




Development of a prediction score (ThyroCOVID) for identifying abnormal thyroid function in COVID-19 patients

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Abstract

Purpose Thyroid dysfunction in COVID-19 carries clinical and prognostic implications. In this study, we developed a prediction score (ThyroCOVID) for abnormal thyroid function (TFT) on admission amongst COVID-19 patients.

Methods Consecutive COVID-19 patients admitted to Queen Mary Hospital were prospectively recruited during July 2020–May 2021. Thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) were measured on admission. Multivariable logistic regression analysis was performed to identify independent determinants of abnormal TFTs. ThyroCOVID was developed based on a clinical model with the lowest Akaike information criteria.

Results Five hundred and forty six COVID-19 patients were recruited (median age 50 years, 45.4% men, 72.9% mild disease on admission). 84 patients (15.4%) had abnormal TFTs on admission. Patients with abnormal TFTs were more likely to be older, have more comorbidities, symptomatic, have worse COVID-19 severity, higher SARS-CoV-2 viral loads and more adverse profile of acute-phase reactants, haematological and biochemical parameters. ThyroCOVID consisted of five parameters: symptoms (malaise), comorbidities (ischaemic heart disease/congestive heart failure) and laboratory parameters (lymphocyte count, C-reactive protein, and SARS-CoV-2 cycle threshold values). It was able to identify abnormal TFT on admission with an AUROC of 0.73 (95% CI 0.67–0.79). The optimal cut-off of 0.15 had a sensitivity of 75.0%, specificity of 65.2%, negative predictive value of 93.5% and positive predictive value of 28.1% in identifying abnormal TFTs on admission amongst COVID-19 patients.

Conclusion ThyroCOVID, a prediction score to identify COVID-19 patients at risk of having abnormal TFT on admission, was developed based on a cohort of predominantly non-severe COVID-19 patients.

Keywords COVID-19 · SARS-CoV-2 · Clinical decision rules · Thyroid function tests · Euthyroid sick syndromes · Thyroiditis

Introduction

As of 17 March 2022, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected over 458 million people globally, causing over 6 million deaths [1]. Cumulative evidence has revealed a spectrum of altered thyroid function in COVID-19, associated with clinical implications [2].

The most common pattern of abnormal thyroid function tests (TFTs) in acute COVID-19 is non-thyroidal illness syndrome (NTIS), characterised by low free triiodothyronine (fT3) levels with/without concomitant low thyroid-stimulating hormone (TSH) levels. NTIS has been shown to bear prognostic implications in COVID-19 across the whole spectrum of severity [3]: amongst COVID-19 patients in the

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community [4], non-intensive care hospitalised COVID-19 patients [5], and severe COVID-19 patients (including those requiring intensive care) [6].

Since the first case of SARS-CoV-2-related subacute thyroiditis reported in May 2020, many similar cases have been reported to occur at or soon after the diagnosis of COVID-19 [2, 7]. Another form of SARS-CoV-2-related atypical thyroiditis, resembling painless thyroiditis, has also been described [8]. These cases of SARS-CoV-2-related thyroiditis could present as either overt or subclinical thyrotoxicosis. The causal link between COVID-19 and thyroiditis has been strengthened by reports of SARS-CoV-2 in the thyroid tissues amongst patients who died from COVID-19 [9], and studies demonstrating ACE2 mRNA expression in thyroid cells [10, 11]. It is crucial to identify SARS-CoV-2-related thyroiditis, given its potential evolution into hypothyroidism requiring thyroxine replacement [2].

Besides thyroiditis, autoimmune thyroid diseases (AITD) have also been linked to COVID-19. Cases of Graves' disease [12] and Hashimoto's thyroiditis [13] have been reported after the diagnosis of COVID-19, where these patients required treatment with anti-thyroid drugs and thyroxine, respectively.

Although the World Health Organization (WHO) did not recommend routine thyroid function testing in COVID-19 patients [14, 15], certain subgroups are at risk of abnormal TFTs. For instance, SARS-CoV-2-related atypical thyroiditis was preferentially reported in hospitalised COVID-19 patients requiring intensive care [8]. Given the clinical relevance and implications of the spectrum of thyroid function alteration in COVID-19, it is helpful to identify those COVID-19 patients at risk of abnormal TFTs on admission. Developing a prediction score for COVID-19 patients at risk of thyroid dysfunction may facilitate a more focussed approach in ordering TFTs for COVID-19 patients.

