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Role of non-thyroidal illness syndrome in predicting adverse outcomes in COVID-19 patients predominantly of mild-to-moderate severity

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Abstract

Objective: Existing studies reported the potential prognostic role of non-thyroidal illness syndrome (NTIS), characterized by low triiodothyronine (T3) with normal/low thyroid-stimulating hormone (TSH), mainly in severe COVID-19. None considered the significant impact of SARS-CoV-2 viral load on adverse outcomes. We aimed to clarify the prognostic role of NTIS among predominantly mild-to-moderate COVID-19 patients.

Design: A prospective study of COVID-19 patients.

Patients and Measurements: Consecutive adults admitted to Queen Mary Hospital for confirmed COVID-19 from July to December 2020 were prospectively recruited. SARS-CoV-2 viral load was represented by cycle threshold (Ct) values from real-time reverse transcription-polymerase chain reaction of the respiratory specimen on admission. Serum TSH, free thyroxine and free T3 were measured on admission. The outcome was deterioration in clinical severity, defined as worsening in ≥1 category of clinical severity according to the Chinese National Health Commission guideline.

Results: We recruited 367 patients. At baseline, 75.2% had mild disease, and 27 patients (7.4%) had NTIS. Fifty-three patients (14.4%) had clinical deterioration. Patients with NTIS were older, had more comorbidities, worse symptomatology, higher SARS-CoV-2 viral loads and worse profiles of inflammatory and tissue injury markers. They were more likely to have clinical deterioration ($p < .001$). In multivariable stepwise logistic regression analysis, NTIS independently predicted clinical deterioration (adjusted odds ratio 3.19, $p = .017$), in addition to Ct value <25 ($p < .001$), elevated C-reactive protein ($p = .004$), age >50 years ($p = .011$) and elevated creatine kinase ($p = .017$).

Conclusions: Non-thyroidal illness syndrome was not uncommon even in mild-to-moderate COVID-19 patients. NTIS on admission could predict clinical deterioration in COVID-19, independent of SARS-CoV-2 viral load, age and markers of inflammation and tissue injury.

KEYWORDS
COVID-19, euthyroid sick syndromes, prognosis, SARS-CoV-2, thyroid function tests, thyroid gland

1 | INTRODUCTION

The occurrence of non-thyroidal illness syndrome (NTIS), characterized by low triiodothyronine (T3) along with normal or low thyroid-stimulating hormone (TSH),[1] was reported in several cohorts of patients with coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Although it was well demonstrated that NTIS occurred more frequently among patients with more severe COVID-19,[3] whether the occurrence of NTIS on admission predicts adverse clinical outcomes in COVID-19 patients is more clinically relevant.

Since October 2020, several studies evaluating the predictive value of NTIS in the clinical course of COVID-19 have been published. Preliminary findings from a retrospective analysis of a small Chinese cohort revealed that 25 patients with thyroid dysfunction (predominantly, but not exclusively, NTIS) had worse biochemical and inflammatory profiles, and a higher risk of mortality than those without thyroid dysfunction.[4] Further studies have shown that lower free T3 (fT3) levels, but not free thyroxine (fT4) or TSH, were associated with COVID-19-related adverse events such as severe disease, ventilatory requirement and mortality,[5,6] echoed by another study revealing that NTIS predicted disease severity.[7] However, all these studies focused on COVID-19 patients with more severe disease, whereas most COVID-19 patients belonged to the mild disease spectrum.[8] Notably, none of these studies considered the significant impact of SARS-CoV-2 viral load on admission on COVID-19-related adverse outcomes.[9]

We have previously reported thyroid dysfunction in 191 patients with COVID-19, which included mainly patients with low TSH suggestive of subclinical thyrotoxicosis due to thyroiditis, and those with low fT3 compatible with NTIS.[10] Patients with low fT3 were more likely to have clinical deterioration than those with normal fT3. In contrast, the likelihood of clinical deterioration was comparable between patients with low TSH and those with normal TSH. While these findings suggested that among the categories of thyroid dysfunction in COVID-19, NTIS appeared to hold a unique prognostic role in COVID-19, further evaluation of the independent prognostic role of NTIS was limited by the sample size.[10]

Hence, we carried out the current prospective study, an extension to our previous study[10] with a longer recruitment period and a significantly larger sample size, to examine the frequency of NTIS, and clarify the prognostic significance of NTIS in COVID-19 patients predominantly of mild-to-moderate severity, taking into consideration a range of COVID-19-related prognostic markers.

