
بنام خداوند جان و خرد

COVID-19 and Thyroid

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Agenda

- Introduction
- Thyroid dysfunction in patients with COVID-19
- Thyrotoxicosis
- Hypothyroidism
- Non thyroidal illness syndrome
- Atypical thyroiditis
- Thyroid cancer patients in the time of COVID-19
- Conclusion


Introduction

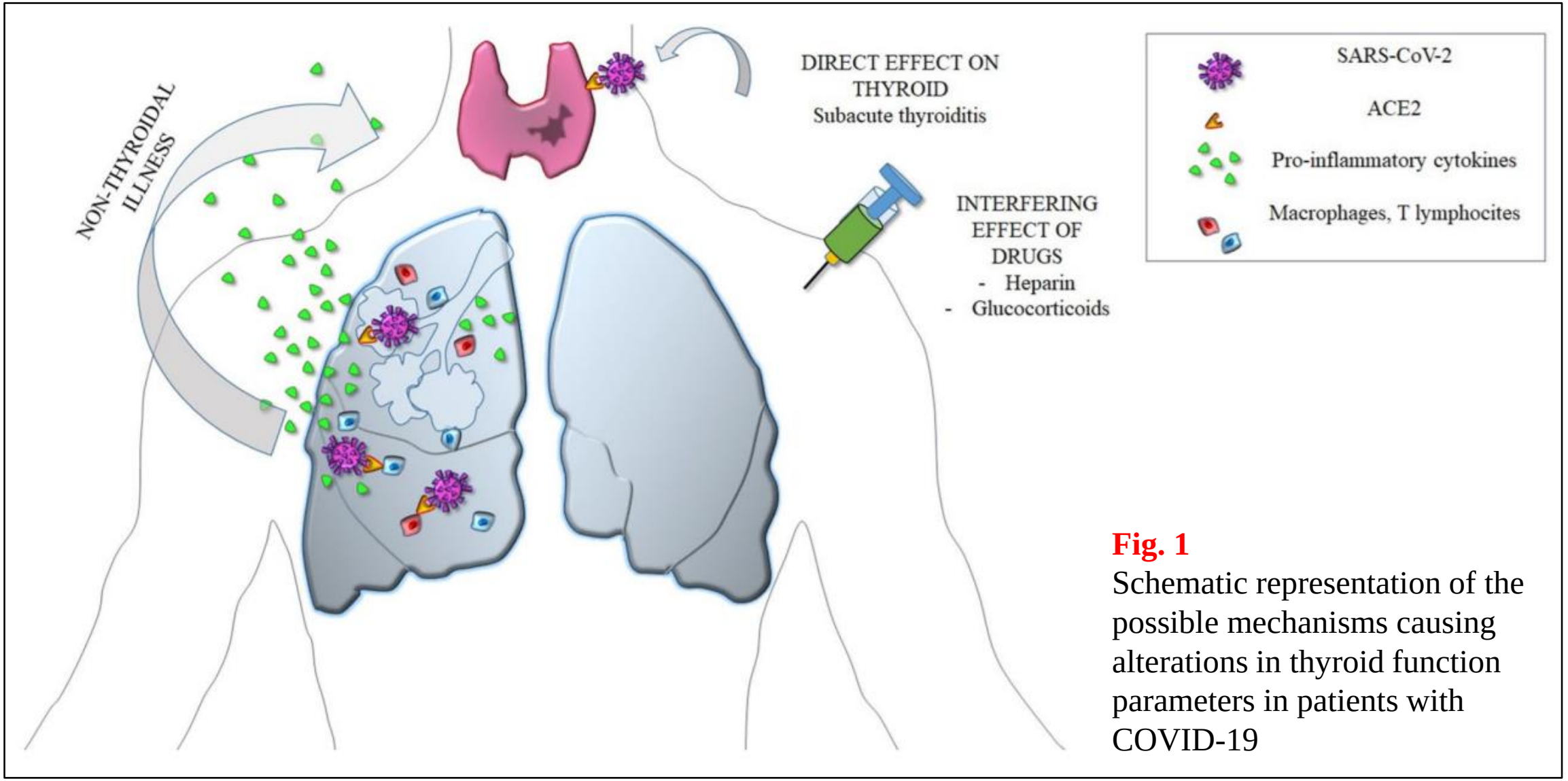
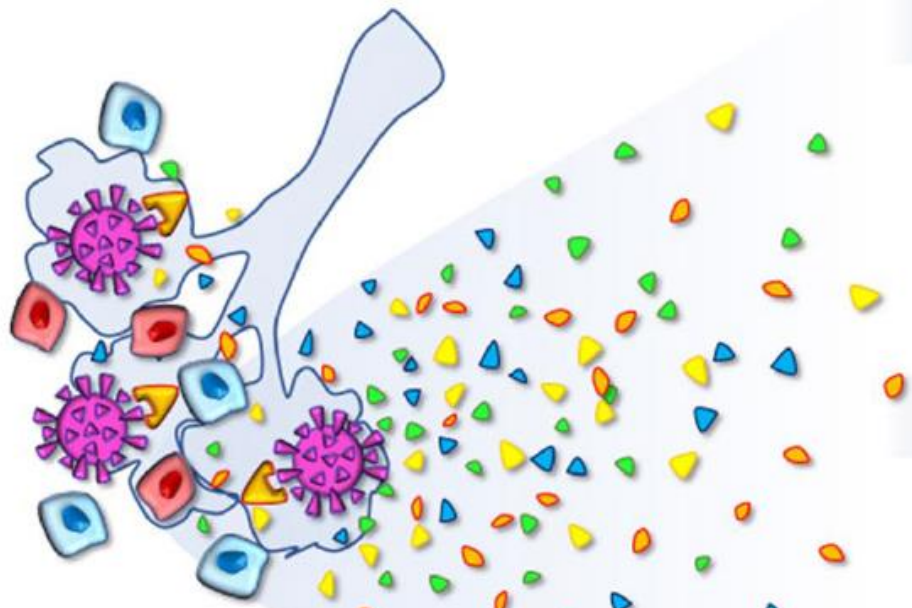


Fig. 1
Schematic representation of the possible mechanisms causing alterations in thyroid function parameters in patients with COVID-19



SARS-COV-2 INFECTION

CYTOKINE STORM

SARS-CoV-2
ACE-2
IL-1 beta
TNF-α
IL-6
IFN-γ
Macrophages
T lymphocites

PITUITARY/HIPOTHALAMUS

↓ TRH secretion and pulsatility
↓ TSH secretion and pulsatility
↑DIO2 activity→increased conversion of T4 to T3→negative feedback on TRH and TSH secretion

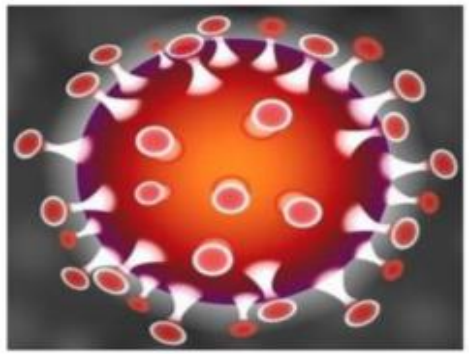
THYROID

↓ iodide uptake
↓ T3 secretion
↓ mRNA expression of thyroid-specific genes
↓ DIO1 and DIO2 expression and activity →decreased conversion of T4 to T3
↑ DIO3 activity expression and activity →increased conversion of T3 to rT3

LIVER

↓ DIO1 and DIO2 expression and activity →decreased conversion of T4 to T3
↑ DIO3 expression and activity →increased conversion of T3 to rT3
↓ secretion of transport proteins

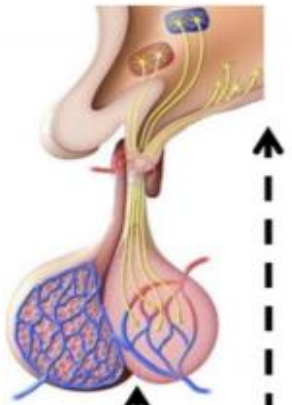
Fig. 1 Schematic representing potential mechanisms of hypothalamic–pituitary–thyroid (HPT) axis injury by SARS-CoV-2 infection

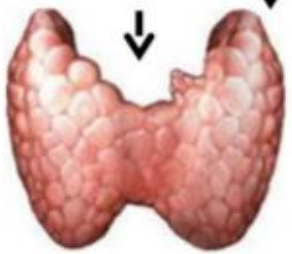


SARS-CoV-2

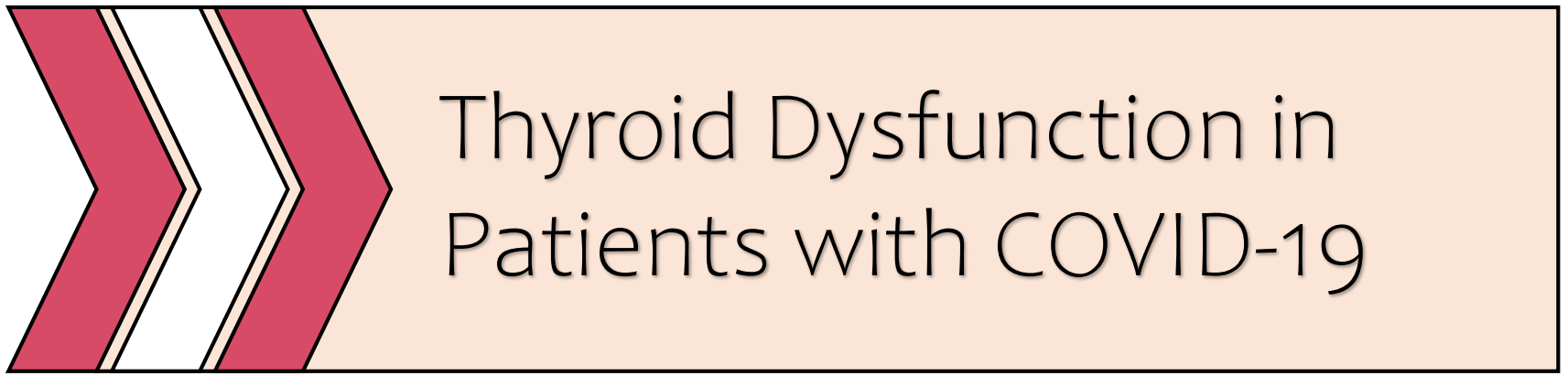
-Direct virus infection or via immune cells

-Immune-inflammatory responses to the virus





HPT axis


Thyroid Dysfunction in
Patients with COVID-19

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ORIGINAL STUDIES
THYROID FUNCTION AND DYSFUNCTION

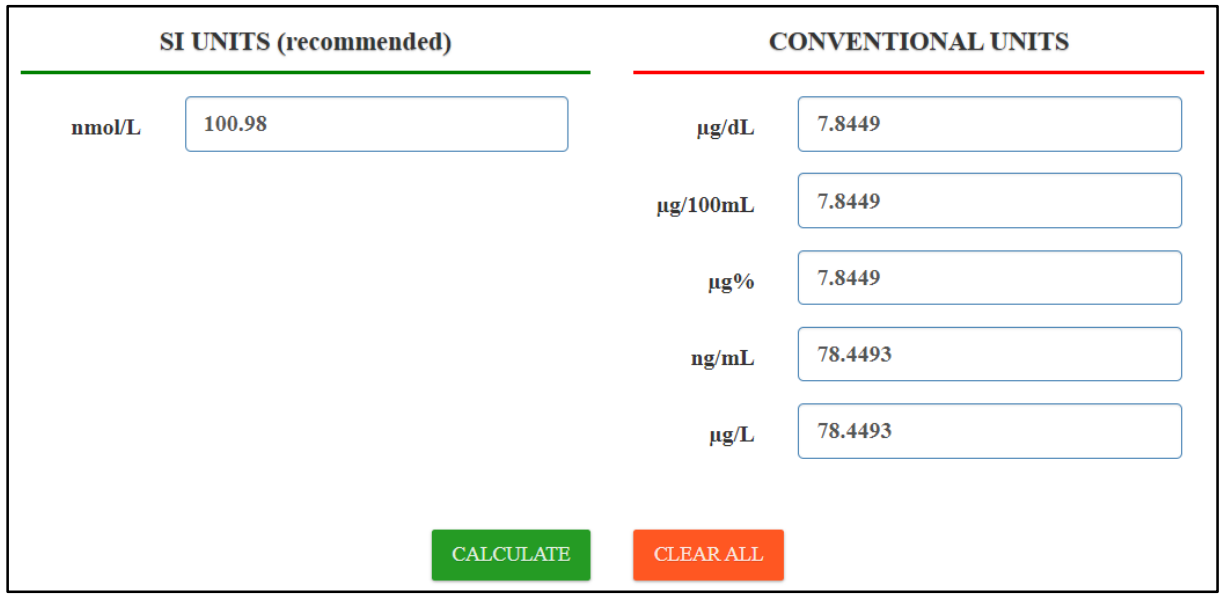
Thyroid Function Analysis in 50 Patients with COVID-19: A Retrospective Study

Min Chen,* Weibin Zhou,* and Weiwei Xu

Background: The aim of this study was to evaluate thyroid function in patients with COVID-19.

Methods: Clinical manifestations, laboratory results, and chest computed tomography scans were retrospectively reviewed for 50 patients with laboratory-confirmed COVID-19 without a history of thyroid disease who underwent thyroid function testing during their course of COVID-19 infection and after recovery. They were admitted to the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China, between January and March 2020. Healthy participants who underwent routine physical checkups and non-COVID-19 pneumonia patients with a similar degree of severity during the same period were included in the study as the control group. Thyroid hormone and thyrotropin (TSH) levels were analyzed and compared between the COVID-19 and control groups.

Thyroxine (total T4)



Triiodothyronine (T3)

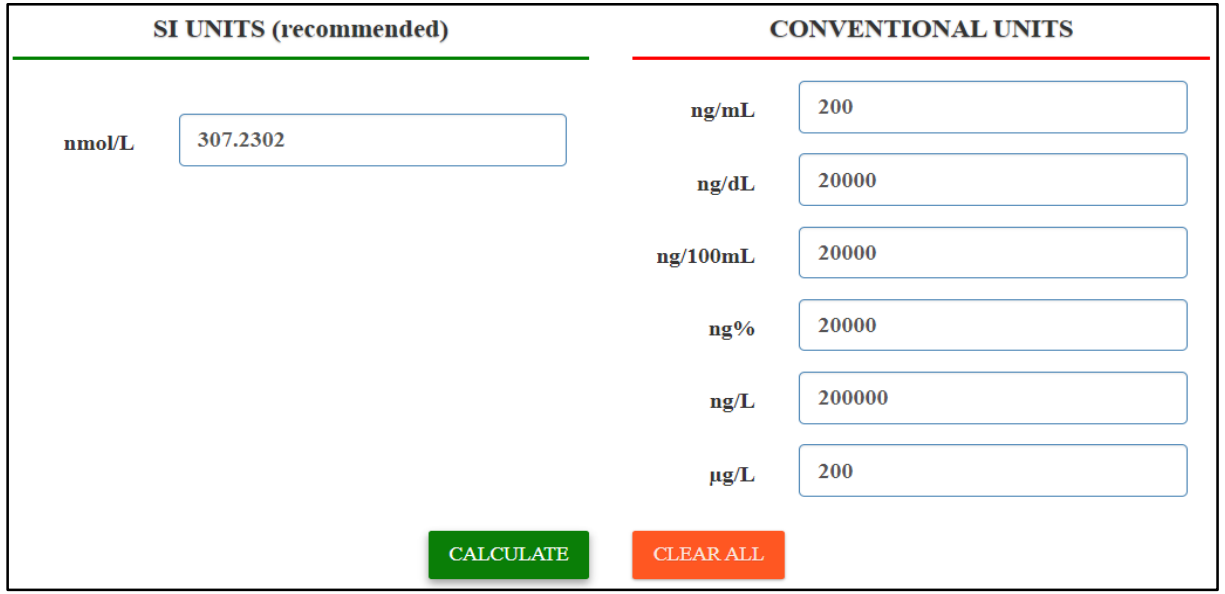


TABLE 1. COMPARISON OF SERUM TSH, TT3, AND TT4 BETWEEN COVID-19 AND HEALTHY CONTROL GROUP AND NON-COVID-19 PNEUMONIA PATIENTS

	COVID-19 (n = *50*)	*Healthy control* (n = *54*)	*Non-COVID-19* (n = *50*)
Alb (g/L)	38.15 [34.57, 43.10]**	46.15 [43.98, 48.05]	38.70 [33.67, 40.95]
TSH (mIU/L)	0.30 [0.15, 0.86]**,##	1.57 [1.03, 1.97]	1.18 [0.68, 1.91]
TT3 (nmol/L)	0.98 [0.84, 1.22]**,#	1.58 [1.49, 1.73]	1.28 [0.82, 1.43]
TT4 (nmol/L)	97.41 [78.71, 113.73]	97.11 [85.73, 108.76]	90.37 [69.16, 105.83]

**$p < 0.01$ compared with healthy control.

#$p < 0.05$, ##$p < 0.01$ compared with non-COVID-19 pneumonia patients.

The median [first quarter, third quarter] of continuous variables was used.

