

RESEARCH

Long-term outcome of thyroid abnormalities in patients with severe Covid-19

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Abstract

Objective: We have previously observed thyroid dysfunction, i.e. atypical thyroiditis (painless thyrotoxicosis associated with non-thyroidal illness syndrome), in patients with severe acute respiratory syndrome coronavirus 2 disease (Covid-19). This study aimed to analyse the evolution of thyroid dysfunction over time.

Methods: One hundred eighty-three consecutive patients hospitalised for severe Covid-19 without known thyroid history were studied at hospital admission (baseline). Survivors were offered 12-month longitudinal follow-up including assessment of thyroid function, autoantibodies and ultrasound scan (US). Patients showing US focal hypoechoic areas suggestive of thyroiditis (focal hypoechogenicity) also underwent thyroid ^{99m}Tc or ¹²³I uptake scan.

Results: At baseline, after excluding from TSH analysis, 63 out of 183 (34%) Covid-19 patients commenced on steroids before hospitalisation, and 12 (10%) showed atypical thyroiditis. Follow-up of 75 patients showed normalisation of thyroid function and inflammatory markers and no increased prevalence of detectable thyroid autoantibodies. Baseline US (available in 65 patients) showed focal hypoechogenicity in 28% of patients, of whom 82% had reduced thyroid ^{99m}Tc/¹²³I uptake. The presence of focal hypoechogenicity was associated with baseline low TSH ($P = 0.034$), high free-thyroxine (FT4) ($P = 0.018$) and high interleukin-6 (IL6) ($P = 0.016$). Focal hypoechogenicity persisted after 6 and 12 months in 87% and 50% patients, respectively, but reduced in size. After 9 months, thyroid ^{99m}Tc/¹²³I uptake partially recovered from baseline (+28%) but was still reduced in 67% patients.

Conclusions: Severe Covid-19 induces mild transient thyroid dysfunction correlating with disease severity. Focal hypoechogenicity, associated with baseline high FT4, IL6 and low TSH, does not seem to be related to thyroid autoimmunity and may persist after 1 year although decreasing in size. Long-term consequences seem unlikely.

Key Words

- ▶ Covid-19
- ▶ SARS-CoV-2
- ▶ thyroiditis
- ▶ thyroid

Introduction

The pandemic of coronavirus disease 2019 (Covid-19), determined by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan (Hubei, China) in December 2019 and later spread worldwide (1). One of the first severely hit countries was Italy, especially the region of Lombardy and Milan's area where our institution is based, experiencing a dramatic rapid increase in hospitalised Covid-19 patients with severe respiratory distress (2).

The angiotensin-converting enzyme 2 (ACE2) is the entry receptor used by SARS-CoV-2 to infect the host cell (3, 4). Both ACE2 and the transmembrane protease serine 2 (TMPRSS2), necessary for SARS-CoV-2 internalisation and activation, are highly expressed in the thyroid tissue (5, 6). Thus, a direct infection and damage of the thyroid gland is a plausible mechanism of thyroid dysfunction induced by SARS-CoV-2, also supported by the autoptic findings of SARS-CoV-2 genome (7) and proteins (8) expression within thyroid follicular cells. Furthermore Covid-19 disease, especially in its severe forms, triggers a systemic inflammatory-immune response with the release of several cytokines and chemokines (9) that can indirectly affect the thyroid function (10). Indeed, SARS-CoV-2 infection and Covid-19 disease have been associated with several thyroid disorders, ranging from subacute thyroiditis to thyroid autoimmune diseases (10, 11, 12, 13, 14).

Furthermore, critically ill patients show alterations in thyroid function tests in the context of euthyroidism, due to a complex combination of adaptive and maladaptive mechanisms, known as non-thyroidal illness syndrome (NTIS) and characterised by low serum concentrations of total and free-triiodothyronine (FT3), associated with low or normal values of thyroid-stimulating hormone (TSH) and free-thyroxine (FT4) (15, 16). Thus, Covid-19 may trigger thyroid dysfunction with several different mechanisms (13, 17).

In a previous study, we provided the first description of atypical painless thyroiditis occurring in 15% of patients affected with severe Covid-19, characterised by mild thyrotoxicosis coexisting with NTIS, that may be also associated with the presence of focal hypoechoogenicity at thyroid ultrasound scan (US) or reduced uptake at thyroid scintigraphy scan (18). In this extension study, we have followed survivors up to 1 year after the SARS-CoV-2 infection, to monitor the evolution of thyroid involvement over time. We have also performed imaging and functional evaluation of the thyroid gland

and correlated the thyroid dysfunction detected at hospitalisation with several parameters of Covid-19 disease severity.