Hence, we carried out the current study to develop a prediction score—'ThyroCOVID'—for abnormal TFTs on admission amongst COVID-19 patients.

Methods

Our institution, Queen Mary Hospital, is one of the major centres in Hong Kong receiving confirmed COVID-19 patients. Consecutive adult patients (aged ≥ 18 years) admitted to Queen Mary Hospital for COVID-19 between 21 July 2020 and 20 May 2021 were prospectively recruited [16–18]. During the recruitment period, the public health ordinance in Hong Kong required all patients tested positive for COVID-19 to be admitted to the hospital [19], including those detected on contact tracing and Universal Community Testing Programme [20], regardless of symptoms. The presence of SARS-CoV-2 was confirmed in all patients by

RT-PCR from the nasopharyngeal swab (NPS) and/or deep throat saliva (DTS), using the LightMix SarbecoV E-gene assay (TIB Molbiol, Berlin, Germany), which targeted the envelope protein (E) gene of SARS-CoV-2 as we described previously [21]. Patients were excluded if they (i) had a history of thyroid, pituitary or hypothalamic disorders; (ii) were on anti-thyroid drugs or thyroid hormone replacement; or (iii) were on medications with potential impact on thyroid function, including systemic steroids, amiodarone, heparin and dopamine. Each patient had blood tests within 24 h after admission, before the initiation of COVID-19 treatments.

Serum TSH, free thyroxine (fT4) and fT3 were measured with immunoassays ADVIA Centaur[®] TSH3-Ultra, FT4 and FT3 assays, respectively (Siemens Healthcare Diagnostics Inc., USA). The reference ranges for TSH, fT4 and fT3 were 0.35–4.8 mIU/L, 12–23 pmol/L and 3.2–6.5 pmol/L, respectively. Anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) antibody titres were measured with QUANTA Lite[®] Thyroid T and TPO enzyme-linked immunosorbent assay, respectively (Inova Diagnostics, USA). Positive anti-Tg and anti-TPO were defined by > 100 units. Anti-TSH receptor antibody (anti-TSHR) titre was measured with Anti-TSH Receptor (TRAb) Fast ELISA (IgG) test kit (EUROIMMUN Medizinische Labordiagnostika AG, Germany), using porcine TSHR. Anti-TSHR was considered positive if > 1 IU/L. NTIS was defined by low fT3 with normal/low TSH [22].

Basic haematology and biochemistry panel, glycated haemoglobin (HbA1c) and C-reactive protein (CRP) were measured. Lymphopenia was defined according to the laboratory reference range, i.e. if absolute lymphocyte count $< 1.06 \times 10^9/L$. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in all individuals [23]. Elevated CRP was defined by > 0.76 mg/dL. Abnormalities in the haematological and biochemical parameters were defined by their respective laboratory reference ranges.

Demographics and major comorbidities were recorded. Obesity was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 278.0. Diabetes was defined by a known diagnosis of diabetes or HbA1c $\geq 6.5\%$ on admission. COVID-19-related symptoms were evaluated with a standard checklist. Respiratory rate, baseline oxygen saturation by pulse oximetry, and oxygen requirement on admission were captured. Chest X-ray was performed in each patient on admission. Cycle threshold (Ct) values were obtained from the qualitative LightMix SarbecoV E-gene assay (TIB Molbiol, Berlin, Germany) performed on specimens from NPS and/or DTS (whichever was lower) on admission. The Ct value represents the number of cycles required for a gene target or a PCR product to be detected. Whilst viral loads

were not directly measured with a dedicated quantitative RT-PCR assay in this analysis, studies have shown a good correlation between Ct values and SARS-CoV-2 viral loads [24, 25], such that the lower the Ct values, the higher the viral loads. COVID-19 severity was classified into mild, moderate, severe and critical according to the ‘Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition)’ published by the Chinese National Health Commission (NHC) [26]. Each patient's clinical outcome was captured.

All statistical analyses were performed with R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) and IBM® SPSS® version 26 (IBM Corp., Armonk, NY, USA). In all statistical tests, two-sided p values < 0.05 were considered statistically significant. Data were presented as median with interquartile range (IQR) or number with percentage as appropriate. Data not conforming to normal distributions were logarithmically transformed before analyses. Between-group comparisons were performed with t test for continuous variables and Chi-square or Fisher's exact test for categorical variables as appropriate.