Alb, albumin; COVID-19, coronavirus disease 2019; non-COVID-19: non-COVID-19 pneumonia patients; TSH, thyrotropin; TT3, total triiodothyronine; TT4, total thyroxine.

TABLE 2. COMPARISON OF SERUM TSH, TT3, AND TT4 AMONG DIFFERENT CLINICAL CLASSIFICATION OF COVID-19 ACCORDING TO SEVERITY

	TSH (mIU/L)	*TT3 (nmol/L)*	*TT4 (nmol/L)*
Control ($n=54$)	1.57 [1.03, 1.97]	1.58 [1.49, 1.73]	97.11 [85.73, 108.76]
Moderate ($n=15$)	0.50 [0.22, 1.58]	1.33 [1.02, 1.53]	98.67 [85.59, 112.63]
Severe ($n=23$)	0.286 [0.13, 0.77]	0.95 [0.88, 1.12]	100.98 [72.73, 114.27]
Critical ($n=12$)	0.23 [0.085, 0.42]	0.83 [0.68, 0.96]	85.05 [78.33, 118.70]
p-value*	<0.001	<0.001	0.756
p-trend#	<0.001	<0.001	—

Moderate: moderate COVID-19; severe: severe COVID-19; critical: critical COVID-19; The median [first quarter, third quarter] of continuous variables was used.

*The *p*-value means that there is difference as compared among all the groups.

#*p*-trend means that there is a trend for the more severe the COVID-19, the lower the TSH and TT3 levels were.

TABLE 3. COMPARISON OF SERUM TSH, TT3, AND TT4 BETWEEN DIFFERENT CLINICAL CLASSIFICATION OF COVID-19 AND NON-COVID-19 PNEUMONIA PATIENTS WITH A SIMILAR DEGREE OF SEVERITY

	Moderate	p	*Severe*	p	*Critical*	p
Albumin (g/L)	43.40 [37.90, 44.90]	0.290	38.20 [35.60, 41.40]	0.462	34.40 [32.05, 37.45]	0.204
	41.40 [39.60, 43.10]		37.70 [35.20, 40.70]		33.50 [30.75, 37.35]	
TSH (mIU/L)	0.50 [0.22, 1.58]	0.067	0.286 [0.13, 0.77]	0.000	0.23 [0.085, 0.42]	0.003
	0.99 [0.70, 1.90]		1.17 [0.51, 1.93]		1.42 [0.39, 1.92]	
TT3 (nmol/L)	1.33 [1.02, 1.53]	0.281	0.95 [0.88, 1.12]	0.051	0.83 [0.68, 0.96]	0.707
	1.39 [1.29, 1.53]		1.28 [0.91, 1.42]		0.80 [0.69, 1.20]	
TT4 (nmol/L)	98.67 [85.59, 112.63]	0.787	100.98 [72.73, 114.27]	0.097	85.05 [78.33, 118.70]	0.273
	95.74 [86.09, 105.85]		85.04 [68.10, 105.57]		83.31 [59.56, 100.61]	

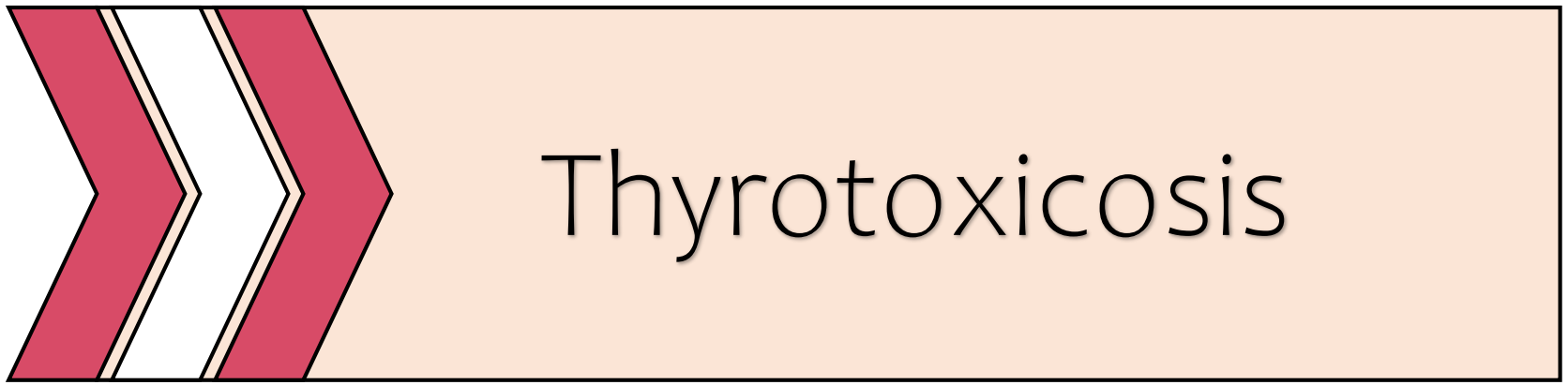
The upper line was for COVID-19, the lower line for non-COVID-19 pneumonia patients. The median [first quarter, third quarter] of continuous variables were used.

Conclusion

TSH lower than the normal range was present in 56% (28/50) of the patients with COVID-19. The levels of TSH and serum total triiodothyronine (TT3) of the patients with COVID-19 were significantly lower than those of the healthy control group and non-COVID-19 pneumonia patients. The more severe the COVID-19, the lower the TSH and TT3 levels were, with statistical significance ($p<0.001$). The degree of the decreases in TSH and TT3 levels was positively correlated with the severity of the disease.

After recovery, no significant differences in TSH, TT3, TT4, free triiodothyronine (fT3), and free thyroxine (fT4) levels were found between the COVID-19 and control groups.

The changes in serum TSH and TT3 levels may be important manifestations of the courses of COVID-19.


Thyrotoxicosis

IF:5.30

Eur J Endocrinol. 2020 Oct;183(4):381-387.

Thyrotoxicosis in patients with COVID-19: the THYRCOV study

Andrea Lania[1,2], Maria Teresa Sandri[3], Miriam Cellini[1], Marco Mirani[1], Elisabetta Lavezzi[1] and Gherardo Mazziotti[1,2] on behalf of Humanitas COVID-19 Task Force

[1]Endocrinology, Diabetology and Medical Andrology Unit, Humanitas Clinical and Research Center, IRCCS, Milan, Italy, [2]Department of Biomedical Sciences, Humanitas University, Milan, Italy, and [3]Laboratory Medicine, Humanitas Clinical and Research Center, IRCCS, Milan, Italy

- **Objective:** This study assessed thyroid function in patients affected by COVID-19, based on the hypothesis that the cytokine storm associated with COVID-19 may influence thyroid function and/or SARS-CoV-2 may directly act on thyroid cells, such as previously demonstrated for SARS-CoV-1 infection.

- **Design and methods:** This single-center study was retrospective and consisted in evaluating thyroid function tests and serum interleukin-6 (IL-6) values in 287 consecutive patients (193 males, median age: 66 years, range: 27-92) hospitalized for COVID-19 in non-intensive care units.

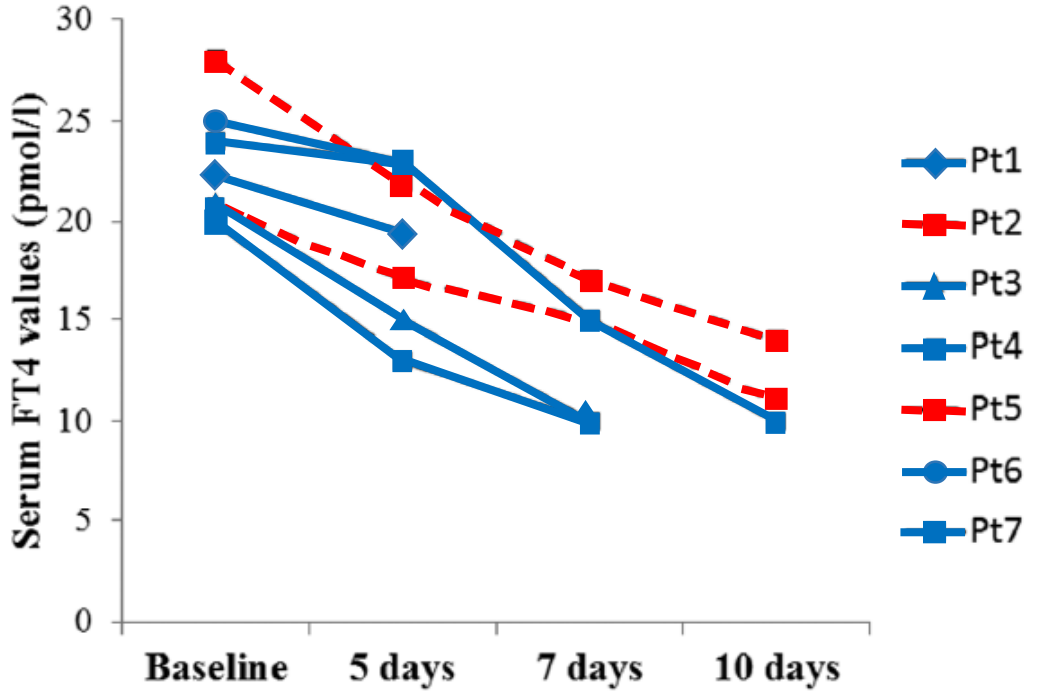
Table 1 Demographical and clinical data of COVID-19 patients at the study entry.

n	287
Age (years)	66 (27–92)
Sex (F/M)	94/193
Duration of COVID-19 (days) before hospitalization	5 (1–15)
Arterial hypertension on treatment	142 (49.5%)
Diabetes mellitus on treatment	70 (24.4%)
Dyslipidemia on treatment	63 (22.0%)
Active cancer	9 (3.1%)
Chronic obstructive pulmonary disease	35 (12.2%)
Prior coronary artery disease	41 (14.3%)
Prior stroke	20 (7.0%)
Prior venous thromboembolism	11 (3.8%)

Continuous data were presented as median and range.

Figure 1

Individual outcomes of serum-free thyroxine (FT4) values in seven patients with overt thyrotoxicosis in the course of COVID-19 who were sequentially evaluated for thyroid function. Two patients (dashed line) were treated with thiamazole, whereas the other five patients (solid line) were not treated with thyroid-targeting drugs.



- Patients with overt thyrotoxicosis showed higher serum FT4 values as compared to those with subclinical thyrotoxicosis, without significant difference in serum FT3 values .

- Serum TRAb, TgAb and TPOAb were measured in nine patients and in all of them, they resulted negative.

- Overt thyrotoxicosis was accompanied by atrial fibrillation with high heart rate in ten patients (32.3%). Moreover, five patients with overt thyrotoxicosis developed thromboembolic events (ischemic stroke in two cases, venous thromboembolism in three cases).

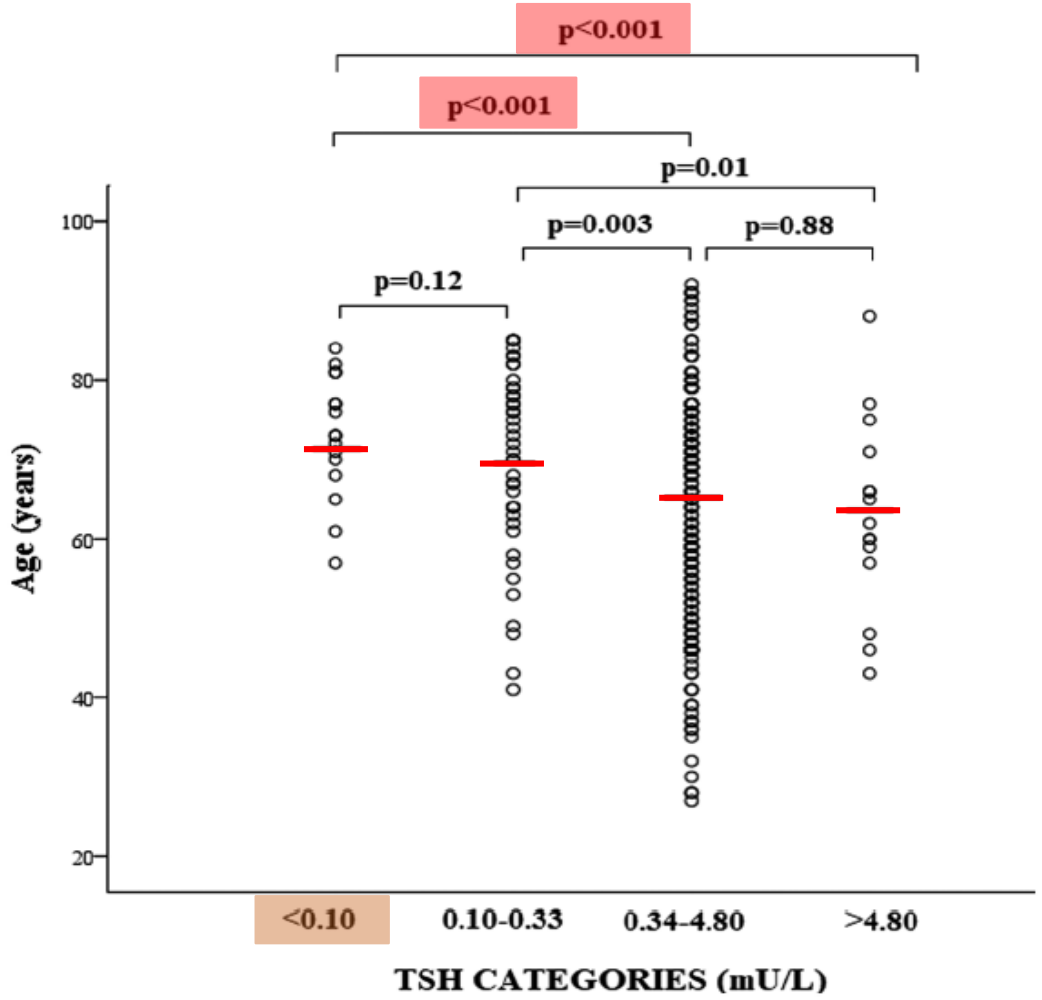


Figure 2

Scatter plot of age in COVID-19 patients stratified for serum thyrotropin (TSH) values. The solid lines identified the median values in each group. Comparisons were performed by Kruskal–Wallis' and Mann–Whitney's tests.

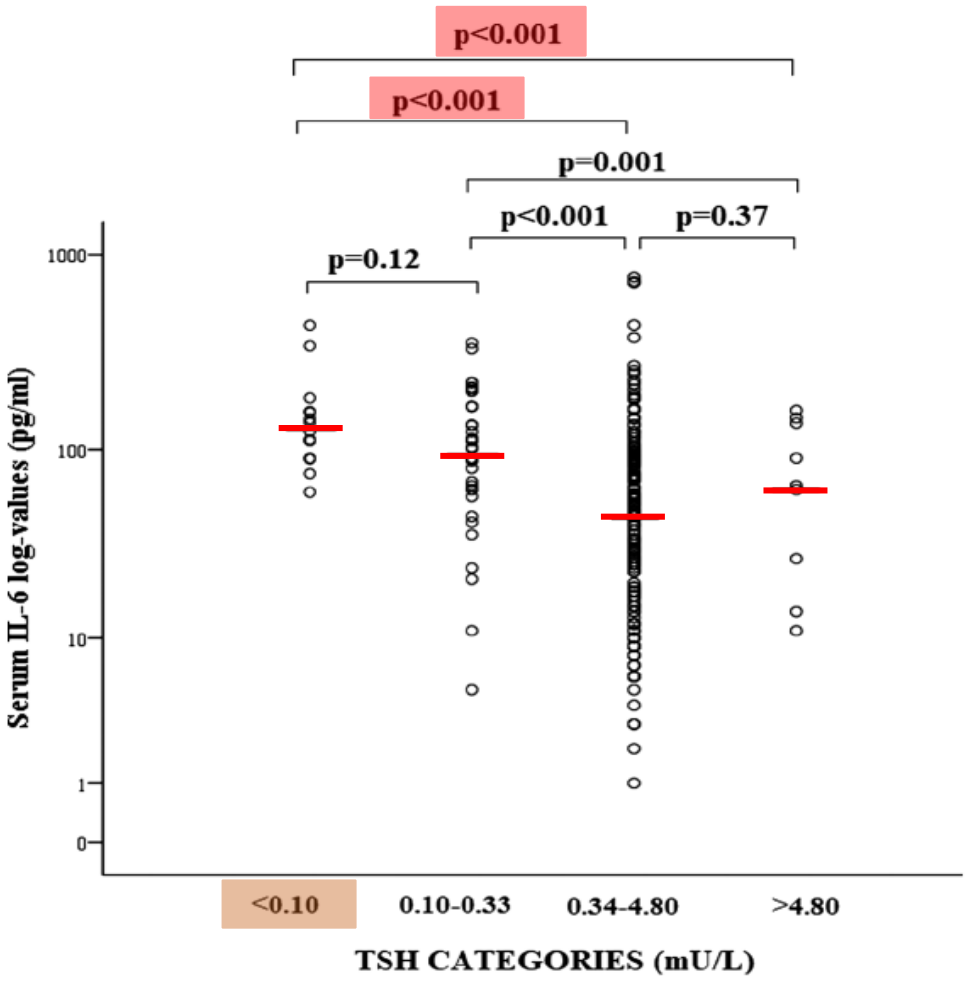


Figure 3

Scatter plot of serum interleukin-6 (IL-6) values expressed in log-scale in COVID-19 patients stratified for serum thyrotropin (TSH) values. The solid lines identified the median values in each group. Comparisons were performed by Kruskal–Wallis' and Mann–Whitney's tests.