2 | MATERIALS AND METHODS

Public health ordinance in Hong Kong required all patients tested positive for COVID-19 be admitted to hospital,[11] including those detected on contact tracing and Universal Community Testing Programme,[12] regardless of symptoms. 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 21 December 2020 were prospectively recruited.[10] 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.[13] Patients were excluded if they (i) had history of thyroid, hypothalamic or pituitary disorders; (ii) were on anti-thyroid drugs or thyroid hormone replacement; and (iii) were on medications with potential impact on thyroid function including systemic steroid, amiodarone, heparin and dopamine. Each patient had blood tests within 24 h after admission, before the initiation of COVID-19 treatments.

Serum TSH, 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 the Anti-TSH Receptor (TRAb) Fast ELISA (IgG) test kit (EUROIMMUN Medizinische Labordiagnostika AG, Germany), using porcine TSHR. Anti-TSHR >1 IU/L was considered positive. Patients with abnormal thyroid function tests (TFTs; defined by any abnormalities in TSH, fT4 or fT3) could therefore be classified into three groups. The first included patients with NTIS as defined by low fT3 with normal/low TSH.[1] The second were those with likely pre-existing autoimmune thyroid disorders as defined by (i) overt/subclinical hypothyroidism in the presence of positive anti-TPO and/or anti-Tg, or (ii) overt/subclinical thyrotoxicosis with positive anti-TSHR. The third group consisted of patients with abnormal TFTs compatible with different phases of thyroiditis.[14]

Basic haematology and biochemistry panel, glycated haemoglobin (HbA1c) and C-reactive protein (CRP) were measured. Abnormal laboratory parameters were defined according to their respective reference ranges: abnormal white blood cell (WBC) count if <3.89 or >9.93 × 10^9/L; abnormal absolute neutrophil count if <2.01 or >7.42 × 10^9/L; lymphopenia if absolute lymphocyte count <1.06 × 10^9/L; thrombocytopenia if platelet count <168 × 10^9/L; elevated alanine aminotransferase if >58 U/L in men, >36 U/L in women aged ≤50 years, or >45 U/L in women aged >50 years; elevated aspartate aminotransferase (AST) if >38 U/L in men, >30 U/L in women aged ≤50 years, or >37 U/L in women aged >50 years; elevated lactate dehydrogenase (LDH) if >221 U/L in men, >218 U/L in women aged ≤50 years, or >280 U/L in women aged >50 years; elevated creatine kinase (CK) if >355 U/L in men, or >161 U/L in women; elevated troponin T if >100 ng/L; elevated CRP if >0.76 mg/dL. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in all individuals.[15]

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 ≥6.5% on admission. Charlson comorbidity index was calculated for each patient. 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. While 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,[16,17] such that the lower the Ct values, the higher the viral loads.

COVID-19 severity was classified according to the 'Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition)' published by the Chinese National Health Commission (NHC).[18] Mild disease was defined by mild clinical symptoms without manifestations of pneumonia on imaging. Moderate disease was defined by fever and respiratory symptoms, and manifestations of pneumonia on imaging. Severe disease was defined by any of the following: respiratory rate ≥30/min, SpO_2 ≤93% at rest and >50% progression in 48 h on imaging. Critical disease was defined by respiratory failure requiring mechanical ventilation, shock and intensive care unit (ICU) admission.

Each patient's clinical outcomes, including radiological progression, supplementary oxygen requirements, ICU admission and death, were captured. The primary outcome of interest was clinical deterioration, defined as worsening in ≥1 category of clinical severity according to the Chinese NHC guideline. Hence, the definition of clinical deterioration incorporated radiological deterioration, new-onset oxygen requirement, ICU admission and death.

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. All participants gave informed consent.

All statistical analyses were performed with IBM® SPSS® version 26. Two-sided *p*-values <.05 were considered statistically significant. Data were presented as median with interquartile range (IQR), or number with percentage as appropriate. Between-group comparisons were performed with the Mann-Whitney *U* test for continuous variables and chi-square or fisher's exact tests for categorical variables as appropriate. Multivariable stepwise logistic regression analysis was used to identify the variables independently associated with clinical deterioration. All variables with statistical significance in the univariate analysis were included in multivariable regression analysis.

