***This is the peer reviewed version of the article published online 30 July 2020 in final form in The Lancet Diabetes & Endocrinology*, DOI** https://doi.org/10.1016/S2213-8587(20)30266-7, *found at* https://www.thelancet.com/journals/landia/article/PIIS2213-8587(20)30266-7/fulltext*. This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record."*

SARS-CoV-2-related atypical thyroiditis

Ilaria Muller MD PhD[1,2], Daniele Cannavaro MD[3], Davide Dazzi MD[4], Danila Covelli MD[1], Giovanna Mantovani MD PhD[1,3], Antonio Muscatello MD[5], Emanuele Ferrante MD[1], Emanuela Orsi MD[1], Veronica Resi MD[1], Virgilio Longari MD[6], Marco Cuzzocrea MD[6], Alessandra Bandera MD PhD[5,7], Elisa Lazzaroni MD[1], Alessia Dolci MD[1], Ferruccio Ceriotti MD[8], Tiziana E Re MD[9], Andrea Gori MD[5,7], Maura Arosio MD PhD[1,3], Mario Salvi MD[1]

1 Endocrinology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

2 Thyroid Research Group - Division of Infection & Immunity, Cardiff University School of Medicine, Cardiff, UK

3 Department of Clinical Sciences and Community Health, University of Milan, Italy

4 Internal Medicine, Ospedale di Vaio, Fidenza, Italy

5 Infectious Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

6 Nuclear Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

7 Department of Pathophysiology and Transplantation, University of Milan, Italy

8 Clinical Laboratory, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

9 Medicine - Acute Medical Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

CORRESPONDING AUTHOR

Dr Ilaria Muller

Endocrinology (UOC Endocrinologia)

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Via Francesco Sforza 35,

20122 Milan, Italy

Email: ilaria.muller@policlinico.mi.it

Phone: +39 02 55033332, Fax: +39 02 50320605

The Covid-19 pandemic determined by the severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2)[1,2] is a global emergency that has seriously affected Northern Italy, where we are based. Preliminary data analysis of Covid-19 patients hospitalised in our Institution requiring high intensity of care (HICU), frequently showed low-suppressed serum thyroid stimulating hormone (TSH), with and without elevated free thyroxine (FT4) concentrations, suggestive for thyrotoxicosis. It is known that critically ill patients often show alterations of thyroid function tests known as non-thyroidal illness syndrome (NTIS)[3,4]. Alternatively, thyrotoxicosis might result from SARS-CoV-2 directly infecting the thyroid gland as described in other viral infections. This event is known as subacute thyroiditis and is characterised by self-limiting thyrotoxicosis of variable duration (weeks/months), followed by hypothyroidism with final restoration of euthyroidism[5,6].

In this study, we aimed to assess the prevalence of thyrotoxicosis, suggestive for subacute thyroiditis, in patients admitted in HICU units in relation to the presence or absence of Covid-19, by comparing HICU patients hospitalised in 2020 for Covid-19 disease (HICU-20), with those hospitalised in the same HICU units in 2019, thus SARS-CoV-2 negative (HICU-19). Considering a 0.5% prevalence of subacute thyroiditis in HICU-19, in line with general population[5], and a 10% estimated prevalence in HICU-20 patients, a total of 166 patients were needed to obtain a 80% statistical power and a significance of 0.05 (two tails).

Thyroid function was assessed at hospital admittance (within two days average) in 93 HICU-20 and 101 HICU-19 consecutive patients hospitalised for Covid-19 disease. Fifty-two Covid-19 patients hospitalised in low intensity of care units (LICU-20) were also studied (**Table 1A appendix**). HICU-20 patients were younger (65.3±12.9 years, $P<0.01$) and predominantly male (68.8%, $P=0.04$) compared with HICU-19 (73.0±15.2 years, 56.4%) and LICU-20 patients (70.3±18.1 years, 48.1%). Consistently with the known female preponderance of thyroid disease, patients with pre-existing thyroid disorders (N=42) were more frequent in HICU-19 (22.8%) and LICU-20 (21.1%) compared with HICU-20 (8.6%, $P=0.02$), and were excluded from the thyroid