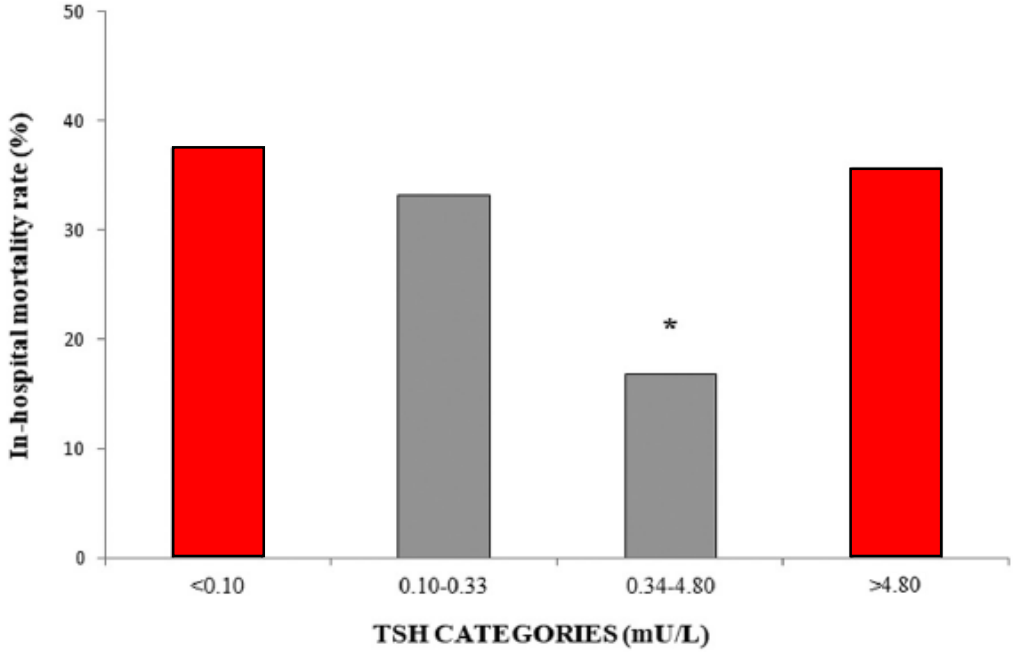


Figure 4

In-hospital mortality rate in COVID-19 patients stratified for serum thyrotropin (TSH) values. *$P < 0.05$ vs the other groups.

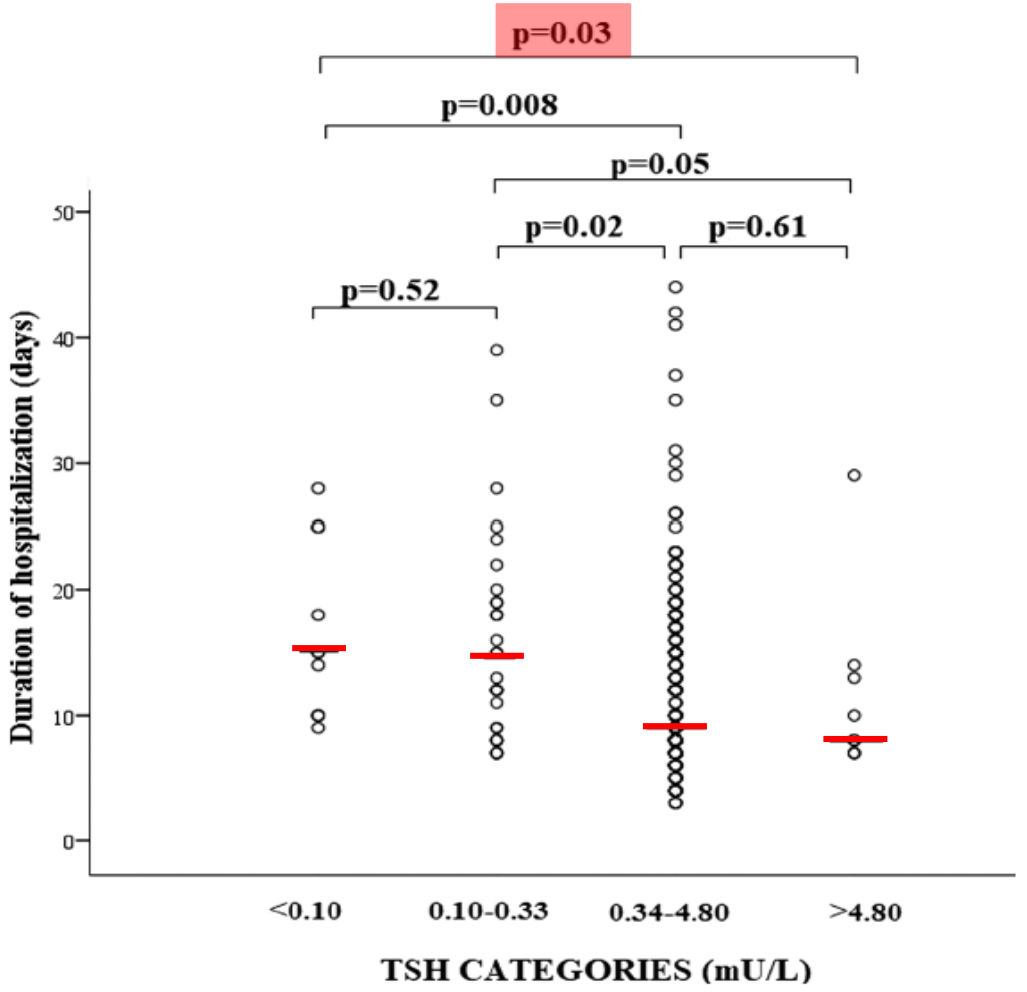


Figure 5

Scatter plot of hospitalization length in COVID-19 patients stratified for serum thyrotropin (TSH) values. The solid lines identified the median values in each group. Comparisons were performed by Kruskal–Wallis' and Mann–Whitney's tests.

In the multivariate logistic regression analysis, thyrotoxicosis resulted to be significantly associated with higher IL-6 (OR: 3.25, 95% CI: 1.97–5.36; P < 0.001) but not with the age of patients (OR: 1.03, 95% CI: 0.99–1.06; P = 0.09).

- IL-6 was shown to decrease T3 secretion possibly contributing to the normal levels of FT3 in our thyrotoxicotic patients.
- These findings suggest that COVID-19 may favor the development of thyrotoxicosis at a higher incidence than that expected in the general population.
- It is reasonable to hypothesize that thyrotoxicosis was caused by destructive thyroiditis. This hypothesis was supported by the findings that thyrotoxicosis was often mild and improved spontaneously during follow-up.
- The close relationship between thyrotoxicosis and higher serum IL-6 in our patients suggests that thyroid gland inflammation might be triggered and sustained by the cytokine storm associated with COVID-19, mimicking thyroid disorders developing during the course of immunotherapies.

limitation

In several patients, thyroid function was assessed in the course of treatment with low-molecular-weight heparin for prevention of venous and arterial thromboembolic complications of COVID-19.

One could argue that the use of heparin may have favored the elevation of FT4 in our patients as an effect of displacement of the thyroid hormone from the binding proteins.

J Clin Endocrinol Metab. 2020 Jul 1;105(7):dgaa276.

IF:5.39

CLINICAL RESEARCH ARTICLE

Subacute Thyroiditis After Sars-COV-2 Infection

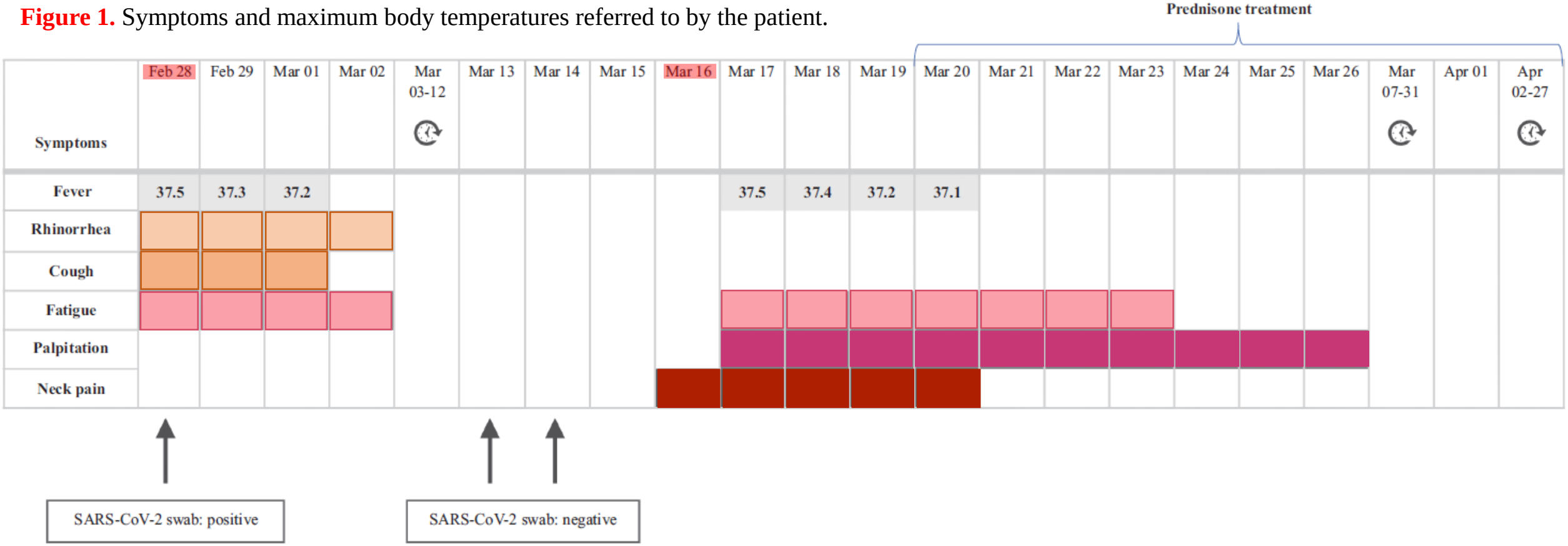
Alessandro Brancatella,[1] Debora Ricci,[1] Nicola Viola,[1] Daniele Sgrò,[1] Ferruccio Santini,[1] and Francesco Latrofa[1]

[1]Endocrinology Unit I, Department of Clinical and Experimental Medicine, University Hospital of Pisa, Pisa 56127, Italy

Objectives:

The objective of this work is to report the first case of SAT related to SARS-CoV-2 infection.

Figure 1. Symptoms and maximum body temperatures referred to by the patient.



Results: At physical examination the patient presented with a slightly increased heart rate and a painful and enlarged thyroid on palpation. At laboratory exams free thyroxine and free triiodothyronine were high, thyrotropin undetectable, and inflammatory markers and white blood cell count elevated. Bilateral and diffuse hypoechoic areas were detected at neck ultrasound. One month earlier, thyroid function and imaging both were normal. We diagnosed SAT and the patient started prednisone. Neck pain and fever recovered within 2 days and the remaining symptoms within 1 week. Thyroid function and inflammatory markers normalized in 40 days.

Table 1. Clinical laboratory results

Measure	Reference range	February 21	March 19	April 1	April 27
FT4, nmol/L	11-23	15.4	27.2	21.7	16.2
FT3, pmol/L	4.6-8.4	5.5	8.7	7.5	5.3
TSH, mIU/L	0.5-4.1	2.1	< 0.04	0.2	2.9
TgAb, IU/mL	< 30	< 30	120.2		
TPOAb, IU/mL	< 10	< 10	< 10		
TRAb, IU/mL	< 1.5		< 1.5		
Tg, µg/L			5.6		
White cell count, per L	3800-11 000		11 200	6900	6600
ESR, mm/h	0-13		90	28	2
CRP, mg/L	< 2		6.9	1.2	0.9

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FT3, free triiodothyronine; FT4, free thyroxine; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; TPOAb, thyroperoxidase antibodies; TRAb, TSH receptor antibodies; TSH, thyrotropin.

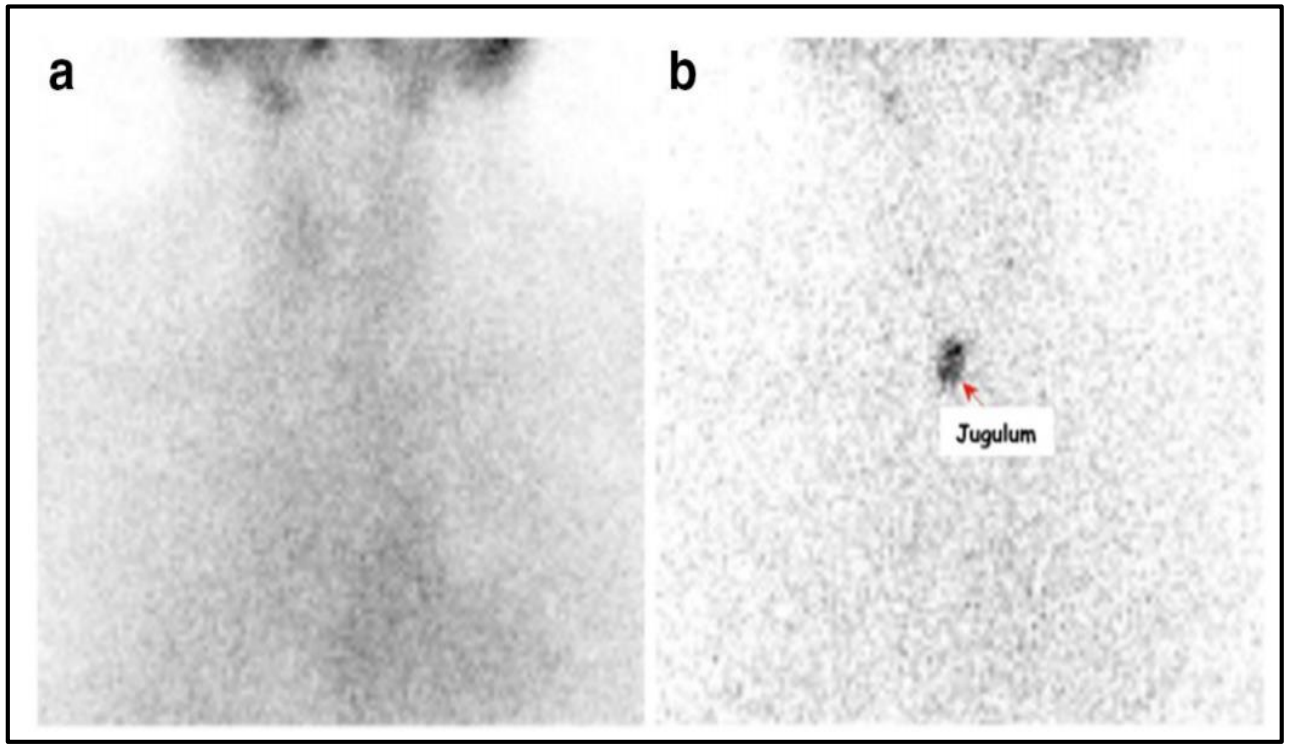


Fig. 1 ^{99m}Tc-pertechnetate scintigraphy obtained using a single-head gamma camera equipped with low-energy high-resolution parallel-hole collimator (LEHR-PAR). Panel **A**. Static image (magnification 1; matrix 256 × 256, acquisition frame 100 Kc) obtained in anterior view 10 min after radiotracer administration (111 MBq). No significant ^{99m}Tc-pertechnetate uptake in thyroid parenchyma was noted. Panel **B**. To better identify the thyroid bed, a jugular radioactive mark was used

Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. Hormones (Athens). 2020 Jul 16 : 1–3.