A few sensitivity analyses were performed. Firstly, we repeated the multivariable stepwise logistic regression analysis by including not only the variables with statistical significance in the univariate analysis, but also those with biological plausibility which included obesity, age, cardiovascular diseases, pulmonary diseases, diabetes, hypertension, smoking and male.[19] Secondly, we repeated the multivariable stepwise logistic regression analysis by using Charlson comorbidity index, a composite score of comorbidities, instead of individual comorbidities. Thirdly, we repeated the multivariable stepwise logistic regression analysis by using thyroid hormones (fT4 and fT3) as continuous variables instead of NTIS as a categorical variable.

3 | RESULTS

A total of 367 patients with a complete panel of TSH, fT4 and fT3 were included, with a median age of 54 years (IQR: 38–65) and 172 men (46.9%). Hypertension was present in 89 patients (24.3%), diabetes in 60 patients (16.3%), coronary artery disease/heart failure in 20 patients (5.4%), obesity in 19 patients (5.2%), history of or current malignancy in 17 patients (4.6%), pulmonary diseases in 13 patients (3.5%) and history of stroke/transient ischaemic attack in 10 patients (2.7%). The median Ct value was 24.87 (IQR: 18.30–30.82). Most patients had mild disease on admission (*n* = 276, 75.2%), while 77 had moderate disease (21.0%) and 14 had severe disease (3.8%). None was critically ill on admission; that is, all patients were initially admitted to the non-intensive care unit. Most patients were symptomatic (*n* = 263, 71.7%). The most common symptoms were cough (*n* = 148, 40.3%), fever (*n* = 128, 34.9%), sore throat (*n* = 98, 26.7%), malaise (*n* = 54, 14.7%), rhinorrhoea (*n* = 51, 13.9%), diarrhoea (*n* = 48, 13.1%) and anosmia and/or ageusia (*n* = 45, 12.3%).

Abnormal TFTs were observed in 62 patients (16.9%). None had overt thyrotoxicosis/hypothyroidism. Twenty-seven patients (7.4%) had NTIS. Five patients likely had pre-existing autoimmune thyroid disorders: 3 of them had subclinical hypothyroidism with strongly positive anti-TPO (>5 times upper limit of normal), suggesting pre-existing Hashimoto's thyroiditis, while another 2 had suppressed TSH levels (<0.01 mIU/L) with high-normal fT4 and fT3 as well as elevated anti-TSHR (2.2 IU/L and 9.9 IU/L, respectively), raising the possibility of subclinical hyperthyroidism due to Graves' disease. Thirty patients (8.2%) had abnormal TFTs compatible with different phases of thyroiditis: 21 patients had isolated low TSH, with high-normal fT4 and normal fT3; 5 patients had isolated mildly elevated fT4 (24-25 pmol/L); 2 patients had mildly elevated fT3 (6.6–6.7 pmol/L), high-normal fT4 and normal TSH levels; and the remaining 2 patients had isolated low fT4 of 11 pmol/L. Among these 30 patients having abnormal TFTs compatible with thyroiditis, 25 were negative for anti-TPO and anti-Tg, favouring TFTs changes related to COVID-19 rather than pre-existing autoimmune thyroid disorders.

Of all 367 patients, 53 patients (14.4%) had clinical deterioration, the primary outcome of our study. Thirty-five patients (9.5%) had radiological deterioration, 28 patients (7.6%) developed desaturation requiring supplemental oxygen, 11 patients (3.0%) required intensive care unit admission, and 4 patients (1.0%) died during hospitalization. The median length of hospitalization was 8 days (IQR: 6–13). Notably, comparing with patients with normal TFTs, those with NTIS had a higher likelihood of clinical deterioration ($p < .001$), mainly driven by the higher likelihood of oxygen requirement ($p < .001$) and

intensive care unit admission (p = .005). In contrast, there was no significant difference in clinical outcomes between patients with normal TFTs and those with pre-existing autoimmune thyroid disorders or with abnormal TFTs compatible with thyroiditis. (Table 1).

