Subacute thyroiditis following recovery from COVID-19 infection: novel clinical findings from an Eastern Indian cohort

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ABSTRACT

Objective Recent reports have suggested a link between COVID-19 infection and subacute thyroiditis (SAT). We aimed to describe variations in clinical and biochemical parameters in patients developing post-COVID SAT.

Design Ours was a combined retrospective-prospective study on patients presenting with SAT within 3 months of recovery from COVID-19 infection, who were subsequently followed up for a further 6 months since diagnosis of SAT.

Results Out of 670 patients with COVID-19, 11 patients presented with post-COVID-19 SAT (6.8%). Those with painless SAT (PLSAT, n=5) presented earlier, had more severe thyrotoxic manifestations and exhibited higher C-reactive protein, interleukin 6 (IL-6), neutrophil-lymphocyte ratio and lower absolute lymphocyte count than those with painful SAT (PFSAT, n=6). There were significant correlations of total and free T4 and total and free T3 levels with serum IL-6 levels (p_{all} <0.04). No differences were observed between patients with post-COVID SAT presenting during the first and second waves. Oral glucocorticoids were needed for symptomatic relief in 66.67% of patients with PFSAT. At 6 months of follow-up, majority (n=9, 82%) achieved euthyroidism, while subclinical and overt hypothyroidism were found in one patient each.

Conclusions Ours is the largest single-centre cohort of post-COVID-19 SAT reported until, demonstrating two distinct clinical presentations—without and with neck pain—depending on time elapsed since COVID-19 diagnosis. Persistent lymphopaenia during the immediate post-COVID recovery period could be a key driver of early,painless SAT. Close monitoring of thyroid functions for at least 6 months is warranted in all cases.

INTRODUCTION

The SARS-CoV-2 virus has been shown to affect multiple endocrine organs including the thyroid.[1 2] Diverse alterations of thyroid functions have been observed during and following COVID-19 infection, of which some are transient while others are associated with a permanent sequelae.[1 2] Subacute thyroiditis (SAT) is a form of granulomatous thyroiditis which can occur during or after a viral illness.[3] Several case reports of post-COVID thyroiditis have been published, and potential pathophysiological mechanisms have been proposed. The ACE2 and transmembrane serine protease 2 (TMPRSS2), which serve as entry points for the SARS-CoV-2, have been identified in the thyroid follicular cells, and their expression levels have been found to be even higher than that in the lungs, though their exact pathogenetic role in post-COVID thyroiditis warrants further investigations.[4]

Thyroiditis has been reported both during the active phase as well as postviral follow-up phase after COVID-19 infection. The initial reports of COVID-19-associated SAT were suggestive of a similar presentation to other aetiologies of postviral SAT, with neck pain being a prominent feature.[5–7] However, in a recent observational study on patients admitted with COVID-19 in the intensive care units (ICUs), the authors have reported an atypical 'painless' presentation with the absence of local symptoms.[8] The few cases of COVID-19-related thyroiditis reported from various parts of India almost uniformly presented with significant neck pain, though differing in other clinical and biochemical features.[9 10]

In this study, we aimed to assess the diverse clinical and biochemical characteristics in patients presenting with SAT within 3 months of recovery from COVID-19 infection, and compare these characteristics between painless and painful varieties of SAT, as also between those presenting during the first and second waves of COVID-19, respectively. Further, prospective evaluation of these patients for further 6 months was done to elucidate progressive changes in their clinical and biochemical characteristics.

METHODOLOGY

Study design

This was a combined retrospective-prospective study conducted over a period of 20 months since April 2020 to November 2021. Initially, a retrospective review of electronic records of all patients, attending a tertiary care hospital in Eastern India with an reverse transcription PCR (RT-PCR) confirmed diagnosis of COVID-19 between April 2020 and May 2021, was done. The study included only those patients for whom data were available regarding pre-COVID-19 thyroid function tests (TFTs), evidence of recovery from COVID-19 in the form of a negative SARS-CoV-2 RT-PCR test and at least 3 months of follow-up data after recovery from COVID-19 infection. Patients with a clinical and biochemical diagnosis of SAT within 3 months of recovery from COVID-19 infection were included in the final analysis (figure 1). Patients with known pre-existing thyroid disorders or on medications for the same, history of COVID-19 vaccination, history

