al. [62], including 191 patients with COVID-19 (mean age  $53.5 \pm 17.2$  years; 51.8% male), ten patients had isolated low TSH, suggestive of subclinical thyrotoxicosis due to thyroiditis, although the contribution of autoimmunity was likely in 2 of them, whereas ten patients had isolated low fT3, likely related to NTI. A subsequent study, conducted in an Indian tertiary care teaching hospital, assessed thyroid function tests in 60 COVID-19 hospitalized patients and found that most patients were euthyroid, but 35% of them had one or more abnormality in the thyroid function, low TSH being the most common (11 patients or 18.33%); one patient had characteristic pattern of thyroiditis [63]. No significant correlation emerged between thyroid function tests (TFTs) and severity of COVID-19 [63]. The Authors concluded that alterations of TFTs may occur during COVID-19 infection, even in absence of preexisting thyroid diseases, the most common alteration being a combination of thyroiditis and NTI [63]. However, in both studies very few data were available concerning clinical features and management of the patients with alterations of TFTs [62,63] (Table 2). In another study by Khoo et al. [64] most patients (86.6%) with COVID-19 were euthyroid, with no case of thyrotoxicosis recorded (Table 2). In the study by Khoo et al. [64] as well as in a previous retrospective study by Chen et al. [65], COVID-19 patients had lower TSH and FT3 levels compared to those without COVID-19, NTI being the most common thyroid function alteration recorded. Similarly, in a single-center study including 144 COVID-19 patients [66], half of them had normal thyroid function tests both at admission and on follow-up, while 39% of patients were found to have low TSH levels either at admission or during hospitalization, associated with low FT3 in half of them. In this series, the finding of low TSH was more likely due to NIT rather than to destructive thyroiditis [66]. Such variability in the prevalence of SAT among studies may depend on differences and limitations in data collection, patients' setting (i.e. HICU patients compared to non HICU hospitalized patients), and/or interfering factors, such as drugs or iodine-containing contrast agents. Large epidemiological multicenter studies are needed to better evaluate the prevalence of thyrotoxicosis related to SAT in the course of COVID-19.

Thyroid inflammation/damage may be the consequence of a direct action of the SARS-CoV-2 virus on the gland, based on the recent evidence that SARS-CoV-2 RNA is present in the serum from COVID-19 patients, indicating episodes of viremia [67] and the virus receptor, the angiotensin-converting enzyme 2 (ACE2), is highly expressed in thyroid follicular cells [68]. Recent pathological data demonstrate that despite the SARS-CoV-2 is mainly distributed in the lung, the infection also damages several

**Table 1.** Summary of the demographic and clinical features, biochemical and imaging data, treatment and follow-up of patients diagnosed with subacute thyroiditis related to SARS-Cov2 infectious, as extracted from case reports and case series available in the literature.

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
<b>Ippolito S et al. Italy</b>	F	69	Yes (goiter)	5	No fever palpitations, insomnia, agitation	TSH 0.08 mIU/L FT3 5.5 pg/ml (n v 2-4.4) FT4 24.6 nmol/L (nv 0.3-1.7) TgAb, TPOAb and TRAb	US: enlarged hypoechoic thyroid, decreased vascularity. TS: no 99mTc-perthecnetate uptake	Intravenous methylprednisolone 40 mg/days for 3 days, oral prednisone (25 mg/d as starting dose) progressively tapered over 4 weeks Clinical and biochemical thyrotoxicosis improved within 10 days	[44]
<b>Asfuroglu Kalkan E et al. Turkey</b>	F	41	No	0	Tenderness to palpation of thyroid	TSH <0.008 mIU/L FT3 7.7 pm/L (nv 3.1-6.8) FT4 25.7 pmol/L (nv 7-22) TgAb, TPOAb and TRAb undetectable Elevated ESR and CRP	US: diffuse decrease of vascularity and heterogeneous parenchyma TS: not performed	Oral prednisolone (16 mg daily) gradually tapered within 4 weeks, with significant improvement of clinical condition.	[45]
<b>San Millan RB et al. Spain</b>	M	52	No	0	Fever	TSH 0.10 pg/mL FT3 3.21 pg/mL (nv 1.8-4.6) FT4 1.83 ng/dL (nv 0.93-1.7) TgAb, TPOAb and TRAb undetectable Elevated ESR and CRP	TS: no 99mTc-perthecnetate uptake	Beta-blockers (propranolol)	[46]

(Continued)

Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
Mathews et al. USA	M	67	No	0	AF, acute HF, weight loss, fatigue, and diarrhea. No neck pain.	TSH 0.029 uIU/mL FT4 2.1 ng/dL ( <i>n.v.</i> 0.8–1.7 ng/dL) TgAb, TPOAb and TRAb undetectable Elevated ESR and CRP	US: mildly enlarged thyroid gland with no increased vascularity and 5-mm bilateral cysts TS: not performed	MMI and oral prednisolone (20 mg daily) gradually tapered within 6 months, with significant improvement of clinical condition and normalization of TFTs	[47]
Davoodi L et al. Iran	M	33	No	6	Fever (38.5°C), sore throat, sinus tachycardia, anterior neck pain.	TSH < 0.001 mIU/L, tT4 23.1 µg/dL ( <i>n.v.</i> 4–11 µg/dL) tT3 236 ng/dL ( <i>n.v.</i> 75–195 ng/dL) TgAb, TPOAb and TRAb undetectable Elevated ESR and CRP	US: heterogeneous thyroid gland with bilateral ill-defined hypoechoic areas TS: not performed	Dexamethasone 4 mg every 8 hours for 5 days. After that, oral prednisone (25 mg daily) gradually tapered. At last follow up, 45 days later, TFTs were within normal ranges.	[48]
Brancatella A et al. Italy	F	18	No	17	Fever, anterior neck pain, fatigue, palpitations,	TSH < 0.04 mIU/L FT3 8.7 pmol/L ( <i>n.v.</i> 4.6–8.4) FT4 27.2 nmol/L ( <i>n.v.</i> 11–23) Tg 5.6 pg/ml TgAb 120.2 IU/mL ( <i>n.n.</i> <30) TPOAb and TRAb undetectable Elevated ESR and CRP	US: bilateral and diffuse hypoechoic areas TS: not performed	Oral prednisone (25 mg/d as the starting dose, gradually tapered) TFTs and inflammatory indexes normalized within 12 days	[49]

