



Impact of the COVID-19 pandemic on the incidence, seasonal distribution, and characteristics of subacute thyroiditis

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Abstract

Purpose An increasing number of cases of subacute thyroiditis (SAT) related to the coronavirus disease 2019 (COVID-19) and its vaccines continue to be published. The aim of this study was to investigate any change in the incidence and characteristics of SAT by comparing the pre-pandemic and pandemic periods.

Methods This retrospective, single-center study included 432 newly-diagnosed SAT patients between January 2018 and December 2021. The annual frequency of SAT was calculated as the number of newly-diagnosed SAT cases divided by the total number of outpatients that year.

Results The frequencies of newly-diagnosed SAT were 0.136% in 2018, 0.127% in 2019, 0.157% in 2020, and 0.114% in 2021 ($p = 0.19$). While SAT patients were clustered in the autumn (35.1%) in 2018 and 2019, it was found that this cluster shifted to the winter (33.0%) in 2020 and 2021, in parallel with COVID-19 case peaks ($p = 0.017$). The patients were separated into two groups as pre-COVID-19 pandemic SAT ($n = 272$) and COVID-19 pandemic SAT ($n = 160$). The mean ages of the groups were similar. There were more male patients in the COVID-19 pandemic SAT group than in the pre-pandemic group (30.6% vs. 18.7%, $p = 0.005$). Frequencies of overt hyperthyroidism and median free-thyroxine levels were significantly higher in the COVID-19 pandemic SAT group ($p = 0.029$, $p = 0.001$). Treatment modalities, recurrence rates, and permanent hypothyroidism were similar in both groups.

Conclusion With the COVID-19 pandemic, although there was a change in seasonal variation of SAT and an increase in the number of male patients, there was no change in the incidence and clinical course of SAT.

Keywords Subacute thyroiditis · Thyrotoxicosis · Hyperthyroidism · Recurrence · Persistent hypothyroidism · SARS-CoV-2

Introduction

Subacute thyroiditis (SAT) is an inflammatory disease of the thyroid gland that mostly affects women (female to male ratio of 4:1), with peak incidence in the 4th and 5th decades of life [1, 2]. Although it is a self-limiting pathology, neck pain and thyrotoxicosis symptoms can sometimes last for

months in untreated patients. In a comprehensive study conducted in Olmsted, MN, USA, the incidence of SAT was found to be 3.6 cases per 100,000/year in the 1990s [3]. Another single-center study conducted in an Endocrinology and Metabolism unit in Italy reported that 0.3% of the patients admitted to the outpatient clinic were diagnosed with SAT [4]. Some studies have claimed that there is a seasonal clustering in the diagnosis of SAT, especially during the summer and autumn [5, 6]. Although the etiology has not been clearly established, it is thought that viral pathogens (H1N1 influenza, some enteroviruses, Epstein Barr, and mumps virus) may be responsible [1, 2, 7, 8]. It is known that SAT can develop during or within 2–8 weeks following viral infections, especially those involving the upper respiratory tract. However, while viral infections affect a very large population, very few of these patients develop SAT. Some studies have shown that individuals

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with certain human leukocyte antigen (HLA) alleles are more likely to develop SAT [9, 10].

The coronavirus disease 2019 (COVID-19) pandemic, which has caused the biggest health system problem in recent years, has affected more than half a billion people worldwide. Turkey was one of the countries severely affected by COVID-19, ranking 10th among the most affected countries [11]. In addition to the fatal complications of COVID-19, autoimmune/inflammatory events that developed during or after the infection have been carefully followed. During the pandemic, COVID-19 infection and vaccination-associated endocrine dysfunctions were reported for several endocrine organs such as pituitary, thyroid, pancreas, and adrenal gland, thus the “endocrine phenotype” of COVID-19 has gained popularity and increased clinical concerns [12].

Considering the possible relationship of SAT with viral pathogens, it can be expected that this pathology may also occur as a late complication of COVID-19. There are reports in the literature of SAT cases developing post-COVID-19 infection and even after COVID-19 vaccines [12–17]. These reported cases also raise the question of whether there has been an increase in the incidence of SAT and/or a variation in its character during the pandemic. Therefore, the primary aim of this study was to observe whether there was any change in the incidence and seasonal distribution of SAT by comparing the 2-year period of the pandemic with the previous 2 years. Second, it was aimed to examine the possible effects of the COVID-19 pandemic on classical SAT characteristics by comparing the clinical, laboratory, ultrasonographic, and follow-up features of SAT patients before and during the pandemic.