Materials and methods

Study population and design

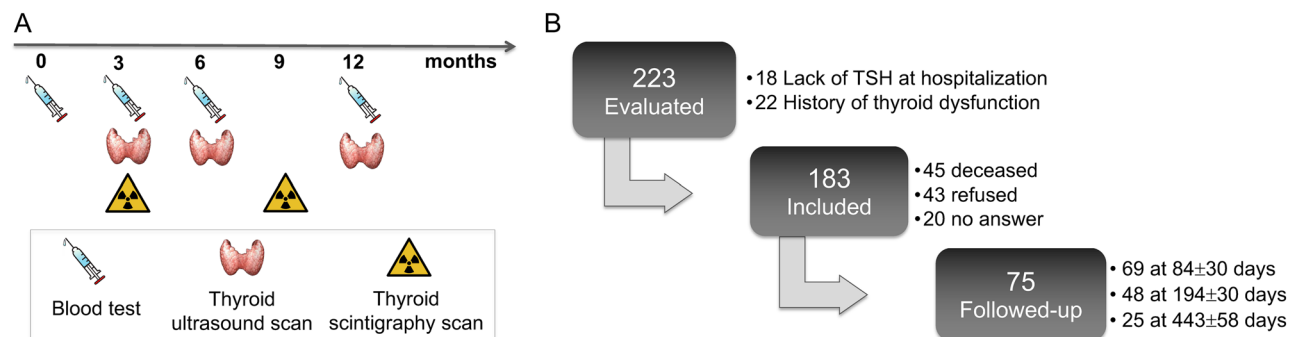
This single-centre observational study is the extension of the study 'Tiro-Covid-19' approved by the Ethics Committee of Milano Area 2 (Milan, Italy), ID 375_2020 (18). Consecutive patients (hospitalised for Covid-19 in the Department of Medicine – High Intensity of Care Unit of Fondazione IRCCS Ca' Granda Ospedale Policlinico Maggiore of Milan (Italy) during the pandemic waves one (W1) from March to September 2020, two (W2) from October to December 2020 and three (W3) from March to May 2021) were included in the study after receiving a full explanation of the purpose and nature of the research and providing written consent. SARS-CoV-2 infection was diagnosed by real-time reverse transcriptase polymerase chain reaction conducted on nasal and pharyngeal swab specimens or broncho-alveolar lavage fluid.

The patients' electronic clinical records were analysed for clinical and pharmacological history, length of hospitalisation and final outcome. Patients with a lack of TSH measurement at hospital admission (baseline) and known history of thyroid dysfunction were excluded.

Survivors were invited to attend the follow-up visits at different time points (Fig. 1A): as soon as negative at SARS-CoV-2 test and physically restored (2–3 months after hospital admission) and after 6 and 12 months. The follow-up visits included biochemical tests and thyroid imaging.

Patient characteristics

The study included 183 consecutive Covid-19 patients (Fig. 1B), 119 (65%) from W1, 36 (20%) from W2 and 28 (15%) from W3. They had a mean (\pm S.D.) age of 67.5 ± 13.8 years and were predominantly males ($n=124$, 68%). The National Early Warning Score 2 (NEWS2) assessed at hospital admission was low in 84 (47%), medium in 60 (33%) and high in 36 (20%) patients and the median (interquartile range (IQR)) length of hospitalisation was 20 (12-30) days. Oxygen support was administered low-flow in 40 (22%) patients, while 111 (61%) and 20 (11%) patients required continuous positive airway pressure (CPAP)/high-flow nasal cannula (HFNC) and invasive mechanical ventilation, respectively. Treatment

**Figure 1**

Study design. (A) Thyroid assessments were planned at different time points following the hospitalisation for Covid-19 (time 0). (B) Numbers of patients evaluated at the time of hospital admission for Covid-19, included in the study at baseline and attending at least one follow-up time point. TSH, thyroid-stimulating hormone.

approaches changed significantly during the different Covid-19 waves: W1 patients were predominantly treated with paracetamol, hydroxychloroquine, anakinra and antivirals, while such treatments were discontinued and substituted with steroids and heparin during W2/W3. Similarly, W2/W3 patients were more frequently treated with CPAP/HFNC than W1 patients, and none was intubated (0% W2/W3 vs 13% W1). Following the preliminary recommendations for Covid-19 disease management emerged by the RECOVERY Collaborative Group (19), from September 2020 onwards steroid treatment, usually oral dexamethasone 6 mg daily, had been commenced by the general practitioner before hospital admission in 63/183 (34%) patients: 4/119 (3.4%) W1, 33/36 (91.7%) W2 and 26/28 (92.9%) W3.

Seventy-five patients agreed to be followed up on at least one occasion; 69 at 3 months, 48 at 6 months and 25 at 12 months following hospitalisation for Covid-19 (Fig. 1B). They were mostly males (65%) and younger when compared to the whole study cohort (62 ± 10.9 years, $P < 0.01$).

