Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Endocrine Practice 27 (2021) 894–902

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org

Original Article

Long COVID in Patients With Mild to Moderate Disease: Do Thyroid Function and Autoimmunity Play a Role?

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ARTICLE INFO

Article history:
Received 8 May 2021
Received in revised form
25 June 2021
Accepted 28 June 2021
Available online 6 July 2021

Key words:
post–acute COVID-19 syndrome
COVID-19
SARS-CoV-2
thyroid function tests
autoimmunity
autoantibodies

ABSTRACT

Objective: Post-acute sequelae of coronavirus disease 2019 (COVID-19) or long COVID (LC) is an emerging global health issue. Fatigue is a common feature. Whether thyroid function and autoimmunity play a role is uncertain. We aimed to evaluate the prevalence and predictors of LC and the potential role of thyroid function and autoimmunity in LC.

Methods: We included consecutive adults without a known thyroid disorder who were admitted to a major COVID-19 center for confirmed COVID-19 from July to December 2020. Thyroid function tests and antithyroid antibodies were measured for all patients on admission and at follow-up. LC was defined by the presence or persistence of symptoms upon follow-up.

Results: In total, 204 patients (median age, 55.0 years; 95 men [46.6%]) were reassessed at a median of 89 days (interquartile range, 69-99) after acute COVID-19. Of the 204 patients, 41 (20.1%) had LC. Female sex (adjusted odds ratio, 2.48; $P = .018$) and severe acute respiratory syndrome coronavirus 2 polymerase chain reaction cycle threshold value of <25 on admission (adjusted odds ratio, 2.84; $P = .012$) independently predicted the occurrence of LC. Upon follow-up, most abnormal thyroid function tests in acute COVID-19 resolved, and incident thyroid dysfunction was rare. Nonetheless, we observed incident antithyroid peroxidase (anti-TPO) positivity. Although baseline or follow-up thyroid function tests were not associated with the occurrence of LC, among 172 patients with symptomatic acute COVID-19, symptom resolution was more likely in those with positive anti-TPO upon follow-up ($P = .043$).

Conclusion: LC is common among COVID-19 survivors, with females and those with higher viral load in acute COVID-19 particularly being vulnerable. The observation of incident anti-TPO positivity warrants further follow-up for thyroid dysfunction. Whether anti-TPO plays a protective role in LC remains to be elucidated.

Introduction

The coronavirus disease 2019 (COVID-19), due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic.[1] Many COVID-19 survivors continue to experience a range of symptoms after recovery from the acute COVID-19 illness, variably described as "long COVID," "post–acute sequelae of SARS-CoV-2," or "post–acute COVID-19 syndrome."[2,3] This phenomenon has been referred to as "long COVID" in this article.

Abbreviations: aOR, adjusted odds ratio; CDARS, Clinical Data Analysis and Reporting System; COVID, coronavirus disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Ct, cycle threshold; fT3, free triiodothyronine; fT4, free thyroxine; ICD-9-CM, International Classification of Diseases; Ninth Revision, Clinical Modification; IgG, Immunoglobulin G; IQR, interquartile range; LC, long coronavirus disease; PCR, polymerase chain reaction; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TFT, thyroid function test; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

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https://doi.org/10.1016/j.eprac.2021.06.016
1530-891X/

Typical presentations include fatigue and dyspnea.[2] Long COVID can represent the following: (1) residual symptoms that persist after recovery from acute infection or (2) new symptoms or syndromes that develop after initial asymptomatic or mild infection.[4] As the population of COVID-19 survivors is growing, long COVID could evolve into a "pandemic of the pandemic."[5] It is crucial to identify those prone to develop long COVID for the appropriate allocation of health care resources.

As acute COVID-19 is associated with multisystem involvement by SARS-CoV-2, it is also increasingly recognized that sequelae may occur in multiple systems after acute COVID-19 illness.[2,6] The hypothalamic-pituitary-thyroid axis has attracted clinical interest in its relevance in acute COVID-19.[7] The volume of literature is growing regarding thyroid dysfunction in acute COVID-19, which mainly includes nonthyroidal illness and thyroiditis. However, relatively few studies have addressed the thyroid status in the convalescent phase of COVID-19, mainly reporting the resolution of thyroid dysfunction. Recently, the potential incident thyroid dysfunction and autoimmunity among 122 patients with COVID-19 during convalescence has been described.[8] As manifestations of long COVID include fatigue, and immune dysregulation is one of the postulated mechanisms of long COVID, it would be helpful to investigate whether thyroid function and autoimmunity play a role in long COVID.[9]

Hence, we conducted this prospective study to evaluate the prevalence and predictors of long COVID and the role of thyroid function and autoimmunity among COVID-19 survivors who have had long COVID.

Methods

This study included COVID-19 survivors who were reassessed at approximately 3 months after acute COVID-19. The inclusion and exclusion criteria have been detailed in the following sections. 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.

The public health ordinance in Hong Kong required all patients to test positive for COVID-19 to be admitted to the hospital, including those detected on contact tracing and the Universal Community Testing Programme, regardless of symptoms.[10] Our institution is one of the major centers in Hong Kong receiving patients with confirmed COVID-19. Consecutive adult patients (aged ≥18 years) admitted to our institution for COVID-19 between July 21, 2020, and December 21, 2020, were prospectively recruited. The presence of SARS-CoV-2 was confirmed in all patients via reverse transcription-polymerase chain reaction (PCR) from the nasopharyngeal swab or deep throat saliva, using the LightMix SarbecoV E-gene assay (TIB Molbiol), which targeted the envelope protein (E) gene of SARS-CoV-2.[10,11] Exclusion criteria were as follows: (1) a history of thyroid, hypothalamic, or pituitary disorders; (2) the use of antithyroid drugs or thyroid hormone replacement; and (3) the use of medications that may impact thyroid function, including systemic steroid, amiodarone, heparin, and dopamine. Each patient had baseline blood tests taken within 24 hours after admission before starting COVID-19 treatments.