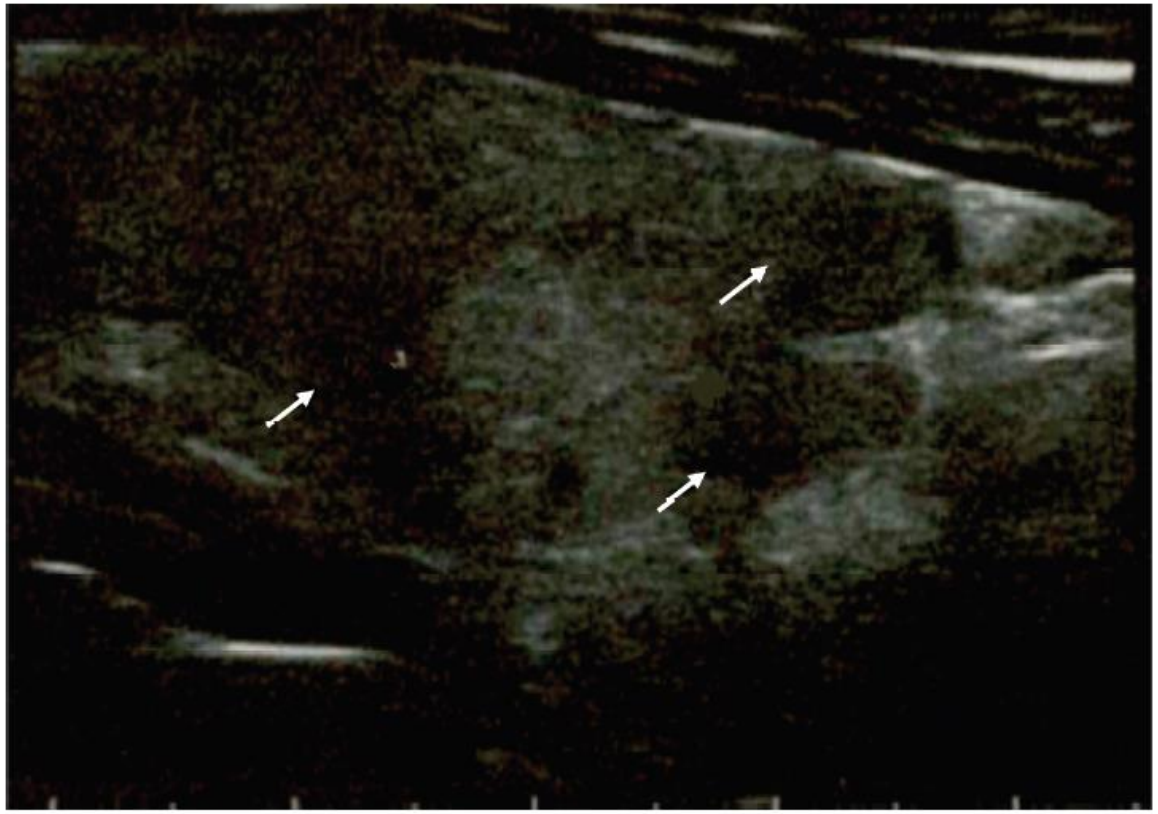


Figure 2. Thyroid ultrasound performed during the thyrotoxic phase, showing multiple hypoechoic areas (arrows).

Subacute Thyroiditis After Sars-COV-2 Infection. J Clin Endocrinol Metab. 2020 Jul 1;105(7):dgaa276.

Case Series

IF:5.39

J Clin Endocrinol Metab. 2020 Oct 1;105(10):dgaa537.

Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection?

Insights from a case series

Alessandro Brancatella[1], M.D., Debora Ricci[1], Ph.D., Daniele Cappellani[1], M.D., Nicola Viola[1], M.D., Daniele Sgrò[1], M.D., Ferruccio Santini[1], M.D., Francesco Latrofa[1], M.D.

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ORIGINAL STUDIES
THYROID FUNCTION AND DYSFUNCTION

Thyroid Function Analysis in 50 Patients with COVID-19: A Retrospective Study

Min Chen,* Weibin Zhou,* and Weiwei Xu

Case Series

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-020-01312-7

IF:3.39

LETTER

SARS-CoV-2: a potential trigger for subacute thyroiditis? Insights from a case report

S. Ippolito[1] · F. Dentali[2] · M. L. Tanda[1]

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-020-01316-3

IF:3.39

LETTER

A case of subacute thyroiditis associated with Covid-19 infection

E. Asfuroglu Kalkan[1] · I. Ates[1]

Case Series

Hormones
https://doi.org/10.1007/s42000-020-00230-w

IF:1.96

LETTER TO THE EDITOR

Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic

Rosaria Maddalena Ruggeri[1] · Alfredo Campennì[2] · Massimiliano Siracusa[2] · Giuseppe Frazzetto[3] · Damiano Gullo[3]

BMJ Case Rep. 2020 Aug 25;13(8):e237336.

New disease

IF:--

Case report

Subacute thyroiditis associated with COVID-19

Shaikh Abdul Matin Mattar ,[1] Samuel Ji Quan Koh,[1] Suresh Rama Chandran,[2] Benjamin Pei Zhi Cherng[3]

Table 1 Analysis of cases of COVID-19-related subacute thyroiditis (SAT) reported in the literature to date

Case, (ref.)	1, (35)	2, (36)	3, (36)	4, (36)	5, (36)	6, (38)	7, (39)	8, (40)	9, (41)
Sex	F	F	F	F	F	F	F	F	M
Age (yr)	18	38	29	29	46	69	41	43	34
Thyroid disease before Covid-19	no	no	no	no	no	nodules	no	no	no
Covid-19 test	swab	swab	swab, sIg	swab, sIg	swab	swab	swab	swab, sIg	swab
Covid-19 manifestations	mild	mild	mild	mild	mild	pneumonia	mild	mild	mild
Time from Covid-19 to SAT onset (days)	17	16	30	36	20	during Covid-19	during Covid-19	40	during Covid-19
SAT manifestations	typical, neck pain, fever (37.5 °C)	typical, neck pain, fever (38.5 °C), AF	typical, neck pain	typical, neck pain	typical, neck pain, fever (37.2 °C)	typical, no neck pain	typical, neck pain, fever (38.5 °C)	typical, neck pain, fever (37.5 °C)	typical, neck pain
Biochemical profile	TSH 0.004 FT4 27.2 FT3 8.7	TSH 0.1 FT4 29.3 FT3 8.0	TSH 0.01 FT4 31.8 FT3 8.9	N.A.	TSH 0.01 FT4 27.8 FT3 6.9	TSH 0.08 FT4 31.6 FT3 7.0	TSH 0.08 FT4 25.7 FT3 7.7	TSH 0.006 FT4 34.6 FT3 9.0	TSH 0.01 FT4 41.8 FT3 13.4
	TgAb+ TPOAb- TRAb-	TgAb- TPOAb- TRAb-	TgAb+ TPOAb- TRAb-		TRAb-	TgAb- TPOAb- TRAb-	TgAb- TPOAb- TRAb-	TgAb- TPOAb- TRAb-	TPOAb- TRAb-
Inflammatory markers	WBC 11.2, CRP 6.9	CRP 11.2	CRP 7.9	N.A.	CRP 8	N.A.	WBC 15.6, CRP 101	WBC 6.6, CRP 8.8	WBC 11.6, CRP 122
Resolutive therapy	prednisone	prednisone	prednisone, propanolol	ibuprofen	prednisone	prednisone	prednisolone	prednisone	prednisolone, atenolol
Thyroid function after SAT	normal	normal	hypothyroidism	hypothyroidism	normal	N.A.	N.A.	normal	normal
Relapse of Covid-19	no	no	no	no	no	swab+	N.A.	no	N.A.

COVID 19 & Graves

Case Presentation

- A 47-year-old female with a 12-year history of GD and GO relapsed on concomitantly being infected with COVID-19 in May 2020. MMI treatment with 40 mg/daily quickly stabilized her thyroid status without complications.

- The second patient was a 61-year-old female with atrial fibrillation and GD since 2004. One month after being infected with COVID-19, she was admitted to the hospital with suspected heart infarction, which was ultimately not confirmed. Florid hyperthyroidism was diagnosed and treated with MMI 10 mg/daily for 3 months, thus achieving euthyroidism.

- Two female patients, 53 and 61 years old, were also reported. The first, whose GD had remained 30 years in remission, was infected with COVID-19 in April 2020 and had a relapse of GD a month later. The second, who had no history of thyroid disease, developed GD 2 months after COVID-19 infection, her entire immunological and thyroid hormone assessment being concordant with GD. She was successfully treated with methimazole 10 mg/day.

- Generally speaking, patients with hyperthyroidism, of which GD is the most common form, and particularly those subjects being treated or with recurrent disease, are not considered to be at higher risk of contracting COVID-19.
- Patients with Graves ophthalmopathy (GO) receiving steroid medication may, due to immunosuppression, theoretically be more prone to being infected.
- Future studies monitoring patients with active moderate-to-severe GO considered for treatment with teprotumumab, a human monoclonal antibody against the insulin-like growth factor type I receptor (IGF-IR) with a low side effects profile.

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Teprotumumab for the Treatment of Active Thyroid Eye Disease

❖ BACKGROUND

Thyroid eye disease is a debilitating, disfiguring, and potentially blinding periocular condition for which no Food and Drug Administration–approved medical therapy is available. Strong evidence has implicated the insulin-like growth factor I receptor (IGF-IR) in the pathogenesis of this disease.

❖ METHODS

In a randomized, double-masked, placebo-controlled, phase 3 multicenter trial, we assigned patients with active thyroid eye disease in a 1:1 ratio to receive intravenous infusions of the IGF-IR inhibitor teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks; the last trial visit for this analysis was at week 24.

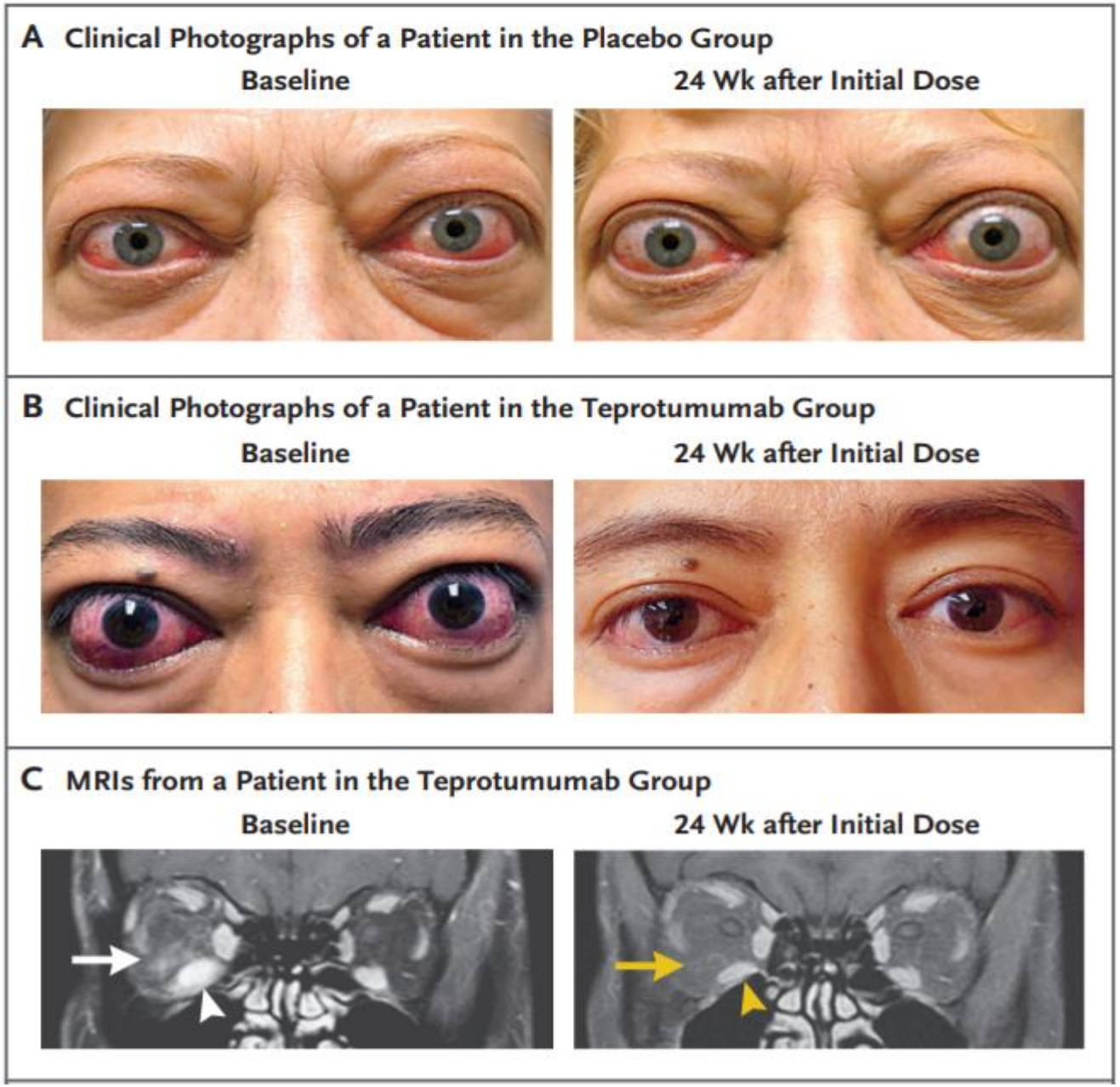
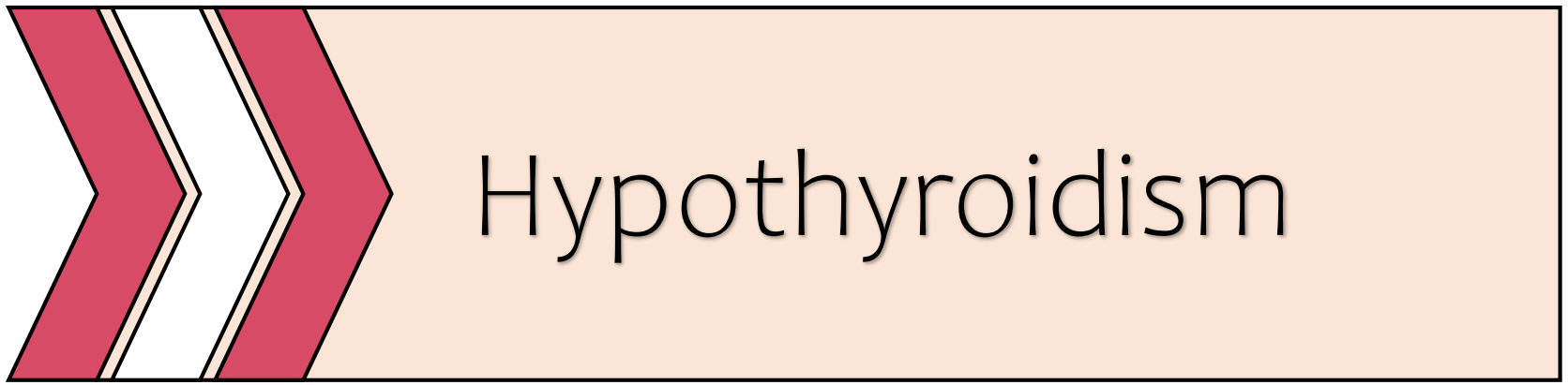


Figure 3.
Clinical Photographs and MRIs at Baseline and 24 Weeks after the Initial Dose of Placebo or Teprotumumab. Panel A shows the clinical photographs of a patient in the placebo group. At baseline, the patient had considerable proptosis (29 mm in the left eye and 27 mm in the right eye), edema, and multiple inflammatory signs (Clinical Activity Score of 7 in the left eye and 5 in the right eye). At week 24, the patient still had considerable proptosis (28 mm in the left eye and 26 mm in the right eye) and inflammatory signs (Clinical Activity Score of 5 in the left eye and 5 in the right eye). Panel B shows the clinical photographs of a patient in the teprotumumab group. At baseline, the patient had considerable proptosis (24 mm in each eye), upper and lower eyelid retraction, edema, and multiple inflammatory signs (Clinical Activity Score of 5 in each eye). At week 24, the patient had considerable reductions in both proptosis (−5 mm) and Clinical Activity Score (−4 points) in each eye.

- One concern regarding patients recovering from GD or GO might be the finding that interferon (IFN-γ),TNF-α, and IL-6 cytokines, which are involved in the pathogenesis of both diseases, could potentially have a combined synergistic action in susceptible subjects, leading to recurrence of their disease and/or exacerbation of the virus infection.
- Importantly, thyrotoxicosis left untreated can increase the risk for LVH and CHF. Hyperthyroidism elevates circulating marker of endothelial dysfunction, including IL-6, IL-12, IL-18, fibrinogen, PAI-1,vWf, and sVCAM-1, which were found to be significantly increased in patients with both overt and subclinical hyperthyroidism. This may precipitate the hypercoagulable state which characterizes COVID-19 and increase the incidence of cardiovascular complications.
- Patients receiving ATD therapy, presenting even mild-moderate neutropenia, could be at risk for a worse outcome if they contract COVID-19 since their COVID-19 symptoms may be more severe due to immune derangement, this possibly aggravating the neutropenia and resulting in cytokine storm cascade.

- Another concern is treatment options with ATD, including the titration regimen with the lowest possible dose of methimazole.
- These cases presenting GD with a temporal sequence in relation to COVID-19 infection strongly suggest that GD may be triggered by SARS-CoV-2 infection. Viral infections (yersiniosis, HIV, hepatitis C) have been cited as major environmental factors implicated in the pathogenesis of AITD.
- In addition, the hyperinflammatory state associated with severe SARS-CoV-2 infection could have triggered an immunological cascade with reactivation of GD, as has been described in other autoimmune disorders. It is of interest that whereas the hyperinflammation induced by SARS-CoV-2 is likely to be mainly mediated by Th-1 cytokines as well as IL-6, the pathogenesis of GD is apparently mediated by a Th-2 autoimmune response. This implies that the SARS-CoV-2 may trigger GD by altering the immune system in susceptible individuals.


Hypothyroidism

- In contrast to the rapidly accumulating literature regarding thyrotoxicosis and thyroiditis associated with COVID-19 infection, there are relatively few studies addressing hypothyroidism associated with this infection.