(Continued)

Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
Ruggeri RM et al. Italy	F	43	No	30	Fever, anterior neck pain, fatigue, tremors, palpitations	TSH 0.006 mU/L FT3 7.03 pg/mL FT4 2.69 ng/dL ( <i>nv</i> 1.71–3.71) Tg 188 pg/mL ( <i>nv</i> 0.7–1.48) Tg 188 pg/mL ( <i>nv</i> 0–40) TgAb, TPOAb and TRAb undetectable Elevated ESR and CRP	US: enlarged and diffusely hypoechoogenic thyroid gland. TS: markedly reduced <sup>99m</sup> Tc-perthecnetate uptake	Oral prednisolone (25 mg/day as the starting dose, gradually tapered). Thyroid functional tests and inflammatory indexes normalized within four weeks	[50]
Campos-Barrera E et al. Mexico	F	37	No	30	Anterior neck pain, fatigue	Undetectable TSH FT4 1.6 ng/dL ( <i>nv</i> 0.7–1.4) TPOAb and TgAb negative Elevated ESR and CRP	TS: no iodine uptake	No treatment. One month after the diagnosis, the patient was asymptomatic, but her lab tests were still relevant for high ESR and low TSH	[51]
Mattar SAM et al. Singapore	M	34	No	9	Anterior neck pain, tachycardia	TSH <0.01 mU/L FT3 13.4 pmol/L ( <i>nv</i> 3.2–5.3) FT4 41.8 pmol/L ( <i>nv</i> 8.8–14.4) TRAb and TPOAb undetectable	US: enlarged thyroid gland with heterogeneous echotexture. TS: not performed	Oral prednisolone 20 mg/day, beta-blockers (atenolol 25 mg every morning). TFTs and inflammatory symptoms normalized within ten weeks	[52]

(Continued)

Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
Ruano R et al. Spain	F	28	No	14	Fever, anterior neck pain, palpitations, severe asthenia	TSH <0.001 mIU/L FT4 67.5 pmol/L ( <i>n.v.</i> 7–16) TgAb, TPOAb and TRA undetectable Elevated ESR and CRP	TS: absent 99mTc-perthecnetate uptake	Pain-killers (aspirin) and betablockers (propranolol 40 mg every 6 h). Thyroid functional tests and inflammatory indexes normalized within two weeks	[53]
Brancatella A et al. Italy Patient 1	F	38	No	16	Anterior neck pain, fever asthenia, anorexia, palpitations, atrial fibrillation	TSH 0.1 mIU/mL ( <i>n.v.</i> 0.4–4.) FT4 29.3 nmol/L ( <i>n.v.</i> 6–16) FT3 8.0 pmol/L ( <i>n.v.</i> 2.3–4.2) Tg 75.3 µg/L ( <i>n.v.</i> < 35) TgAb, TPOAb and TRAb undetectable Elevated ESR and CRP	US: an enlarged thyroid gland with multiple hypoechoic areas and absent vascularization at color doppler. TS: not performed	Oral prednisone (25 mg/day), gradually tapered Symptoms disappeared within 2 weeks After two months, while taking prednisone 15 mg/d, patient was asymptomatic and TFTs and inflammatory markers were in the normal range	[54]

(Continued)



Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
<b>Patient 2</b>	F	29	No	30	Anterior neck pain, fever, palpitations, asthenia, sweating	TSH < 0.01 mIU/mL (n.v. 0.4–4.5) FT4 31.8 nmol/L (n.v. 6–16) FT3 8.9 pmol/L (n.v. 2.3–4.2) Tg 80 µg/L (n.v. < 35 µg/L) TgAb, TPOAb and TRAB undetectable Elevated ESR and CRP	US: multiple diffuse hypoechoic areas and low vascularization at color Doppler TS: no 99mTc-perthecnetate uptake	Oral prednisone (25 mg/d), gradually tapered and propranolol (40 mg/d) Symptoms disappeared within 2 weeks. Two month later, while taking 15 mg/d of prednisone, patient was asymptomatic, inflammatory markers were in the normal range, whereas TFTs were consistent with subclinical hypothyroidism	
<b>Patient 3</b>	F	29	Yes (goiter)	36	Anterior, neck pain, palpitations, sweating	NA	US: enlarged thyroid with multiple hypoechoic areas TS: not performed	No treatment. Symptoms disappeared within two weeks. After 10 weeks, inflammatory markers were in the normal range, and TFTs were consistent with subHypoand L-T4 therapy was started	
<b>Patient 4</b>	F	46	No	20	Anterior neck pain, fever, palpitations, asthenia, insomnia, anxiety, weight loss	TSH < 0.01 mIU/mL (n.v. 0.4–4.5) FT4 27.8 nmol/L (n.v. 6–16) FT3 6.9 pmol/L (n.v. 2.3–4.2) TRAB undetectable	US: not performed TS: not performed	Prednisone (25 mg/d), gradually tapered Symptoms disappeared within two weeks. Two months later, while taking 20 mg/d of prednisone, patient was asymptomatic and both inflammatory markers and TFTs were unremarkable	
<b>San Juan MDJ et al. Philippines</b>	M	47	NA	0	Anterior neck pain associated with tenderness and goiter. No sign and/or symptoms of thyrotoxicosis	TSH 0.05 mIU/mL (n.v. 0.47–4.85) FT4 1.68 pg/ml (n.v. 0.78–2.19) T3 1.4 ng/dl (n.v. 0.97–1.69) TgAb, TPOAb and TRAB undetectable	US: slightly enlarged right thyroid lobe, hypoechoogenicity and normal vascularity in both lobes TS: not performed	Mefenamic acid, later shifted to celecoxib due to epigastric pain. After two months, overt hypothyroidism occurred (TSH 94.30 mIU/mL, FT4 0.23 pg/ml)	[55]

(Continued)

Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
Khatri A et al. USA	F	41	No	30	Tender neck swelling, odynophagia, neck pain, fevers, fatigue, hand tremors, palpitations	TSH <0.001 mIU/mL (n.v.) 0.7–4.20 FT4 63.21 pmol/L (n.v.) 11.61–23.22 FT3 4.10 nmol/L (n.v.) 1.232–3.08 TPOAb 96.71 IU/mL (n.v. ≤ 34.9) TRAb undetectable Elevated ESR and CRP	US: heterogenous thyroid gland with Bilateral patchy ill-defined hypoechoic area TS: not performed	She was started on oral ibuprofen, 600 mg every 6 h, and prednisone 40 mg daily (followed by a 4-week taper). Complete symptom resolution at last follow-up visit 45 days from hospital discharge	[56]
Sohrabpour S et al. Iran Patient 1	F	26	N.A.	30	Anterior neck pain, fever fatigue, palpitations	TSH 0.07 mIU/mL (n.v. 0.4–4.) FT4 19.5 pmol/L (n.v. 12–21) FT3 18.9 pmol/L (n.v. 3.1–6.8) TgAb, TPOAb, TRAb: N.A. Elevated ESR and CRP	US: bilateral hypoechoic areas. TS: not performed	Oral prednisone (25 mg/day), gradually tapered within 4 weeks Symptoms disappeared within 1 week and TFTs normalized within 1 month.	[57]

(Continued)

Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
<b>Patient 2</b>	F	37	N.A	15	Anterior neck pain, fever fatigue, palpitations	TSH < 0.01 mIU/mL (n.v. 0.4–4.4.) FT4 22.3 pmol/L (n.v. 12–21) FT3 25.4 pmol/L (n.v. 3.1–6.8) TgAb, TPOAb, TRAb: N.A. Elevated ESR and CRP	US: bilateral hypoechoic areas. TS: not performed	Oral prednisone (25 mg/day), gradually tapered within 4 weeks Symptoms disappeared within 1 week and TFTs normalized within 1 month.	
<b>Patient 3</b>	M	35	N.A	30	Anterior neck pain, fever fatigue, palpitations	TSH 0.12 mIU/mL (n.v. 0.4–4.4.) FT4 24.7 pmol/L (n.v. 12–21) FT3 19.7 pmol/L (n.v. 3.1–6.8) TgAb, TPOAb, TRAb: N.A. Elevated ESR and CRP	US: bilateral hypoechoic areas. TS: not performed	Oral prednisone (25 mg/day), gradually tapered within 4 weeks Symptoms disappeared within 1 week and TFTs normalized within 1 month.	
<b>Patient 4</b>	F	41	N.A	15	Anterior neck pain, fever fatigue, palpitations	TSH < 0.01 mIU/mL (n.v. 0.4–4.4.) FT4 21.9 pmol/L (n.v. 12–21) FT3 23.7 pmol/L (n.v. 3.1–6.8) TgAb, TPOAb, TRAb: N.A. Elevated ESR and CRP	US: bilateral hypoechoic areas. TS: not performed	Oral prednisone (25 mg/day), gradually tapered within 4 weeks Symptoms disappeared within 1 week and TFTs normalized within 1 month.	

(Continued)

Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
<b>Patient 5</b>	M	52	N.A	15	Anterior neck pain, fever fatigue, palpitations	TSH 0.17 mIU/mL ( <i>n.v.</i> 0.4–4.) FT4 26.7 pmol/L FT3 21.6 pmol/L ( <i>n.v.</i> 3.1–6.8) TgAb, TPOAb, TRAb: N.A. Elevated ESR and CRP	US: bilateral hypoechoic areas. TS: not performed	Oral prednisone (25 mg/day), gradually tapered within 4 weeks Symptoms disappeared within 1 week and TFTs normalized within 1 month.	
<b>Patient 6</b>	F	34	N.A	30	Anterior neck pain, fever fatigue, palpitations	TSH 0.23 mIU/mL ( <i>n.v.</i> 0.4–4.) FT4 18.4 pmol/L ( <i>n.v.</i> 12–21) FT3 18.1 pmol/L ( <i>n.v.</i> 3.1–6.8) TgAb, TPOAb, TRAb: N.A. Elevated ESR and CRP	US: bilateral hypoechoic areas. TS: not performed	Oral prednisone (25 mg/day), gradually tapered within 4 weeks Symptoms disappeared within 1 week and TFTs normalized within 1 month.	
<b>Chakraborty U et al. India</b>	M	58	Euthyroid nodular goiter	Not known	Anterior neck pain, fever	TSH <0.005 mIU/mL ( <i>n.v.</i> 0.27–4.2) FT4 20.11 µg/dL ( <i>n.v.</i> 5.10–14.1) FT3 2.88 ng/ml ( <i>n.v.</i> 0.80–2.0) TgAb, TPOAb, TRAb: N.A. Elevated ESR and CRP	US: diffuse bilateral enlargement of thyroid with hypoechoogenicity and increased vascularity on color Doppler TS: poor and patchy 99mTc-perthecnetate uptake, with high background radioactivity	Propranolol, 40 mg/day Oral prednisolone (30 mg/day), gradually tapered over next 1 month and then stopped. After two months, overt hypothyroidism occurred (TSH 21.90 mIU/mL) and L-T4 therapy was started.	[58]

(Continued)

Table 1. (Continued).

Case, Place	Gender	Age	Preexisting thyroid disease	Time from COVID to SAT onset (days)	Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref. no.
Dworakowska D et al. UK	F	57	Euthyroid multinodular goiter	90	Anterior neck pain, tremors and palpitations, neck swelling	TSH 0.001 mIU/mL (n.v. 0.35–4.94) FT4 23.4 pmol/L (n.v. 9–19) FT3 8.5 PM/L (n.v. 2.9–4.9) TgAb 6.61 IU/mL (n.v. 0–4.11) TPOAb 71.80 IU/mL (n.v. 0–5.61) TRAb <0.80 IU/L (n.v. 1.51–3) Elevated ESR and CRP	US: normal-sized thyroid with patchy areas of variably-reduced parenchymal echogenicity bilaterally TS: poor poor tracer uptake within the neck and thyroid bed	The patient managed her symptoms with simple analgesics and propranolol. During follow-up in primary care she developed sub-clinical hypothyroidism, and low-dose thyroxine treatment was started with 25ug daily.	[59]

AF = atrial fibrillation; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FT4 = free thyroxine; FT3 = free triiodothyronine; HF = heart failure; IL-6 = interleukin-6; L-T4 = Levo-thyroxine; Pts = patients; SAT = subacute thyroiditis; Subhypo = subclinical hypothyroidism; tT4 = total thyroxine; tT3 = total tri-iodothyronine; TFTs = thyroid function tests; Tg = thyroglobulin; TgAb = thyroglobulin antibodies; TPOAb = thyroperoxidase antibodies; TRAb = TSH receptor antibodies; TS = Thyroid-stimulating hormone; TS = Thyroid scintigraphy; US = ultrasonography; N.A. = not available.