Multivariable logistic regression analysis was performed to evaluate the independent determinants of abnormal TFTs with their respective odds ratio (OR) and 95% confidence interval (CI). Variables with $p < 0.1$ in the univariate analysis were included in the multivariable logistic regression analysis. ThyroCOVID was developed based on a clinical model with the lowest Akaike information criteria (AIC), indicating the most parsimonious model in the multivariable logistic regression analysis. The optimal cut-off was derived based on the point with maximum Youden j index (y) on ROC curve with $y = [\text{sensitivity} - (1 - \text{specificity})]$.

Sensitivity analyses were done to evaluate the performance of ThyroCOVID in predicting (i) NTIS and (ii) subclinical thyrotoxicosis suggestive of thyroiditis amongst COVID-19 patients.

Results

In total, 546 COVID-19 patients were included in this analysis. The median age was 50 years (IQR: 30–63), and 45.2% were men. The most common comorbidities were hypertension (21.1%), diabetes (16.2%), obesity (5.1%) and ischaemic heart disease/heart failure (IHD/CHF; 4.4%). On admission, 400 patients (72.9%) had mild disease, 131 (23.9%) had moderate disease and 18 (3.3%) had severe disease. Three hundred and eighty six patients (70.3%) were symptomatic on presentation: the most common symptoms being cough ($n = 222$, 40.4%), fever ($n = 181$, 33.0%), sore throat ($n = 136$, 24.8%) and malaise ($n = 71$, 12.9%). Regarding the laboratory parameters on admission, the median SARS-CoV-2 Ct value was 24.76 (IQR: 18.13–31.20), lymphocyte count was

$1.22 \times 10^9/L$ (IQR: 0.90–1.66), eGFR was 96 mL/min (IQR: 82–109), and CRP was 0.58 mg/dL (IQR: 0.31–2.04).

Eighty-four patients (15.4%) had abnormal TFTs on admission (any of abnormal TSH, fT4 and fT3). These fell largely into three categories. (i) 8 patients likely had AITD: 1 patient had overt thyrotoxicosis (TSH < 0.01 mIU/L, fT4 51 pmol/L, fT3 15 pmol/L) with positive anti-TPO and anti-Tg and elevated anti-TSHR titre at 3.6 IU/L, likely representing Graves' disease diagnosed upon admission for acute COVID-19; 7 patients had subclinical hypothyroidism—three of them positive for anti-TPO. (ii) 40 patients had low fT3 compatible with NTIS [37 had isolated low fT3, 2 had concomitant low TSH, and one had concomitant mildly raised fT4 (24 pmol/L)]. (iii) 26 patients had a biochemical picture suggestive of subclinical thyrotoxicosis, i.e. isolated low TSH with normal fT4 and fT3. These were compatible with thyroiditis as their fT3/fT4 ratio was < 0.3 (in the context of thyrotoxicosis, fT3/fT4 ratio < 0.3 has been reported to be more likely thyroiditis than Graves' disease [27]) and/or anti-TPO and anti-Tg were negative. (iv) 10 patients were considered to have abnormal TFTs which could be compatible with thyroiditis, although assay variability could not be completely excluded: 3 patients had mildly elevated fT3 [2 patients had isolated high fT3 (6.6–6.7 pmol/L); 1 patient had mildly elevated fT4 (25 pmol/L) and fT3 (6.6 pmol/L)]; 3 patients had isolated low fT4 (11 pmol/L); 4 patients had isolated elevated fT4 (24 pmol/L).

The comparison between patients with and without abnormal TFTs is summarised in Table 1. Patients with abnormal TFTs were older, had more comorbidities such as diabetes, and were more likely to be symptomatic. Regarding the characteristics of COVID-19, patients with abnormal TFTs were more likely to have worse COVID-19 severity (in terms of radiological involvement and oxygen requirement), higher SARS-CoV-2 viral loads, more adverse profiles of acute-phase reactants (higher CRP and lower albumin), haematological parameters (including lower lymphocyte and platelet counts) and biochemical parameters (including lower eGFR).