Table 1. Reports of the finding of hypothyroidism associated with COVID-19

Author, year	Type of study	Total number of patients with COVID-19	Number (%) of patients with hypothyroidism	Definition of Hypothyroidism (number overt)	Comments
Lania, 2020	Retrospective, single center	287	15(5.2%)	TSH>4.8(2)	Mortality higher in those with hypothyroidism
Daraei, 2020	Retrospective, single center	390	21(5.4%)	Not provided (not provided)	Not effect of hypothyroidism on mortality
Muller, 2020	Single center, observational	126	7(5.5%)	TSH>4.3 (not provided)	7 of 78(9%) ICU patients without COVID-19 developed hypothyroidism
Lui, 2020	Prospective, single center	191	1(0.5%)	TSH>4.8 (0)	Patient with TSH of 11 and TPO antibodies of 18,719
Tee, 2020	Case report	1	1	Not provided (1)	TSH 6.49, TPO antibodies>2,000
Dixit, 2020	Case report	1	1	TSH>4.7 (1)	Myxedemacoma, FT4 low, TPO antibodies 33 (normal<20)
Cuven, 2021	Prospective, signal center	250	4(3%)	TSH>4.2(3)	No effect of hypothyroidism on mortality

- A study of patients in Iran found that 5.4% of patients hospitalized for COVID-19 had hypothyroidism. This group of patients were mostly over 50 years of age and did not have higher mortality than the non-hypothyroid group.

- In a study of those with mild versus severe COVID-19 pneumonia, none of those hospitalized with mild pneumonia had hypothyroidism, compared with 3.2% of those with severe pneumonia (2.4% overt; 0.8% subclinical). Hypothyroidism did not appear to affect outcomes.

Non Thyroidal Illness Syndrome

frontiers in Endocrinology

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ORIGINAL RESEARCH
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Thyroid Function Abnormalities in COVID-19 Patients

Weibin Wang[1†], Xingyun Su[2†], Yongfeng Ding[2†], Weina Fan[3†], Weibin Zhou[4], Junwei Su[5], Zhendong Chen[1], Hong Zhao[5], Kaijin Xu[5], Qin Ni[5], Xiaowei Xu[5], Yunqing Qiu[5] and Lisong Teng[1*]*

Purpose: The novel coronavirus COVID-19, has caused a worldwide pandemic, impairing several human organs and systems. Whether COVID-19 affects human thyroid function remains unknown.

Methods: Eighty-four hospitalized COVID-19 patients in the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China) were retrospectively enrolled in this study, among which 22 cases had complete records of thyroid hormones. In addition, 91 other patients with pneumonia and 807 healthy subjects were included as controls.

TABLE 1 | Comparison of clinical features among COVID-19, non-COVID-19 pneumonia patients and healthy subjects.

Characteristics	COVID-19 patients (N = 84)	Non-COVID-19 pneumonia patients (N = 91)	Healthy subjects (N = 807)	*p* value	
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	COVID-19 vs. Non-COVID-19	COVID-19 vs. Healthy subjects
Mean age (yrs)	57.3 ± 14.5	60.1 ± 16.7	57.7 ± 13.0	0.472	0.782
Gender					
Male	53 (63.1%)	60 (65.9%)	474 (58.7%)	0.695	0.695
Female	31 (36.9%)	31 (34.1%)	333 (41.3%)		
Clinical classifications					
Mild and moderate	21 (25.0%)	24 (26.4%)	–	0.835	–
Severe and critical	63 (75.0%)	67 (73.6%)	–		–
Thyroid Function					
TT4 (nmol/L)	99.04 ± 25.96	82.28 ± 26.47	97.25 ± 17.13	***0.000***	0.391
TT3 (nmol/L)	1.02 ± 0.32	0.92 ± 0.38	1.59 ± 0.24	0.059	***0.000***
TSH (mIU/L)	0.62 ± 0.62	1.07 ± 0.94	1.55 ± 0.94	***0.001***	***0.000***

TT4, total thyroxine or tetraiodothyronine, normal range 62.68–150.84 nmol/L; TT3, total triiodothyronine normal range 0.89–2.44 nmol/L; TSH, thyroid-stimulating hormone, normal range 0.35–4.94 nmol/L.

p values were False Discovery Rate (FDR)-corrected. p value in bold was regarded as statistically significant.

FIGURE 1

The relationship of TT3 and TSH levels on admission.

The TT3 and TSH levels in COVID-19 patients are positively correlated ($R = 0.575$, $P < 0.001$).

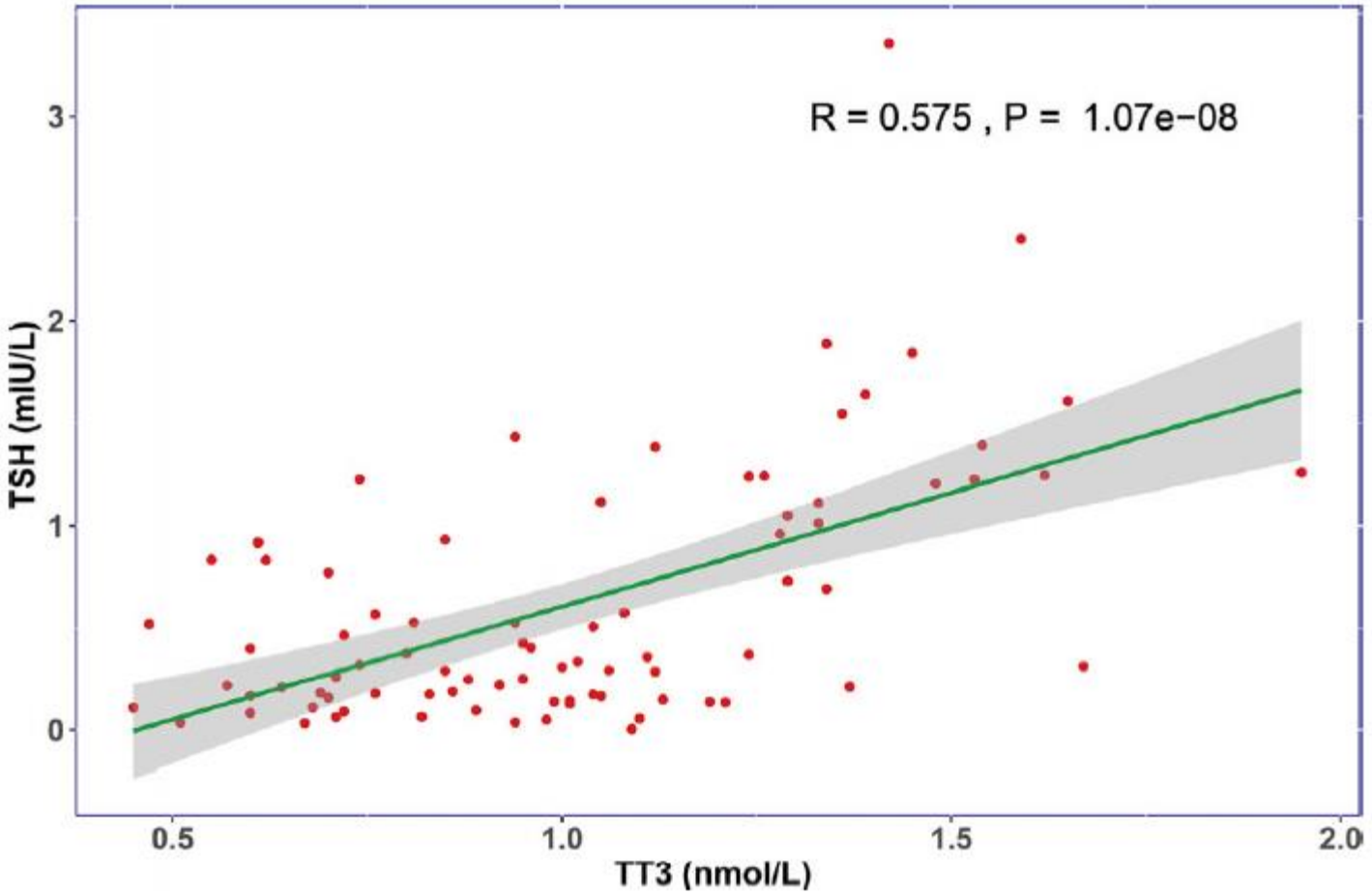

TABLE 2 **Clinical characteristics and selected laboratory abnormalities of COVID-19 patients with and without thyroid dysfunction.**

	Thyroid dysfunction* (N = 52) Mean ± SD or n (%)	Normal (N = 32) Mean ± SD or n (%)	P value
Gender			
Male	35 (66.0%)	18 (34.0%)	0.308
Female	17 (54.8%)	14 (45.2%)	
Clinical classifications on admission			
Mild and moderate	5 (23.8%)	16 (76.2%)	***0.000***
Severe and critical	47 (74.6%)	16 (25.4%)	
Viral nucleic acid cleaning time (days)	14.1 ± 9.4	10.6 ± 8.3	0.088
Thyroid auto-antibodies			
TPOAb (IU/ml, normal range 0–5.61)	23.95 ± 38.12	24.71 ± 57.08	0.945
TGAb (IU/ml, normal range 0–4.11)	35.05 ± 142.01	20.98 ± 47.31	0.613
Cytokines			
IL-6 (pg/ml; normal range 0–6.61)	59.27 ± 98.24	51.99 ± 95.17	0.748
IL-10 (pg/ml; normal range 0–2.31)	8.15 ± 10.92	6.11 ± 7.58	0.378
TNF-α (pg/ml; normal range 0–33.27)	69.14 ± 259.33	31.27 ± 38.23	0.438
IFN-γ (pg/ml; normal range 0–20.06)	32.92 ± 73.10	30.92 ± 47.39	0.895
Blood routine tests			
Leucocytes ($x10^9$/L; normal range 4–10)	8.71 ± 5.33	4.92 ± 1.64	***0.000***
Neutrophils ($x10^9$/L; normal range 2–7)	7.97 ± 5.30	3.40 ± 1.51	***0.000***
Lymphocytes ($x10^9$/L; normal range 0.8–4)	0.62 ± 0.33	1.09 ± 0.41	***0.000***
Platelets ($x10^9$/L; normal range 83–303)	189.13 ± 71.13	209.38 ± 75.93	0.221
Haemoglobin (g/L; normal range: male 131–172, female 113–151)	132.50 ± 17.14	137.16 ± 15.69	0.216
Infection-related biomarkers			
Procalcitonin (ng/L; normal range 0–0.5)	0.22 ± 0.46	0.06 ± 0.45	0.054
C reactive protein (mg/ml; normal range 0–8)	38.14 ± 37.01	15.60 ± 17.73	***0.002***
Blood biochemistry			
Globulin (g/L; normal range 20–40)	29.34 ± 5.85	27.82 ± 4.16	0.204

TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumor necrosis factor α; IFN-γ, interferon-γ.
p value in bold was regarded as statistically significant.
**Thyroid dysfunction indicates any abnormalities in the levels of TT4, TT3, or TSH.*

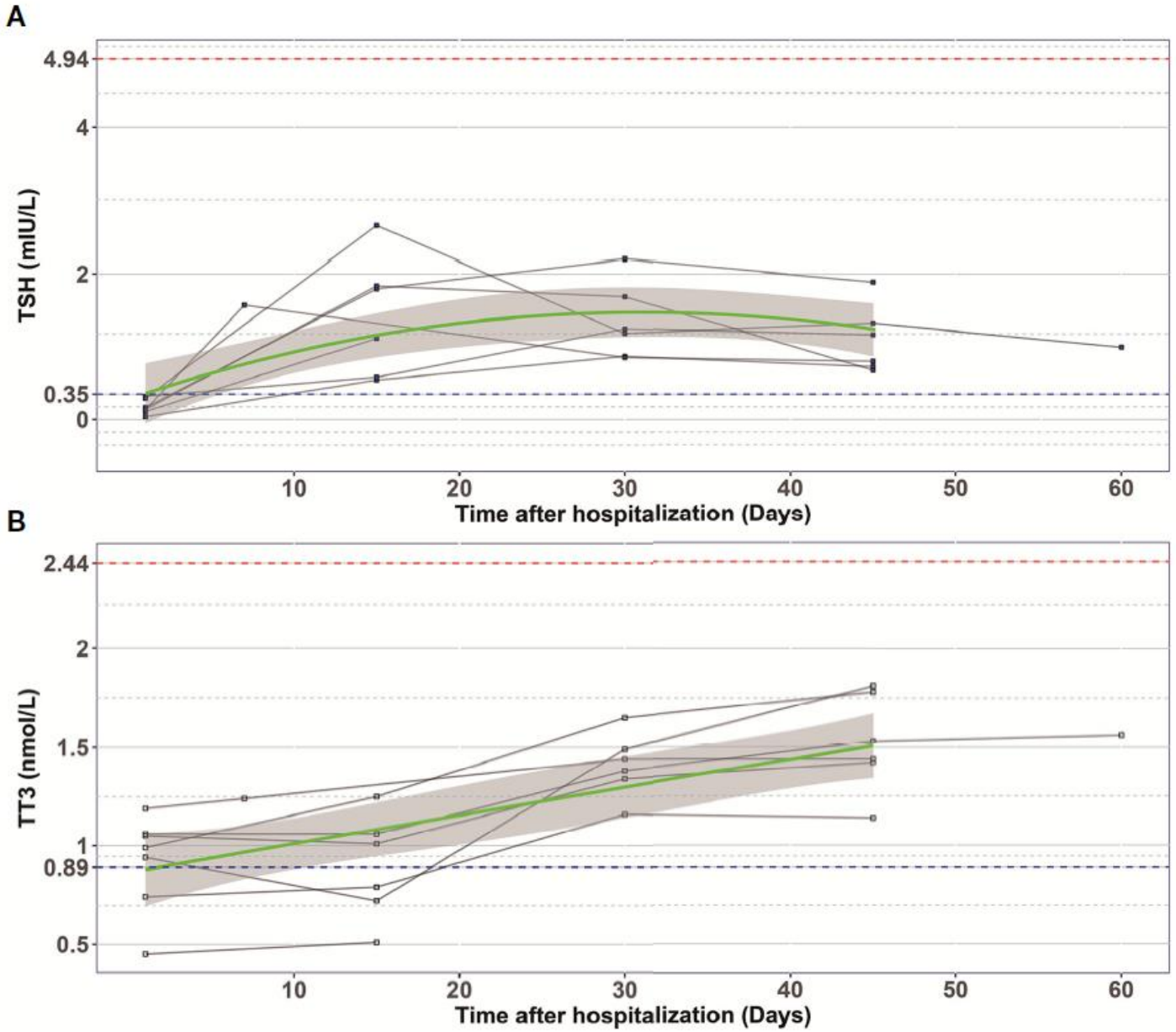

Figure 2

The changes of TSH (**A**) and TT3 (**B**) levels during hospitalization in COVID-19 patients with abnormal TSH level on admission. Every polyline represents the variation trend of TSH or TT3 level of one patient. Dashed blue lines, the lower limit of normal TSH (0.35 mIU/L) and TT3 (0.89 nmol/L) value; Dashed red lines, the upper limit of normal TSH (4.94 mIU/L) and TT3 (2.44 nmol/L) value; Green curves represent the fitting of data; Grey shaded areas, depict the 95% confidence band for the fitted curve.

- Nonthyroidal illness syndrome presents as abnormal thyroid function in serious diseases other than thyroid disorders, including infection, cancer, cardiovascular and gastrointestinal disease, burn, and trauma.
- It is well established that NTI is a consequence of an acute phase response to severe systemic illness or macronutrient restriction and usually presents as decreased plasma T3 level, or low or normal T4 and TSH levels.
- The phenomenon of decreased T3 and TSH in COVID-19 patients was consistent with NTI. In COVID-19 patients, a profile of cytokines, such as IL-2, IL- 6, IL-7, INF-g, and TNF-a, is associated with disease severity and mortality of patients.
- Our results also showed that thyroid dysfunction was associated with increased inflammation biomarkers including CRP and leucocytes, indicating inflammatory reaction played an important role in thyroid dysfunction of COVID-19. Therefore, serious infection in COVID-19 is a primary cause of NTI.

The molecular basis of the non-thyroidal illness syndrome

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(2015) 225, R67–R81

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The ‘sick euthyroid syndrome’ or ‘non-thyroidal illness syndrome’ (NTIS) occurs in a large proportion of hospitalized patients and comprises a variety of alterations in the hypothalamus–pituitary–thyroid (HPT) axis that are observed during illness. One of the hallmarks of NTIS is decreased thyroid hormone (TH) serum concentrations, often viewed as an adaptive mechanism to save energy. Downregulation of hypophysiotropic TRH neurons in the paraventricular nucleus of the hypothalamus and of TSH production in the pituitary gland points to disturbed negative feedback regulation during illness. In addition to these alterations in the central component of the HPT axis, changes in TH metabolism occur in a variety of TH target tissues during NTIS, dependent on the timing, nature and severity of the illness. Cytokines, released during illness, are known to affect a variety of genes involved in TH metabolism and are therefore considered a major determinant of NTIS.