tissues and organs, including the thyroid gland [69,70]. Extrapolation can also be made from SARS-CoV-1 data since in previous autopsy studies SARS-CoV-1 was responsible for follicular cell destruction, extensive apoptosis, and fibrosis in the absence of lymphocytic infiltration, representing the histopathological hallmarks of destructive thyroiditis [71]. Alternatively, thyroid inflammation might be caused by the cytokine storm associated with COVID-19, as above reported [14]. In the acute phase, increased concentrations of pro-inflammatory cytokines, and in particular of IL-6, may trigger thyroiditis and related thyrotoxicosis, the prevalence of which has been shown to correlate with IL-6 elevation [34,72]. Indeed, in the study by Lania et al. [60] a close relationship between thyrotoxicosis and increased serum levels of IL-6 was found: serum IL-6 levels were inversely correlated with TSH values ( $\rho$  0.41;  $P < 0.001$ ) and thyrotoxicosis was significantly associated with higher levels of the cytokine in the multivariate analysis.

In the above-mentioned patients diagnosed with SAT, SARS-CoV-2 infection was demonstrated by reverse transcriptase-PCR (polymerase chain reaction) assay of oropharyngeal or nasopharyngeal swabs to detect the presence of viral RNA in all patients, along with the measurement of antibodies to SARS-CoV-2 in a number of them. In the case series from Iran [57] the PCR tests of nasopharyngeal swabs were negative in all patients but both IgM and IgG were positive for SARS-CoV-2 (COVID-19). In all cases, SARS-CoV-2 was not directly evidenced in the thyroid tissue, but PCR positivity and seroconversion indicated recent infection with SARS-CoV-2 and supported its role in the pathogenesis of SAT. Moreover, it should underline that searching the virus in the thyroid is not currently required for the diagnosis of SAT. In some cases, screening serology testing for other viral infections, including respiratory viral panel, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus was performed and was negative, thus reinforcing the causal relationship.

In non-hospitalized cases, COVID-19 clinical manifestations were absent or mild (fever, cough, coryza), with only one patient having experienced interstitial pneumonia. The main clinical features of SAT during COVID-19 included: higher incidence in females in isolated case reports but not in HICUs patients, where more were male; no relevance of preexisting thyroid disorders; both typical and silent cervical forms; increased frequency of heart rhythm disorders (atrial fibrillation) and thromboembolic events in hospitalized patients. As shown in Tables 1, 17 out of 24 individual case reports of SAT associated with SARS-CoV-2 were female aged 18–69 years (median age 37.5 years). The medical history was unremarkable for preexisting thyroid disorders in most of them, only two patients being previously diagnosed with nontoxic goiter [44,49]. Most patients from Table 1 presented with fever, typical neck pain, and a tender goiter and experienced severe discomfort, only a minority presenting with silent cervical forms, while none of the two cohorts of hospitalized patients complained of the neck pain nor local signs and/or symptoms of SAT were recorded at clinical evaluation (Table 2) [60,61]. Müller et al. hypothesized that lymphocytopenia, commonly

encountered in SARS-CoV-2 infection, may decrease lymphoplasmocytic infiltration of the thyroid gland, thereby decreasing the pain symptoms in the anterior cervical region in hospitalized, that is, more serious, patients [61]. In addition, interfering factors as clinical conditions and concurrent drugs may be responsible for this 'atypical' presentation. Indeed, in patients with severe form of COVID-19, specific treatments (heparin, glucocorticoids) may modify the parameters of the thyroid function and make the diagnosis of thyrotoxicosis more difficult. Symptoms and/or signs of thyrotoxicosis (palpitations, tremors, fatigue, insomnia, and so on) occurred in about 70% of patients from isolated case series; one patient experienced atrial fibrillation (AF), a rather infrequent complication of SAT thyrotoxicosis, especially in a young woman [50], whereas another patient, a 67-year-old male with a past medical history of chronic heart failure (HF), experienced HF exacerbation and acute onset of AF [47] (Table 1). In hospitalized COVID-19 patients with thyrotoxicosis, Lania et al. [60] reported a high prevalence of AF and a rate of thromboembolic events more than two folds higher than that registered in hospitalized COVID-19 patients without thyrotoxicosis (Table 2). Thus, despite a high incidence of arrhythmias that have been reported among COVID-19 patients in the context of more severe disease [73], SAT thyrotoxicosis is relevant for the onset of cardiovascular complications and negatively impacts the clinical course of COVID-19 patients. Noteworthy, thyrotoxicosis may favor the development of fatal arrhythmias in the presence of prolonged QT interval, a common event in COVID-19 [2,74]. Moreover, a longer duration of hospitalization and a higher rate of in-hospital mortality were recorded in COVID-19 thyrotoxic patients compared to those with normal thyroid function [60].

At the hormonal level, patients from isolated case series displayed the typical features of SAT, with suppressed or low TSH, increased levels of both FT3 and FT4, and increase serum thyroglobulin, in the absence of anti-thyroid autoantibodies. Inflammatory markers, when checked, were altered (Table 1). In hospitalized patients, low or rarely undetectable TSH levels were associated with increased FT4 but low-normal FT3. Such a 'T4-thyrotoxicosis' may be due to the passive release of the stored hormone in the bloodstream because of gland inflammation, along with a decrease/disruption in deiodinase activity in the COVID-19 infectious context, responsible for a decrease in FT3 levels. Thus, in COVID-19 patients requiring hospitalization and/or high intensity of care, SAT thyrotoxicosis may present with atypical features because of an underlying NTI. Also, concurrent interfering factors, like drugs or iodine-containing contrast agents, should be taken into account in this setting of patients (Table 2) [61]. As concerns imaging studies, when allowed to perform them in isolated patients, thyroid ultrasonography often demonstrated a heterogeneous hypoechoic, non-vascularized gland, while scintigraphy revealed a reduced or near-absent uptake, representing the diagnostic hallmark of SAT [31,44,46,48,53,59,61]. While some patients were followed up without any specific treatment or received only symptomatic treatment with beta-blockers, an anti-inflammatory therapy with corticosteroids or

**Table 2.** Demographic, clinical, biochemical and imaging features of hospitalized patients with SARS-Cov2-related thyroiditis and thyrotoxicosis from cohort studies.