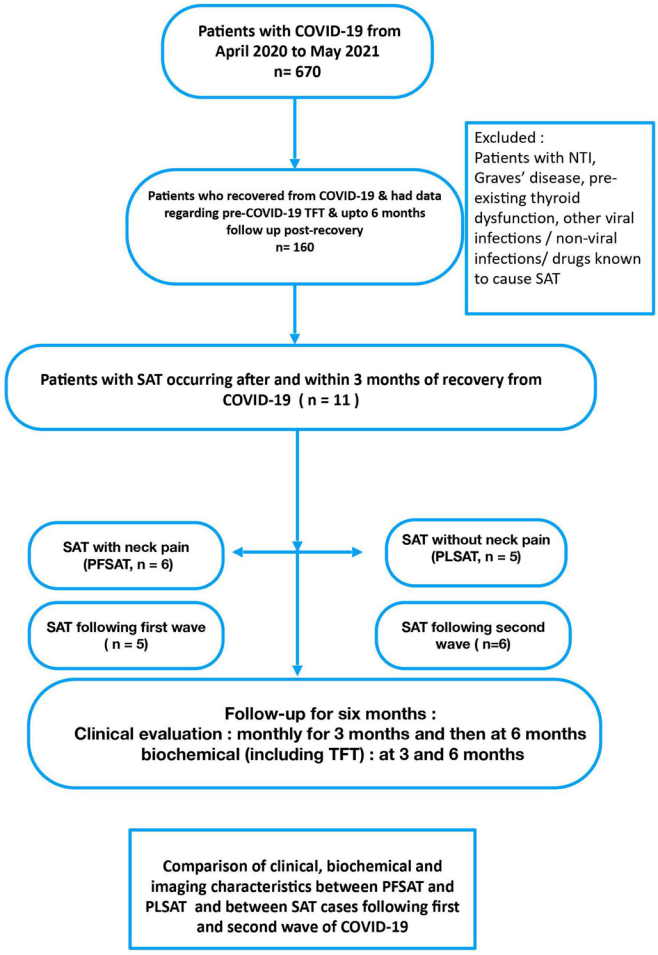

Figure 1 Study design. NTI, non-thyroidal illness; PFSAT, painful subacute thyroiditis; PLSAT, painless subacute thyroiditis; SAT, subacute thyroiditis; TFT, thyroid function test.

of other non-COVID-19 viral or bacterial infections (recurrence of fever with sore throat or skin rash or joint pains or any localised source of infections) or disorders known to cause SAT (eg, malaria, vasculitis) and history of having received medications like interferons or immunosuppressants within the time period between recovery from COVID-19 and the diagnosis of SAT were excluded. We also excluded patients with low thyroid-stimulating hormone (TSH) due to non-thyroidal illness, the latter being diagnosed by a combination of low TSH with low total and free T3, low or normal total and free T4 and normal ultrasonography (USG) Doppler of the thyroid gland. Those with hyperthyroidism due to Graves' disease, diagnosed from clinical findings of thyroid-associated orbitopathy, dermopathy or clubbing with positive TSH-receptor antibody (TRAb)(TRAb >1.22 IU/L) and/or increased vascularity on USG colour Doppler and/or increased 99mTc scan uptake were also excluded.

Patients thus included were prospectively followed up monthly for 3 months and then at 6 months following the diagnosis of SAT in the Endocrinology outpatient clinic. Clinical evaluation was done every month, while biochemical evaluation including TFT, complete blood count (CBC) and erythrocyte sedimentation rate (ESR) were done for all patients at 6 weeks, 3 months and 6 months following diagnosis. All the patients with SAT were started on beta-blockers, while those who had neck pain were initially prescribed non-steroidal anti-inflammatory drugs (NSAIDs) (aceclofenac 100 mg or ibuprofen 200 mg two times per day) for symptomatic relief. Those with persisting symptoms of neck pain or difficulty in swallowing after 5 days of NSAIDs were started on oral glucocorticoids.[3] Prednisolone was started at a dose of 1 mg/kg daily orally (with a maximum initial dose of 50 mg) which was continued for 10 days, followed by a rapid taper over a period of 4–6 weeks, depending on the clinical response.[3]

Definitions used

Diagnosis of COVID-19 infection was based on positive results of oropharyngeal and nasopharyngeal swab samples, assessed by PCR test for SARS-CoV-2 on an isothermal cartridge-based nucleic acid amplification test. Recovery from COVID-19 was defined as the absence of fever and a documented negative COVID-19 RT-PCR report.[11] Severity of COVID-19 was defined as per national guidelines.[11] The study period encompassed two periods of significant upsurge of COVID-19 cases in the country, described as the first and second waves, occurring during the months of September 2020 to January 2021 and March 2021 to July 2021, respectively.[12–14]

We considered patients to be having a diagnosis of SAT if they had a combination of features including at least one each of the following clinical, imaging and biochemical findings:

- Clinical findings included neck pain, palpable thyroid swelling, symptoms of thyrotoxicosis, including palpitations, new-onset heart failure, ECG documentation of atrial fibrillation or sinus tachycardia, weight loss with increasing appetite, new-onset tremor, hyperdefecation or fever.
- Biochemical abnormalities included raised ESR and/or C reactive protien (CRP) values along with TFTs consistent with a diagnosis of SAT, as evidenced by a low TSH along with raised total T4 and/or free T4, raised/normal total T3 and/or free T3 levels, T3 (ng/dL) to T4 (μg/dL) ratio of less than 20[3 15] and TRAb levels <1.22 IU/L.
- Imaging abnormalities included an USG with colour Doppler of the thyroid suggestive of heterogeneous echotexture and reduced vascularity in a diffusely enlarged or normal-sized thyroid gland, and/or a 99mTc thyroid uptake study showing patchy uptake with the overall uptake value of less than 5%.

In addition, anti-thyroid peroxidase antibodies (anti-TPO-Abs), ESR, interleukin 6 (IL-6), CRP, absolute lymphocyte count (ALC) and neutrophil-lymphocyte ratio (NLR) levels (calculated from the CBC) were obtained in all patients at the time of diagnosis of SAT. Patients who had neck pain at the time of diagnosis of SAT were designated as painful SAT (PFSAT) and those without neck pain as painless SAT (PLSAT).

Assay methods

Serum TSH, total and free T4, total and free T3, anti-TPO Ab and TRAb tests were done using electrochemiluinescence assay on Roche E411 analyser (Roche Diagnostics, Switzerland; Co-efficient of variation [(CV) 3%)]. Anti-TPO Ab was considered positive if values were more than 35 IU/mL and TSH-receptor antibody was considered positive at a level >1.22 IU/L. Total and differential blood counts were done using electrical impedance and DII channel scattergram using SYSMEX XN 350 analyser (CV 2.5%). Serum CRP was measured using particle-enhanced immunoturbidimetry by Integra 400+ analyser. Serum IL-6 was estimated by eletrochemiluminescenece assay using Cobas e411 analyser (Roche Diagnostics; CV 2.5%), while ESR was measured by modified Westergren tube (Vesmatic 30; CV 15%). Diagnostic ultrasound imaging of the thyroid was performed with the Philips Affinity 70G model with 8 MHz linear probes,

and vascularity assessed in colour Doppler mode. Diagnostic radionuclide scintigraphy of the thyroid was done using 4.4 mCi 99mTcO4, with overall uptake values exceeding 5% considered as increased thyroid uptake.

Statistical methods

Comparisons of clinical and biochemical characteristics between PFSAT and PLSAT were done using unpaired t-test (or Mann-Whitney when non-parametric) for quantitative variables and Fisher's exact test for categorical variables. Results were expressed as mean (SD) for quantitative variables. Correlation between variables was expressed using Spearman's r correlation coefficient. Statistical analysis was done using GraphPad Prism V.8 for Mac with $p<0.05$ considered significant.

RESULTS

Out of a total of 670 patients with COVID-19 infection who visited the hospital during the study period, baseline TFTs and adequate follow-up data for 6 months after recovery were available for n=160 patients. Among the latter, a total of 11 patients (6.8%) were diagnosed with COVID-19-associated thyroiditis, within 3 months of infection. Majority were women (n=7, 63.63%) and the mean age of presentation was 44.09 years (SD: 16.62). Clinical manifestations, biochemical and imaging findings at the time of presentation are summarised in table 1.

The mean duration since recovery from COVID-19 to the diagnosis of SAT was 23.8 days (SD 14.8), with the shortest and longest durations being that of 6 days and 48 days, respectively (table 2). While majority had a history of moderate or severe COVID-19 infection (n=5 for moderate, n=5 for severe cases, 45.4% for both), one case of PFSAT occurred after asymptomatic COVID-19 infection. Four cases with PFSAT (two severe COVID-19, two moderate COVID-19) and two cases of PLSAT (both severe COVID-19) had received oral or parenteral glucocorticoids in the form of either injection methylprednisolone or dexamethasone in their recommended doses during COVID-19 infection.[11]