Variables were selected into ThyroCOVID based on the model with the best performance, as reflected by the lowest AIC values (Table 2). ThyroCOVID consisted of five parameters: symptoms (malaise), comorbidities (IHD/CHF), and laboratory parameters (CRP, lymphocyte count and Ct values) incorporated into the

$$\frac{1}{1 + \exp[-1.38 - 0.98$$

following equation: $\times (\text{if IHD/CHF present}) - 0.58$
(if malaise present) $+ 1.03 \times \log(\text{Ct value}) + 0.72$

$\times \log(\text{lymphocyte count}) - 0.46 \times \log(\text{CRP})]$. ThyroCOVID identified abnormal TFTs on admission with an AUROC of 0.73 (95% CI 0.67–0.79). In the current study, with a prevalence of 15% for abnormal TFT amongst

Table 1 Baseline characteristics of COVID-19 patients with and without abnormal thyroid function tests in acute COVID-19

	All	Normal TFT	Abnormal TFT	<i>p</i> value
Number	546	462	84	–
Age (years)	50 (36–63)	49 (35–62)	56 (43–69)	0.002
Male	248 (45.4%)	209 (45.2%)	39 (46.4%)	0.840
Comorbidities				
Hypertension	116 (21.2%)	96 (20.8%)	20 (23.8%)	0.532
Diabetes	89 (16.3%)	68 (14.7%)	21 (25.0%)	0.019
Obesity	28 (5.1%)	24 (5.2%)	4 (4.8%)	0.999
IHD/CHF	24 (4.4%)	17 (3.7%)	7 (8.3%)	0.076
Stroke/TIA	13 (2.4%)	11 (2.4%)	2 (2.4%)	0.999
Cancer	22 (4.0%)	15 (3.2%)	7 (8.3%)	0.062
Symptomatic presentation	384 (70.3%)	317 (68.6%)	67 (79.8%)	0.040
Fever	181 (33.2%)	141 (30.5%)	40 (47.6%)	0.002
Myalgia	58 (10.6%)	48 (10.4%)	10 (11.9%)	0.678
Malaise	71 (13.0%)	18 (21.4%)	53 (11.5%)	0.013
Rhinorrhoea	68 (12.5%)	54 (11.7%)	14 (16.7%)	0.204
Cough	221 (40.5%)	180 (39.0%)	41 (48.8%)	0.091
Dyspnoea	33 (6.0%)	25 (5.4%)	8 (9.5%)	0.146
Sore throat	136 (24.9%)	119 (25.8%)	17 (20.2%)	0.282
Headache	56 (10.3%)	46 (10.0%)	10 (11.9%)	0.588
Nausea/vomiting	19 (3.5%)	18 (3.9%)	1 (1.2%)	0.334
Diarrhoea	59 (10.8%)	53 (11.5%)	6 (7.1%)	0.240
Anosmia/ageusia	63 (11.5%)	53 (11.5%)	10 (11.9%)	0.909
Viral load				
SARS-CoV-2 PCR Ct value*	24.9 (18.2–30.98)	25.5 (18.40–31.50)	22.20 (16.8–27.83)	0.003
Acute phase reactants				
C-reactive protein* (mg/dL)	0.58 (0.31–2.03)	0.48 (0.31–1.54)	1.55 (0.39–4.87)	< 0.001
Albumin (g/L)	42 (40–45)	42 (40–45)	41 (38–44)	0.005
Haematological parameters				
Lymphocyte* ($\times 10^9/L$)	1.22 (0.90–1.66)	1.28 (0.96–1.70)	1.00 (0.72–1.29)	< 0.001
Platelet* ($\times 10^9/L$)	216 (172–268)	219 (175–272)	192 (156–236)	0.001
Prothrombin time (s)	11.8 (11.4–12.2)	11.7 (11.4–12.2)	12.0 (11.6–12.4)	0.691
Biochemical parameters				
Sodium (mmol/L)	140 (138–141)	140 (139–141)	138 (135–140)	< 0.001
Potassium (mmol/L)	3.7 (3.4–4.0)	3.7 (3.5–4.0)	3.8 (3.3–4.0)	0.812
Urea (mmol/L)	3.9 (3.1–4.8)	3.9 (3.0–4.8)	4.2 (3.4–5.3)	0.014
eGFR (mL/min)	96 (82–109)	97 (84–110)	89 (70–98)	< 0.001
ALT* (U/L)	25 (17–39)	26 (17–40)	23 (17–33)	0.213
AST* (U/L)	27 (21–37)	27 (21–36)	31 (24–39)	0.022
LDH* (U/L)	212 (179–262)	208 (178–255)	235 (192–291)	0.001
Creatine kinase* (U/L)	98 (67–154)	97 (68–151)	106 (66–168)	0.823
Abnormal chest x-ray on admission	147 (26.9%)	110 (23.8%)	37 (44.0%)	< 0.001
Oxygen requirement on admission	17 (3.1%)	10 (2.2%)	7 (8.3%)	0.008