<b>Cohort studies, Place</b>	<b>Patients with thyroiditis</b>	<b>Mean Age</b>	<b>Preexisting thyroid disease</b>	<b>Clinical presentation</b>	<b>Laboratory findings</b>	<b>Imaging studies</b>	<b>Treatment and follow-up</b>	<b>Ref no.</b>
<b>Lania A et al. Italy</b>	58/287 (20.2%)	66 yr	Yes 3 pts, goiter	No neck pain Palpitations AF, 30.2% Thromboembolic events, 19.3%	TSH low or undetectable FT4 increased FT3 normal TgAb, TPOAb TRAb undetectable Elevated ESR and CRP	US: signs of thyroid inflammation in two pts, no significant alteration in three pts TS: not performed	Most pts were followed-up without any treatment and thyroid function improved spontaneously. Four pts received thiamazole	[60]
<b>Muller I et al. Italy</b>	13/85 HICU pts (15%) 9 M 1/41 LICU pts (2%) M	65 yr	Yes (not specified)	No neck pain	Increased IL-6 TSH low or undetectable FT4 increased FT3 normal or low TgAb, TPOAb TRAb negative Elevated CRP	US: diffuse mild hypoechoic pattern with focal markedly hypoechoic areas. TS: reduced 99mTc-perthecnetate uptake	Not specified anti-inflammatory treatments. The six pts who were followed-up had normal thyroid function and negative thyroid autoantibodies after a mean of 55 days from discharge;	[61]
<b>Liu DTW et al. UK</b>	10/191 (0.5%) 4 M	53 yr	Not specified	N.A.	TSH low or undetectable FT4 increased FT3 normal or low TgAb, TPOAb TRAb negative	N.A.	N.A.	[62]
<b>Sen K et al. India</b>	1/60 (1/11 pts with low TSH)	N.A.	Not specified	N.A.	TSH low or undetectable FT4 increased FT3 increased TgAb, TPOAb TRAb N.A.	N.A.	N.A.	[63]

COVID-19 = coronavirus disease 2019; SAT = subacute thyroiditis; Pts = patients; M = male; F = female; HICU = high intensity of care units; LICU = low intensity of care units; FT4 = free thyroxine; FT3 = free triiodothyronine; TSH = Thyroid-stimulating hormone; TgAb = thyroglobulin antibodies; TPOAb = thyroperoxidase antibodies; TRAb = TSH receptor antibodies; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; IL-6 = interleukin-6; US = ultrasonography; TS = Thyroid scintigraphy; AF: atrial fibrillation.  
N.A. = not available.

non-steroidal drugs (NSAID) was prescribed in those who experienced a severe discomfort and have developed SAT after the resolution of COVID-19 symptoms (or were asymptomatic for COVID-19). All patients from isolated case series had a good response to anti-inflammatory and corticosteroid therapy, when administered, and an overall favorable outcome. Reassuring, none of them experienced a relapse of COVID-19. All patients recovered from SAT within 4–8 weeks, even if a few patients were still taking low dose oral corticosteroids after two months. At the last available follow-up, normal thyroid function was restored in most patients from isolated case series; subclinical hypothyroidism was recorded in four patients, requiring L-thyroxine therapy in two (Table 1). Also, in most hospitalized patients, thyroid function recovered during follow up, only two patients (25%) presenting with hypothyroidism (Table 2) [61]. Long-term prospective studies should clarify if SARS-CoV-2 infectious may be also able to trigger thyroid autoimmunity as a long-term sequela of destructive thyroiditis. Indeed, the development of chronic autoimmune thyroiditis and permanent hypothyroidism following SAT has been reported, suggesting that virus infection may trigger an aberrant immune response against the thyroid gland in genetically predisposed individuals [45]. Noteworthy, SAT has been associated with the de-novo appearance of anti-thyroid antibodies, mainly TgAb [75].

## 5. Autoimmune thyroid disorders and COVID-19

One of the most intriguing possible clinical outcomes of SARS-CoV-2 is the induction of an autoimmune disease that may persist long after the resolution of acute viral infection in a subpopulation of patients. The occurrence of autoimmune complications, including anti-phospholipid syndrome, autoimmune thrombocytopenia, hemolytic anemia, Guillain-Barré, has been described in patients following SARS-CoV-2 infection [76–79]. Moreover, latent autoimmunity was checked by measuring a panel of rheumatic, thyroid, and phospholipid auto-antibodies in sera samples from 120 hospitalized patients with COVID-19 in comparison to pre-pandemic samples from 100 healthy individuals [80]. Compared to controls COVID-19 patients displayed latent autoimmunity mediated by a higher frequency of autoantibodies, such as TPOAb, rheumatoid factor (RF), and antinuclear antibodies (ANAs), to mention a few. A meta-analysis of selected studies confirmed such an increased prevalence of autoantibodies in COVID-19 patients, being RF and ANAs the most common autoantibodies [80]. These findings suggest a role of SARS-CoV-2 infection in promoting/amplifying autoimmune disorders (AIDs) and support further post-COVID studies to evaluate the development of overt autoimmunity.

The molecular mechanisms that could make the development of AITDs more likely in patients with COVID-19 patients are the same underlying the induction of autoimmunity by severe viral infection: molecular mimicry, viral and bacterial superantigens altering the T cell repertoire, and lymphocyte apoptosis followed by expansion of autoreactive lymphocytes [81]. Recently, Vojdani and coworkers provided evidence of a possible molecular mimicry between COVID-19 viral proteins and