Biochemical analysis and thyroid function

Serum TSH, FT4 and FT3 concentrations (reference intervals 0.28–4.30 mIU/L for TSH, 8–17 ng/L for FT4 and 2–5 ng/L for FT3) were measured by electrochemiluminescence immunoassay (Cobas® e801, Roche Diagnostics). Serum TSH concentrations were routinely measured in all patients; per the automated setting of the hospital laboratory ('reflex TSH'), FT4 and FT3, or FT4 only, were measured for TSH concentrations < 0.45 mIU/L or > 3.50 mIU/L, respectively. Autoantibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) were measured by enzyme-linked immunosorbent assay (ThermoFisher)

and autoantibodies to TSH receptor (TRAb) by Immulite 2000/2000 XPi TSI (Siemens). Normal reference ranges were < 35 KIU/L (TPOAb), < 60 KIU/L (TgAb) and < 0.55 KIU/L (TRAb).

Thyrotoxicosis was defined as TSH < 0.28 mIU/L and/or FT4 > 17 ng/L, while hypothyroidism as TSH > 4.30 mIU/L and FT4 ≤ 17 ng/L.

The following parameters were also assessed with automated assays: full blood count with lymphocyte and neutrophil counts (XN-9000™, Sysmex, Lincolnshire, Illinois, USA), serum C-reactive protein (CRP; turbidimetry Cobas® c702, Roche Diagnostics), interleukin-6 (IL6; electrochemiluminescence Elecsys®, Roche Diagnostics) and albumin (colorimetric assay, Cobas® c501, Roche Diagnostics). Normal reference ranges were 1.2–3.4 10^9 /L for lymphocytes, 1.5–6.5 10^9 /L for neutrophils, < 0.5 mg/dL for CRP, 0–10 ng/L for IL6 and 3.4–4.8 g/dL for albumin.

Thyroid imaging

The US of the thyroid gland was performed by the same operator with a MyLab™25Gold ultrasound machine (Esaote, Genoa, Italy). Thyroid scintigraphy with 99m-technetium-pertechnetate (^{99m}Tc) or iodine-123 (^{123}I) and SPECT tomographic acquisitions of the thyroid gland (triple head gamma camera, Irix, Philips Medical Systems) was also performed in patients showing focal hypoechoic areas at US, suggestive of thyroiditis.

Disease severity assessment

The respiratory support was divided into four categories: (i) none required, (ii) low-flow oxygen therapy, (iii) CPAP or HFNC and (iv) invasive mechanical ventilation.

The disease severity was also assessed using the NEWS2, categorised as low (0–4), medium (5–6) or high (≥ 7), according to the respiration rate, oxygen saturation, systolic blood pressure, heart rate, level of consciousness and body temperature (20).

Statistical analysis

Variables were assessed for their distribution and summarised using the sample mean \pm s.d. when approximately normally distributed or using the sample median and IQR otherwise. Categorical variables were summarised using percentages, and the statistical significance of associations between them was calculated using the Fisher's exact test. We also applied the Kruskal–Wallis test with Mann–Whitney *U* tests or one-way analysis of variance with *post hoc* Bonferroni correction, depending on the distribution of variables. Spearman's rank correlation coefficient was used for non-parametric data to analyse the relationship between biochemical parameters. The data were analysed in STATA, version 12 (StataCorp LLC). *P* values < 0.05 were considered statistically significant.

Results

Thyroid dysfunction at hospital admission

Table 1 summarises the thyroid function measured at hospital admission (baseline) in patients with or without steroid treatment. As expected, patients on steroids had significantly lower TSH and FT4 serum concentrations than those untreated, while FT3 concentrations were similar. Thus, the 63 patients on steroid treatment before hospital admission were excluded from the analysis of thyroid dysfunction at baseline. The mean serum FT4 concentrations were not different in patients receiving (12.3 ± 2.7 ng/L) or not receiving (13.4 ± 4.3 ng/L; $P=0.11$) heparin treatment, which was administered at least 8 h before blood draw. Compared with the whole study population (Table 1A), the 75 patients attending at least one follow-up visit (Table 1B) had similar serum TSH ($P=0.67$) and FT4 ($P=0.22$), but higher FT3 serum concentrations ($P < 0.01$) assessed at hospital admission.

As shown in Fig. 2, at baseline the median serum TSH concentrations positively correlated with albumin ($P=0.02$) and lymphocyte count ($P < 0.01$), but not with serum IL6 ($P=0.10$) and CRP ($P=0.12$) concentrations (not shown). They were also inversely correlated to

Table 1 Baseline thyroid function assessed at hospital admission according to the absence or presence of steroid treatment in the entire patient cohort (A, $n = 183$) and in the subgroup of survivors seen at follow-up (B, $n = 75$). In brackets is reported the number (*n*) of patients in whom hormone measurement was available. *P* values have been calculated between patients taking vs not taking steroids at the time of thyroid assessment.