function analysis (**Table 1B appendix**). As many as 13/85 (15.3%) HICU-20 patients were thyrotoxic, compared to 1/78 (1.3%) HICU-19 (P<0.01) and 1/41 (2.4%) LICU-20 (P=0.02). Among Covid-19 thyrotoxic patients, 9/14 (64.3%) were men and 5/14 (35.7%) women (P=0.02). Serum TSH concentrations were skewed towards lower values in HICU-20 compared with HICU-19 and LICU-20 patients (P<0.02, **Figure 1A**). Mean serum FT4 concentrations were higher in HICU-20 than LICU-20 (P<0.02), but not HICU-19 patients (P=0.38; **Table 1B appendix**). Stratification for sex and age did not affect the results (not shown). Although the dramatic increase of patients requiring hospitalization due to the Covid-19 pandemic emergency may have selected HICU-20 patients in more critical conditions compared with HICU-19, the thyroid dysfunction observed in HICU-20 patients unlikely relates to NTIS only. Serum FT3 concentrations, the main NTIS indicator, were in fact low in all groups, not only HICU-20 (P=0.71; **Table 1B appendix**). Furthermore, in NTIS normal/low serum concentrations of TSH and T3 are usually associated with low concentrations of T4[3,4], but not normal/elevated as observed in our patients. A transient (hours) T4 increase may occur in acute conditions, usually associated with normal/high serum TSH concentrations[3], but not low as observed in this study. It is plausible that our patients may have a combination of thyrotoxicosis and NTIS, described as T4 thyrotoxicosis[4].

To elucidate the diagnostic hypothesis, eight Covid-19 patients with any thyroid dysfunction observed at hospital admission were followed-up after a mean of 51 days, when discharged and negative for SARS-CoV-2 (**Table 2 appendix**). Two were confirmed hypothyroid and had typical marked diffuse hypoechogenicity and heterogeneity at thyroid ultrasound, consistent with autoimmune thyroiditis. All other patients with low/suppressed TSH or thyrotoxicosis at baseline had normal thyroid function and negative thyroid autoantibodies at follow-up; none reported neck pain ever. All had a diffuse mild hypoechoic pattern at thyroid ultrasound; focal markedly hypoechoic areas were present in 3/6 (50%) cases. Such areas corresponded to focal reduced uptake at SPECT imaging, and the thyroid gland showed a general low-normal or reduced ^{99m}Tc uptake, suggestive for subacute thyroiditis (**Figure 2 appendix**). It is plausible that we may have missed some typical

imaging features of subacute thyroiditis in the other three patients, due to the time elapsed between hospital admission and follow-up, and the anti-inflammatory treatments received.

This study suggests that a substantial proportion of Covid-19 patients, requiring high intensity of care, present with thyrotoxicosis and low serum TSH concentrations, likely as a consequence of subacute thyroiditis induced by SARS-CoV-2, in an underlying setting of NTIS. They also had a lower prevalence of pre-existing thyroid disorders (autoimmune and not) compared with HICU-19 patients; this suggests that such conditions are not a risk factor for Covid-19 disease. In these patients, serum FT4 concentrations were not as elevated, and serum TSH concentrations not as suppressed, as classically described in subacute thyroiditis[6]. These patients also did not complain of neck pain, consistent with silent thyroiditis, did not have leucocytosis, but had lymphopenia as observed with Covid-19 infection (**Table 2 appendix**)[2]. These features differ from those described in a single case report of late-onset thyroiditis after mild SARS-CoV-2 infection[7] and in classic subacute thyroiditis, characterised by a pathognomonic infiltration of giant cells (congregates of lymphocytes, histiocytes and colloid) with swelling of thyroid follicles, stretching of thyroid capsule and consequent neck pain[6]. Rather, in SARS-CoV-2 induced thyroiditis giant cells might not form due to lymphopenia, and thyroid cells may be damaged by apoptosis as observed with SARS-associated coronavirus (SARS-CoV)[8]. The angiotensin-converting enzyme 2 (ACE-2) is a host-cell entry receptor for both SARS-CoV and SARS-CoV-2[1] and might be in part responsible for a common pathogenic pathway. ACE-2 is even more highly expressed in thyroid than lung cells, and in women such expression negatively correlates with signatures of immune cell enrichment[9]. This might in part explain why in this study the most severe forms of Covid-19 pneumonia[2], and associated thyroid dysfunction, affected predominantly men (HICU-20), but not women as in the classic viral subacute thyroiditis[6].