The mean (SD) total and free T4 levels at the time of presentation were 20.51 μg/dL (5.24) and 2.27 ng/dL (0.76), respectively, while mean total and free T3 levels were 173.49 ng/dL (24.42) and 5.8 pg/mL (2.5), respectively. The mean T3 : T4 (μg/dL : ng/dL) ratio was 8.77 (1.79). While TRAb were negative in all, TPO Abs were seen in three patients. On USG of the thyroid gland, findings included diffuse enlargement of the thyroid gland (n=7, 63.6%), patchy hypoechoic areas (n=11, 100%) and/or reduced vascularity (n=4, 36.4%). All patients with PLSAT and one patient with PFSAT had 99mTc scan of the thyroid gland which revealed overall reduced uptake in the thyroid gland with patchy areas of uptake. The mean values of ESR in first hour, CRP and IL-6 levels were 70 mm (SD: 19.40), 134.22 mg/dL (SD: 108.74) and 77.5 (SD: 46.91), respectively. One patient, aged 69 years, presented with congestive cardiac failure which resolved following correction of the thyrotoxic phase. There were significant correlations of total T4, free T4 and total T3 with serum IL-6 levels (Spearman's $\rho=0.67$, 0.62 and 0.71, respectively, $p_{all}<0.04$) and of free T3 levels with both serum IL-6 and CRP levels (Spearman's $\rho=0.87$ and 0.84, $p_{both}<0.04$).

Comparison between PFSAT and PLSAT

Comparison between patients who presented with PFSAT (n=6) and those with PLSAT (n=5) revealed that the mean duration to onset of SAT since recovery from COVID-19 was significantly lesser for PLSAT (10.6 days vs 34.8 days, $p=0.001$). Patients with PLSAT had significantly higher levels of IL-6, CRP, NLR and lower ALC compared with PFSAT (110 vs 50.4 pg/mL, 212.3 vs 69.1 mg/dL, 2.80 vs 1.83 and 1.59×10^3 vs 2.68×10^3/μL, $p_{all}<0.03$). Clinical and biochemical findings at presentation and final outcomes in the two groups are outlined in table 3. There was a slightly higher prevalence of severe COVID-19 infection in cases of PLSAT compared with those with PFSAT (60% vs 33.3%, $p=0.23$). There were no significant differences in any of the other characteristics including occurrence during the first or second wave of infection. In spite of the small sample size, when analysed separately, the correlation of free T4 with IL-6 levels and of free T3 with CRP levels were found to be significant only for the PLSAT group (Spearman's $\rho=0.9$, $p_{both}<0.04$).

Comparison of SAT cases following COVID-19 infection during first and second waves

There were no significant differences between cases of SAT occurring following COVID-19 infection in the first (n=5) and second waves (n=6) in the country with regards to age, clinical symptomatology, thyroid hormone levels or levels of proinflammatory markers, neither were their final outcomes at 6 months difference ($p_{all}>0.3$). Half of the cases of SAT following COVID-19 during the second wave were PLSAT (n=3 out of 6, 50%) while majority of the SAT cases following COVID-19 during first wave were PFSAT (n=4 out of 5, 80%).

Outcome of patients

Out of the six patients presenting with PFSAT, four patients (66.7 %) required a short course of oral glucocorticoids (prednisolone) started at a dose of 1 mg/kg/day for 10 days, and then tapered off over a mean duration of 4.5 weeks. At their 3 months' follow-up, 7 out of 11 patients with SAT had become euthyroid (63.7%). Out of the remaining four, three patients (75%) had subclinical hypothyroidism while one (25%) had developed overt hypothyroidism. At their 6 months' follow-up, 7 patients with euthyroid continued to remain so, while out of the three patients with subclinical hypothyroidism, two regained euthyroid status while one continued to evidence biochemical features of subclinical hypothyroidism. The patient developing overt hypothyroidism at 3 months was treated with oral levothyroxine (1.6 μg/kg daily) and became euthyroid on medication at 6 months. Overall, after 6 months since their diagnosis of SAT, 9 out of 11 patients became euthyroid (81.82%), while 1 developed overt hypothyroidism requiring treatment and 1 with subclinical hypothyroidism continued to remain on close follow-up. There were no differences in outcomes between the group that received glucocorticoids compared with the group that did not. Both the patients with residual hypothyroidism (1=overt, 1=subclinical) at 6 months had a history of severe COVID-19, TPO Ab positivity, painful presentation and history of treatment with oral glucocorticoids, with SAT developing after 35 days and 40 days since recovery from COVID-19, respectively.