Serum thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) were measured using immunoassays ADVIA Centaur TSH3-Ultra, FT4, and FT3 assays (Siemens Healthcare Diagnostics Inc), respectively. The reference ranges for TSH, fT4, and fT3 were 0.35 mIU/L to 4.8 mIU/L, 12 pmol/L to 23 pmol/L, and 3.2 pmol/L to 6.5 pmol/L, respectively. Antithyroglobulin (anti-Tg) and antithyroid peroxidase (anti-TPO) antibody titers were measured using QUANTA Lite Thyroid T and TPO enzyme-linked immunosorbent assay (Inova Diagnostics), respectively. Positive anti-Tg and anti-TPO were defined as >100 units. Basic hematology and biochemistry panel, glycated hemoglobin A1C, and C-reactive protein (CRP) were measured. Abnormal laboratory parameters were defined according to their respective reference ranges.[10] Elevated CRP level was defined as >0.76 mg/dL. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[12] Antinuclear antibody titers were measured using Kallestad human epithelial cell (HEp-2) immunofluorescence assays (Bio-Rad Laboratories Inc), with titers of >1:80 considered positive.

Demographics and major comorbidities were recorded. Obesity was defined as per 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 hemoglobin A1C value of ≥6.5% (≥48 mmol/mol) on admission. The 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. A chest x-ray was performed for each patient on admission, and abnormal chest radiographs were graded as mild (opacities in 1-2 lung zones), moderate (opacities in 3-4 lung zones), and severe (opacities in >4 lung zones).[13] Cycle threshold (Ct) values were obtained from the qualitative LightMix SarbecoV E-gene assay performed on specimens from nasopharyngeal swab or deep throat saliva (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. Although viral loads were not directly measured with a dedicated quantitative reverse transcription-PCR assay in this analysis, studies have shown a good correlation between Ct values and SARS-CoV-2 viral loads, such that lower Ct values correlate with higher 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.[14–16] Patients' clinical outcomes were captured.

COVID-19 survivors were offered a follow-up visit at a dedicated COVID-19 clinic approximately 3 months after admission, in which they were systematically evaluated for symptoms with a standard checklist. At the follow-up, all patients had a reassessment for chest x-ray, and their CRP, thyroid function tests (TFTs), and antithyroid antibody levels were re-evaluated. Immunoglobulin G (IgG) antibodies specific to the SARS-CoV-2 spike protein receptor-binding domain (RBD; anti-SARS-CoV-2 RBD IgG) were measured using a live virus microneutralization assay, an in-house assay developed by the University of Hong Kong.[17] A titer of ≥1:20 was considered positive. Reassessment chest radiograph was classified as follows according to the British Society of Thoracic Imaging guidance in comparison with the chest radiograph obtained during acute COVID-19: (1) normal/resolved, (2) ≥50% improvement, (3) <50% improvement, and (4) worsening.[18]

Comparison of the Current Cohort With Adult Patients With COVID-19 Admitted to Other Centers

Hospitalization records of adults admitted for COVID-19 in the matched period (between July 21, 2020, and December 21, 2020) in Hong Kong were retrieved from the territory-wide anonymized electronic health database of the Hospital Authority of Hong Kong—the Clinical Data Analysis and Reporting System (CDARS). ICD-9-CM codes are used as the standard in Hong Kong. Data validation has demonstrated high coding accuracy in CDARS.[19] With the help of CDARS, high-quality large population-based studies have been published.[19–22] The Hospital Authority of Hong Kong is the only publicly funded health care provider providing management to all COVID-19 cases in Hong Kong. Cases of COVID-

19 were identified using a combination of ICD-9-CM codes 519.8, 079.89, and V75.9, with a valid SARS-CoV-2 PCR Ct value. However, information on the clinical severity of COVID-19 could not be retrieved from CDARS. Nevertheless, the SARS-CoV-2 PCR Ct value has been reported to correlate with COVID-19 severity.[23] Thus, age, sex, and SARS-CoV-2 PCR Ct values were compared between our cohort and the patients admitted to other centers.

Definition of Long COVID

Long COVID was defined in our study as the presence or persistence of symptoms after acute COVID-19. Long COVID can represent the following: (1) residual symptoms that persist after recovery from acute infection or (2) new symptoms or syndromes that develop after initial asymptomatic or mild infection.[4] Hence, in this study, patients were also categorized into the following: (1) those who had symptomatic acute COVID-19 (group A) and (2) those who had asymptomatic mild acute COVID-19 (group B).

Statistical Analyses

All statistical analyses were performed using SPSS version 26 (International Business Machines Corporation). Two-sided *P* values of <.05 were considered statistically significant. Data were presented as median with interquartile range (IQR) or number with the percentage, as appropriate. Comparisons between groups were performed using a *t* test or Mann-Whitney *U* test for continuous variables, as appropriate, and χ^2 test or Fisher exact test for categorical variables, as appropriate. Multivariable logistic regression analysis was used to identify variables independently associated with long COVID. All variables with statistical significance in the univariate analysis ($P < .05$) were included in the multivariable regression analysis.