human tissues antigens [82]. They demonstrated that SARS-CoV-2 antibodies reacted with several different human tissues, including the thyroid [82]. By selective epitope mapping they showed similarities and homology between spike, nucleoprotein, and many other SARS-CoV-2 proteins and the thyroid tissue antigen TPO, among the others [82]. This extensive immune cross-reactivity between SARS-CoV-2 antibodies and different antigen groups may contribute to precipitate the onset of autoimmunity in susceptible subgroups, and potentially exacerbate autoimmunity in subjects with preexisting AIDs in the course of COVID-19 [82]. Another intriguing mechanism proposed for AID induction is the presence of so-called superantigens within SARS-CoV-2, which stimulate excessive activation of the adaptive immune system and induce a nonspecific expansion of T-cells by directly binding T cell receptors (TCR) as well as expansion of plasmablasts, which may produce autoreactive IgG. The expansion of a population of T-cells with a skewed TCR repertoire consistent with superantigen activation, as well as an increased number of proliferating plasmablasts, appeared to correlate with elevated pro-inflammatory cytokines associated with cytokine storm in children who developed a rare secondary inflammatory syndrome, now known as multisystem inflammatory syndrome in children (MIS-C), after severe COVID-19 [83]. It is hypothesized that a zonulin-dependent increased mucosal permeability allows the paracellular passage of large intact viral molecules, including SARS-CoV-2-derived spike proteins, into the lamina propria, acting as superantigens and thus triggering a cytokine storm and autoimmunity. In this light, it has been emphasized it has been emphasize the critical role of type 1 IFN in controlling viral load [84,85]. Another hypothesis for the development of post-COVID-19 autoimmunity is based on the consequences of severe lymphopenia during acute infection. Lymphocyte apoptosis may lead to transient immunosuppression (both of innate and acquired immunity) in which self-tolerance is lost, followed by a skewed expansion of the repertoire with normalization of lymphocytes once the infection is controlled. Both this transient immunosuppression and an inappropriate form of immune reconstitution may lead to the expansion of autoreactive lymphocytes and the occurrence of autoimmune conditions in predisposed individuals [86]. Finally, as above reported, interesting parallels have been emerged between COVID-19 immune responses and autoimmune disorders, including thyroid disorders [6]. However, data supporting a correlation between thyroid autoimmunity and COVID-19 are still scanty. Autoimmune thyroid disorders (AITDs) have been described as complications of COVID-19, even in patients with mild manifestations. As detailed in Table 3, a case of Hashimoto's thyroiditis (HT) in the course of COVID-19 was reported by Tee and coworkers [87], while Mitzuno et al. [88] described a case of postpartum thyroiditis (PPT) in a young woman, who has been already diagnosed with HT. The two case reports are quite



**Table 3.** Summary of the demographic, clinical, biochemical and imaging features, treatment and follow-up of patients diagnosed with autoimmune thyroid disorders (AITDs) related to SARS-Cov2 infectious, as extracted from case reports and case series available in the literature.

Case, Place	Sex	Age	Preexisting thyroid disease	Time from COVID to AITD onset (days)	Disease/ Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref no.
<b>Tee LY et al.</b> Singapore	M	45	No	7	HT Generalized fatigue, muscle weakness	TSH 6.49 $\mu$ IU/ low FT4 9.19 pmol/L TPOAb >2000 IU/l	N.A.	L-Thyroxine therapy was started	[87]
<b>Mizuno S et al.</b> Japan	F	29	Yes (TH)	33	PPT Generalized fatigue	TSH 0.020 $\mu$ IU/ mL FT3 5.44 pg/ mL ( <i>nv</i> 2.3–4.0) FT4 2.0 ng/ dL ( <i>nv</i> 0.9–1.7) Tg 5.26 pg/ ml ( <i>nv</i> <33.7) TgAb 12.24 IU/mL ( <i>nv</i> <5) TPOAb and TRAb undetectable	US: coarse echotexture.	Thyroid function returned to normal after 36 days without any specific drug therapy	[88]
<b>Mateu Salat Met al.</b> Spain <b>Patient 1</b>	F	60	Yes (GD)	30	GD Palpitations, nervousness, fatigue	TSH <0.01 mIU/mL ( <i>nv</i> 0.3–5) FT3 7.93 pmol/L ( <i>nv</i> 2.63–5.7) FT4 16 pmol/L ( <i>nv</i> 9–19) TRAb 2.13 IU/L ( <i>nv</i> <1.75) TPOAb 1343 IU/mL ( <i>nv</i> <100) TgAb 199 IU/mL ( <i>nv</i> <138)	TS: Thyroid 131iodine uptake was increased to 30% and 45.7% at 2 and 24 h after administration of 100 $\mu$ Ci I131	Therapy with thiamazole and propranolol was started with improvement of both symptoms and thyroid function indexes.	[89]
<b>Patient 2</b>	F	53	No	60	GD Asthenia, tremor, palpitations	TSH <0.01 mIU/mL ( <i>nv</i> 0.3–5) FT4 36.5 pmol/L ( <i>nv</i> 9–19) TRAb 2.13 IU/L ( <i>nv</i> <1.75) TPOAb 3239 IU/mL ( <i>nv</i> <100) TgAb 1617 IU/mL ( <i>n.v.</i> <138)	TS: Thyroid 131iodine uptake was increased to 61% and 62% at 2 and 24 h after administration of 100 $\mu$ Ci I131	Therapy with thiamazole and propranolol was started with improvement of symptoms and thyroid function indexes.	
<b>Harris A et al.</b> USA	F	21	No	17	GD tachycardia, palpitations, anxiety, shortness of breath, heat intolerance, sweating	TSH 0.01 mIU/ ml ( <i>nv</i> 0.30–5.00) FT3 2.8 ng/dl ( <i>nv</i> 0.6–1.6) TRAb 2.6 IU/ mL ( <i>nv</i> <1.3)	N.A.	Therapy with beta-blockers and methimazole was started, achieving clinical and laboratory improvement.	[90]

(Continued)

Table 3. (Continued).

Case, Place	Sex	Age	Preexisting thyroid disease	Time from COVID to AITD onset (days)	Disease/Clinical presentation	Laboratory findings	Imaging studies	Treatment and follow-up	Ref no.
<b>Jimenez Blanco S et al. Spain</b>									[91]
<b>Patient 1</b>	F	45	Yes (GD, GO)	concurrent	GD Palpitations, nervousness,	TSH <0.005 mIU/mL (nv 0.27–4.2) FT4 > 7.7 ng/dl (nv 0.93–1.7) TRAb 28.7 IU/mL (nv <1.5)	US: diffuse hypervascularization	Therapy with thiamazole and propranolol was started with improvement of both symptoms and thyroid function indexes. No deterioration of her ophthalmopathy	
<b>Patient 2</b>	F	61	Yes (GD)	30	GD Asthenia, tremor, palpitations	TSH <0.001 mIU/mL (nv 0.27–4.2) FT4 2.66 ng/dl (nv 0.93–1.7) TRAb 1.31 IU/mL (nv <0.5)	US: diffuse hypervascularization TS: increased uniform tracer uptake	Therapy with thiamazole and propranolol was started with improvement of symptoms and thyroid function indexes.	
<b>Pastor S et al. Spain</b>	F	45	Yes (GD)	30	Thyroid storm Palpitations (180 bpm), sleep difficulty, nervousness, excessive sweating, heat intolerance, flushing. Bilateral proptosis	TSH <0.01 mIU/ml (nv 0.55–4.78) FT3 3.29 ng/dl (nv 0.89–1.76)	N.A.	Therapy with atenolol 50 mg every 12 hours, paracetamol and hydrocortisone 100 mg every eight hours and thiamazole at an initial loading dose of 30 mg followed by 30 mg every six hours was started, achieving normal heart rate (100 bpm) and no central nervous system symptoms within the following hours. No data on long-term follow-up.	[92]