DISCUSSION

In the current study, we found that around 7% of patients having no pre-existing thyroid dysfunction developed SAT within 3 months of being diagnosed with COVID-19. Most of the patients were middle-aged women and had suffered from moderate or severe COVID-19. The time since recovery from COVID-19 to the onset of SAT ranged from 6 to 48 days, with a median of 24 days. Our findings were very similar to data from two recent

Table 1 Clinical, biochemical and imaging findings of patients at the time of presentation with post-COVID-19 subacute thyroiditis

Age and gender	Time since COVID-19	Presenting symptoms	Laboratory investigations		Imaging
26/F	6	Palpitation, tremor	Total T4: 16.15 Free T4: 1.59 Total T3: 155.2 Free T3: 4.5 TSH: <0.001 TPO antibody: positive (67.8)	ESR: 67 CRP: 99.9 IL-6: 68.1 NLR: 3.03 ALC: 1267	USG thyroid: diffusely enlarged thyroid gland, reduced vascularity, patchy hypoechoic areas 99mTc scan of thyroid: overall uptake 2.3%, patchy uptake
54/M	7	Fever	Total T4: 24.78 Free T4: 3.61 Total T3: 200.9 Free T3: 8.6 TSH: 0.003 TPO antibody: negative	ESR: 36 CRP: 347.22 IL-6: 187.9 NLR: 2.5 ALC: 1780	USG thyroid: normal-sized thyroid gland, reduced vascularity, patchy hypoechoic areas 99mTc scan of thyroid: overall uptake <2%, patchy uptake
28/F	12	Palpitation, tremor	Total T4: 32.35 Free T4: 2.99 Total T3: 207.5 Free T3: 0.73 TSH: <0.001 TPO antibody: negative	ESR: 85 CRP: 219.58 IL-6: 138 NLR: 3.08 ALC: 1450	USG thyroid: normal-sized thyroid gland, patchy hypoechoic areas 99mTc scan of thyroid: overall uptake <3%
49/F	21	Palpitation, tremor	Total T4: 24.91 Free T4: 2.33 Total T3: 199.5 Free T3: 6.2 TSH: 0.005 TPO antibody: negative	ESR: 94 CRP: 109.93 IL-6: 98 NLR: 2.1 ALC: 2200	USG thyroid: diffusely enlarged thyroid gland, patchy hypoechoic areas 99mTc scan of thyroid: overall uptake of thyroid 3.5%, patchy areas of uptake seen
25/M	7	Palpitation, tremor, diarrhoea	Total T4: 17.09 Free T4: 2.2 Total T3: 168.55 Free T3: 6.5 TSH: <0.001 TPO antibody: negative	ESR: 51 CRP: 284.95 IL-6: 58 NLR: 3.3 ALC: 1254	USG thyroid: normal-sized thyroid gland, patchy hypoechoic areas 99mTc scan of thyroid: diminished uptake in thyroid bed (<2%)
26/F	48	Pain and tenderness over neck, fever	Total T4: 20.5 Free T4: 2.2 Total T3: 170.1 Free T3: 5.9 TSH: 0.003 TPO antibody: positive (59.9)	ESR: 82 CRP: 69.24 IL-6: 61.74 NLR: 1.81 ALC: 2689	USG thyroid: diffusely enlarged thyroid gland, reduced vascularity, patchy hypoechoic areas 99mTc scan of thyroid: NA
69/M	28	Pain and tenderness over neck, palpitation, congestive cardiac failure	Total T4: 21.81 Free T4: 2.45 Total T3: 128.4 Free T3: 5.1 TSH: 0.001 TPO antibody: negative	ESR: 80 CRP: 74.5 IL-6: 42.72 NLR: 1.56 ALC: 2156	USG thyroid: diffusely enlarged thyroid gland, patchy hypoechoic areas 99mTc scan of thyroid: poor, patchy uptake in thyroid gland (2.2%)
48/F	35	Pain and tenderness over neck, palpitation, fever	Total T4: 15.7 Free T4: 1.81 Total T3 : 148.2 Free T3 : 4.1 TSH : 0.02 TPO antibody: positive (75.6)	ESR: 76 CRP: 6.1 IL-6: 53 NLR: 2.13 ALC: 2320	USG thyroid: diffusely enlarged thyroid gland, patchy hypoechoic areas 99mTc scan of thyroid: NA
59/F	28	Pain and tenderness over neck, tremor, fever	Total T4: 19.6 Free T4: 2.1 Total T3: 185.6 Free T3: 4.8 TSH: <0.001 TPO antibody: negative	ESR: 73 CRP: 154.49 IL-6: 45 NLR: 1.78 ALC: 3100	USG thyroid: diffusely enlarged thyroid gland, patchy hypoechoic areas 99mTc scan of thyroid: NA
36/M	26	Pain and tenderness over neck, fever	Total T4: 18.29 Free T4: 1.72 Total T3: 162.5 Free T3: 4.9 TSH:<0.001 TPO antibody: negative	ESR: 40 CRP: 10.51 IL-6: 32 NLR : 2.2 ALC : 2800	USG thyroid: diffusely enlarged thyroid gland, reduced vascularity, patchy hypoechoic areas 99mTc scan of thyroid: NA
65/F	44	Pain and tenderness over neck, tremor	Total T4: 14.5 Free T4: 1.87 Total T3: 182 Free T3: 5.5 TSH: 0.03 TPO antibody: negative	ESR: 85 CRP: 99.9 IL-6: 68 NLR: 1.5 ALC: 3015	USG thyroid: normal-sized thyroid gland, patchy hypoechoic areas 99mTc scan of thyroid: NA