A	No steroids	Steroids	<i>P</i>
TSH mIU/L	1.12 (0.57–1.99)	0.51 (0.34–1.03)	< 0.01
median (IQR)	(<i>n</i> = 120)	(<i>n</i> = 63)	
FT4 ng/L	13.7 ± 3.8	12.1 ± 3.1	0.02
mean \pm s.d.	(<i>n</i> = 38)	(<i>n</i> = 57)	
FT3 ng/L	1.87 ± 0.37	1.71 ± 0.42	0.11
mean \pm s.d.	(<i>n</i> = 24)	(<i>n</i> = 57)	
B	No steroids	Steroids	<i>P</i>
TSH mIU/L	1.15 (0.54–1.77)	0.56 (0.36–0.78)	< 0.01
median (IQR)	(<i>n</i> = 57)	(<i>n</i> = 18)	
FT4 ng/L	15.0 ± 4.1	12.0 ± 3.7	0.04
mean \pm s.d.	(<i>n</i> = 14)	(<i>n</i> = 17)	
FT3 ng/L	2.0 ± 0.37	1.88 ± 0.51	0.50
mean \pm s.d.	(<i>n</i> = 10)	(<i>n</i> = 17)	

FT3, free-triiodothyronine; FT4, free-thyroxine; IQR, interquartile range; s.d., standard deviation; TSH, thyroid-stimulating hormone.

the increased need for oxygen support ($P=0.02$), but not to the NEWS2 score ($P=0.17$, not shown) and did not change in relation to the length of hospitalisation ($P=0.06$) and in deceased patients compared to survivors ($P=0.61$) (not shown).

Thyrotoxicosis was observed in 12/120 (10%) patients (mean age 68 ± 11 years, 9 males and 3 females) untreated with steroids at hospital admission; none complained of neck pain and were therefore diagnosed with atypical thyroiditis. Hypothyroidism was observed in 7/120 (6%) patients (mean age 78 ± 12 years, 3 males and 4 females).

Thyroid imaging

Thyroid US was performed at the earliest feasible time following hospital discharge in 65 patients (mean \pm s.d. 84 ± 30 days). Focal hypoechoic areas suggestive of thyroiditis were present in 18/65 (28%) patients and were more frequent among patients with baseline TSH below the lower cut-off for automated reflex TSH assay (< 0.45 mIU/L), compared with those with normal TSH (60% versus 25%, respectively, $P=0.034$, Fig. 3). In patients with focal hypoechoic areas at US, baseline serum concentrations of FT4 ($P=0.018$) and IL6 ($P=0.016$) were higher compared to those in patients with a normal US thyroid pattern (Fig. 3). Seventeen out of 18 (94%) patients with focal hypoechoic areas at US

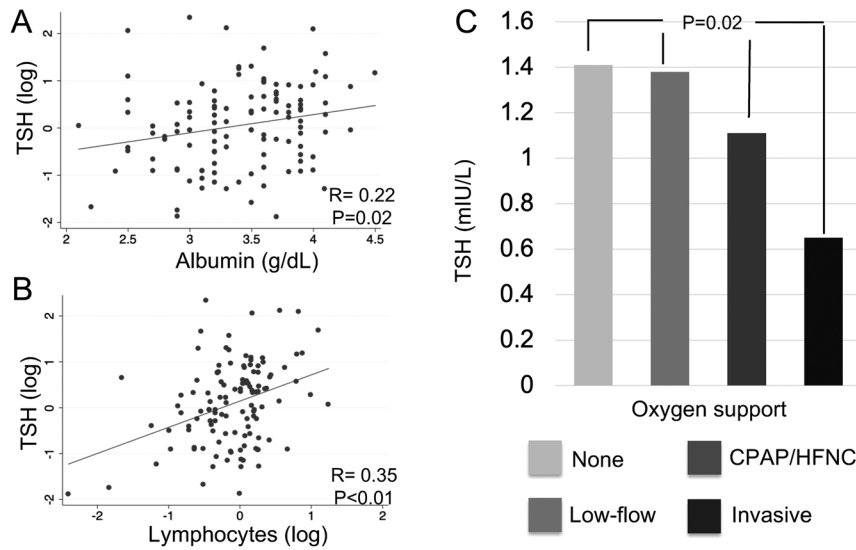


Figure 2 Correlation between thyroid-stimulating hormone (TSH) assessed at hospital admission and Covid-19 disease severity. Scatter plots of correlations between serum concentrations of TSH and albumin (A) and lymphocyte count (B). Bar graphs of median TSH serum concentrations measured in patients grouped according to the different type of oxygen support required (C). CPAP/HFNC, continuous positive airway pressure or high-flow nasal cannula.