Bold values denote statistical significance at $p < 0.05$

IHD ischaemic heart disease, *CHF* congestive heart failure, *TIA* transient ischaemic attack, *Ct* cycle threshold, *eGFR* estimated glomerular filtration rate, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *LDH* lactate dehydrogenase

*Logarithmically transformed before analysis

Table 2 The prediction score for abnormal thyroid function: ThyroCOVID

Variables in the prediction score	Odds ratio (95% confidence interval)	P value
Malaise	1.78 (0.93–3.31)	0.075
IHD/CHF	2.65 (0.94–6.83)	0.050
C-reactive protein (mg/dL)*	1.58 (1.27–1.96)	<0.001
Lymphocyte count ($\times 10^9/L$)*	0.49 (0.25–0.92)	0.027
SARS-CoV-2 PCR Ct value*	0.36 (0.15–0.83)	0.018

The model also included age, comorbidities (diabetes, cancer), symptoms (symptomatic presentation, cough), laboratory parameters (albumin, platelet, sodium, urea, aspartate aminotransferase, lactate dehydrogenase, estimated glomerular filtration rate), and COVID-19 severity (radiological involvement, oxygen requirement). Variables were selected in ThyroCOVID score based on Akaike information criteria

The prediction score ThyroCOVID is calculated with the equation:
 $1 / \{1 + \exp[-1.38 - 0.98 \times (\text{if IHD/CHF present}) - 0.58 \times (\text{if malaise present}) + 1.03 \times \log(\text{Ct value}) + 0.72 \times \log(\text{lymphocyte count}) - 0.46 \times \log(\text{CRP})]\}$

IHD ischaemic heart disease, CHF congestive heart failure, Ct cycle threshold

*Logarithmically transformed before analysis

COVID-19 patients, which was similar to that reported amongst the first 191 patients in this cohort [16], the optimal cut-off of 0.15 based on the Youden index had a sensitivity of 75.0%, specificity of 65.2%, negative predictive value (NPV) of 93.5% and positive predictive value (PPV) of 28.1% in identifying abnormal TFTs on admission amongst COVID-19 patients. A low cut-off value of 0.11 identified abnormal TFT with a higher sensitivity of 82% and corresponding specificity of 49%, such that ThyroCOVID score < 0.11 classifies COVID-19 patients to be at low risk of thyroid dysfunction. On the other hand, a high cut-off value of 0.21 identified abnormal TFT with a higher specificity of 80% and corresponding sensitivity of 44%, such that ThyroCOVID score ≥ 0.21 classifies COVID-19 patients to be at high risk of thyroid dysfunction.

Subgroup analyses were performed to evaluate the performance of ThyroCOVID for (i) NTIS and (ii) subclinical thyrotoxicosis suggestive of thyroiditis respectively (Table 3), showing a similar AUROC of 0.78 (95% CI 0.71–0.86) for NTIS and 0.76 (95% CI 0.67–0.85) for subclinical thyrotoxicosis presumably due to thyroiditis respectively.

For the convenience of application, we have also converted ThyroCOVID to a more user-friendly scoring system. The continuous variables were converted to categorical variables, such that the beta coefficient of the variables was as follows: IHD/CHF (1.07), malaise (0.48), Ct value < 30 (0.72), lymphopenia (0.73), elevated CRP (0.74). The

Table 3 The performance of ThyroCOVID in predicting (A) non-thyroidal illness syndrome and (B) subclinical thyrotoxicosis

	(A) Non-thyroidal illness syndrome	(B) Subclinical thyrotoxicosis
Total number of patients*	502	488
No. of cases	40	26
AUROC (95% CI)	0.78 (0.71–0.86)	0.76 (0.67–0.85)
Sensitivity	75.0%	76.9%
Specificity	66.9%	66.9%
Positive predictive value	16.5%	11.6%
Negative predictive value	96.8%	98.1%

*Total number of patients = number of patients with normal thyroid function ($n=462$) + number of patients with the thyroid function abnormality in question (scenario A: non-thyroidal illness syndrome; scenario B: subclinical thyrotoxicosis)