COVID-19 = coronavirus disease 2019; FT4 = free thyroxine; FT3 = free triiodothyronine; GD = Graves' disease; GO = Graves' ophthalmopathy; PPT = post-partum thyroiditis; TgAb = thyroglobulin antibodies; TH = Hashimoto's thyroiditis; TPOAb = thyroperoxidase antibodies; TRAb = TSH receptor antibodies; TS = Thyroid scintigraphy; TSH = Thyroid-stimulating hormone; US = ultrasonography;

descriptive and do not allow to establish a causal association between SARS-CoV-2 infection and development of AITD, also taking into account that HT itself is a major risk factor for subsequent development of PPT. Thus, it remains to be determined whether the viral infection represents an epiphenomenon or a trigger of autoimmunity.

Two cases of autoimmune hyperthyroidism (Graves' disease) occurring after SARS-CoV-2 infection were described by Mateu-Salat et al. (Table 3) [89]. Of the two patients, a 60-year-old woman had been diagnosed with Graves' disease at the age of 23 and has been in remission since the age of 25. One month after the clinical onset of COVID-19 she experienced a relapse of autoimmune hyperthyroidism requiring medical treatment. The other patient, a 53-year-old woman, developed a new-onset Graves' disease 1 month after the onset of COVID-19 [89]. A similar case of de-novo occurrence of GD following mild symptomatic COVID-19 was reported in a 21-year-old woman [90], whereas Jimenez-Blanco and coworkers [91]

reported two further cases of relapse of GD after SARS-CoV-2 infection in two women, aged 45 and 61 years, respectively, who have already been diagnosed with GD and had maintained a normal thyroid function for about 4 years prior to contracting SARS-CoV-2 infection (Table 3). Finally, a thyroid storm probably precipitated by COVID-19 infection has been recently reported in a 45-year-old Caucasian woman, with a previous history of Graves' disease in stable remission for more than four years. The patient reported the onset of respiratory symptoms more than one month before, and her nasopharyngeal swab was still positive when the thyrotoxic crisis occurred (Table 3) [92]. In all patients, the temporal sequence suggests that GD could have been triggered by SARS-CoV-2 infection. Viral infections are frequently cited as a major environmental trigger involved in the pathogenesis of autoimmune thyroid diseases [20]. In addition, the hyperactivation of immune response and the hyperinflammatory state associated with SARS-CoV-2 infection could have triggered an immunological cascade leading to appearance or reactivation

or thyroid autoimmunity in subjects with a genetic predisposition, as it has been described in other autoimmune disorders [76–79]. Other potential mechanisms, such as stress, could have also had a role in the GD recurrence in the course of COVID-19 [20].

In this light patients with preexisting autoimmune diseases should be prone to experience a relapse of the disorder (for instance, recurrence of hyperthyroidism and/or thyroid storm in Graves' disease patients) or new onset of the related disorder (the occurrence of PPT in the woman suffering from Hashimoto's thyroiditis) after SARS-CoV-2 infectious and attentive monitoring of thyroid function should be recommended, to avoid overlooking the diagnosis and delaying treatment. On the other hand, preexisting autoimmune diseases do not seem to affect the risk for contracting SARS-CoV-2 infectious nor for developing more severe COVID-19 disease [93,94]. Findings from the recent literature suggest that the overall course of the COVID-19 disease is not far worse, as was initially assumed, in patients with a preexisting autoimmune inflammatory disease, either thyroidal or not [60,94,95]. Possible connections and mutual relationships between SARS-CoV-2 and thyroid autoimmunity deserve investigation by future prospective studies, also in order to evaluate the development of overt autoimmunity.

## 6. Impact of COVID-19 on preexisting thyroid diseases: how they affect each other

Robust studies providing clear evidence regarding the link between thyroid disease and COVID-19 are still lacking. Despite a higher prevalence of thyroid disorders has not clearly detected in patients with COVID-19, a recent meta-analysis reported that thyroid disease seems to be associated with an enhanced risk of severe COVID-19 infection (OR = 2.48; 95% CI 1.32, 4.66) [96]. It has emerged that the occurrence of thyroid dysfunction (TD) has a negative prognostic value since it has been associated with higher clinical severity of COVID-19, a higher fatality rate and longer hospitalization in patients with COVID-19 [96]. However, despite including 2169 individual COVID-19 cases from 8 studies, this meta-analysis has some limitations: it includes a limited number of retrospective studies or case series; a minority of patients (less than 3%) were reported to suffer from (not always well defined) thyroid disorders, and among them were included also subjects who have developed a low-T3 syndrome (that is, not a preexisting disorder) during the course of COVID-19. In a subsequent study by Zhang et al. [97], the whole spectrum of TD, including either overt or subclinical hypo- and hyperthyroidism, and not only the NTI, was considered and was found to be associated with poor outcomes. Patients with TD presented with more complications such as ARDS, acute cardiac and kidney injury and as a result, received more medical treatments, and mechanical ventilation, and were more likely to stay in the hospital for more than 28 days than were those without any thyroid dysfunction [97]. These findings are in line with the study by Lania et al. [60], showing an increased risk of cardiac rhythm disturbances and thromboembolic complications in patients with TD compared to those without TD,

but are rather different from those emerged from other single-center studies. A more recent review evaluated the prevalence of thyroid dysfunction in patients with COVID-19, including 1237 individual patients with COVID-19 from seven studies [98]. Most COVID-19 patients assessed in the included studies (from 44 to 94%) were euthyroid with TSH levels in the normal range. The prevalence of TD, defined as abnormal thyroid function tests, largely varied from 13% to 64% of COVID-19 patients, being significantly higher than in control groups only in three studies [64–66]. Low TSH levels were reported in up to 54% of patients with COVID-19, related mainly to a concurrent NTI, and a significant correlation between TD (namely decrease in TSH levels) and clinical severity of COVID-19 was found in four studies [60,65,96,99]. However, a significant heterogeneity across the studies was found and controversial findings were reported when the correlation between TD and mortality was assessed in patients with COVID-19 [98]. Thus, at present, there are not enough data to affirm that patients suffering from thyroid diseases are at higher risk of COVID-19, despite a higher prevalence of thyroid disease in patients with COVID-19 has been emerging.