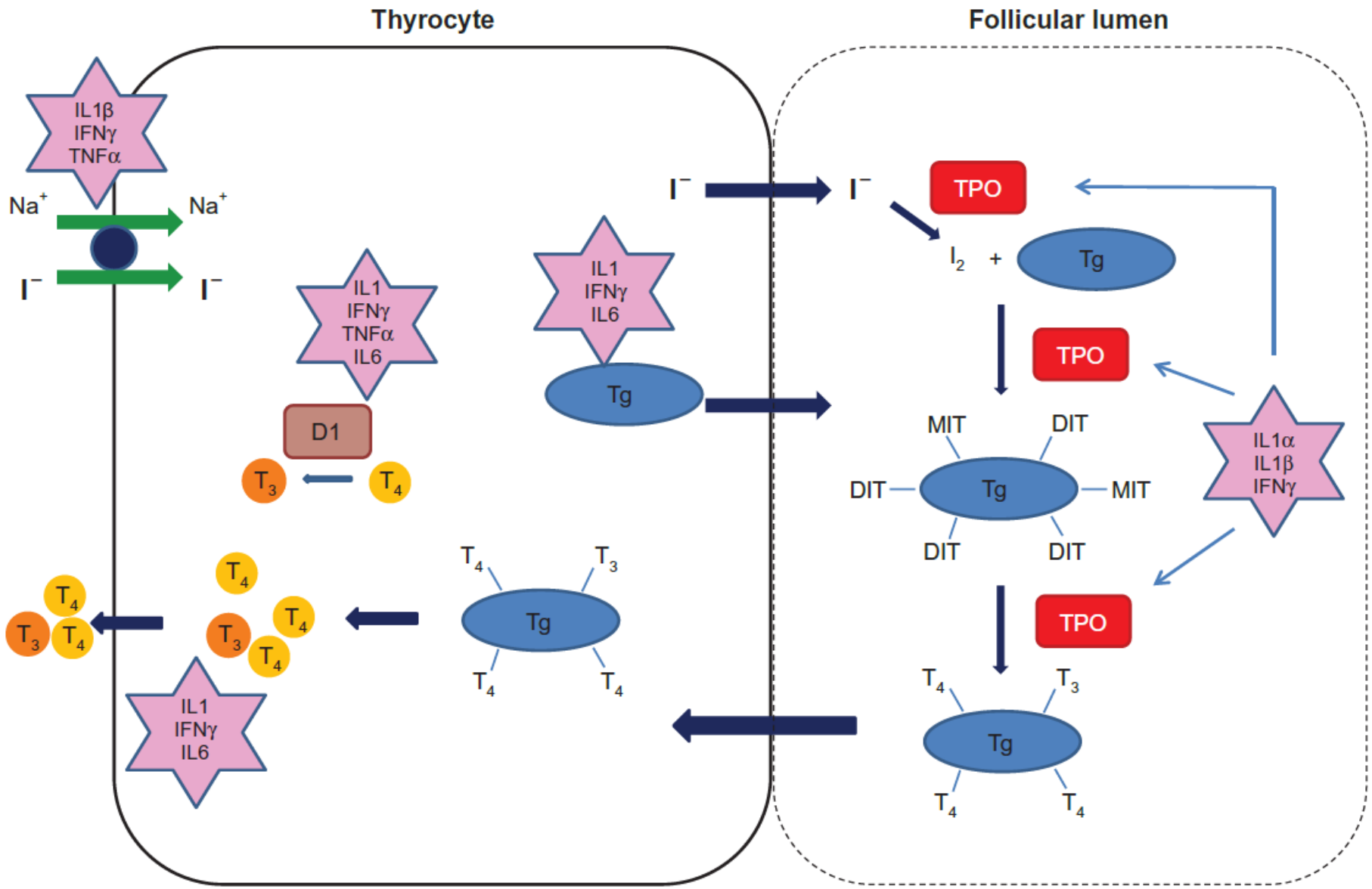


FIG 1

Cytokines have direct inhibitory effects on components of the thyroid hormone synthesis pathway in the thyrocyte. Cytokines diminish the uptake of iodide by the natrium/iodide symporter (NIS). Thyroglobulin (Tg) is synthesized within the follicular cells and is transported into the follicular lumen. The transcription of Tg is inhibited by cytokines. In the lumen, thyroid peroxidase (TPO) is a key enzyme in the formation of TH. It oxidizes I^- to I_2 and subsequently organifies the I_2 by linking it to the tyrosin residues on the Tg protein forming mono-iodotyrosine (MIT) and di-iodotyrosine (DIT). TPO subsequently combines MIT and DIT to form triiodothyronine (T_3) or two DIT residues to form thyroxine (T_4). TPO expression and function is inhibited by cytokines. After endocytosis into the follicular cell, Tg is broken down thereby releasing T_4 and T_3. Additional T_3 is formed by deiodination of T_4 by type 1 deiodinase (D1) which is also inhibited by cytokines.

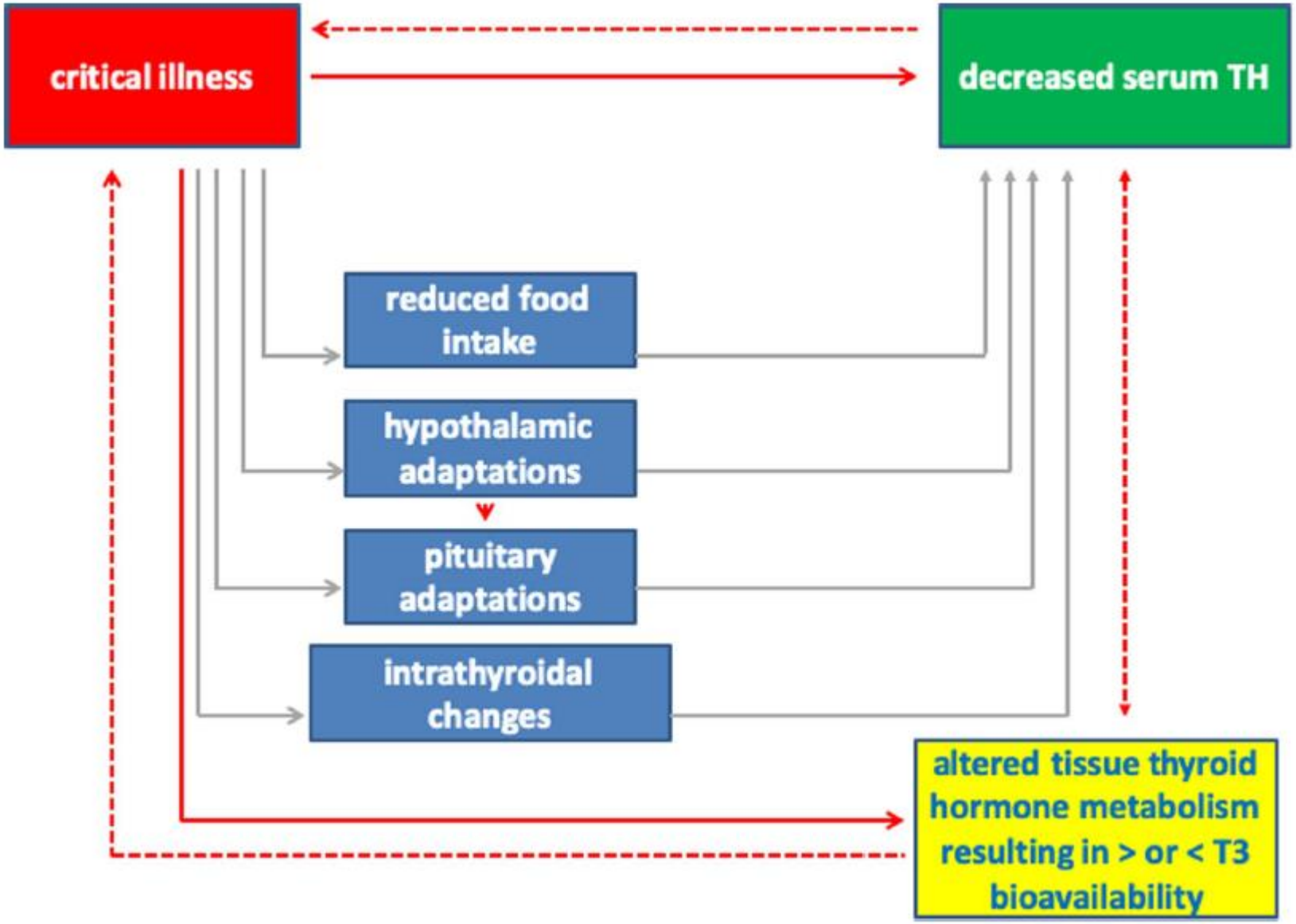
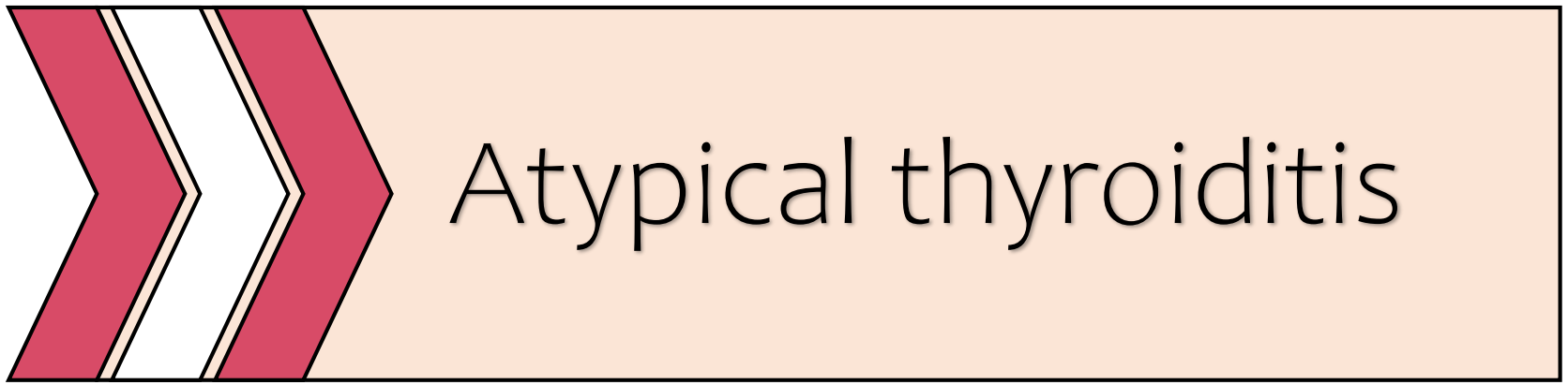


FIG 1
Schematic representation of the variety of changes occurring during critical illness. Solid lines represent a causal relation, while a dashed line represents a probable effect. The scheme is based on both experimental and human studies. The net result of altered tissue TH metabolism may be beneficial or maladaptive, dependent on disease duration and severity.


Atypical thyroiditis

Lancet Diabetes Endocrinol. 2020 Sep;8(9):739-741. doi: 10.1016/S2213-8587(20)30266-7. Epub 2020 Jul 30. **IF: 25.34**

SARS-CoV-2-related atypical thyroiditis

Ilaria Muller [1], Daniele Cannavaro [2], Davide Dazzi [3], Danila Covelli [4], Giovanna Mantovani [5], Antonio Muscatello [6], Emanuele Ferrante [4], Emanuela Orsi [4], Veronica Resi [4], Virgilio Longari [7], Marco Cuzzocrea [7], Alessandra Bandera [8], Elisa Lazzaroni [4], Alessia Dolci [4], Ferruccio Ceriotti [9], Tiziana E Re [10], Andrea Gori [8], Maura Arosio [5], Mario Salvi [4]

"Tiro-Covid-19"

STUDY DESIGN AND PATIENTS

This is a single center observational study with a longitudinal component. Consecutive patients hospitalized 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.

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.

A		HICU-19 Covid-NEG N = 101	HICU-20 Covid-POS N = 93	LICU-20 Covid-POS N = 52	ALL 3 GROUPS P	HICU-20 vs HICU-19 P	HICU-20 vs LICU-20 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**

Table 1:
As many as 13 (15%) of 85 patients in the HICU-20 group were thyrotoxic, compared with one (1%) of 78 patients in the HICU-19 group (p=0·002) and one (2%) of 41 patients in the LICU-20 group (p=0·025).

Of the 14 patients with COVID-19 and thyrotoxicosis, more were men (nine [64%] men and five [36%] women; p=0·017).

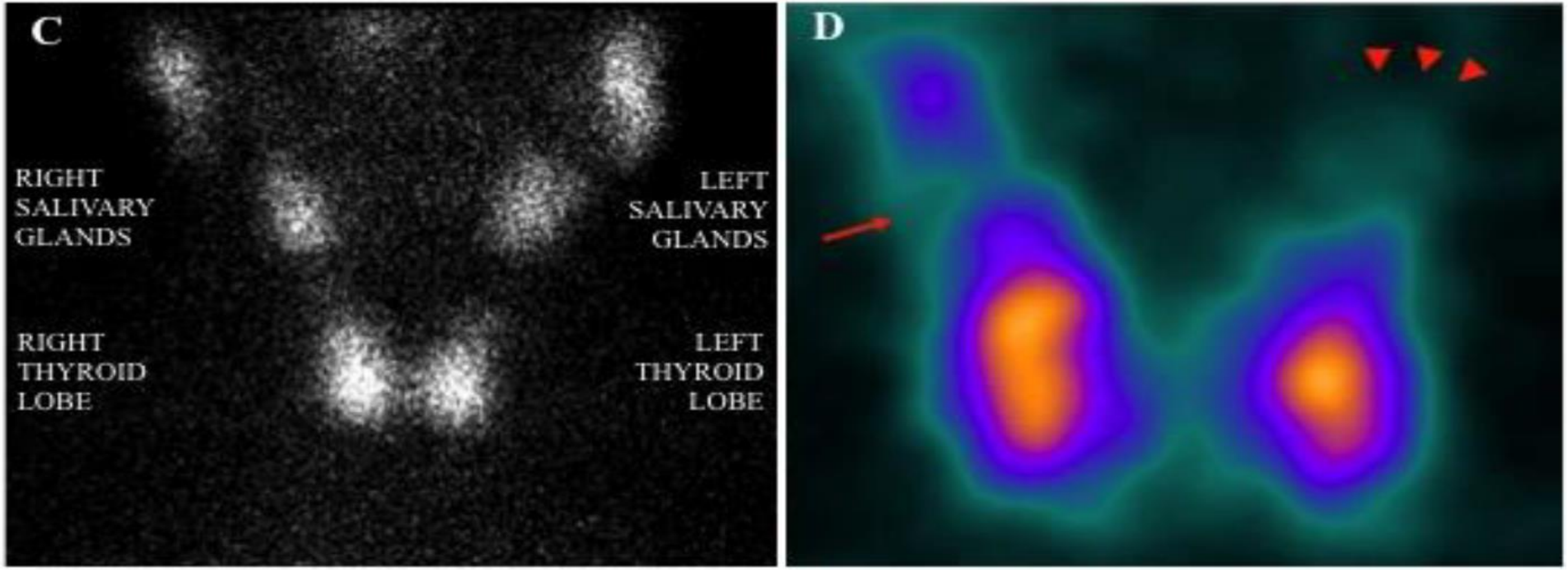


Figure 1

Panel **C**: Thyroid scintigraphy with 99m-technetium-pertechnetate (99mTc) showing only slightly increased uptake of 99mTc (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 99mTc 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.

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	THERAPY H	THERAPY A+M	THERAPY 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

To test this hypothesis, eight patients with COVID-19 and any thyroid dysfunction observed at hospital admission were followed up after a mean of 55 (SD 8) days following discharge when negative for SARS-CoV-2 (appendix p 6).

Two (25%) patients were confirmed to have hypothyroidism and had marked diffuse hypoechogenicity and heterogeneity at thyroid ultrasound, characteristic features of autoimmune thyroiditis.

The six (75%) patients with low or suppressed thyroid stimulating hormone concentrations or thyrotoxicosis at baseline had normal thyroid function and were negative for thyroid autoantibodies at follow-up; none reported neck pain ever.