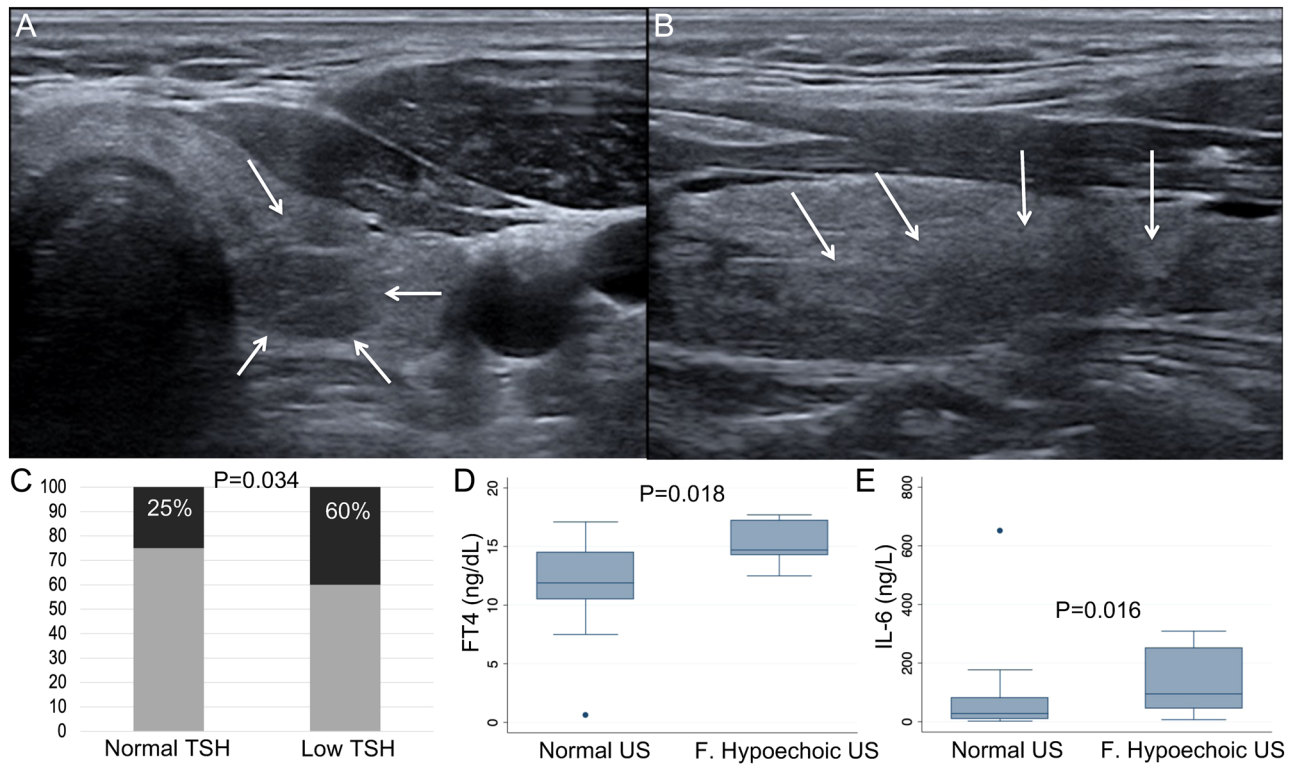


Figure 3 Thyroiditis-like areas (focal hypoechoic areas). Representative images in transverse (A) and longitudinal (B) planes at thyroid ultrasound (US) showing focal hypoechoic areas (white arrows). (C) Bar graphs showing the prevalence of focal hypoechoic areas at thyroid US (black if present, grey if absent) in patients with serum concentrations at hospital admission of thyroid-stimulating hormone (TSH) < 0.45 mIU/L, the lower cut-off for automated reflex TSH assay (low TSH), or above 0.45 mIU/L and within the normal reference range (normal TSH). Box plots of the association between the presence or absence of focal areas of hypoechoic areas at US (F. Hypoechoic US) and serum concentrations at hospital admission of free-thyroxine (FT4; D) and interleukin-6 (IL-6; E).