We further characterized patients with NTIS and studied the prognostic implication of NTIS, with reference to patients with normal TFTs. Table 2 summarizes the baseline characteristics of patients with normal TFTs and those with NTIS. Patients with NTIS were older and had worse baseline clinical severity. More patients with NTIS had fever, malaise and shortness of breath. More patients with NTIS had abnormal WBC count, lymphopenia, elevated LDH and CRP.

To identify the potential predictors of clinical deterioration, we first compared the baseline characteristics of patients who did and did not develop clinical deterioration. (Table 3) More patients with NTIS developed clinical deterioration (p < .001). Furthermore, patients who had clinical deterioration were older, had more comorbidities (hypertension, diabetes and history of stroke/TIA), worse symptomatology (fever, cough, nausea/vomiting), higher SARS-CoV-2 viral load (reflected by more patients having low Ct values) and a worse profile of inflammatory and tissue injury markers (lymphopenia, renal impairment and elevated AST, CK and CRP). Charlson comorbidity index was higher in the group with clinical deterioration (p = .001). Of note, the presence of anti-TPO/Tg was not associated with clinical deterioration (p = .797).

We then included all the 14 variables showing univariate significance in Table 3 into the multivariable stepwise logistic regression analysis to identify the independent predictors of clinical deterioration. In the multivariable stepwise logistic regression analysis (Table 4), NTIS remained to be an independent predictor of clinical deterioration (adjusted odds ratio [OR] 3.19, 95% CI 1.23–8.26, p = .017), in addition to Ct value <25 (adjusted OR 7.05, p < .001), elevated CRP (adjusted OR 3.04, p = .004), age >50 years (adjusted OR 2.88, p = .011) and elevated CK (adjusted OR 3.13, p = .017).

3.1 | Sensitivity analyses

Firstly, we repeated the multivariable stepwise logistic regression analysis by further including variables with biological plausibility selected a priori, that is, obesity, age, cardiovascular diseases, pulmonary diseases, diabetes, hypertension, smoking and male. In the final model, NTIS again remained as an independent predictor of clinical deterioration (adjusted OR 2.90, 95% CI 1.11–7.58, p = .029), in addition to Ct value <25 (adjusted OR 6.62, 95% CI 2.85–15.4, p < .001), elevated CRP (adjusted OR 3.09, 95% CI 1.44–6.63, p = .004), age >50 years (adjusted OR 2.81, 95% CI 1.25–6.29, p = .012) and elevated CK (adjusted OR 3.07, 95% CI 1.18–8.00, p = .022).

Secondly, we repeated the multivariable stepwise logistic regression analysis by using Charlson comorbidity index instead of individual comorbidities. In the final model, NTIS again remained as an independent predictor of clinical deterioration (adjusted OR 3.18, 95% CI 1.23–8.25, p = .017), in addition to Ct value <25 (adjusted OR 7.02, 95% CI 3.02–16.3, p < .001), elevated CRP (adjusted OR 3.03, 95% CI 1.43–6.43, p = .004), age >50 years (adjusted OR 2.89, 95% CI 1.28–6.52, p = .011) and elevated CK (adjusted OR 3.03, 95% CI 1.43–6.43, p = .018). Charlson comorbidity index was not independently associated with clinical deterioration.

Thirdly, we repeated the multivariable stepwise logistic regression analysis by using thyroid hormones (fT4 and fT3) as continuous variables instead of NTIS as a categorical variable. In the final model, fT3, but not fT4, showed an independent inverse association with clinical deterioration (adjusted OR 0.48, 95% CI 0.27–0.85, p = .011), in addition to Ct value <25 (adjusted OR 6.32, 95% CI 2.72–14.6, p < .001), elevated CRP (adjusted OR 2.49, 95% CI 1.14–5.47, p = .023) and age >50 years (adjusted OR 2.46, 95% CI 1.08–5.63, p = .033).