Total T4 measured in µg/dL (normal: 5.44–11.73), free T4 is measured in ng/dL (normal: 0.61–1.72), total T3 is measured in ng/dL (normal: 78–136), free T3 measured in pg/mL (normal: 2.2–4.2), TSH in µIU/mL (normal: 0.34–4.25) (TPO (thyroid peroxidase/microsomal) Ab measured in IU/mL (normal: 0–35). ESR reported as millimetres in first hour, CRP as mg/L (normal: <5), IL-6 levels in pg/mL (normal: <7).NA = Data not available
Ab, antibody; ALC, absolute lymphocyte count; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; F, female; IL-6, interleukin 6; M, male; NLR, neutrophil-lymphocyte ratio ; TSH, thyroid-stimulating hormone; USG, ultrasonography.

systematic reviews involving 17 case reports and two case series of COVID-19-associated patients with SAT.[5 6] In them, around two-thirds were women, and the time of onset since COVID-19 ranged from 3 to 60 days.

In the recent review,[16] the authors have described several novel trends in the clinical course of SAT triggered by SARS-CoV-2 and updated their prior diagnostic criteria for SAT based on the new findings, particularly focusing on the absence of neck pain.[16 17] Our defining criteria for post-COVID SAT, which mandated the presence of at least one each of the different clinical, biochemical and imaging characteristics described, were more stringent than that suggested by Stasiak and colleagues. Owing to logistic

Table 2 Summary of characteristics of patients with SAT following COVID-19

Mean age in years	44.09 (16.07)
Gender	M: 4, F: 7
Clinical features at the time of presentation with SAT	Neck pain (n=6, 54.5%) Palpitation (n=6, 54.5%), Tremor (n=5, 45.4%), fever (n=5, 45.5%), diarrhoea (n=2, 18.1%)
Mean times since recovery from COVID-19	23.8 days (range: 6–48 days)
Severity of COVID-19	Severe COVID-19: 5, moderate COVID-19: 5, mild COVID-19: 0, asymptomatic COVID-19: 1
Treatment received	Beta-blockers=11, NSAIDs=2, glucocorticoids=4
Occurrence following first or second wave of COVID-19 in India	Following first wave: 5 Following second wave: 6
Outcome at 6 months	Euthyroidism=9 Subclinical hypothyroidism=1 Overt hypothyroidism=1

F, female; M, male; NSAIDs, non-steroidal anti-inflammatory drugs; SAT, subacute thyroiditis.

constraints, all of our patients couldn't get radionuclide thyroid imaging and fine needle aspiration biopsy (FNAB) done though these are parts of the additional criteria laid down by these authors for the diagnosis of SAT. However, we adhered strictly to the remaining criteria to ensure exclusion of false-positive cases. While the authors recommend considering the possibility of SAT in any patient developing new-onset/worsening tachyarrythmias or fatigue with/after SARS-CoV-2 infections, these features were not included in our diagnostic criteria owing to the high prevalence of post-COVID-19 fatigue, particularly following the second wave.[18]

We found two distinct presentations of SAT—with and without neck pain, and the presentation differed according to the time of occurrence of SAT since recovery from COVID-19 infection. Those with the painless variant presented sooner after recovery and had significantly higher levels of serum CRP and IL-6 levels than those with PFSAT. Although not statistically significant, most of the patients with PFSAT had received parenteral glucocorticoids during COVID-19. In one of the first case reports of post-COVID-19 SAT, Ruggeri *et al* described a 43-year-old woman presenting with painful goitre and thyrotoxic symptoms being diagnosed with SAT 6 weeks after COVID-19.[19] Most of the initial case reports of COVID-19-associated SAT had reported severe neck discomfort.[6 7 20] The review by Trimboli *et al* reports nearly universal occurrence of neck pain in their cohort of 27 patients (n=25 out of 27 cases).[5] However, they included cases till April 2021 and majority of the cases occurred following mild COVID-19. In another series, which considered only patients with COVID-19 admitted in ICU, Muller and coauthors described a pattern of 'atypical' PLSAT.[8] They have proposed that due to COVID-19-associated lymphopaenia, there is a lack of lymphocytic infiltration and giant cell formation within the thyroid gland, leading to the lack of tension of the thyroid capsule and consequently a non-painful presentation of inflammatory thyroiditis.[8 21] In the current study, we found a