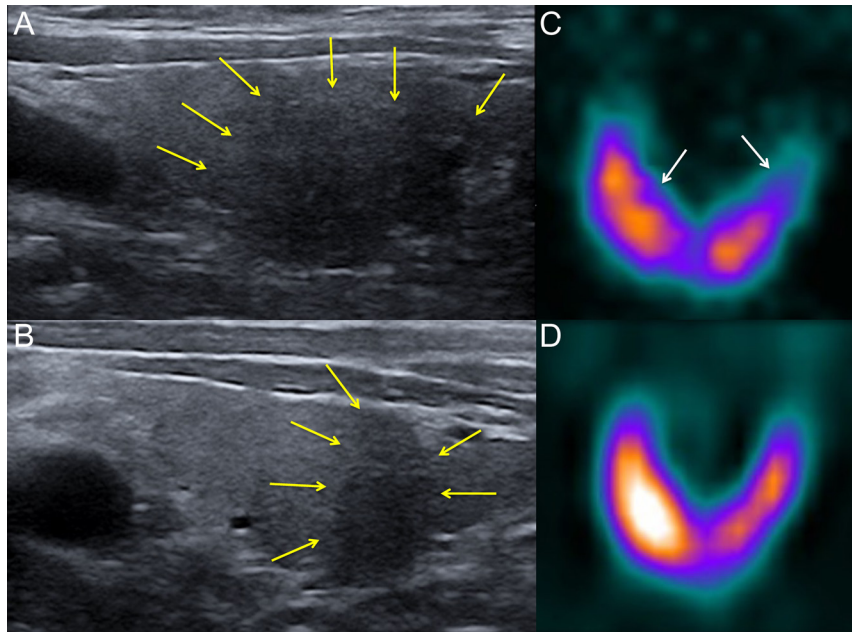


Figure 4

Evolution of thyroiditis-like features at thyroid ultrasound and scintigraphy scans during follow-up. Representative images of thyroid ultrasound scan (A and B) and SPECT tomographic acquisitions of thyroid scintigraphy scan with iodine-123 (C and D) at baseline and follow-up. Yellow arrows indicate hypoechoic areas suggestive of thyroiditis at ultrasound, reduced in size at the 6-month follow-up (B) compared with baseline (A). Thyroid scintigraphy images at 9-month follow-up (D) show an overall increased iodine-123 uptake and disappeared areas of focally reduced uptake (white arrows) in the middle region of the right lobe and middle/polar region of the left lobe, compared with baseline (C).

were further investigated with thyroid scintigraphy (15 with ¹²³I and 2 with ^{99m}Tc) and the thyroid uptake was found to be reduced in 14/17 (82%) patients: focally in 9 and diffusely in 5 of them (Fig. 4).

In the majority of cases the areas of focal hypoechoogenicity at thyroid US scan were monitored during follow-up and at 6 and 12 months they were still

present, even if often reduced in size (Fig. 4), in 13/15 (87%) and 6/12 (50%) patients, respectively. The thyroid uptake scan was repeated after a mean of 284 ± 20 days in 8 patients. Despite four of them (50%) still presented a focally reduced uptake, the mean thyroid uptake showed a +28 ± 27% (range 11–91%) recovery when compared with the baseline scan (Fig. 4).

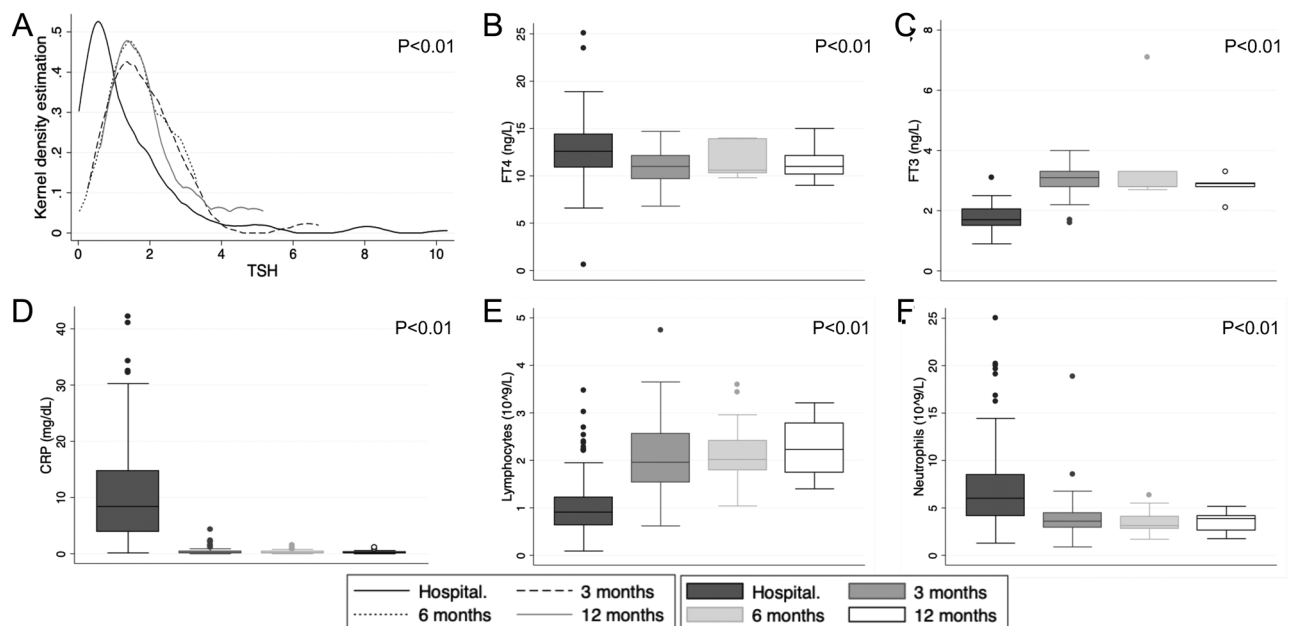


Figure 5

Longitudinal evolution of biochemical parameters. Kernel density plot of thyroid-stimulating hormone (TSH, A) and box plots of free-thyroxine (FT4, B), free-triiodothyronine (FT3, C), C-reactive protein (CRP, D), lymphocyte count (E) and neutrophil count (F) measured at the time of hospital admission (Hospital.: day 0), after 3 months (days +84), 6 months (days +194) and 12 months (days +443). P values refer to the comparison between Hospital. and 3 months time point (t test).