The serum CRP concentration is a general non-specific marker of inflammation, subacute thyroiditis[10] and Covid-19 disease severity[2]. Median serum CRP concentrations were significantly higher in HICU-20 compared with HICU-19 ad LICU-20 patients ($P<0.01$; **Figure 1B**, **Table 1B**

appendix). In Covid-19 patients, serum CRP, but not TSH and FT4 concentrations, were significantly higher in deceased patients than in survivors (median[IQR] 190[94 - 256] mg/L vs 73[33 - 136] mg/L respectively, P<0.01). This difference was not observed in HICU-19 patients (P=0.27). It could be speculated that patients with higher serum CRP concentrations may have a systemic spread of SARS-Cov-2, that is more likely to affect the thyroid gland.

This study has some limitations: i) serum FT4/FT3 concentrations were measured only in case of abnormal TSH; ii) thyroid imaging was conducted nearly two months after baseline TSH measurement because of prolonged post-discharge persistence of SARS-Cov-2 positivity; iii) serum TSH was not available in all LICU patients. This study has several strengths: i) first comprehensive description of thyroid alterations in hospitalised Covid-19 patients; ii) focused study design; iii) initial longitudinal follow-up.

In conclusion, we suggest to routinely assess thyroid function in patients affected with Covid-19 requiring high intensity of care, because they frequently present with thyrotoxicosis due to a peculiar form of subacute thyroiditis induced by SARS-CoV-2. Considering the currently ongoing pandemic emergency, future studies are encouraged to confirm, or counter, these results. Thyroid cytology or histology and longitudinal studies of thyroid (dys)function in these patients would be particularly informative.

CONTRIBUTORS' STATEMENT

IM, MS, DCa, DD, DCo, GM and MA contributed to study conception and design, literature search, data collection, data analysis, data interpretation, figures and manuscript writing.

VL, MC contributed to data collection, data analysis, data interpretation, figures and manuscript writing.

AM, EF, EO, VR, AB, EL, AD, FC, TR, AG contributed to data collection, data analysis, data interpretation and manuscript writing.

DISCLOSURE STATEMENT

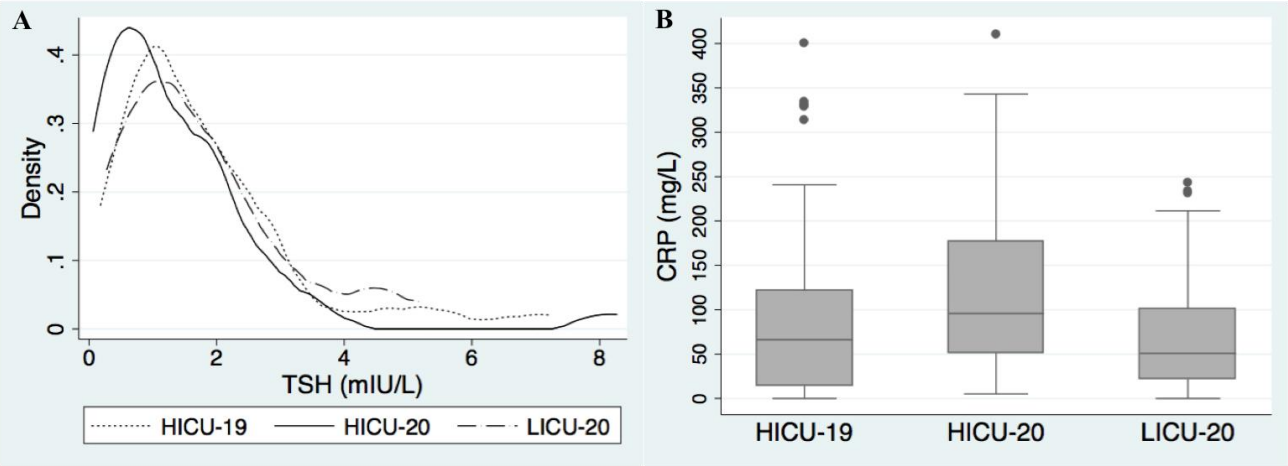
Authors have nothing to disclose.