3.2 | Reassessment TFTs for patients with initial abnormal TFTs

Reassessment TFTs were arranged at around 3 months after discharge to assess for resolution or progression. Forty-three of the 62 patients with initial abnormal TFTs had reassessment TFTs. Among the 27 patients categorized as NTIS, 20 had reassessment TFTs. Eighteen recovered, but two still had abnormal TFTs. One patient had NTIS upon reassessment when he was admitted for fluid overload and clinically ill. The other patient developed T3-toxicosis at 3 months, followed by spontaneous resolution another 3 months

TABLE 1 Comparison of clinical outcomes in COVID-19 patients with different thyroid function profiles

	Normal TFTs	Non-thyroidal illness syndrome	Likely pre-existing autoimmune thyroid disorder	Abnormal TFTs compatible with thyroiditis
Number of patients	305	27	5	30
Clinical deterioration	37 (12.1%)	11 (40.7%)[b]	0 (0%)	5 (16.7%)
Radiological deterioration	29 (9.5%)	4 (14.8%)	0 (0%)	2 (6.7%)
Oxygen requirement	19 (6.2%)	7 (25.9%)[b]	0 (0%)	2 (6.7%)
Intensive care unit admission	6 (2.0%)	4 (14.8%)[a]	0 (0%)	1 (3.3%)
Death	4 (1.3%)	0 (0%)	0 (0%)	0 (0%)

Note: Data presented as number (percentage).

Abbreviation: TFTs, thyroid function tests.

[a]p < .01, [b]p < .001 compared with patients with normal thyroid function tests.

TABLE 2 Baseline characteristics of patients with normal thyroid function tests and those with non-thyroidal illness syndrome

	Patients with normal TFTs	Patients with NTIS	*p*-value
Number of patients	305	27	---
TSH (mIU/L)	1.20 (0.87–1.70)	0.91 (0.56–1.60)	**.017**
fT4 (pmol/L)	18 (16–19)	16 (14–17)	**<.001**
fT3 (pmol/L)	4.2 (3.8–4.7)	2.9 (2.5–3.0)	**<.001**
fT3/fT4 ratio	0.237 (0.214–0.271)	0.172 (0.140–0.200)	**<.001**
Age (years)	53 (37–63)	62 (50–70)	**.002**
Male	141 (46.2%)	12 (44.4%)	.858
Smoking	46/266 (17.3%)	3/23 (13.0%)	.776
Obesity	17 (5.6%)	1 (3.7%)	.999
Charlson comorbidity index			
0	232 (76.1%)	19 (70.4%)	.158
1	45 (14.8%)	2 (7.4%)	
2	16 (5.2%)	4 (14.8%)	
≥3	12 (3.9%)	2 (7.4%)	
Comorbidities			
Hypertension	72 (23.6%)	9 (33.3%)	.259
Diabetes	45 (14.8%)	6 (22.2%)	.302
IHD/CHF	16 (52.5%)	2 (7.4%)	.649
Stroke/TIA	9 (3.0%)	0 (0%)	.999
Malignancy	11 (3.6%)	3 (11.1%)	.095
Pulmonary disease	11 (3.6%)	1 (3.7%)	.999
Symptomatology			
Symptomatic	213 (69.8%)	23 (85.2%)	.203
Fever	96 (31.5%)	15 (55.6%)	**.011**
Myalgia	32 (10.5%)	5 (18.5%)	.204
Malaise	40 (13.1%)	8 (29.6%)	**.019**
Rhinorrhoea	40 (13.1%)	5 (18.5%)	.432
Cough	117 (38.4%)	12 (44.4%)	.534
Shortness of breath	16 (5.2%)	5 (18.5%)	**.007**
Sore throat	85 (27.9%)	6 (22.2%)	.529
Headache	29 (9.5%)	2 (7.4%)	.999
Nausea/vomiting	9 (3.0%)	1 (3.7%)	.577
Diarrhoea	43 (14.1%)	3 (11.1%)	.999
Anosmia and/or ageusia	38 (12.5%)	2 (7.4%)	.756
Baseline clinical severity			
Mild	238 (78.0%)	13 (85.2%)	**<.001**
Moderate	58 (19.0%)	11 (40.7%)	
Severe	9 (3.0%)	3 (11.1%)	
Baseline laboratory parameters			
Cycle threshold value	25.50 (18.56–31.39)	22.20 (17.00–28.06)	.125
Abnormal white blood cell count	62 (20.3%)	11 (40.7%)	**.014**
Abnormal neutrophil count	48 (15.7%)	5 (18.5%)	.705
Lymphopenia	108 (35.4%)	19 (70.4%)	**<.001**
Thrombocytopenia	59 (19.3%)	6 (22.2%)	.718
eGFR <60 ml/min	15 (4.9%)	4 (14.8%)	.058