Results

Baseline Characteristics

In total, 204 patients with COVID-19 were included. Their baseline clinical characteristics have been summarized in Table 1. The median age was 55.0 years (IQR, 44.3-63.0), and 95 patients (46.6%) were men. Of the 204 patients, 172 (84.3%) were symptomatic in the acute COVID-19, whereas 32 (15.7%) had asymptomatic mild acute COVID-19. The most common comorbidities were hypertension (23.0%), diabetes (13.7%), and obesity (7.4%). Most patients (n = 157; 77.0%) had a Charlson comorbidity index of 0. Regarding the severity of acute COVID-19, 147 patients (72.1%) had mild disease, 49 (24.0%) had moderate disease, and 8 (3.9%) had severe disease. The median Ct value was 25.55 (IQR, 19.10-29.90). Most patients ($n = 147$; 72.1%) received treatment during acute COVID-19, usually with interferon beta-1b ($n = 126$; 61.8%) and ribavirin ($n = 98$; 48.0%). The median length of stay was 8 days (IQR, 6-12). Only 5 patients required intensive care unit admission.

In the matched inclusion period (from July 21, 2020, to December 21, 2020), we identified 5199 adult patients with COVID-19 who were admitted to other centers with valid Ct values. Comparison with our cohort ($n = 204$) revealed a comparable sex distribution (46.6% male in our cohort vs 47.5% male in other

Table 1
Baseline Characteristics of the Cohort

Clinical parameters	All	Symptomatic in acute COVID-19 illness (group A)	Asymptomatic in acute COVID-19 illness (group B)	*P* value[a]
Number	204	172	32	…
Age, y	55.0 (44.3-63.0)	56.0 (45.0-63.0)	53.5 (32.0-64.5)	.243
Female	109 (53.4%)	90 (52.3%)	19 (59.4%)	.463
Charlson comorbidity index				.333
0	157 (77.0%)	132 (76.7%)	25 (78.1%)	
1	27 (13.2%)	21 (12.2%)	6 (18.8%)	
≥2	20 (9.8%)	19 (11.0%)	1 (3.1%)	
Acute COVID-19 illness				
Baseline clinical severity				<.001[b]
Mild	147 (72.1%)	115 (66.9%)	32 (100%)	
Moderate	49 (24.0%)	49 (28.5%)	0 (0%)	
Severe	8 (3.9%)	8 (4.7%)	0 (0%)	
SARS-CoV-2 PCR Ct value	25.55 (19.10-29.90)	23.85 (19.00-28.51)	28.48 (17.97-33.05)	.199
TSH (mIU/L)	1.10 (0.76-1.70)	1.10 (0.72-1.68)	1.30 (1.00-1.88)	.080
fT4 (pmol/L)	17 (16-19)	17 (16-19)	18 (16-20)	.470
fT3 (pmol/L)	4.1 (3.5-4.5)	4.0 (3.4-4.4)	4.3 (3.9-4.9)	.002[b]
Abnormal TFT	43 (21.1%)	38 (22.1%)	5 (15.6%)	.410
Anti-TPO positivity	40/200 (20.0%)	32/171 (18.7%)	8/29 (27.6%)	.269
Anti-Tg positivity	21/200 (10.5%)	18/171 (10.5%)	3/29 (10.3%)	.999
ANA positivity	20/80 (25.0%)	16/69 (23.2%)	4/11 (36.4%)	.454
COVID-19 treatment	147 (72.1%)	129 (75.0%)	18 (56.3%)	.030[b]
Reassessment				
Interval from acute COVID-19 (days)	89 (69-99)	90 (71-101)	88 (33-97)	.390
Long COVID	41 (20.1%)	34 (19.8%)	7 (21.9%)	.785
TSH (mIU/L)	1.40 (0.95-1.98)	1.45 (0.96-2.00)	1.40 (0.88-1.78)	.512
fT4 (pmol/L)	17 (16-19)	17 (15-19)	18 (16-19)	.199
fT3 (pmol/L)	4.7 (4.4-5.1)	4.7 (4.3-5.0)	4.9 (4.4-5.2)	.187
Abnormal TFT	12 (5.9%)	11 (6.4%)	1 (3.1%)	.696
Anti-TPO positivity	38/162 (23.5%)	28/139 (20.1%)	10/23 (43.5%)	.014[b]
Anti-Tg positivity	18/162 (11.1%)	16/139 (11.5%)	2/23 (8.7%)	.999

Abbreviations: ANA = antinuclear antibody; COVID = coronavirus disease; COVID-19 = coronavirus disease 2019; Ct = cycle threshold; fT3 = free triiodothyronine; fT4 = free thyroxine; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TFT = thyroid function test; Tg = thyroglobulin; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

[a] Comparison between groups A and B.

[b] Statistically significant ($P > .05$).