REFERENCES

1. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**(7798): 270-3.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**(18): 1708-20.
3. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. *Thyroid* 2014; **24**(10): 1456-65.
4. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet D & E* 2015; **3**(10): 816-25.
5. Desailloud R, Hober D. Viruses and thyroiditis: an update. *Virol J* 2009; **6**: 5.
6. Guimarães VC. Subacute and Riedel's Thyroiditis. In: Jameson JL, De Groot LJ, eds. *Endocrinology Adult and Pediatric*. 7 ed. Philadelphia: Elsevier Saunders; 2016: 1528-39.
7. Brancatella A, Ricci D, Viola N, Sgro D, Santini F, Latrofa F. Subacute thyroiditis after SARS-CoV-2 infection. *J Clin Endocrinol Metab* 2020; **105**(7): 1-4.
8. Wei L, Sun S, Xu CH, et al. Pathology of the thyroid in severe acute respiratory syndrome. *Hum Pathol* 2007; **38**(1): 95-102.
9. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020; **9**(1): 45.
10. Pearce EN, Bogazzi F, Martino E, et al. The prevalence of elevated serum C-reactive protein levels in inflammatory and noninflammatory thyroid disease. *Thyroid* 2003; **13**(7): 643-8.

FIGURES

Figure 1: Graphical representation of the main thyroid-related laboratory findings in the three groups of patients (excluded those with known thyroid disorders at hospitalisation).



HICU-19 = high intensity of care units in 2019 (N=78). HICU-20 = high intensity of care units in 2020 (N=85). LICU-20 = low intensity of care units in 2020 (N=41).

A: Distribution of serum thyroid stimulating hormone (TSH) concentrations (mIU/L), expressed as median (IQR): 1.43 (0.88 - 2.37) mIU/L in HICU-19, 1.04 (0.47 - 1.80) mIU/L in HICU-20 and 1.43 (0.71 - 2.28) in LICU-20 ($p<0.02$), with differences between HICU-20 and HICU-19 being highly significant ($P<0.01$) and between HICU-20 and LICU-20 moderately significant ($P<0.05$).

B: Box plots of median [IQR] CRP concentrations in HICU-19 (66 [15 - 121] mg/L), HICU-20 (96 [51 - 177] mg/L) and LICU-20 patients (52 [22 - 103] mg/L) ($P<0.01$).

APPENDIX

METHODS

STUDY DESIGN AND PATIENTS

This is a single centre observational study with a longitudinal component. Consecutive patients hospitalised for Covid-19 from March 3rd to April 28th 2020 in HICU (HICU-20) and LICU (LICU-20) units and, as controls, in the same HICU units during the equivalent period of 2019 (HICU-19), were included in the study, as they had serum TSH routinely measured at hospital admittance. Patients with severe respiratory distress received predominantly oxygen supply in LICU and Continuous Positive Airway Pressure (CPAP) in HICU units; in LICU and HICU units a minority of patients were treated with intubation and invasive mechanical ventilation.

The electronic clinical records of HICU-19, HICU-20 and LICU-20 patients were then analysed for clinical and pharmacological history, length of hospitalisation and final outcome. Patients with no available clinical data were excluded from the study. Patients with known history of any thyroid disease (autoimmune or not) before hospital admittance were also excluded from the analyses addressing the main study endpoints.

HICU-20 and LICU-20 patients showing abnormal thyroid function tests at hospital admittance were contacted for follow-up after discharge when negative at SARS-CoV-2 test and after providing informed consent. The follow-up visit included biochemical tests and ultrasound scan of the thyroid gland using a MyLab™25Gold ultrasound machine (Esaote, Genoa, Italy). Thyroid scintigraphy with 99m-technetium-pertechnetate (^{99m}Tc) and SPECT tomographic acquisitions of thyroid gland (triple head gamma camera, Irix, Philips Medical Systems, US) was also performed as a functional test in patients showing focal hypoechoic areas at ultrasound.

This study, named "Tiro-Covid-19", was approved by the Ethics Committee of Milano Area 2 (Milan, Italy), ID 375_2020.

BIOCHEMICAL ANALYSIS

Serum thyroid-stimulating hormone (TSH), free-thyroxine (FT4) and free-triiodothyronine (FT3) concentrations were measured by electrochemiluminescence immunoassay (Cobas® e801, Roche Diagnostics, Germany). Reference intervals were 0.28 – 4.30 mIU/L for TSH, 10.3 - 21.9 pmol/L for FT4 and 3.1 - 7.7 pmol/L for FT3. As per the automated setting of the hospital laboratory, FT4 and FT3, or FT4 only, were measured for TSH concentrations <0.45 mIU/L or >3.50 mIU/L, respectively. The serum C reactive protein (CRP) was measured by turbidimetry (Cobas® c702, Roche Diagnostics, Germany) and considered normal if <5 mg/L.