(Continues)

TABLE 2 (Continued)

	Patients with normal TFTs	Patients with NTIS	*p*-value
Elevated alanine aminotransferase	46 (15.1%)	2 (7.4%)	.396
Elevated aspartate aminotransferase	78 (25.6%)	9 (33.3%)	.380
Elevated lactate dehydrogenase	105 (34.4%)	21 (77.8%)	**<.001**
Elevated creatine kinase	33 (10.8%)	3 (11.1%)	.999
Elevated troponin T	1 (0.3%)	0 (0%)	.999
Elevated C-reactive protein	124 (40.7%)	22 (81.5%)	**<.001**
Anti-TPO/Tg positivity	65/293 (22.2%)	6/26 (23.1%)	.916

Note: Data presented as number (percentage) or median (interquartile range) as appropriate.

Values reaching statistical significance are in bold.

Abbreviations: CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; fT3, free triiodothyronine; fT4, free thyroxine; IHD, ischaemic heart disease; NTIS, non-thyroidal illness syndrome; Tg, thyroglobulin; TIA, transient ischaemic attack; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

later, suggestive of painless thyroiditis. Among the 30 patients with initial abnormal TFTs compatible with thyroiditis, 19 had reassessment. Fifteen recovered, while the remaining four still had subclinical thyrotoxicosis (low TSH with normal fT4 and fT3 levels). Among the 5 patients with likely pre-existing autoimmune thyroid disorder, 4 had reassessment. The 3 patients with subclinical hypothyroidism on admission had persistent subclinical hypothyroidism upon reassessment, while the TFTs of the remaining patient who initially presented with subclinical thyrotoxicosis subsequently normalized.

4 | DISCUSSION

To our knowledge, this is the largest prospective cohort of COVID-19 patients with complete TFT profiles including fT3, the classical indicator of NTIS. Thus, our study was able to validate the unique prognostic role of NTIS among the different patterns of thyroid dysfunction in COVID-19, taking into consideration multiple other prognostic factors. We demonstrated that NTIS predicted clinical deterioration even in patients with predominantly mild-to-moderate COVID-19, extending the current understanding of NTIS in COVID-19. Importantly, even after taking into account the significant impact of SARS-CoV-2 viral load on admission, NTIS remained to be an independent predictor of clinical deterioration, in addition to age and markers of inflammation and tissue injury.

The frequency of NTIS in our cohort of mild-to-moderate COVID-19 was 7.4%, in line with the previous report of 5.9% among 34 non-severe COVID-19 patients in a Chinese cohort.[5] Not surprisingly, the frequency of NTIS was lower than that among patients with more severe baseline clinical severity, which has been reported to occur in up to 20%–30% among severe COVID-19 patients.[4,7] The baseline clinical profile of patients with NTIS, in comparison with patients with normal TFTs, was similar to those reported in cohorts of more severe COVID-19 patients,[6,7] in that patients with NTIS were older, more symptomatic with fever and shortness of breath, and had more lymphopenia, higher markers of inflammation and tissue injury.

Identifying independent risk factors of COVID-19-related adverse outcomes helps clinicians triage at-risk patients for more intensive monitoring and aggressive therapy. Some of the more consistently reported risk factors were older age,[20–23] higher levels of inflammatory markers including CRP,[24] higher levels of tissue injury markers[21,23] including CK[25] and worse symptoms.[23] Recently, SARS-CoV-2 viral load has also been shown to have an important prognostic implication in COVID-19,[9,26] which is an important factor to consider when studying outcomes of a viral illness. We showed that NTIS remained to be an independent predictor of clinical deterioration even after considering the SARS-CoV-2 viral load, in addition to those consistently reported in the literature (older age, higher markers of inflammation and tissue injury). Nonetheless, NTIS ranked below the top three independent predictors identified in our study. In particular, higher SARS-CoV-2 viral loads, defined by low Ct values <25, was a highly significant predictor, associated with 7 times the risk of clinical deterioration, whereas the rest were associated with only 2-3 times the risk of clinical deterioration. The potential implication from our study findings is to encourage clinicians to be alerted to the Ct values reported upon the diagnosis of COVID-19, in addition to patients' age and biochemical profiles, whereas TFT especially fT3, if available on admission, can help to refine the clinicians' risk assessment. Nonetheless, as the OR of NTIS for clinical deterioration is in the same order as elevated CRP, we do not have sufficient evidence to advise on routine assessment of fT3 on admission in every COVID-19 patient, given the potential cost-effectiveness concern.