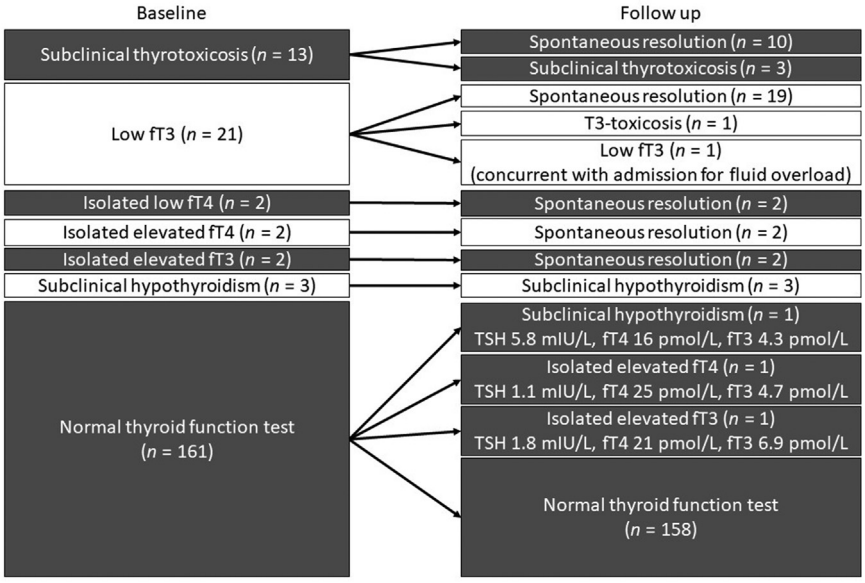

Fig. The evolution of thyroid function in all 204 patients. *fT3* = free triiodothyronine; *fT4* = free thyroxine; *T3* = triiodothyronine; *TSH* = thyroid-stimulating hormone.

centers; $P = .788$) and baseline Ct values (25.55 [IQR, 19.10-29.90] in our cohort vs 23.24 [IQR, 18.60-28.92] in other centers; $P = .245$), although patients admitted to other centers were slightly younger (49.0 years [IQR, 35.0-62.0] in other centers vs 55.0 years [IQR, 44.3-63.0] in our cohort; $P < .001$).

Results of Reassessment

Upon reassessment at a median interval of 89 days (IQR, 69-99) after acute COVID-19, 41 patients (20.1%) reported at least 1 symptom upon reassessment, that is, having long COVID. Symptoms, in descending order of frequency, included dyspnea ($n = 16$), cough ($n = 16$), anosmia ($n = 11$), malaise/fatigue ($n = 7$), loose stools ($n = 1$), headache ($n = 1$), and palpitation ($n = 1$). Regarding symptom burden, 31 patients reported 1 symptom, 8 reported 2 symptoms, and 2 reported 3 symptoms.

The evolution of the TFTs in all 204 patients has been summarized in the Figure. Of the 204 patients, 43 had abnormal TFTs on admission for acute COVID-19; 35 of them (81.4%) recovered spontaneously, subsequently. Thirteen patients had subclinical thyrotoxicosis in acute COVID-19; 10 of them spontaneously resolved upon follow-up, whereas 3 remained in subclinical thyrotoxicosis. Twenty-one patients had isolated low fT3 levels, suggestive of nonthyroidal illness; of these patients, 19 recovered. One patient had nonthyroidal illness upon reassessment when he was admitted for fluid overload and was clinically ill. In the other patient, triiodothyronine toxicosis developed at 3 months, followed by spontaneous resolution 3 months later, suggestive of painless thyroiditis. Six patients had isolated mildly abnormal fT4 or fT3 levels in acute COVID-19; all subsequently normalized upon follow-up. All 3 patients with subclinical hypothyroidism in acute COVID-19 had positive anti-TPO, likely representing a pre-existing autoimmune thyroid disorder. All 3 patients had persistent subclinical hypothyroidism upon reassessment; 1 required thyroxine replacement because their TSH level was persistently >10 mIU/L. Incident TFT abnormalities detectable at 3 months were rare. Among 161 patients with normal TFTs in acute COVID-19, only 3 (1.9%) had abnormal TFTs upon follow-up: 1 had subclinical hypothyroidism (TSH, 5.8 mIU/L; fT4, 16.0 pmol/L; fT3, 4.3 pmol/L), 1 had mildly elevated fT4 (TSH, 1.1 mIU/L; fT4, 25.0 pmol/L; fT3, 4.7 pmol/L), and 1 had mildly elevated fT3 (TSH, 1.8 mIU/L; fT4, 21.0 pmol/L; fT3, 6.9 pmol/L). Although the TFT changes in these 3 cases could be compatible with different phases of thyroiditis, in the latter 2 cases, assay variability could not be excluded entirely. None of these 3 patients required treatment.

In total, 159 of all 204 patients (77.9%) had anti-TPO and anti-Tg assessed at baseline and follow-up. Baseline characteristics were largely comparable between patients with and without anti-TPO data—percentage of male ($P = .988$), clinical severity of COVID-19 ($P = .860$), SARS-CoV-2 PCR Ct value ($P = .849$), and Charlson comorbidity index ($P = .562$)—except for younger age in those with missing anti-TPO data (49.0 years [IQR, 36.0-61.5] vs 57.0 years [IQR, 46.0-64.0]; $P = .029$). Among the 159 patients with paired antithyroid antibody data, 32 were positive for anti-TPO and 18 were positive for anti-Tg in acute COVID-19. Interestingly, in 7 of the 127 patients (5.5%) with a negative anti-TPO in acute COVID-19, incident anti-TPO positivity developed upon follow-up, whereas only 1 patient positive for anti-TPO in acute COVID-19 became negative upon follow-up. On the other hand, regarding anti-Tg status, only 1 patient's anti-Tg status changed from negative to positive, and another patient's anti-Tg status changed from positive to negative.