## 7. Conclusions

COVID-19 is associated with a systemic immune and inflammatory response, involving also coagulation and complement systems, and is characterized by elevated serum levels of several proinflammatory cytokines (IL-6, IL-1 $\beta$ , TNF- $\alpha$ , to mention a few), the so-called 'cytokine storm' which is responsible for more severe complications of SARS-COV-2 infection and multiorgan involvement. The cytokine pathways and the immune responses described in COVID-19 seem to resemble, at least in part, the immune activation that occurs in immune-mediated thyroid diseases. Specifically, a hyperactivation of Th1 and Th17 response in peripheral lymphocytes has been described in patients with autoimmune and drug-induced thyroiditis and an increase in IL-6 was reported in the course of destructive thyroiditis. As a consequence, thyroid function test alterations are quite common in the course of COVID-19 as a consequence of either NTI or thyroidal gland involvement in the context of cytokine storm, due to hyperinflammatory response (subacute thyroiditis) or T-lymphocyte triggered autoimmunity (painless thyroiditis). Thyroid inflammation/damage may be also the consequence of a direct action of the SARS-CoV-2 virus on thyroid cells through ACE2 receptor. COVID-19-related thyroid disorders include destructive thyroiditis and onset or relapse of autoimmune thyroid disorders, leading to a broad spectrum of T ranging from thyrotoxicosis to hypothyroidism, that may worsen COVID-19 clinical course and affect prognosis.

## 8. Expert opinion

COVID-19 has been a great challenge for clinicians all over the world due to its rapid worldwide spread, the high disease-specific mortality and the wide spectrum of clinical severity, ranging from asymptomatic presentations to severe forms rapidly evolving toward ARDS and multi-organ failure and

even death. The most intriguing aspect of SARS-CoV-2 infectious is its potential to induce a systemic inflammation, thought excess cytokine production and hyper-activation of immune responses, determining multi-organ effects, that further contribute to the complexity of clinical presentation of COVID-19, impacting patients' management and outcome and amplifying the spectrum of possible complications and long-term *sequelae*.

Among the various clinical effects of SARS-CoV-2 infectious, thyroid involvement has been emerged as the most common endocrine manifestation. Alterations of thyroid function and structure occur during COVID-19 as a consequence of direct or indirect effects of SARS-CoV-2 infection on the gland or as a consequence of the systemic illness (NTI). Patients with COVID-19 may be affected by a combination of the above-mentioned pathways, and knowledge of their different pathophysiological mechanisms and mutual relationship is needed to carefully evaluate thyroid function tests and correctly guide the treatment of these patients, when needed. Moreover, critical conditions and medical management of COVID-19, including heparin, remdesivir and glucocorticoid, may alter thyroid function parameters and make their correct interpretation more difficult.

Although on 13 March 2020 the World Health Organization did not recommend the systematic evaluation of thyroid function in COVID-19 patients, increasing evidence from the literature justifies performing TFTs in these patients, mostly in those hospitalized in high intensity of care units, and referring to an endocrinologist in case of abnormal values.

Clinicians should be aware of the different thyroid manifestations potentially associated with COVID-19 since this could impact the patient's outcomes and the clinical approaches. In particular, SAT, often underdiagnosed disorder, has been reported as a possible endocrine complication triggered by SARS-CoV-2 infectious during the COVID-19 pandemic and a high index of suspicion is needed for its early diagnosis and appropriate management. Although the disorder is often self-limiting, early recognition and prompt treatment of SAT should be relevant for clinical outcomes. Indeed, when a destructive thyroiditis occurs in the setting of hospitalized patients with more severe presentation, the subsequent thyrotoxicosis may worsen the COVID-19 clinical course, increasing the risk of cardiovascular and thromboembolic complications and in-hospital mortality along with the duration of hospitalization. Early recognition and rapid treatment of the underlying thyroiditis is important in this setting of patients to improve the respiratory and cardiovascular outcomes. Indeed, a timely diagnosis is also warranted in patients with a mild SARS-CoV-2 infection to avoid/prevent adverse events (i.e. episode of AF). Moreover, in isolated cases, most patients are not able to recall a known exposure or are asymptomatic and confirming COVID-19 diagnosis may significantly decrease the risk of further transmission of SARS-CoV-2.

Some limitations and weakness of the available literature in the thyroid field should be highlight: data concerning SAT occurrence mainly rely on case reports or short case series, whereas data from large cohort studies are often incomplete and insufficient to correctly characterize thyroid alterations and suffer from several interfering factors, including critical conditions, NTI and medical treatments. As a consequence,

the real frequency and nature of thyroid involvement in COVID-19 patients is far to be defined as well as its impact on clinical outcomes. Large epidemiological studies should be performed to define the true prevalence of thyroid disorders in the course of COVID-19.

Moreover, the long-term impact of COVID-19 on the thyroid gland remains to be fully elucidated in the following years. Indeed, the hyperactivation of immune response and the hyperinflammatory state during COVID-19 may act as a trigger of latent or new-onset autoimmunity and preexisting autoimmune diseases seems to represent a risk factor for developing thyroid autoimmune complications during COVID-19. Also, chronic autoimmune disease may develop over the years as a long-term sequela of destructive thyroiditis in susceptible individuals. Long-term prospective studies should clarify if SARS-CoV-2 infectious may be also able to trigger thyroid autoimmunity and future research would investigate the intriguing connections and mutual relationships between SARS-CoV-2 and thyroid autoimmunity.

### Declaration of 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. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Author agreement

All authors have seen and approved the final version of the manuscript and warrant that the article is the authors' original work, has not received prior publication and is not under consideration for publication elsewhere.

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