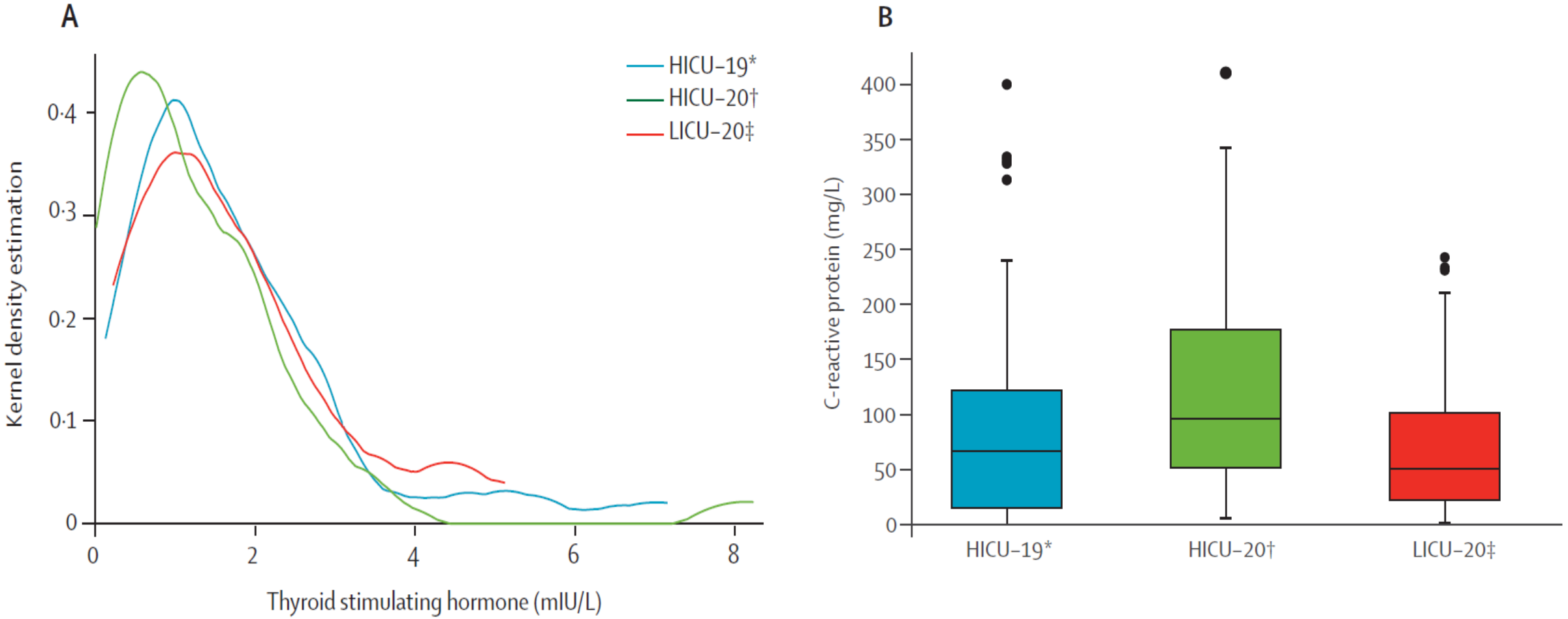


Figure 1: Distribution of serum thyroid stimulating hormone (A) and box plots of C-reactive protein (B) concentrations in patients admitted to high or low intensity of care units.

The HICU-20 group had a lower thyroid stimulating hormone concentration than the HICU-19 group (p=0·009) and the LICU-20 group (p=0·045). (B) C-reactive protein concentrations were 66 (15–121) mg/L in the HICU-19 group; 96 (51–177) mg/L in the HICU-20 group; and 52 22–103 mg/L in the LICU-20 group (p=0·0038).

patients with higher serum C-reactive protein concentrations might have a systemic spread of SARS-CoV-2 that is more likely to affect the thyroid gland.

Main Findings

- The thyroid dysfunction observed in the HICU-20 group is unlikely to be related to non-thyroidal illness syndrome only. There was no significant difference between the free T3 concentrations, the main non-thyroidal illness syndrome indicator, which were low in all groups.
- In patients with non-thyroidal illness syndrome, normal or low serum concentrations of TSH and low concentrations of T3 are usually associated with low concentrations of T4; however, in our cohort of patients with COVID-19, low concentrations of TSH and T3 were associated with normal or elevated concentrations of T4.
- It is plausible that our patients might have had a combination of thyrotoxicosis and non-thyroidal illness syndrome, described as thyroxine thyrotoxicosis.

Main Findings

- Our work suggests that a substantial proportion of patients with COVID-19, requiring high intensity of care, present with thyrotoxicosis and low serum TSH concentrations, possibly as a consequence of SAT induced by SARS-CoV-2, in an underlying setting of NTI.
- These patients also did not complain of neck pain (consistent with silent thyroiditis), did not have leucocytosis, but did have lymphopenia, as observed with COVID-19 infection.
- In SARS-CoV-2 related thyroiditis, giant cells might not form because of lymphopenia and thyroid cells might be damaged by apoptosis, as observed with severe acute respiratory syndrome coronavirus (SARS-CoV).
- we suggest routine assessment of thyroid function in patients with COVID-19 requiring high intensity care, because they frequently present with thyrotoxicosis due to a form of subacute thyroiditis related to SARS-CoV-2.

Thyroid Cancer Patients in the Time of COVID-19

Multidisciplinary Team

Virtual Tumor Boards

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Head & Neck

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SPECIAL ISSUE

WILEY

Thyroid surgery during COVID-19 pandemic: Principles and philosophies

Ashok R. Shaha MD

- As a matter of fact, the ATA endorsed observation as a definitive approach in proven microcarcinomas.
- If we use the analogy of management of thyroid cancer during pregnancy and delaying the treatment by 9 to 10 months, it would be the same philosophy of managing these patients during the COVID-19 pandemic.

❖ Anaplastic thyroid cancer

- Patients with rapidly growing thyroid tumors with proven anaplastic thyroid cancer will obviously require emergent management. The decision regarding surgical intervention should be made based on the extent of the disease and cross-sectional imaging.
- If the tumor appears to be unresectable there is no reason to bring these patients to the operating room. The definitive diagnosis could easily be made with ultrasound guided core biopsy

❖ Medullary thyroid cancer

- Appropriate evaluation of extent of the disease with calcitonin, CEA, ultrasound and cross-sectional imaging is very important before consideration of timely surgical intervention. If the disease appears to be limited and calcitonin levels are not high (<400) patients can be monitored for a few months without surgical intervention hoping for COVID-19 peak to settle??

❖ **Low and intermediate risk in differentiated thyroid carcinomas**

- These patients can wait for surgery for a period of time (**3-6 months**) until we have a better handle on COVID-19, and they are not a risk to the health care workers. If the patients need extended period of observation, a repeat imaging with ultrasound in 3 to 4 months will encourage the patients to delay the surgery further.

❖ **Microcarcinomas**

- As reported by a large series of patients, these patients with microcarcinomas can definitely be observed.
- Most of these patients can be encouraged not only to delay the surgery but to remain under active surveillance or deferred intervention. Again, appropriate ultrasound will define the exact location of the disease and the need for active intervention.

❖ **Recurrent thyroid carcinoma**

- The majority of the recurrences especially in the central compartment nodes or lateral neck nodes are essentially the persistent diseases. They could be observed for an extended period of time with repeat imaging studies in 4 to 6 months. Alternate treatment choices such as **alcohol injection** and **radio frequency ablation** may be considered.

❖ **Indeterminate thyroid nodules**

- Most of these patients will be in the group of Bethesda III and IV categories. These patients can be easily monitored and if the tumors are small, could be monitored for a period of time before active surgical intervention.

❖ **Patients with large primary tumors and bulky nodal disease**

- The history of the presence of tumor and the duration of the nodal metastasis would be quite helpful to project the best timing of surgery in these patients. Again, appropriate cross-sectional imaging and approximation of the tumor to the vital structures is critical in making the best decision regarding appropriate timing of surgery in these patients.

❖ **Large goiters**

- The majority of the large goiters have generally been there for a long period of time and surgery could be easily avoided even with tracheal deviation and mild compression unless there is rapid progression, major compression symptoms, or impending acute airway issues.

❖ **Benign thyroid conditions**

- Benign thyroid nodules, Hashimoto's thyroiditis, or Graves' disease could be managed appropriately as before and probably may not be in-person consultation. The majority of these patients can be easily consulted on telephone, Skype, or Facetime, which will give them a sense of confidence and make them feel that the treating physician is actively involved in their care and follow-up.

IF: 5.30

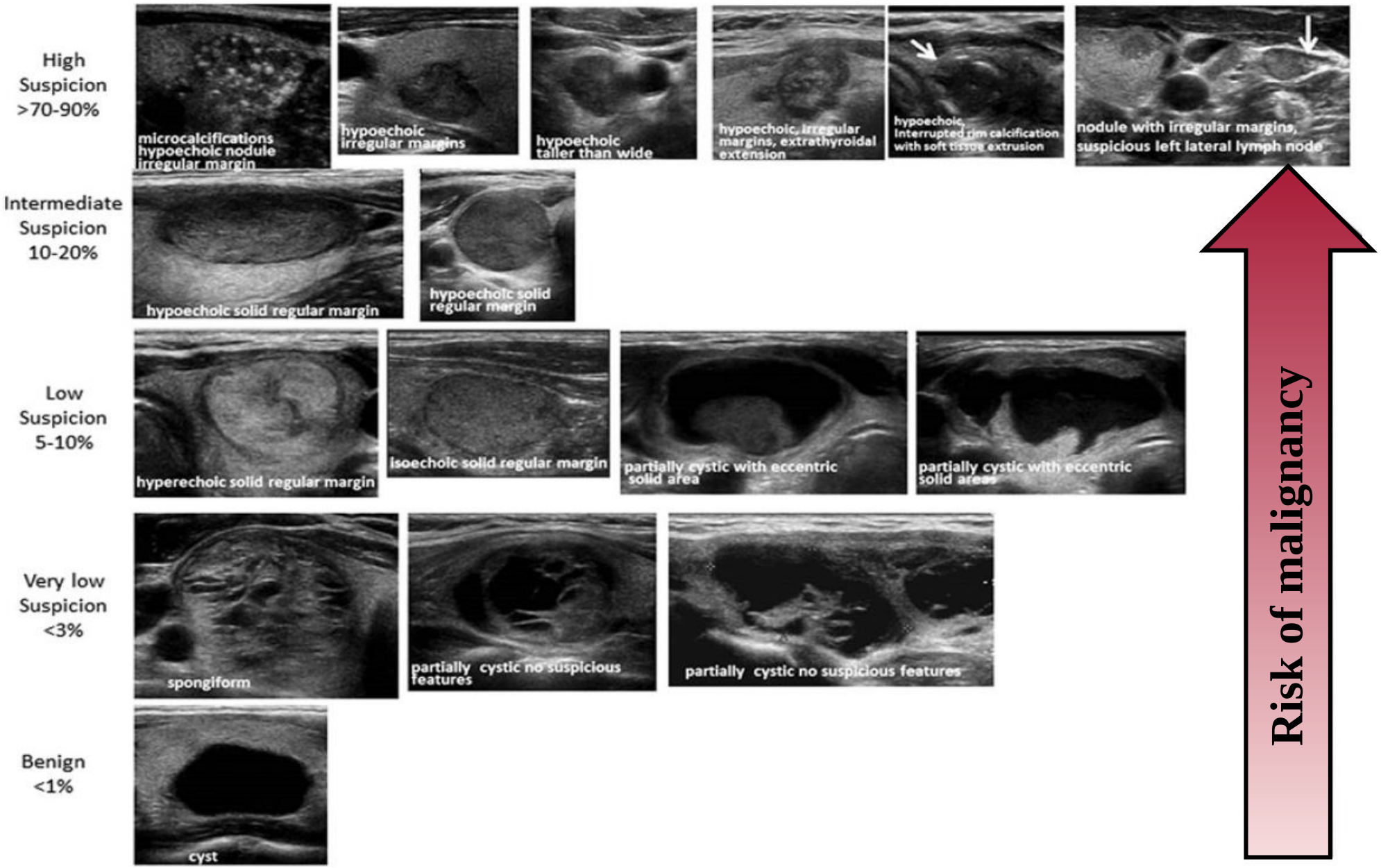
Thyroid. 2016 Jan;26(1):1-133.

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer

Bryan R. Haugen,[1,*] Erik K. Alexander,[2] Keith C. Bible,[3] Gerard M. Doherty,[4] Susan J. Mandel,[5] Yuri E. Nikiforov,[6] Furio Pacini,[7] Gregory W. Randolph,[8] Anna M. Sawka,[9] Martin Schlumberger,[10] Kathryn G. Schuff,[11] Steven I. Sherman,[12] Julie Ann Sosa,[13] David L. Steward,[14] R. Michael Tuttle,[15] and Leonard Wartofsky[16]

FIG. 2.
ATA nodule sonographic patterns and risk of malignancy.



2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016 Jan;26(1):1-133.

TABLE 6. SONOGRAPHIC PATTERNS, ESTIMATED RISK OF MALIGNANCY, AND FINE-NEEDLE ASPIRATION GUIDANCE FOR THYROID NODULES

Sonographic pattern	*US features*	*Estimated risk of malignancy, %*	*FNA size cutoff (largest dimension)*
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE	>70–90[a]	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, ETE, or taller than wide shape	10–20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate, or high suspicion patterns	<3	Consider FNA at ≥2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	<1	No biopsy[b]

US-guided FNA is recommended for cervical lymph nodes that are sonographically suspicious for thyroid cancer (see Table 7).
[a]The estimate is derived from high volume centers, the overall risk of malignancy may be lower given the interobserver variability in sonography.
[b]Aspiration of the cyst may be considered for symptomatic or cosmetic drainage.
ETE, extrathyroidal extension.

TABLE 11. ATA 2009 RISK STRATIFICATION SYSTEM WITH PROPOSED MODIFICATIONS

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)[a] Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF*^{V600E} mutated (if known)[a]
ATA intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension[a] Multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutated (if known)[a]
ATA high risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

[a]Proposed modifications, not present in the original 2009 initial risk stratification system. See sections [B19]–[B23] and Recommendation 48B.

TABLE 14. CHARACTERISTICS ACCORDING TO THE AMERICAN THYROID ASSOCIATION RISK STRATIFICATION SYSTEM AND AJCC/TNM STAGING SYSTEM THAT MAY IMPACT POSTOPERATIVE RADIOIODINE DECISION-MAKING

ATA risk Staging (TNM)	*Description*	*Body of evidence suggests RAI improves disease-specific survival?*	*Body of evidence suggests RAI improves disease-free survival?*	*Postsurgical RAI indicated?*
ATA low risk T1a N0,Nx M0,Mx	Tumor size ≤1 cm (uni-or multi-focal)	No	No	No
ATA low risk T1b,T2 N0, Nx M0,Mx	Tumor size >1–4 cm	No	Conflicting observational data	Not routine[b]—May be considered for patients with aggressive histology or vascular invasion (ATA intermediate risk).
ATA low to intermediate risk T3 N0,Nx M0,Mx	Tumor size >4 cm	Conflicting data	Conflicting observational data	Consider[b]—Need to consider presence of other adverse features. Advancing age may favor RAI use in some cases, but specific age and tumor size cutoffs subject to some uncertainty.[a]
ATA low to intermediate risk T3 N0,Nx M0,Mx	Microscopic ETE, any tumor size	No	Conflicting observational data	Consider[b]—Generally favored based on risk of recurrent disease. Smaller tumors with microscopic ETE may not require RAI.

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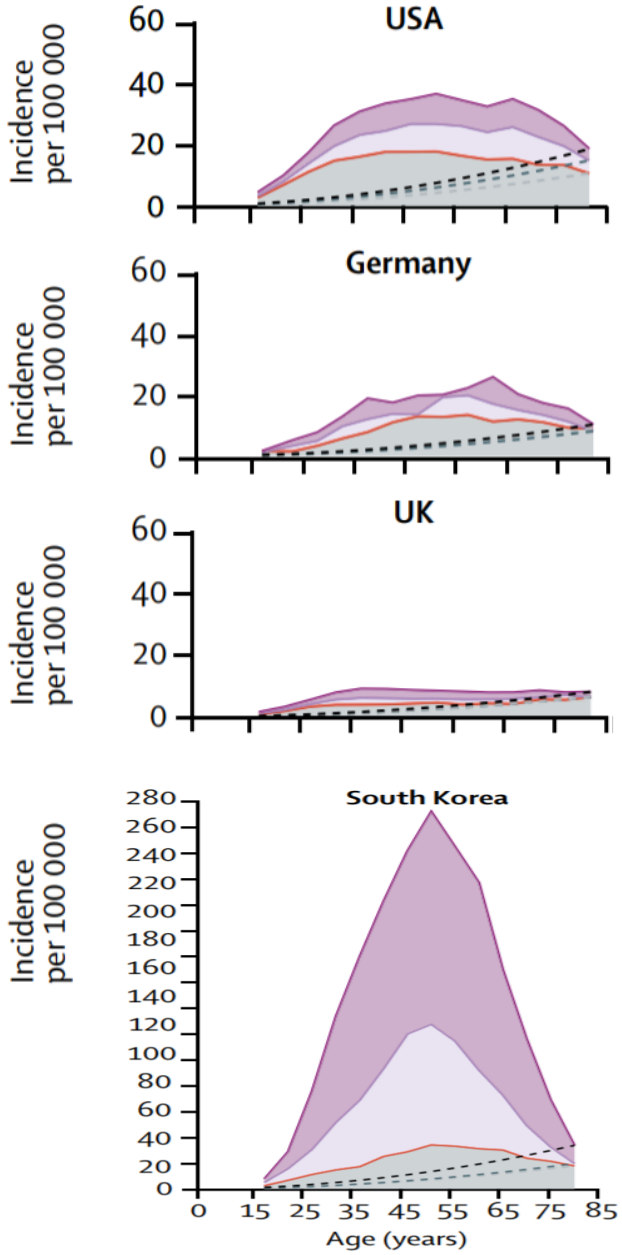
Global trends in thyroid cancer incidence and the impact of overdiagnosis

Mengmeng Li [1], Luigino Dal Maso [2], Salvatore Vaccarella [3]

- In recent decades, the incidence of thyroid cancer in several affluent countries has markedly increased, although mortality from thyroid cancer has remained relatively low and stable or has steadily declined in these and other countries.
- This increase in incidence has predominantly been a reflection of the growing scrutiny of the thyroid gland with ultrasonography and other diagnostic techniques.
- Overdiagnosis is the detection and histological confirmation of a disease that would have otherwise not been diagnosed in a person's lifetime had testing not been done.
- To estimate the effects of overdiagnosis, we identified a so-called historical age-specific curve of symptomatic thyroid cancer incidence before the introduction of ultrasonography, and attributed the progressive departure from the historical pattern (ie, towards an inverted U-shape curve) to the intense search for thyroid nodules in middle-aged individuals that seldom lead to death.