Predictors of Long COVID

We compared patients who did and did not have symptoms upon follow-up (Table 2). We observed female preponderance, higher viral load (represented by Ct value <25), and a higher likelihood of exposure to COVID-19 treatment among those who reported symptoms at the follow-up. Of note, baseline clinical severity ($P = .508$), symptom burden ($P = .293$), laboratory parameters, elevated CRP levels ($P = .233$), chest radiograph severity ($P = .822$), requirement of prolonged stay (≥14 days; $P = .471$), and intensive care unit admission ($P = .056$) in acute COVID-19 were not different between patients with and without long COVID. Elevated CRP levels ($P = .347$), anti-SARS-CoV-2 RBD IgG positivity ($P = .613$), and chest x-ray resolution ($P = .699$) upon follow-up were also not different between patients who did and did not have long COVID. Besides, TFTs and antithyroid antibodies did not differ between the 2 groups. In the multivariable logistic regression analysis, both female (adjusted odds ratio [aOR], 2.48; 95% CI, 1.17-5.27; $P = .018$)

Table 2
Comparison of Clinical Characteristics Between Patients Who Did and Did Not Have Post–Acute COVID-19 Symptoms ($n = 204$)

Clinical parameters	Long COVID	Symptoms resolved	*P* value
Number	41	163	…
Age, >50 y	21 (51.2%)	110 (67.5%)	.052
Female	28 (68.3%)	81 (49.7%)	.033[a]
Charlson comorbidity index			.135
0	28 (68.3%)	129 (79.1%)	…
1	7 (17.1%)	20 (12.2%)	
≥2	6 (14.6%)	14 (8.6%)	
Acute COVID-19 illness			
Ct value <25	30 (73.2%)	78 (47.9%)	.005[a]
TSH (mIU/L)	1.10 (0.85-1.60)	1.10 (0.66-1.70)	.952
fT4 (pmol/L)	17 (15-19)	17 (16-19)	.999
fT3 (pmol/L)	4.0 (3.4-4.3)	4.0 (3.4-4.4)	.643
Abnormal TFT	6 (14.6%)	37 (22.7%)	.258
Anti-TPO positivity	4/39 (10.3%)	36/161 (22.4%)	.118
Anti-Tg positivity	3/39 (7.7%)	18/161 (11.2%)	.771
ANA positivity	2/17 (11.8%)	18/63 (28.6%)	.214
COVID-19 treatment	35 (85.4%)	112 (68.7%)	.034[a]
Interferon	29 (70.7%)	97 (59.5%)	.186
Ribavirin	22 (53.7%)	76 (46.6%)	.420
Remdesivir	9 (22.0%)	30 (18.4%)	.606
Dexamethasone	6 (14.6%)	22 (13.5%)	.850
Clofazimine	1 (2.4%)	4 (2.5%)	.999
Reassessment			
Interval from acute COVID-19 (d)	89 (73-99)	89 (63-101)	.823
TSH (mIU/L)	1.50 (0.91-2.05)	1.40 (0.99-1.90)	.894
fT4 (pmol/L)	17 (16-18)	17 (15-19)	.775
fT3 (pmol/L)	4.6 (4.2-4.9)	4.7 (4.4-5.2)	.174
Abnormal TFT	2 (4.9%)	10 (6.1%)	.999
Anti-TPO positivity	4/32 (12.5%)	34/130 (26.2%)	.160
Anti-Tg positivity	2/32 (6.25%)	16/130 (12.3%)	.530

Abbreviations: ANA = antinuclear antibody; COVID = coronavirus disease; COVID-19 = coronavirus disease 2019; Ct = cycle threshold; fT3 = free triiodothyronine; fT4 = free thyroxine; TFT = thyroid function test; Tg = thyroglobulin; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.
[a] Statistically significant ($P > .05$).

and Ct value of <25 (aOR, 2.84; 95% CI, 1.26-6.42; $P = .012$) independently predicted the occurrence of long COVID, whereas COVID-19 treatment was no longer an independent predictor of long COVID ($P = .272$).

According to the definition of long COVID, the 204 patients identified in this study were categorized into those who were symptomatic in the acute COVID-19 (group A; $n = 172$) and those who had asymptomatic mild acute COVID-19 (group B; $n = 32$).[4]