The association between NTIS and COVID-19-related adverse outcomes could be explained by the cytokine storm, which may suppress central TSH and 5'-deiodinases activity, and in turn be associated with worse clinical outcomes.[7] In our study, patients with NTIS had a higher likelihood of elevated CRP, which in turn independently predicted clinical deterioration. Nonetheless, NTIS independently predicted clinical deterioration in addition to CRP. Thus, the perturbation in thyroid function in NTIS might impact on other

TABLE 3 Comparison of the baseline clinical characteristics of patients who did and did not develop clinical deterioration

	Clinical deterioration	No clinical deterioration	*p*-value
Number of patients	48	284	---
TSH (mIU/L)	0.85 (0.60–1.50)	1.25 (0.92–1.70)	**.002**
fT4 (pmol/L)	17 (15–18)	18 (16–19)	**.001**
fT3 (pmol/L)	3.6 (3.2–4.1)	4.2 (3.7–4.7)	**<.001**
fT3/fT4 ratio	0.218 (0.194–0.243)	0.236 (0.212–0.271)	**.001**
Non-thyroidal illness syndrome	11 (22.9%)	16 (5.6%)	**<.001**
Age >50 years	38 (79.2%)	147 (51.8%)	**<.001**
Male	28 (58.3%)	125 (44.0%)	.066
Smoking	4/39 (10.3%)	45/250 (18.0%)	.231
Obesity	5 (10.4%)	13 (4.6%)	.098
Charlson comorbidity index			
0	29 (60.4%)	222 (78.2%)	**.001**
1	8 (16.7%)	39 (13.7%)	
2	5 (10.4%)	15 (5.3%)	
≥3	6 (12.5%)	8 (2.8%)	
Comorbidities			
Hypertension	20 (41.7%)	61 (21.5%)	**.003**
Diabetes	13 (27.1%)	38 (13.4%)	**.015**
IHD/CHF	5 (10.4%)	13 (4.6%)	.098
Stroke/TIA	4 (8.3%)	5 (1.8%)	**.028**
Malignancy	2 (4.2%)	12 (4.2%)	.999
Pulmonary disease	4 (8.3%)	7 (2.5%)	.059
Symptomatology			
Fever	26 (54.2%)	85 (29.9%)	**.001**
Myalgia	7 (14.6%)	30 (10.6%)	.413
Malaise	6 (12.5%)	42 (14.8%)	.677
Rhinorrhoea	6 (12.5%)	39 (13.7%)	.818
Cough	27 (56.3%)	102 (35.9%)	**.008**
Shortness of breath	5 (10.4%)	16 (5.6%)	.208
Sore throat	15 (31.3%)	76 (26.8%)	.519
Headache	3 (6.3%)	28 (9.9%)	.594
Nausea/vomiting	4 (8.3%)	6 (2.1%)	**.042**
Diarrhoea	4 (8.3%)	42 (14.8%)	.364
Anosmia and/or ageusia	5 (10.4%)	35 (12.3%)	.707
Baseline clinical severity			.447
Mild	36 (75.0%)	215 (75.7%)	
Moderate	8 (16.7%)	61 (21.5%)	
Severe	4 (8.3%)	8 (2.8%)	
Baseline laboratory parameters			
Cycle threshold value <25	39 (81.3%)	125 (44.0%)	**<.001**
Abnormal white blood cell count	11 (22.9%)	62 (21.8%)	.852
Abnormal neutrophil count	7 (14.6%)	46 (16.2%)	.778
Lymphopenia	27 (56.3%)	100 (35.2%)	**.006**
Thrombocytopenia	12 (25.0%)	53 (18.7%)	.306
eGFR <60 ml/min	6 (12.5%)	13 (4.6%)	**.029**

(Continues)

TABLE 3 (Continued)

	Clinical deterioration	No clinical deterioration	*p*-value
Elevated alanine aminotransferase	7 (14.6%)	41 (14.4%)	.979
Elevated aspartate aminotransferase	19 (39.6%)	68 (23.9%)	**.023**
Elevated lactate dehydrogenase	23 (47.9%)	103 (36.3%)	.124
Elevated creatine kinase	10 (20.8%)	26 (9.2%)	**.016**
Elevated troponin T	1 (2.1%)	0 (0%)	.145
Elevated C-reactive protein	34 (70.8%)	112 (39.4%)	**<.001**
Anti-TPO/Tg positivity	10/48 (20.8%)	61/271 (22.5%)	.797

Note: Data presented as number (percentage).