Figure
Observed versus expected changes in the age-specific incidence of thyroid cancer in **women** between 1998 and 2012



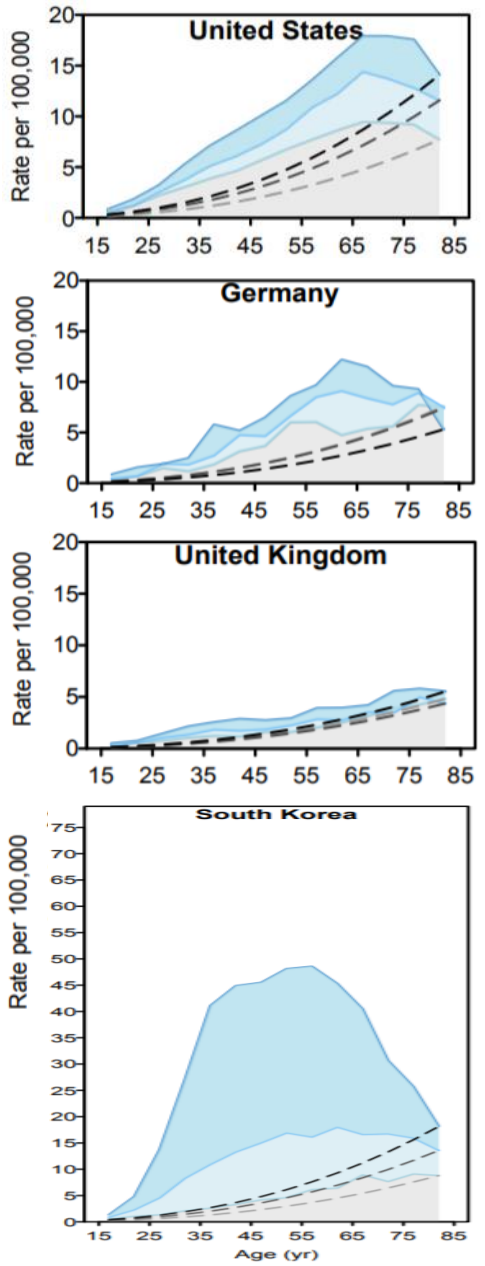


Figure
Observed versus expected changes in age-specific incidence rates of thyroid cancer from 1998 to 2012, in **men**.

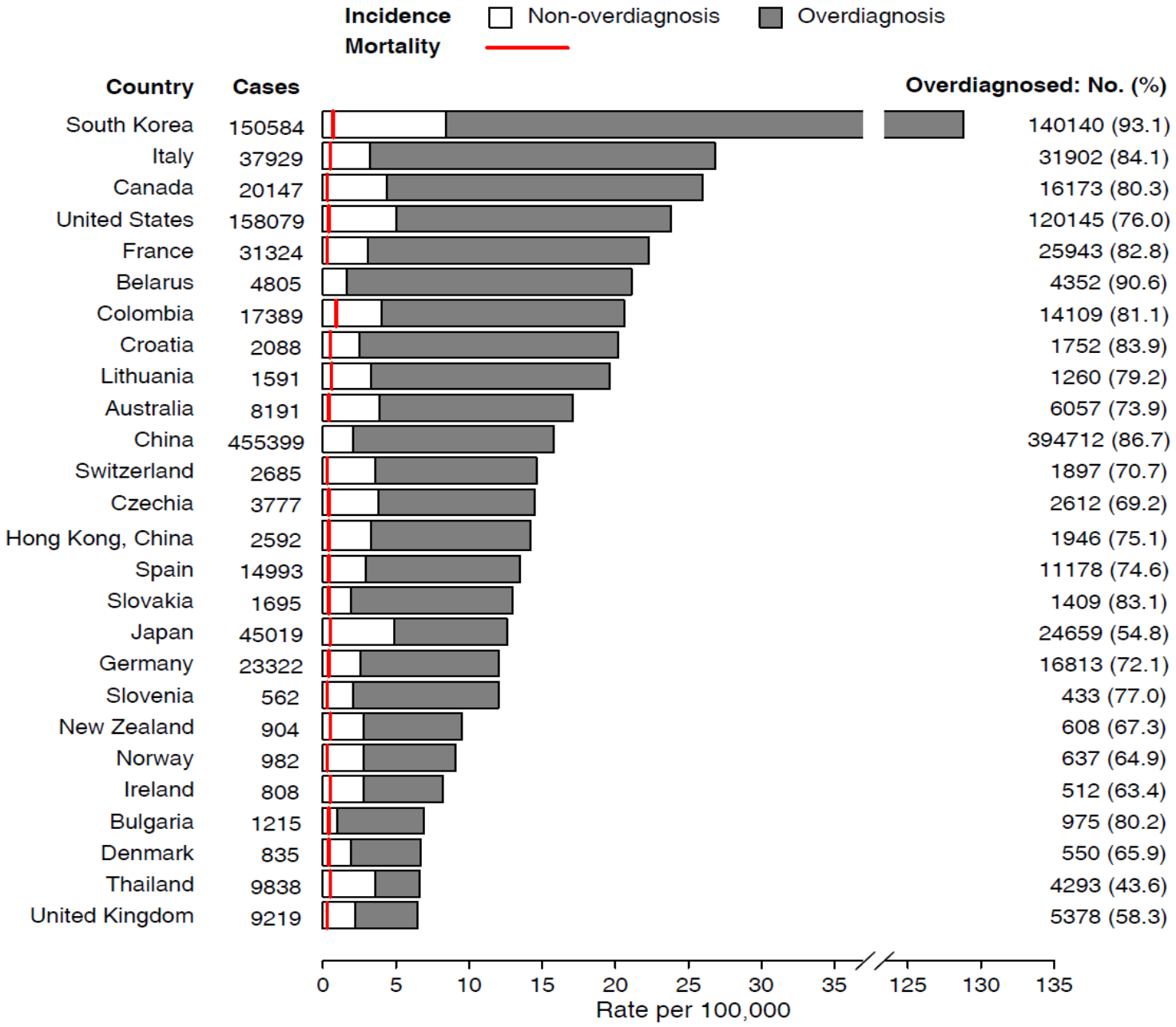


Figure S2:

Age-standardized rates (ASRs, world standard population) of thyroid cancer incidence, with number of cases and proportions attributable to overdiagnosis, and ASRs of thyroid cancer mortality, in women, 2008-2012.

The white and grey bars represent the ASRs of thyroid cancer incidence non overdiagnosed and overdiagnosed, respectively; the red lines denote the observed ASRs of thyroid cancer mortality. Note: agestandardized mortality rates of thyroid cancer were calculated by using data derived from the World Health Organization mortality database (available at https://www.who.int/healthinfo/mortality_data/en/, accessed date 22/05/2019). Mortality data were not available for Belarus and China.

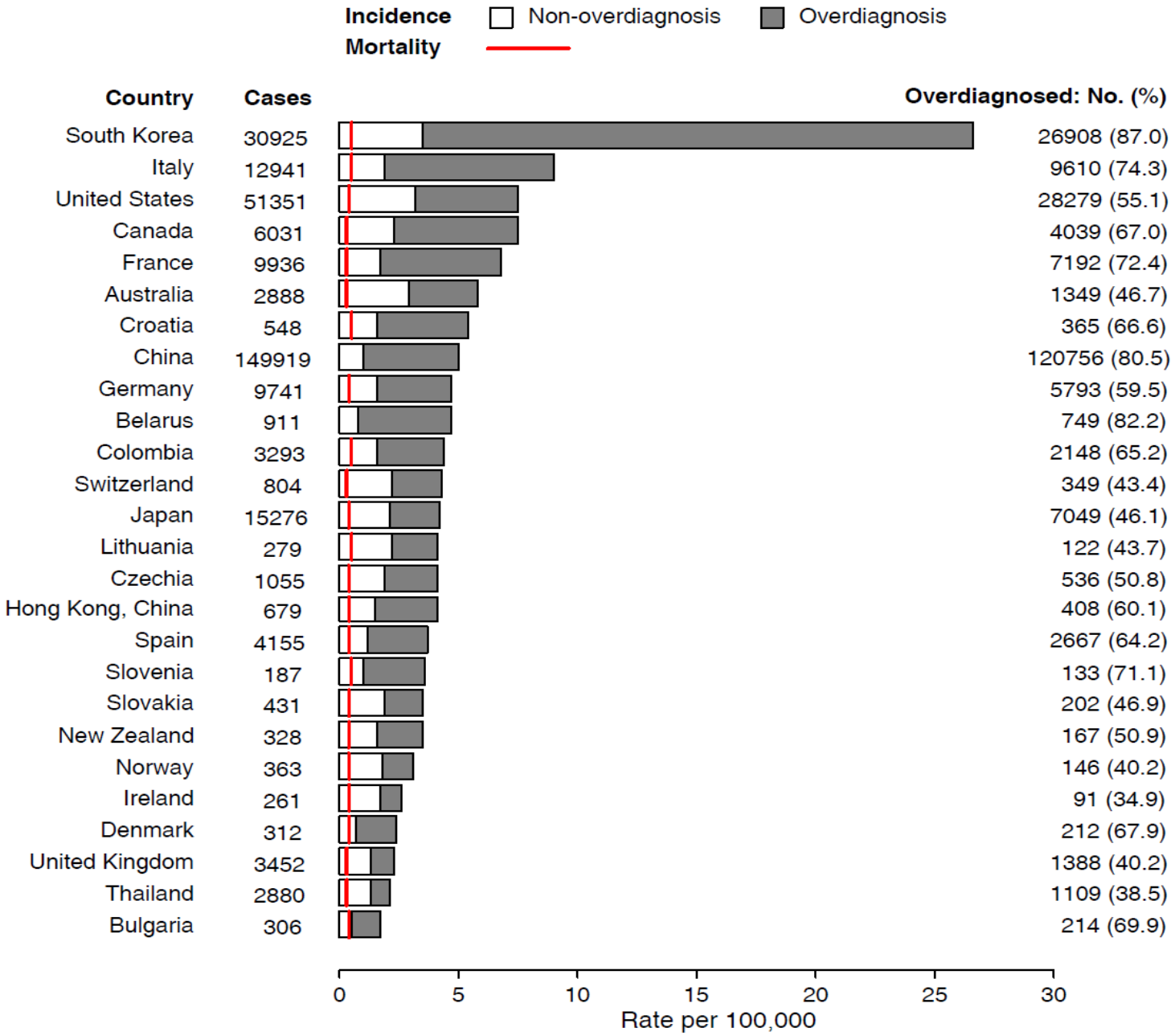


Figure S3:

Age-standardized rates (ASRs, world standard population) of thyroid cancer incidence, with number of cases and proportions attributable to overdiagnosis, and ASRs of thyroid cancer mortality, in men, 2008-2012.

The white and grey bars represent the ASRs of thyroid cancer incidence non-overdiagnosed and overdiagnosed, respectively; the red lines denote the observed ASRs of thyroid cancer mortality. Note: agestandardized mortality rates of thyroid cancer were calculated by using data derived from the World Health Organization mortality database (available at https://www.who.int/healthinfo/mortality_data/en/, accessed date 22/05/2019). Mortality data were not available for Belarus and China.

- The increase in incidence differed across countries, but was always more marked among middle-aged women (ie, those aged 35–64 years), leading to a progressive transformation of the age-specific curves towards an inverted U-shape.
- Scrutiny of the thyroid gland is sometimes commonly done and not regulated, particularly in settings where health-care services are predominantly private and market-based, such as in many middle-income countries undergoing an economic transition.
- We found that overdiagnosis was more common in women than in men, reflecting the systematic differences in incidence between sexes (a female-to-male ratio of approximately 3:1) found in all countries analysed. Mortality was similarly low in both women and men (<1 death per 100 000 individuals), and the prevalence of thyroid cancer identified from autopsies is also similar between men and women.
- Overdiagnosis could turn healthy people into patients, and expose them to unnecessary harms and lifelong treatments.
- Most individuals diagnosed with thyroid cancer undergo a total thyroidectomy and other treatments (eg, radiotherapy and neck lymph node dissection), and a non-negligible proportion of these individuals also have post-surgery complications.

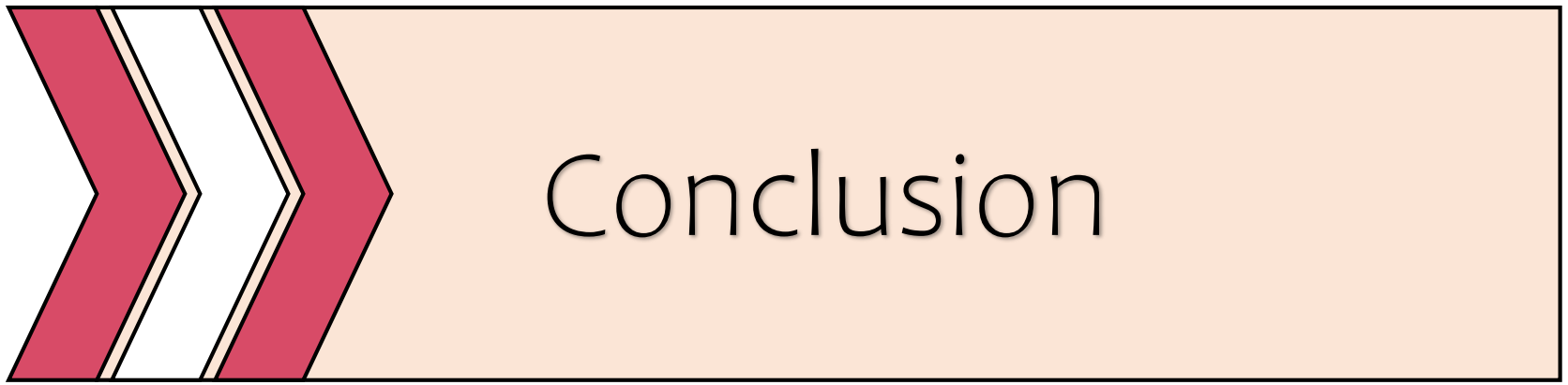

Conclusion

Table 1 Clinical consequences of SARS-CoV-2 infection and pandemic-related management challenges based on background thyroid conditions

Background	Clinical consequences	Management challenges and solutions
No thyroid complaints	Subacute thyroiditis (reversible condition after glucocorticoid treatment)	Recurrent thyroid function checking until euthyroidism has been restored Telemedicine service for data collection and medical prescriptions
Thyroid autoimmunity per se	Possible exacerbation or recurrence due to SARS-CoV-2 infection	Timely update of thyroid function in case of symptoms of new-onset or recurrent hyperthyroidism, especially in home self-isolated patients Telemedicine service for data collection and medical prescriptions
Hypothyroidism per se	Nor additive risks of contracting the infection neither possible progression of COVID-19	Follow-up through telemedicine Levothyroxine can be assumed safely
Uncontrolled hypothyroidism	Higher levels of systemic inflammation and oxidative stress, hypocoagulative imbalance	Timely recognition in both hospitalized and home self-isolated patients Levothyroxine should be started to restore euthyroidism promptly Posology and route of administration (i.e., liquid formulations through a feeding tube; rectal) of levothyroxine according to underlying clinical conditions
Hyperthyroidism per se	Nor additive risks of contracting the infection neither possible progression of COVID-19	Follow-up through telemedicine Thionamides as the first choice. A "block and replace" strategy may reduce frequent thyroid function monitoring or medical consultations Fever or pharyngodynia may be acute manifestations of both SARS CoV-2 infection and agranulocytosis in patients on thionamides Concomitant administration of remdesivir and thionamides may increase acute liver toxicity risk

Table 1 Clinical consequences of SARS-CoV-2 infection and pandemic-related management challenges based on background thyroid conditions

Background	Clinical consequences	Management challenges and solutions
Uncontrolled hyperthyroidism	Higher background inflammation, hypercoagulative imbalance, cardiac arrhythmias, hemodynamic instability	Timely recognition in both hospitalized and home self-isolated patients Thionamides as the first choice for promptly restore euthyroidism. Selective beta-blockers should also be prescribed Fever or pharyngodynia may be acute manifestations of both SARS-CoV-2 infection and agranulocytosis in patients on thionamides Concomitant administration of remdesivir and thionamides may increase acute liver toxicity risk
Graves' orbitopathy	Nor additive risks of contracting the infection neither possible progression of COVID-19	Possible delay in recognizing and diagnosing Graves' orbitopathy in patients with ophthalmic manifestations of COVID-19 Prioritize severe ophthalmopathy for intravenous methylprednisolone
Thyroid nodules	Nor additive risks of contracting the infection neither possible progression of COVID-19	Possible delay of the cytological definition of high-risk nodules Neck ultrasound could be required to assess/re-assess nodule characteristics Selection of high-risk nodules for undeferrable fine-needle aspiration and cytology
Thyroid malignancies	Thyroid cancer malignancy is not a risk factor for a poorer prognosis of COVID-19	A careful and structured clinical triage is needed for adequately scheduling the management of patients who require interventions with priority Telemedicine as a tool for TSH and thyroglobulin monitoring in patients with an excellent prognosis


Thanks for
your patience,
dear colleagues!