In group A (Table 3), patients who experienced persistent symptoms upon follow-up were more likely to be female ($P = .017$) and have a higher viral load in acute COVID-19 ($P = .004$), consistent with the findings in the whole cohort. Moreover, we observed a higher proportion of anti-TPO positivity at the baseline and follow-up among patients whose symptoms subsequently resolved, although complete anti-TPO data were only available for approximately 80% of the cohort. Regarding the clinical course of acute COVID-19, there was no difference in the baseline clinical severity ($P = .538$), symptom burden ($P = .165$), elevated CRP levels ($P = .320$), requirement of prolonged stay (≥14 days) ($P = .351$), and intensive care unit admission ($P = .053$). Upon follow-up, there was no difference in the proportion of patients with elevated CRP levels ($P = .257$), anti-SARS-CoV-2 RBD IgG positivity ($P = .977$), and chest x-ray resolution ($P = .464$). In the multivariable logistic regression model, including female, Ct value of <25, and exposure to COVID-19 treatment, the independent predictors of symptom persistence were female (aOR, 2.88; 95% CI, 1.25-6.65; $P = .013$) and Ct value of <25 (aOR, 3.13; 95% CI, 1.24-7.90; $P = .015$) but not exposure to COVID-19 treatment ($P = .318$). To explore the potential role of anti-TPO in symptom persistence, we analyzed a subgroup of 138 patients who had complete anti-TPO status at baseline and reassessment (Table 4). Patients with symptom persistence had a higher Charlson comorbidity index ($P = .048$) and higher viral load in acute COVID-19 ($P = .016$). There was no difference in the baseline clinical severity ($P = .232$), symptom burden ($P = .318$), CRP elevation ($P = .640$), requirement of prolonged stay (≥14 days) ($P = .765$), and intensive care unit admission ($P = .454$) in acute COVID-19. On the follow-up, there was no difference in the proportion of patients with elevated CRP levels ($P = .454$), anti-SARS-CoV-2 RBD IgG positivity ($P = .999$), and chest x-ray resolution ($P = .635$). On the other hand, more patients with symptom resolution had positive anti-TPO at the baseline ($P = .046$) and follow-up ($P = .027$). As anti-TPO positivity at the baseline and follow-up showed a significant and strong correlation (Kendall tau-b = 0.886; $P < .001$), anti-TPO positivity at the baseline and follow-up were separately entered into the multivariable logistic regression analysis models comprising the Charlson comorbidity index and viral load. In the former model, only Ct value of <25 (aOR, 2.88; 95% CI, 1.04-7.99; $P = .043$) remained to be the significant factor associated with symptom persistence but not baseline anti-TPO positivity (aOR, 0.15; 95% CI, 0.18-1.17; $P = .070$) or Charlson comorbidity index ($P = .323$). In the latter model, both Ct value of <25 (aOR, 2.83; 95% CI, 1.02-7.86; $P = .046$) and anti-TPO positivity at follow-up (aOR, 0.12; 95% CI, 0.01-0.94; $P = .043$) were associated with symptom persistence but not the Charlson comorbidity index ($P = .229$).

In group B, the clinical characteristics at baseline and follow-up were not different between patients who remained asymptomatic and those in whom new symptoms developed (data have not been shown).

Discussion

Our study added to the current growing literature on long COVID. We reported a 20% prevalence of long COVID, predicted by

Table 3
Comparison of Clinical Characteristics Between Patients Who Did and Did Not Have Persistent Post–Acute COVID-19 Symptoms ($n = 172$)

Clinical parameters	Long COVID	Symptoms resolved	*P* value
Number	34	138	…
Age, >50 y	18 (52.9%)	95 (68.8%)	.080
Female	10 (29.4%)	72 (52.2%)	.017[a]
Charlson comorbidity index			.070
0	22 (64.7%)	110 (79.7%)	…
1	6 (17.6%)	15 (10.9%)	
≥2	6 (5.9%)	13 (9.4%)	
Acute COVID-19 illness			
Ct value <25	26 (76.5%)	68 (49.3%)	.004[a]
TSH (mIU/L)	1.10 (0.85-1.60)	1.10 (0.66-1.70)	.952
fT4 (pmol/L)	17 (15-19)	17 (16-19)	.999
fT3 (pmol/L)	4.0 (3.4-4.3)	4.0 (3.4-4.4)	.643
Abnormal TFT	5 (14.7%)	33 (23.9%)	.246
Anti-TPO positivity	2/33 (6.1%)	30/138 (21.7%)	.046[a]
Anti-Tg positivity	3/33 (9.1%)	15/138 (10.9%)	.999
ANA positivity	1/14 (7.1%)	15/55 (27.3%)	.162
COVID-19 treatment	30 (88.2%)	99 (71.7%)	.049[a]
Interferon	25 (73.5%)	86 (62.3%)	.221
Ribavirin	18 (52.9%)	65 (47.1%)	.542
Remdesivir	8 (23.5%)	28 (20.3%)	.677
Dexamethasone	6 (17.6%)	22 (15.9%)	.809
Clofazimine	1 (2.9%)	4 (2.9%)	.999
Reassessment			
Interval from acute COVID-19 (d)	90 (73-97)	90 (68-101)	.844
TSH (mIU/L)	1.55 (0.95-2.10)	1.40 (0.98-2.00)	.581
fT4 (pmol/L)	17 (16-18)	17 (15-19)	.946
fT3 (pmol/L)	4.6 (4.2-4.9)	4.7 (4.4-5.1)	.297
Abnormal TFT	1 (2.9%)	10 (7.2%)	.695
Anti-TPO positivity	1/24 (4.2%)	26/108 (24.1%)	.027[a]
Anti-Tg positivity	2/24 (8.3%)	13/108 (12.0%)	.999

Abbreviations: ANA = antinuclear antibody; COVID = coronavirus disease; COVID-19 = coronavirus disease 2019; Ct = cycle threshold; fT3 = free triiodothyronine; fT4 = free thyroxine; TFT = thyroid function test; Tg = thyroglobulin; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.
[a] Statistically significant ($P > .05$).

female and higher SARS-CoV-2 viral loads factors. Importantly, our study was the first to investigate the potential role of thyroid function and autoimmunity in long COVID. We demonstrated that, on follow-up, most thyroid dysfunction in acute COVID-19 had recovered spontaneously, and incident thyroid dysfunction was relatively rare. Nonetheless, we observed incident anti-TPO positivity upon follow-up. Interestingly, subgroup analysis revealed that symptom resolution was more likely among patients with positive anti-TPO at the time of reassessment, suggesting a potential protective role of anti-TPO in long COVID.