The follow-up measurements included TSH, FT4, FT3, CRP, full blood count (XN-9000^{TM}, Sysmex, US), autoantibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) by enzyme-linked immunosorbent assay (ThermoFisher, US) and autoantibodies to TSH receptor (TRAb) by Immulite 2000/2000 XPi TSI (Siemens, Germany). Normal reference ranges were <35 KIU/L (TPOAb), <60 KIU/L (TgAb) and <0.55 KIU/L (TRAb).

STUDY ENDPOINTS

Patients with TSH <0.28 mIU/L and/or FT4 >21.9 pmol/L concentrations were classified as "thyrotoxic", whereas those with TSH <0.45 mIU/L (laboratory automatic cut-off) were classified as "low TSH". Patients with TSH >4.30 mIU/L (and FT4 ≤21.9 pmol/L) and/or FT4 <10.3 pmol/L concentrations were classified as "hypothyroid".

The primary study endpoint was the prevalence of thyrotoxicosis, suggestive for subacute thyroiditis, in patients admitted in HICU in relation with presence or absence of Covid-19, thus comparing HICU-20 and HICU-19. We also studied: i) the prevalence of thyrotoxicosis in less critical Covid-19 patients LICU-20, ii) thyroid (dys)function of Covid-19 patients in relation with inflammatory markers such as the C reactive protein (CRP), length of hospitalization and patient's outcome.

STATISTICAL ANALYSIS

Variables were assessed for their distribution and summarized using the sample mean ± standard deviation (SD) when approximately normally distributed, or using the sample median and interquartile range (IQR) otherwise. Categorical variables were summarized using percentages, and the statistical significance of associations between them calculated using Fisher's exact test. The Kruskal-Wallis test with Mann-Whitney U tests or one-way analysis of variance (ANOVA) with post hoc Bonferroni correction were also applied, depending on the distribution of variables. The 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, US). P values <0.05 were considered statistically significant.

TABLES

Table 1: Clinical characteristics of patients hospitalised in units of high intensity of care during (HICU-20) and in absence (HICU-19) of Covid-19 pandemic, and of low intensity of care during Covid-19 pandemic (LICU-20).

		HICU-19 Covid-NEG	HICU-20 Covid-POS	LICU-20 Covid-POS	ALL 3 GROUPS	HICU-20 vs HICU-19	HICU-20 vs LICU-20
A		**N = 101**	**N = 93**	**N = 52**	**P**	**P**	**P**
Age	years	73.0 ± 15.2	65.3 ± 12.9	70.3 ± 18.1	**<0.01**	**<0.01**	0.06
Female	N (%)	44 (43.6%)	29 (31.2%)	27 (51.9%)	**0.04**	0.08	**0.01**
Length of hospitalisation	days	20.9 ± 15.8	23.8 ± 15.8	22.3 ± 15.5	0.44	0.20	0.60
Deaths [1]	N (%)	12/101 (11.9%)	17/91 (18.7%)	4/51 (7.8%)	0.16	0.18	0.08
Known thyroid disorders	N (%)	23 (22.8%)	8 (8.6%)	11 (21.1%)	**0.02**	**<0.01**	**0.03**
B		**N = 78**	**N = 85**	**N = 41**	**P**	**P**	**P**
Thyrotoxicosis [2]	N (%)	1 (1.3%)	13 (15.3%)	1 (2.4%)	**<0.01**	**<0.01**	**0.02**
Suppressed TSH [3]	N (%)	1 (1.3%)	8 (9.4%)	1 (2.4%)	**0.04**	**0.02**	0.15
Low TSH [4]	N (%)	6 (7.7%)	21 (24.7%)	4 (9.8%)	**<0.01**	**<0.01**	**<0.05**
Hypothyroidism [5]	N (%)	7 (9.0%)	3 (3.5%)	4 (9.8%)	0.28	0.51	0.59
TSH mIU/L	median (IQR) [range]	1.43 (0.88 - 2.37) [0.17 - 14.00]	1.04 (0.47 - 1.80) [0.06 - 10.30]	1.43 (0.71 - 2.28) [0.27 - 10.10]	**<0.02**	**<0.01**	**<0.05**
FT4 pmol/L [6]	mean ± SD [range]	16.2 ± 2.4 [10.8 - 20.1]	18.7 ± 5.4 [8.5 - 32.3]	13.5 ± 4.6 [4.5 - 19.2]	**<0.02**	0.38	**<0.02**
FT3 pmol/L [7]	mean ± SD [range]	2.6 ± 0.8 [1.4 - 3.5]	2.9 ± 0.6 [2.0 - 3.8]	2.9 ± 1.1 [1.8 - 4.0]	0.71	0.50	0.76
CRP mg/L	median (IQR) [range]	66 (15 - 121) [1 - 400]	96 (51 - 177) [5 - 410]	52 (22 - 103) [0 - 243]	**<0.01**	**<0.01**	**<0.01**

Data are presented as mean ± SD or median (IQR), based on normal or non-normal distribution respectively.