ThyroCOVID score could be applied using a scoring system as shown in Table 4 with an optimal threshold of ≥ 18 to define the patients to be at risk of abnormal TFTs on admission. The AUROC was 0.71 (95% CI 0.64–0.77). Furthermore, low and high cut-off values were derived based on higher sensitivity and specificity for clinical use. A low cut-off value of 10 was derived with a higher sensitivity of 79% and corresponding specificity 48% such that ThyroCOVID score < 10 classifies COVID-19 patients to be at low risk of thyroid dysfunction. This low cut-off may be used to screen out patients not requiring TFT measurement if ThyroCOVID score is low. On the other hand, a high cut-off value of 20 was derived with a higher specificity of 80%, and corresponding sensitivity 51% such that ThyroCOVID score ≥ 20 classifies COVID-19 patients to be at high risk of thyroid dysfunction and strongly suggests the need for TFT measurement.

Discussion

To our knowledge, this is the first study to develop a prediction score for abnormal thyroid function in COVID-19 to guide the need to check TFTs on admission for COVID-19 patients. As routine thyroid function testing in each COVID-19 patient on admission may not be cost-effective, we developed this prediction score (ThyroCOVID) consisting of five readily available clinical parameters for potential clinical application.

ThyroCOVID consisted of malaise, IHD/CHF, C-reactive protein, lymphocyte count and SARS-CoV-2 Ct values. These clinical features are players in the relationship between COVID-19 and the thyroid. COVID-19 impacts on the thyroid causing thyroid dysfunction, both directly and indirectly. SARS-CoV-2 uses ACE2 combined with the transmembrane protease serine 2 (TMPRSS2) as the key

Table 4 The proposed user-friendly scoring system of ThyroCOVID in identifying abnormal thyroid function on admission amongst patients with COVID-19

Parameters	Score if feature present
IHD/CHF	+ 11
Malaise	+ 5
SARS-CoV-2 PCR Ct value < 30 (high viral load)	+ 8
Lymphocyte count < $1.06 \times 10^9/L$ (lymphopenia)	+ 8
CRP ≥ 0.76 mg/dL (elevated CRP)	+ 8
Total score: 40	
< 18	Low risk for abnormal TFTs
≥ 18	At risk for abnormal TFTs

Bold values denote statistical significance at $P < 0.05$

A low cut-off of ≥ 10 identifies abnormal TFTs with sensitivity of 79%; a high cut-off of ≥ 20 identifies abnormal TFTs with specificity of 80% (see text)

IHD ischaemic heart disease, *CHF* congestive heart failure, *Ct* cycle threshold, *CRP* C-reactive protein, *TFT* thyroid function test

molecular complex to enter and infect the host cells. Furthermore, as ACE2 and TMPRSS2 expression levels are higher in the thyroid gland than in the lungs, this provides a mechanistic link for the direct thyroid damage causing thyroid dysfunction amongst COVID-19 patients [15]. SARS-CoV-2 has been shown in the thyroid tissues in an autopsy study [9]. Studies have specifically demonstrated the expression of ACE2 mRNA in thyroid cells [10, 11]. The finding of expression of mRNA encoding for the ACE2 receptor in thyroid follicular cells makes them a potential target for SARS-CoV-2 entry, providing a clue to the possible direct viral effect of SARS-CoV-2 on thyroid leading to thyroiditis [10]. This may explain why SARS-CoV-2 Ct value can predict the occurrence of biochemical picture of thyroiditis amongst the abnormal TFTs. COVID-19 can also indirectly impact on the thyroid through immune-inflammatory responses to SARS-CoV-2 [15]. The immune response pathway in COVID-19 includes a range of cytokine release, where in severe form of COVID-19 may lead to cytokine storm. The pro-inflammatory cytokine release contributes to the picture of NTIS [28]. Thus, SARS-CoV-2 Ct value can predict the occurrence of NTIS, another main category of abnormal TFTs in acute COVID-19. In COVID-19 patients who developed thyroiditis, CRP elevation was commonly observed [29]. Higher CRP levels in the context of COVID-19 also correlated with the occurrence of NTIS [30]. Thus, CRP levels contribute significantly to our prediction score. Moreover, COVID-19 patients typically present with malaise [31], which is a common manifestation of viral infection and inflammation, and therefore, is included in ThyroCOVID. Lymphopenia is a common haematological finding in COVID-19, postulated to be related to the direct effect of SARS-CoV-2 on lymphocyte apoptosis, bone marrow impairment and thymic suppression, and cytokine-induced apoptosis of lymphocytes [32]. Thus, lymphopenia, a marker of extra-pulmonary involvement of COVID-19, may predict thyroid dysfunction in