Table 3 Comparison of characteristics between those with painful SAT and those with painless SAT

	Painless SAT (n=5)	Painful SAT (n=6)	Reference ranges
Age in years	36.40 (12.47)	50.5 (16.97)	
Fever	1 (20%)	4 (66.67%)	
Palpitation	4 (80%)	2 (55.55%)	
Tremor	3 (60%)	2 (55.55%)	
Time of onset since recovery from COVID-19 infection in days	10.6 (5.65)*	34.83 (9.26)	
Severity of COVID-19 infection	Mild/asymptomatic=0 Moderate=1 Severe=3	Mild/asymptomatic=1 Moderate=4 Severe=2	
Required glucocorticoids during COVID-19	2 (40%)	4 (66.67%)	
Total T4 in µg/dL	23.05 (5.9)	18.4 (2.8)	5.44–11.73
Total T3 in ng/dL	186.33 (20.58)	162.8 (21.6)	78–136
Free T4 in ng/dL	2.35 (0.85)	2.19 (0.64)	0.61–1.72
Free T3 in pg/mL	6.6 (1.5)	5.1 (0.6)	2.2–4.2
ESR in mm/hour	66.6 (21.2)	72.8 (16.6)	≤15 for men <50 years ≤22 for women <50 years and men ≥50 years ≤29 mm for women ≥50 years
Anti-TPO antibody positivity	1 (20%)	2 (33.33%)	Positive: >35 IU/mL
CRP in mg/L	212.33 (96.29)*	69.12 (55.98)	0–5
IL-6 in pg/mL	110.00 (47.87)*	50.41 (13.20)	0–7
Absolute lymphocyte count	1.59×10^3/µL*	2.68×10^3/µL	
Neutrophil-lymphocyte ratio	2.8*	1.83	
Treatment required for SAT	NSAIDs=0 Glucocorticoids=0	NSAIDs=2 Glucocorticoids=4	
Outcome at 3 months	Euthyroidism=3 Subclinical hypothyroidism=2 Overt hypothyroidism=0	Euthyroidism=4 Subclinical hypothyroidism=1 Overt hypothyroidism (started on LT4)=1	
Outcome at 6 months	Euthyroidism=5 Subclinical hypothyroidism=0 Overt hypothyroidism=0	Euthyroidism=4 Subclinical hypothyroidism=1 Overt hypothyroidism (euthyroid with LT4 replacement)=1	

*Denotes significant difference (p<0.05).
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; LT4, levothyroxine; NSAIDs, non-steroidal anti-inflammatory drugs; SAT, subacute thyroiditis; TPO, thyroid peroxidase.

lower ALC and higher NLR in those with PLSAT. While lymphopaenia is now a well-known severity indicator and prognostic marker in COVID-19, it has been seen to persist for up to several weeks following severe COVID-19.[22 23] Our findings suggest that persistent lymphopaenia immediately after COVID-19, along with glucocorticoid use during active illness, may contribute to relatively painless presentation of early post-COVID-19 SAT. In cases of SAT occurring later, the lymphocyte count returns to normal with rebound lymphocytosis, with the rapid lymphocyte infiltration leading to capsular distension and increase in neck pain. Though not statistically significant, PLSAT was numerically greater during the second wave of COVID-19 pandemic than the first. While multiple factors may have contributed to this, the role of variably mutated viral strains in influencing clinical presentations of SAT needs further evaluation.

Both direct and indirect mechanisms have been proposed for SARS-CoV-2-associated thyroiditis.[21 24] While direct apoptosis of thyroid follicular cells may ensue following viral entry, the indirect mechanism entails destructive thyroiditis due to massive cytokine release during acute infection. A correlation between the severity of COVID-19 and severity of thyrotoxicosis may be less prominent if the apoptotic mechanism is predominant. In the THYROCOV study, authors have reported a significant difference in serum IL-6 levels between those with overt and those with subclinical thyrotoxicosis in patients with COVID-19.[25] In our study, patients with PLSAT had higher IL-6 and CRP levels and more thyrotoxic manifestations compared with those with PFSAT. Though limited by the sample size, we found significant correlation of IL-6 with free T4, total T4 and total T3 levels in the PLSAT group, suggesting that the destructive effects of proinflammatory cytokines may play a role in the causation of PLSAT. Although beyond the scope of our study, our findings indicate that proinflammatory cytokine-mediated destructive mechanisms might be the key regulators of PLSAT, whereas direct SARS-CoV-2 invasion of thyroid follicular cells leading to apoptosis may be more important for PFSAT. The fact that some of the cases presented as late as 48 days after a documented recovery from COVID-19 could indicate the prolonged persistence of SARS-CoV-2 in the thyroid follicular cells long after its clearance from the body.[26] Infection by SARS-CoV-2, by stimulating Th1/Th17 hyperactivity, may trigger the onset of autoimmune disorders,[21 26]though in our study the similar prevalences of anti-TPO antibody levels between the PFSAT and PLSAT groups suggest a less likely pathogenetic role for autoimmunity.