[1] Percentages calculated on denominators after excluding patients still hospitalised at the time of data analysis: 2/93 (2.1%) HICU-20 and 1/52 (1.9%) LICU-20

[2] Defined as TSH <0.28 mIU/L and/or FT4 >21.9 pmol/L

[3] Defined as TSH <0.28 mIU/L

[4] Defined as TSH <0.45 mIU/L

[5] Defined as TSH >4.30 mIU/L (and FT4 ≤21.9 pmol/L) and/or FT4 <10.3 pmol/L

[6] FT4 measured only in patients with TSH <0.45 mIU/L or >3.50 mIU/L (N = 49)

[7] FT3 measured only in patients with TSH <0.45 mIU/L (N = 28)

A = 102 HICU-19, 95 HICU-20 and 61 LICU-20 were initially evaluated; one HICU-19, two HICU-20 and nine LICU-20 had no associated electronic clinical records, thus were excluded from the study. Serum TSH concentrations were routinely measured in all patients in HICU but less frequently in LICU units, due to different standard protocols applied at hospital admittance. All HICU-20 and LICU-20 patients were hospitalised for Covid-19 related pneumonia and respiratory distress. Diagnosis at hospitalisation in HICU-19 patients was pneumonia (34.6%), other respiratory diseases (14.8%), infections/sepsis (12.9%), cardiovascular (9.9%), abdominal (8.9%) and neurological (7.9%) disorders, trauma or haemorragia (7.0%), kidney failure and electrolyte disequilibrium (4.0%). Evidence of viral infection was reported in 16 HICU-19 patients: 7 Influenza A virus, 4 Rhinovirus (in one case associated with influenza B virus), 3 Respiratory

Syncytial Virus RSV (in one case associated with metapneumovirus MPV), 1 viral meningitis not better specified, 1 vasculitis related to HBV.

B = Patients studied after excluding those with pre-existing thyroid disorders. Abbreviations in alphabetical order: CRP = C reactive protein. FT3 = Free tri-iodothyronine. FT4 = Free thyroxine. TSH = Thyroid Stimulating Hormone.

History of steroids started prior to hospital admission was investigated to exclude its potential influence on thyroid function, and found present in 8 HICU-19, 3 HICU-20 and 6 LICU-20 patients, as treatment for several pre-existing disorders including: previous transplantation, rheumatoid arthritis, polymyalgia rheumatica, dermatitis/eczema, pneumonia, prostate cancer, hemolytic anemia, sarcoidosis, cryoglobulinemic vasculitis, pemphigus. The median daily dose was prednisone 5 mg. These 17 patients had normal thyroid function, except for one thyrotoxic patient (HICU-20; prednisone 5 mg daily) and one hypothyroid patient (LICU-20; prednisone 1 mg daily). Considering the small number of patients receiving steroids, predominantly low doses, before baseline assessment, we exclude that such treatment may have influenced the conclusions of the present study.

Table 2: Follow-up clinical parameters of patients hospitalised for Covid-19 showing thyroid dysfunction at admittance