An accurate estimate of the prevalence of long COVID provides essential information to health care authorities for resource planning. The prevalence of long COVID may vary with the different populations studied, the interval from acute COVID-19 to reassessment, and the study instruments used.[24] Earlier studies in the United States, Europe, and China have revealed a prevalence varying from one third to nearly 90%, with the higher prevalence usually reported among cohorts of patients with a more severe acute COVID-19.[2] Our reported prevalence of 20% was at the lower end of this range, which could be explained by the less severe disease spectrum and lower symptom burden in acute COVID-19 in our cohort. This prevalence likely applies to the general population for several reasons. First, vigorous contact tracing by the Centre of Health Protection and active surveillance with the Universal Community Testing Programme, followed by early quarantine and isolation, likely allowed identification of most patients with COVID-19 in the territory. Second, most patients with COVID-19 belonged to the mild disease spectrum.[25] Third, our cohort was largely similar to patients with COVID-19 admitted to other centers in Hong Kong in terms of sex and initial Ct values, except that patients in our cohort were slightly older. We were not able to compare the clinical severity of COVID-19 between our cohort and patients admitted to other centers. Nonetheless, admission to centers for COVID-19 management was arranged according to patients' area of residence and the occupancy of the individual centers but not according to clinical severity. Furthermore, the initial Ct values were similar among patients admitted to our center and those admitted to other centers. As Ct values have been reported to correlate with COVID-19 severity, we do not expect a significant inter-center difference in the clinical severity of COVID-19.[23] Our list of reported symptoms of long COVID was consistent with that of the existing studies, with dyspnea, cough, anosmia/ageusia, and fatigue/malaise more commonly reported.[2]

Although much has been focused on the description of long COVID, the predictors of long COVID still require active research. A large contemporary symptom-based prospective observational cohort study for long COVID in the United Kingdom revealed that older age, higher body mass index, female sex, and high symptom burden during acute COVID-19 predicted long COVID.[26] We took a step further to include a panel of laboratory parameters, viral loads, immune profiles, and radiologic assessments in the study of predictors of long COVID, which may unveil mechanisms of long COVID and improve risk stratification. Consistent with the United Kingdom study, our study showed that female sex was a predictor of long COVID.[26] In addition, a higher baseline SARS-CoV-2 viral load predicted long COVID. Our finding echoed another single-center longitudinal study in China that showed that viral shedding time in acute COVID-19 was associated with specific symptoms upon follow-up (physical decline/fatigue or postactivity polypnoea).[27] On the other hand, we did not identify any association among the panel of hematologic, biochemical, inflammatory, and radiologic markers with the presence of long COVID. These findings may support the hypothesis of a direct viral effect in the pathogenesis of long COVID, analogous to the postulated potential

Table 4
Subgroup Analysis of Patients in Group A With Complete Anti-TPO ($n = 138$)

Clinical parameters	Long COVID	Symptoms resolved	*P* value
Number	25	113	…
Age, >50 y	15 (60.0%)	81 (71.7%)	.251
Female	16 (64.0%)	56 (49.6%)	.191
Charlson comorbidity index			.048[a]
0	16 (64.0%)	91 (80.5%)	…
1	5 (20.0%)	13 (11.5%)	
≥2	4 (16.0%)	9 (8.0%)	
Acute COVID-19 illness			
Ct value <25	19 (76.0%)	56 (49.6%)	.016[a]
TSH (mIU/L)	1.20 (0.77-1.60)	1.05 (0.63-1.70)	.446
fT4 (pmol/L)	18 (16-19)	17 (16-19)	.748
fT3 (pmol/L)	3.8 (3.3-4.1)	4.0 (3.5-4.4)	.398
Abnormal TFT	4 (16.0%)	23 (20.4%)	.784
Anti-TPO positivity	1 (4.0%)	24 (21.2%)	.046[a]
Anti-Tg positivity	2 (8.0%)	14 (12.4%)	.736
ANA positivity	1/11 (9.1%)	10/49 (20.4%)	.670
COVID-19 treatment	22 (88.0%)	86 (76.1%)	.284
Interferon	20 (80.0%)	78 (69.0%)	.274
Ribavirin	17 (68.0%)	60 (53.1%)	.175
Remdesivir	3 (12.0%)	21 (18.6%)	.567
Dexamethasone	4 (16.0%)	17 (15.0%)	.999
Clofazimine	1 (4.0%)	4 (3.5%)	.999
Reassessment			
Interval from acute COVID-19 (d)	91 (84-98)	92 (83-102)	.682
TSH (mIU/L)	1.40 (0.92-2.08)	1.45 (0.93-2.00)	.754
fT4 (pmol/L)	17 (16-18)	17 (15-19)	.668
fT3 (pmol/L)	4.7 (4.3-4.9)	4.7 (4.4-5.2)	.668
Abnormal TFT	1 (4.0%)	7 (6.2%)	.999
Anti-TPO positivity	1 (4.0%)	27 (23.9%)	.027[a]
Anti-Tg positivity	2 (8.0%)	14 (12.4%)	.736

Abbreviations: ANA = antinuclear antibody; COVID = coronavirus disease; COVID-19 = coronavirus disease 2019; Ct = cycle threshold; fT3 = free triiodothyronine; fT4 = free thyroxine; TFT = thyroid function test; Tg = thyroglobulin; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.
[a] Statistically significant ($P > .05$).