In a systematic review of seven studies involving more than 1200 patients with COVID-19, thyroid dysfunction was found in 13% to 64% of the patients, with the most common abnormality detected being a low TSH.[27] There was a correlation between the degree of decrease in TSH levels and severity of the disease. However, majority of the cases were associated with low free T3 and was presumably due to non-thyroidal illness syndrome (NTI), with negative correlations being seen between free T3 and high-sensitive CRP, IL-6 and tumour necrosis factor-α in many studies.[27 28] Our strict inclusion criteria precluded possible cases of NTI and ensured that our study population comprised only cases with a confirmed diagnosis of post-COVID-19 SAT.

At 6-month follow-up, 81.8% of our patients (n=9) had become euthyroid. The outcome did not differ between those with PFSAT or PLSAT, neither were they different based on presentation during the first or second waves. Existing literature is controversial regarding the influence of symptoms of SAT, thyroid function abnormalities, ESR or the use of glucocorticoids on the final outcome of post-viral SAT, though majority studies, similar to our findings, failed to find any correlation.[3] While most of our cases returned to euthyroid state by 3–6 months, the deleterious effects of transient thyrotoxicosis on cardiovascular manifestations including arrhythmias need to be kept in mind, specially in cases presenting soon after COVID-19 infection. Since majority of these are not associated with typical neck pain, close supervision and monitoring of thyroid functions is warranted.

Over the past few years, a group of high-risk human-leukocyte antigen (HLA) alleles have been identified which increases susceptibility for SAT and has effect on the clinical course, recurrence rates and sonographic findings in SAT.[16 29 30]Although majority of the data come from studies in Caucasian populations, the clinical implications may be generalisable to other population as well. All our patients had patchy hypoechoic areas bilaterally on USG, which fits more with the description in the group with HLA haplotype HLA-B*35 and/or HLA-C*04 in the study by Stasiak *et al*.[30] Unfortunately, this could not be substantiated as HLA haplotyping could not be done in our study owing to logistic constraints.

In addition, a relatively small, single-centre study population and lack of universal data on thyroid scintigraphy (I^{123} or 99mTc scan) were limitations of our study. However, estimation of TRAb levels in all our patients prevented misclassification of Graves' disease as SAT in our study.

Overall, our data suggest two distinct clinical subsets of post COVID-19 19 SAT—a painless variety with significant thyrotoxic symptoms, occurring more commonly in disease presenting soon after recovery from COVID-19, and a painful, less thyrotoxic variety, which predominantly occurs long after recovery from COVID-19. Though our findings suggest possible differences in pathogenetic mechanisms underlying these clinical presentations, further multicentric, prospective studies are needed to carefully elucidate the exact aetiopathogenetic mechanisms. Although majority revert to euthyroidism, close clinical

Key messages

What is already known on this topic

- Subacute thyroiditis (SAT) can occur during or following COVID-19.
- Published case reports and series from different countries suggest diverse clinical presentations and outcome.

What this study adds

- We report the largest single-centre case series of post-COVID SAT reported until in literature.
- We found two distinct clinical presentations—with and without neck pain—depending on the time of presentation since diagnosis with COVID-19.
- We postulate pathophysiological mechanisms driving the two different presentations, with persistent lymphopaenia possibly playing a key role in early painless SAT.
- A comparison between cases presenting during the first and second waves of COVID-19 adds further clinical insight into our study.

How this study might affect research, practice or policy

- Pathogenetic differences in post-COVID-19 SAT and SAT following others viral infections.
- Role of autoimmunity in post-COVID-19 SAT.
- Role of genetics including HLA haplotypes in susceptibility to post-COVID-19 SAT.

and biochemical monitoring of thyroid functions for at least 6 months following documented recovery from COVID-19 is warranted, especially in those affected by severe infection.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by Institutional Ethics Committee, HealthWorld Hospitals, Durgapur (reference ID: HWH/IEC-BMHR/005/2021). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	7,8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	1,112
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.