				BASELINE - INPATIENT									INITIAL FOLLOW-UP											
ID	**GROUP**	**Sex**	**Age** years	**TSH** mIU/L	**FT4** pmol/L	**FT3** pmol/L	**CRP** mg/L	**WBC** 10^9/L	**LYMPH** 10^9/L	**H**	**A+M**	**AV**	**Days F.Up[1]**	**TSH** mIU/L	**FT4** pmol/L	**FT3** pmol/L	**CRP** mg/L	**WBC** 10^9/L	**LYMPH** 10^9/L	**AbTg** KIU/L	**AbTPO** KIU/L	**TRAb** KIU/L	**Thyroid US focal hypo-ecoic areas**	**Thyroid □ ^{99m}Tc uptake**
1[2]	HICU-20	M	68	0.19	32.3	2.6	218	9.0	0.6	X	X		18	1.26	18.9	2.5	1	10.5	1.3	NEG	NEG	NEG	NA	NA
2	HICU-20	F	59	0.28	15.3	2.9	109	9.8	1.0	X		X	68	0.96	10.5	4.3	1	5.3	2.0	NEG	NEG	NEG	NO	NA
3	LICU-20	M	24	0.33	9.6	4.0	10	5.9	1.4				46	1.17	10.4	4.9	1	9.2	2.5	NEG	NEG	NEG	YES	YES
4	HICU-20	F	70	0.34	18.5	3.1	139	6.4	0.7	X		X	56	1.80	13.1	3.8	1	5.1	1.5	NEG	NEG	NEG	NO	NA
5	HICU-20	M	61	0.40	16.0	3.8	17	6.0	1.1	X		X	56	0.93	13.5	4.6	4	6.3	1.9	NEG	NEG	NEG	NO	NA
6	LICU-20	F	59	0.40	16.6	2.3	233	7.3	0.4	X	X	X	62	2.07	10.7	5.1	1	4.3	1.7	NEG	NEG	NEG	YES	YES
7	HICU-20	M	66	0.43	22.8	NA	52	6.1	0.9	X		X	42	0.63	16.5	4.8	1	2.7	1.3	NEG	NEG	NEG	YES	YES
8	HICU-20	F	78	8.09	22.8	NA	17	9.7	2.3	X		X	59	6.71	17.4	4.8	1	8.4	1.7	NEG	NEG	NEG	NO	NA
9	HICU-20	F	65	8.27	9.6	NA	176	9.5	1.7	X		X	53	6.10	8.7	4.3	3	8.7	2.8	89	313	NEG	NO	NA

Patients with available follow-up listed by increasing order of serum TSH concentrations measured at hospital admittance. All HICU-20 and LICU-20 patients with thyrotoxicosis (n=14), low TSH (n=10) and hypothyroidism (n=7) detected at hospitalisation were contacted for the initial follow-up. At the time of recruitment, thirteen were still hospitalised or in rehabilitation, four had died, two were still positive for SARS-CoV-2, three were not reached and one declined. In all cases any pharmacological treatment for Covid-19 was started after baseline blood sampling.