of severe acute respiratory syndrome coronavirus 1 for direct neuroinvasion, causing persistent neuropsychiatric sequelae such as postviral fatigue syndrome.[28,29] Moreover, the findings of our study carry potential implications in encouraging clinicians to be alerted to the Ct values reported upon the diagnosis of COVID-19 and to triage female patients with higher initial SARS-CoV-2 viral loads for a more comprehensive assessment and post–acute COVID care.[30]

Although thyroid dysfunction in acute COVID-19 has been better characterized with results from various cohorts, evidence on the longer-term impact of COVID-19 on the thyroid is still eagerly awaited.[7] The latest data from an Italian cohort of 51 patients with COVID-19, presented in ENDO 2021 in March 2021, showed that both inflammatory markers and thyroid function normalized at 3 months; however, one third of patients still had focal hypoechoic areas on thyroid ultrasonography, suggestive of thyroiditis. This ultrasonographic finding has raised concern for the need for longer-term monitoring for potential incident thyroid dysfunction. Our study findings were in agreement with those of the follow-up study that most thyroid dysfunction in acute COVID-19 recovered and that incident thyroid dysfunction was rare. Furthermore, our novel observation of incident anti-TPO positivity post–acute COVID-19 suggested potential perturbation of thyroid autoimmunity after COVID-19, and an additional concern for potential incident thyroid dysfunction as the occurrence of anti-TPO can precede thyroid dysfunction.[31] Hence, our data further supported the need for follow-up TFTs.

Interestingly, anti-TPO positivity at 3 months was associated with a higher likelihood of symptom resolution among patients who were symptomatic in acute COVID-19. A trend toward statistical significance was observed for baseline anti-TPO positivity with symptom resolution. This phenomenon appeared to be confined to thyroid-specific antibodies as no statistically significant difference in antinuclear antibody positivity was observed between patients with and without long COVID. Furthermore, no difference in anti-SARS-CoV-2 RBD IgG positivity was observed between the 2 groups either. A cross-sectional study of 641 community-dwelling older women demonstrated a lower prevalence of frailty with the positivity of thyroid-specific autoantibodies (anti-TPO and anti-Tg) but not with antinuclear antibody positivity (a marker of systemic autoimmunity), independent of thyroid function status.[32] Some symptoms of long COVID, such as malaise/fatigue, are common with features of frailty, such as reduced physical strength and low energy levels. Whether some form of beneficial autoimmunity may play a role in the link between anti-TPO positivity and long COVID remained to be determined. Chronic use of interferon beta-1b was reported to be associated with altered thyroid function and autoimmunity; however, a greater number of patients in the long COVID group were treated with interferon than those with symptom resolution.[33] Hence, the association between anti-TPO positivity and symptom resolution was less likely confounded by the effect of interferon beta-1b on anti-TPO positivity. Nonetheless, the possibility of other residual confounders not measured in this study cannot be excluded.

The strengths of our study included the following. First, we described the prevalence and predictors of long COVID predominantly among patients with mild to moderate disease, generalizable to patients with COVID-19 at large. Second, our study findings were based on structured face-to-face assessments, including blood tests for inflammatory markers and SARS-CoV-2 antibodies and chest x-rays, which allowed a systematic evaluation of residual objective abnormalities post–acute COVID-19, beyond symptoms perceived by patients. Third, our study was

the first to evaluate the role of thyroid function and autoimmunity in long COVID, revealing interesting observations of incident thyroid autoimmunity post–acute COVID-19 and a potential protective role of anti-TPO in long COVID. Nevertheless, our study findings should be interpreted bearing certain limitations. First, SARS-CoV-2 viral loads were represented by Ct values. Despite good correlation, direct quantitative measurements of viral loads would have been preferable, if available.[14,15] Second, obesity, which has been reported to be associated with long COVID, was defined by the 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.[26] Third, high-resolution computed tomography was performed at the physicians' discretion. Thus, the detection of imaging features of pneumonia in our cohort might be less sensitive. Fourth, a control group of non–COVID-19 pneumonia patients was not available for further characterization of the long-term impact of COVID-19. Fifth, we did not have data on the background rate of anti-TPO positivity in the community; however, this has been reported to be 11% to 12% in Taiwan, a region also consisting of Han Chinese and geographically situated near Hong Kong.[34] Although the rate of positive anti-TPO in our cohort (20%) appeared higher than the reported background rate of anti-TPO positivity in Taiwan, a direct comparison was not possible. Lastly, our findings were based on a single-center study with relatively small sample size and follow-up duration of approximately 3 months. Studies with larger sample size and longer follow-up are necessary to provide more definitive conclusions.

In conclusion, long COVID was not uncommon, with female sex and higher viral load in acute COVID-19 being the risk factors. Most thyroid dysfunction during acute COVID-19 recovered. Though incident thyroid dysfunction was rare, we observed incident anti-TPO positivity, suggesting the possibility of COVID-19 triggering autoimmunity. Patients with anti-TPO positivity at reassessment were more likely to have a symptom resolution, the significance of which remains to be elucidated.

Author Contributions

D.T.W.L. wrote the manuscript. D.T.W.L., C.H.L., W.S.C., A.C.H.L, A.R.T., C.Y.L., and E.K.H.L. researched the data. D.T.W.L. and C.H.Y.F. performed statistical analyses. C.H.L., W.S.C., A.C.H.L., K.K.W.T., K.C.B.T., Y.C.W., C.W.L., I.F.N.H., and K.S.L.L. critically reviewed and edited the manuscript. K.S.L.L. initiated and supervised the study, is the guarantor of this work, and as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure

The authors have no multiplicity of interest to disclose.

Data Availability

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

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