Values reaching statistical significance are in bold.

Abbreviations: CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; fT3, free triiodothyronine; fT4, free thyroxine; IHD, ischaemic heart disease; Tg, thyroglobulin; TIA, transient ischaemic attack; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

TABLE 4 Clinical variables associated with clinical deterioration in the final model of the multivariable stepwise logistic regression analysis

Clinical variables	Adjusted odds ratio (95% CI)	*p*-value
Cycle threshold value <25	7.05 (3.06–16.4)	**<.001**
Elevated C-reactive protein	3.04 (1.44–6.45)	**.004**
Age >50 years	2.88 (1.28–6.51)	**.011**
Elevated creatine kinase	3.13 (1.22–8.03)	**.017**
Non-thyroidal illness syndrome	3.19 (1.23–8.26)	**.017**
Nausea/vomiting	4.47 (0.87–22.8)	.072

Note: The model included non-thyroidal illness syndrome, age >50 years, hypertension, diabetes, stroke/transient ischaemic attack, fever, cough, nausea/vomiting, cycle threshold value <25, lymphopenia, estimated glomerular filtration rate <60 ml/min, elevated aspartate aminotransferase, elevated creatine kinase and elevated C-reactive protein.

Values reaching statistical significance are in bold.

Abbreviation: CI, confidence interval.

systems associated with clinical deterioration. In animal model, thyroid hormones have been shown to be associated with the respiratory system, where increased serum T3 levels could enhance pulmonary surfactant synthesis, reduce the alveolar surface tension and improve lung compliance and lung function.[27,28] The ongoing randomized controlled trial of treating critically ill COVID-19 patients with T3[29] may shed light on the association between NTIS and the respiratory system and further extend our understanding of the prognostic role of NTIS in COVID-19.

Our study provided additional insights into the potential prognostic role of NTIS in COVID-19. The findings are generalizable to COVID-19 patients at large as our patients were predominantly of mild-to-moderate severity. However, our results should be interpreted in the light of certain limitations. Firstly, as our cohort comprised mainly mild-to-moderate COVID-19 patients and thus had a low mortality rate, our study was not powered to identify predictors of mortality. Secondly, SARS-CoV-2 viral loads were represented by Ct values. Despite a good correlation,[16,17] direct quantitative measurements of viral loads would have been preferable if available. Thirdly, obesity, increasingly recognized as an important risk factor for COVID-19-related morbidity and mortality,[19] was defined by ICD-9-CM diagnostic code in our study as a categorical variable, instead of body mass index as a continuous variable, and was likely to be underreported. Fourthly, high-resolution computed tomography was done at the physicians' discretion. Thus, the detection of imaging features of pneumonia in our cohort might be less sensitive. Last but not least, a control group of non-COVID-19 pneumonia patients was not included in this study.

5 | CONCLUSIONS

Non-thyroidal illness syndrome was not uncommon, occurring in over 7%, even in COVID-19 patients with predominantly mild-to-moderate disease severity on admission. The occurrence of NTIS on admission could predict clinical deterioration in COVID-19, independent of SARS-CoV-2 viral load, age and markers of inflammation and tissue injury.

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CONFLICT OF INTEREST

The author has no conflict of interest to declare.

AUTHOR CONTRIBUTION

DTWL wrote the manuscript. DTWL, CHL, WSC, ACHL, ART, CYL and EKHL researched the data. DTWL and CHYF performed statistical analyses. CHL, WSC, ACHL, KKWT, KCBT, YCW, CWL, IFNH and KSLL critically reviewed and edited the manuscript. KSLL initiated and supervised the study, is the guarantor of this work and as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

Datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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