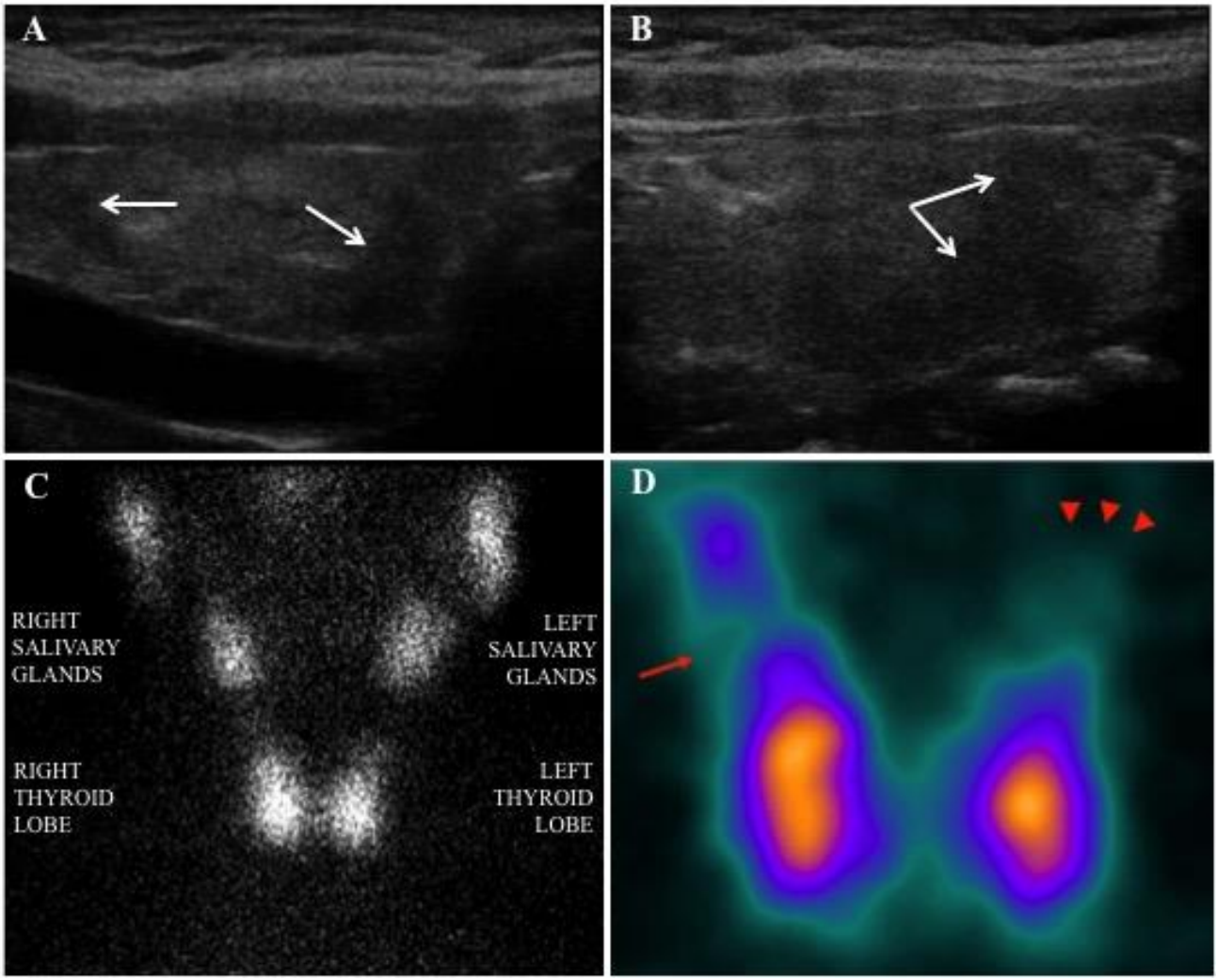
Abbreviations in alphabetical order: AbTg = autoantibodies to thyroglobulin (negative [NEG] if <60 KIU/L). AbTPO = autoantibodies to thyroid peroxidase (negative [NEG] if <35 KIU/L). AV = anti-viral drugs (Lopinar/Ritonavir or Remdesivir). A + M = anakinra (interleukin 1 receptor antagonist) and methylprednisolone. CRP = C reactive protein (normal if <5 mg/L). FT3 = Free tri-iodothyronine (reference intervals 3.1 - 7.7 pmol/L). FT4 = Free thyroxine (reference intervals 10.3 - 21.9 pmol/L). H = hydroxychloroquine. ID = Patient identity code. LYMPH = total lymphocytes count (reference intervals 1.20 - 3.40 *10^9/L). NA = Not available. TRAb = autoantibodies to TSH receptor (negative [NEG] if <0.55 KIU/L). TSH = Thyroid Stimulating Hormone (reference intervals 0.28 – 4.30 mIU/L). WBC = total white blood cells count (reference intervals 4.80 - 10.80 *10^9/L). US = Ultrasound. ^{99m}Tc = 99m-technetium-pertechnetate. □ = low-normal.

[1] Days from baseline TSH to follow-up TSH (F.Up) measurements.

[2] ID1 Could not attend the follow-up visit due to the long Covid-19 clinical course; his thyroid function was re-tested during hospitalisation

SUPPLEMENTAL FIGURES

Figure 2



Imaging of SARS-CoV-2 related subacute thyroiditis obtained in ID6, who had a particularly aggressive clinical course of Covid-19 requiring mechanical invasive ventilation.

Ultrasound imaging of focal hypoechoic areas (white arrows) in the lower and upper portions of the right (panel **A**) and the upper portion of the left (panel **B**) thyroid lobes.

Panel **C**: Thyroid scintigraphy with 99m-technetium-pertechnetate (^{99m}Tc) showing only slightly increased uptake of ^{99m}Tc (0.89%, normal range 0.5-4.0%) in the thyroid gland as compared to that of salivary glands (background). Panel **D**: Thyroid SPECT imaging of two focal areas of reduced ^{99m}Tc uptake in the polar portion of the right lobe (red arrow) and the middle polar region of the left lobe (red triangles), corresponding to the hypoechoic areas shown at ultrasound.

ACKNOWLEDGMENTS

We are extremely grateful to patients who participated in the study and to Valter Monzani, Flora Peyvandi, Nicola Montano, Marina Baldini, Anna Ludovica Francanzani, and their dedicated staff for taking care of patients in such dramatic Covid-19 epidemic emergency and updating their electronic clinical records.

FUNDING

This work was funded by Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.