Long-term biochemical follow-up

As shown in Fig. 5, at all follow-up time-points, the median (IQR) serum concentrations of TSH were significantly higher than baseline (0.86 (0.45–1.63) mIU/L, $P < 0.01$), increasing to 1.70 (1.07–2.32) mIU/L at 3 months, 1.59 (1.21–2.31) mIU/L at 6 months and 1.58 (1.25–2.40) mIU/L at 12 months. All other thyroid and inflammation parameters significantly changed and normalised in nearly all patients (Fig. 5).

TgAb and TPOAb were measured at 3 months post-infection in 65 patients and detected in 8 (12%; 6 TgAb and TPOAb, 2 only TgAb); there was no difference in thyroid autoantibodies prevalence between patients with or without areas of focal hypoechogenicity at US ($P=0.56$). At 6 and 12 months, TgAb and TPOAb were detected in 7/48 (15%) and 3/23 (13%) patients available for follow-up, respectively. TRABs were measured only at 3 months and were all undetectable in the 62 patients tested. Serum TSH concentrations also did not differ in patients with or without persisting focal hypoechogenicity ($P=0.45$ at 6 months and $P=0.96$ at 12 months).

Among the patients with hypothyroidism, only one was available for the follow-up programme; at 3 months, she still presented with overt hypothyroidism and her thyroid autoantibodies were positive. Thus, she was diagnosed with autoimmune hypothyroidism and started on treatment with levothyroxine.

Discussion

To our knowledge, this is the first study of patients with severe Covid-19 that matches biochemical, morphological and functional evaluation of the thyroid gland up to 1 year of follow-up. In our study, the finding of an association between focal hypoechoic areas at US and biochemical markers of thyroiditis and inflammation, such as low TSH, high FT4 and high IL6, confirms the hypothesis of atypical thyroiditis. These findings are consistent with thyroid gland involvement during Covid-19 disease, due to viral infection or systemic inflammation, in addition to the hormonal changes related to NTIS. A viral-related origin of such thyroid involvement is also suggested by the progressive reduction in size or disappearance of focal areas of hypoechogenicity in the months following SARS-CoV-2 infection, as well as the progressive and partial recovery of thyroid uptake at the scintigraphy scan with time. The absence of correlation with thyroid autoantibodies positivity seems to rule out autoimmune etiopathogenesis.

The 28% prevalence of thyroiditis at thyroid US performed 2–3 months after the SARS-CoV-2 infection that we observed is consistent with previous reports of 34% (21). Lui *et al.* found a lower prevalence (13.9%), similar to that observed in SARS-CoV-2 negative controls and in the general population (22). While 90% of patients in Lui's study had mild Covid-19 and none developed thyrotoxicosis, in the present study, patients had a severe form of Covid-19 disease, which is more likely to be associated with thyrotoxicosis than the mild form (18).

The present study has been extended to patients from the pandemic waves W2 and W3 when steroids such as dexamethasone were systematically commenced as an early treatment for Covid-19 (19), and we observed an overall slightly lower prevalence of atypical thyroiditis (10%) than the 15% previously reported when analysing only W1 patients, before such therapeutic change (18). Since steroids have an inhibitory effect on the hypothalamic–pituitary–thyroid axis (23, 24), in the present study, patients already commenced steroid treatment before thyroid assessment at hospitalisation were excluded from the TSH analysis at baseline. Some of them may also have had atypical thyroiditis, explaining why its overall prevalence is slightly lower than previously reported. Heparin, another key treatment for Covid-19 (25), is known to spuriously increase the serum concentrations of FT4 by displacing T4 from the transport protein thyroid binding globulin (26). Heparin treatment in our study cohort did not influence FT4 measurements since it was administered at least 8 h before the time blood was withdrawn for the biochemical assessment when such interference appears to be minimised (27).

The impact of thyroid dysfunction on susceptibility to SARS-CoV-2 infection and Covid-19 disease outcome is controversial (28, 29, 30). Suppressed TSH and low FT3 serum concentrations are associated with fatal outcomes in patients with severe Covid-19 disease (28). Furthermore, recent data show that thyroid hormone may protect the lungs from injury, including that associated with Covid-19 disease (29). In contrast with some previous studies, in our cohort lower serum TSH concentrations measured at hospital admission did not correlate with increased inflammatory cytokines IL6 and CRP (12, 31), or to higher rates of mortality or increased length of hospitalisation for Covid-19 disease (32, 33, 34). Possible reasons for such discrepancies are the small-scale nature of these patient cohorts and the fact that our study was not designed to assess this outcome. However, low serum concentrations of TSH were inversely correlated with increased respiratory failure, as previously observed

for FT3 (31, 33), whereas the positive correlations of TSH with albumin and lymphocyte count are consistent with previous findings (35, 36, 37, 38).