COVID-19. Interestingly, recent studies have demonstrated the associations between lymphopenia and abnormal TFTs [33, 34], suggesting potential interactions between the hypothalamic–pituitary–thyroid axis and the immune system. Hence, lymphopenia may reflect disturbances in the hypothalamic–pituitary–thyroid axis and predict the occurrence of abnormal TFTs. Last but not least, cardiovascular comorbidities have been shown to carry significant prognostic implications in COVID-19 [35]. Specifically, IHD/CHF is an important medical comorbidity in COVID-19 patients [36]. Therefore, patients with IHD/CHF may be prone to thyroid dysfunction including NTIS by virtue of worse pre-morbid status. Furthermore, sensitivity analyses in our study demonstrated the ability of ThyroCOVID in the prediction of abnormal TFTs suggestive of NTIS and abnormal TFTs suggestive of thyroiditis respectively.

We did not observe any influence of gender on abnormal TFTs, such that gender is not included in ThyroCOVID. Interestingly, it has been reported in an Italian cohort of patients admitted to high intensity of care units that SARS-CoV-2 atypical thyroiditis was predominantly observed amongst men [8]. In contrast, our cohort comprised predominantly patients with non-severe COVID-19. The difference in the spectrum of disease severity, along with the fact that gender does not influence on the occurrence of NTIS, may explain the lack of gender effect on abnormal TFTs in our study.

Earlier in the COVID-19 pandemic, WHO did not recommend routine thyroid function testing in COVID-19 patients [14, 15], which is reasonable as the prevalence of abnormal TFTs has been estimated to be around 20–30% in general [37]. Nonetheless, the prevalence of abnormal TFTs increases with worsening severity of COVID-19 [37], such that abnormal TFTs has been reported to occur in up to 60% of the cohort with more severe illness [38]. Furthermore, SARS-CoV-2-related atypical thyroiditis has been reported

to be more frequent amongst COVID-19 patients requiring intensive care [8]. Hence, it has been suggested that COVID-19 patients requiring high-intensity care may benefit from thyroid function testing [8]. However, it remains to be determined regarding COVID-19 patients in non-intensive care settings who are at risk of thyroid dysfunction and may benefit from thyroid function testing given the clinical and prognostic implications of the spectrum of thyroid dysfunction in COVID-19. Our current prediction score, ThyroCOVID, addressed this knowledge gap.

Application of ThyroCOVID can help to identify patients with abnormal TFTs suggestive of thyroiditis who can benefit from interval monitoring of TFTs for possible evolution to hypothyroid phase [39]. On the other hand, whilst identifying patients with more severe disease who undergo a non-thyroid illness alteration of TFTs provides prognostic information, whether interventions such as triiodothyronine replacement in NTIS offer benefits to these patients remain to be evaluated [40–42].

The strengths of the current study include a well-characterised cohort of COVID-19 patients consecutively recruited in a major COVID-19 treatment centre, demonstrated to be a representative cohort of the territory [17]. Moreover, the results are likely generalisable to COVID-19 patients at large as our cohort consists of mostly non-severe COVID-19 patients [31]. However, certain limitations exist in this study. First, as the cohort comprised mainly patients with non-severe COVID-19, the prevalence of abnormal TFTs was only 15%. A larger sample size may improve the power of the prediction score. Second, due to the relatively small number of abnormal TFTs, the construction of prediction scores for specific types of abnormal TFTs is not feasible. Nonetheless, we have demonstrated the potential utility of the prediction score in NTIS and thyroiditis in the sensitivity analyses. Last but not least, our prediction score requires external validation in independent populations to confirm our findings.

Conclusion

We have constructed a five-component prediction score, ThyroCOVID, for abnormal TFTs amongst COVID-19 patients on admission, to identify patients who may benefit from thyroid function testing given the clinical and prognostic implications of thyroid dysfunction in COVID-19.

Author contributions Conceptualization: DTWL, KSL; methodology: DTWL, WSC, ART, CYL, KCBT, YCW, IFNH; formal analysis and investigation: DTWL, CHYF, STMK; writing—original draft preparation: DTWL, CHYF, STMK; writing—review and editing: CHL, WSC, ACHL, CYYC, CYL, KKWT, CWL, KCBT, YCW, IFNH, KSL; supervision: KSL.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The study followed the principles in the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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