It is well known that infections may trigger thyroid dysfunction and autoimmunity (39) and subacute thyroiditis may cause a permanent defect in thyroid hormonogenesis (40), with hypothyroidism occurring in around 25% of patients (41, 42) as a later complication. In our study, primary hypothyroidism was found in 6% of patients at hospitalisation. At follow-up, one woman remained hypothyroid and was diagnosed with autoimmune thyroiditis. The same may be hypothesised for the other hypothyroid patients, consistent with the expected prevalence of autoimmune hypothyroidism in the general population, up to 10% (43). Due to the lack of systematic FT3 measurement, we could not assess the prevalence of NTIS in this study cohort; other studies have observed the presence of reduced serum FT3 concentrations in 7 to 39% of patients with mild-to-moderate and severe Covid-19 disease, respectively (17, 31, 32, 38).

In this study population, Covid-19-induced thyroid dysfunction was transient, with nearly all patients recovering to normal thyroid function as soon as 3 months post-infection, as observed in other short-term follow-up studies of patients surviving moderate-to-severe Covid-19 disease (21, 44, 45). The patients remained euthyroid at 12 months post-infection and the prevalence of thyroid autoantibodies positivity during follow-ups (12–15%) was consistent with that expected in the general population (10–12%) (46) and did not increase with time. Followed-up patients were younger and had higher baseline serum concentrations of FT3 compared with the whole cohort. This bias was inevitable, since many of the patients affected with the most severe forms of diseases, usually the elderly, did not survive or could not be continuously studied due to their persisting poor health conditions after hospital discharge.

Both the prevalence and the size of the focal hypoechoic areas at US decreased with time, but in some patients could still be detected at 12 months following SARS-CoV-2 infection. Similarly, the functional assessment of the thyroid gland by scintigraphy scan in some patients showed only a partial recovery of thyroid uptake over time, even in a euthyroid condition. The long-term effects on thyroid function are unknown, but unlikely clinically significant. Dedicated iodine challenge tests may explore whether a mild defect in thyroid hormonogenesis may persist over time, as previously described for classic subacute thyroiditis (40).

This study has some definite limitations: (i) the lack of thyroglobulin measurement during hospitalisation, one of the main markers of destructive thyroiditis; (ii) the availability of serum FT3 and FT4 assessments only in a proportion of patients; (iii) the delay in performing the first thyroid US (mean 84 days) after the Covid-19 diagnosis, due to restricted access to hospitals during the pandemic emergency peaks. Such delayed assessment might have in fact underestimated, rather than overestimated, the real prevalence of SARS-CoV-2-related features suggestive of thyroiditis at US.

Strengths of this study are (i) the systematic assessment of serum TSH concentrations in all consecutive patients hospitalised for severe Covid-19; (ii) the predominant inclusion of patients of the first wave of the Covid-19 pandemic (W1) studied without the confounding factor of steroid treatment; (iii) the availability of matched biochemical, morphological (US) and functional (scintigraphy scan) thyroid assessments; (iv) the length of follow-up, this being the first study assessing the evolution of thyroid involvement up to one year after the outbreak of Covid-19.

In conclusion, patients with severe Covid-19 may present NTIS as the most frequent thyroid alteration, atypical thyroiditis in 10–15% of cases, and common interferences on the thyroid function due to treatment approaches for Covid-19, which differ across pandemic waves and countries.

In our study, the thyroid dysfunction spontaneously resolved in a period of weeks without treatments. Focal areas of hypoechoicogenicity suggestive of thyroiditis, however, were still observed in the thyroid gland up to 1 year after hospital discharge, albeit less evident and not apparently related to thyroid autoimmunity. Despite the limited available follow-up due to the recent outbreak of Covid-19, long-term thyroid functional consequences are unlikely.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This study was funded by Ricerca Corrente Funds from the Italian Ministry of Health to Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy and the European Society of Endocrinology (ESE) Covid-19 Research Grant to Ilaria Muller.

Author contribution statement

Study conception and design (IM, AD, MV, TER, DD, MS), provision of study materials or patients (IM, AD, MV, TR, SM, EC, FDM, VL, MS), collection and assembly of data (IM, AD, MV, TR, DD, SM, EC, FDM, VL, BD, MC, GM, MA,

MS), data analysis and interpretation (IM, AD, MV, TR, DD, SM, EC, FDM, VL, BD, MC, GM, MA, MS), manuscript writing (IM, AD, MV, DD, VL, MS), administrative support (IM, TR, VL, MC, GM, MA, MS), final approval of manuscript (IM, AD, MV, TR, DD, SM, EC, FDM, VL, BD, MC, GM, MA, MS).

Acknowledgements

In memoriam of Dr Davide Dazzi for his strong commitment to the study and key support in the data analysis. The authors are extremely grateful to patients who participated in this study.

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Received 12 January 2023

Accepted 30 January 2023

Available online 30 January 2023

Version of Record published 10 March 2023