Materials and methods

Study design and patients

This retrospective, cross-sectional, single-center study was conducted in the Department of Endocrinology and Metabolism, University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey. SAT patients were identified by searching our hospital system for International Classification of Diseases system (ICD-10) codes indicating SAT (E06.1) between January 1, 2018, and December 31, 2021. Of the identified patients, only 478 patients aged ≥ 18 years who were diagnosed by our department were examined. The total number of patients admitted to our outpatient clinic during the study period was also determined. Out of 478 patients, 12 relapsed cases diagnosed before 2018 and 34 cases with insufficient diagnostic data were excluded from the study. Consequently, a total of 432 newly-diagnosed SAT patients were included in the study and demographic data, the

season of diagnosis, ultrasonographic, laboratory findings, treatment modalities, and follow-up data were recorded. In line with the recommendations of the 2016 American Thyroid Association guidelines [18], the diagnosis of SAT was made by supporting the typical clinical findings (such as neck pain, fever, sweating, weight loss, palpitations) with laboratory (elevated free thyroid hormone levels, suppressed thyroid-stimulating hormone (TSH) levels, and elevated acute phase reactant levels) and ultrasonographic (devascularized hypoechoic areas on Doppler ultrasonography (US)) findings. Cytopathological verification was performed to rule out painful hashitoxicosis and malignancy in suspected cases.

Follow-up assessments

The reappearance of clinical and laboratory findings of SAT in a patient with recovered clinical findings and improved laboratory findings was accepted as recurrence of the disease. Cases followed up for at least 3 months from the time of diagnosis were included in the recurrence analysis. Hypothyroidism that persisted for at least 3 months and required levothyroxine (LT) replacement was defined as permanent hypothyroidism in patients with improved SAT clinical and laboratory findings. Patients who had not received LT replacement before diagnosis and were followed up for at least 6 months from the time of diagnosis were included in the analysis of permanent hypothyroidism.

Biochemical evaluations

All laboratory tests were performed in the Department of Biochemistry of our Hospital. TSH, free-thyroxine (fT4), free-triiodothyronine (fT3), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-thyroid peroxidase antibody (anti-TPO), and anti-thyroglobulin antibody (anti-Tg) levels were examined at the time of diagnosis and on the development of recurrence. When the treatment of the patients was completed, control examinations were performed and they were followed up afterwards. Patients who developed hypothyroidism were followed up at 3-month intervals for determination of replacement need and/or dose titration. Thyroid functions and thyroid antibodies were measured using direct chemiluminescence immunoassay (Beckman Coulter, CA, USA). Normal reference ranges were defined as follows: TSH: 0.27–4.20 mIU/l, fT4: 0.93–1.70 ng/dl, fT3: 2.0–4.4 ng/l, ESR: 0–20 ml/h, CRP: 0–5 mg/l, anti-TG: 0–40 IU/ml, and anti-TPO: 0–35 IU/ml.

Ultrasonographic assessments

In the current study, all US evaluations were performed at the time of diagnosis and in follow-up visits by the authors

Table 1 Comparisons of SAT patients diagnosed before and during the COVID-19 pandemic

Variables	All patients (<i>n</i> = 432)	Pre-COVID-19 pandemic SAT (<i>n</i> = 272)	COVID-19 pandemic SAT (<i>n</i> = 160)	<i>p</i> value
<i>N</i> (%)	432 (100)	272 (63)	160 (37)	
Age, mean ± SD, years	43.5 ± 9.8	43.4 ± 10	43.5 ± 9.5	0.98
Male gender, <i>n</i> (%)	100 (23.1)	51 (18.7)	49 (30.6)	0.005^a
Disease involvement, <i>n</i> (%)				0.32
Unilateral	145 (33.6)	96 (35.3)	49 (30.6)	
Bilateral	287 (66.4)	176 (64.7)	111 (69.4)	
Thyroid volume, mean ± SD, cm ³	20.8 ± 9.5	20.9 ± 8.8	20.7 ± 10.6	0.83
Thyroid hormone status, <i>n</i> (%)				0.029^a
Overt hyperthyroidism	285 (66.0)	171 (62.8)	114 (71.2)	
Subclinical hyperthyroidism	51 (11.8)	40 (14.7)	11 (6.9)	
Euthyroidism	84 (19.4)	57 (20.9)	27 (16.8)	
TSH, median (IQR), mIU/l	0.02 (0.01–0.16)	0.02 (0.01–0.21)	0.02 (0.01–0.10)	0.44
fT4, median (IQR), ng/dl	2.03 (1.41–2.86)	1.88 (1.22–2.72)	2.20 (1.62–3.03)	0.001^a
fT3, median (IQR), ng/l	4.91 (3.79–6.83)	4.77 (3.79–6.33)	5.32 (3.84–7.37)	0.16
ESR, mean ± SD, mm/h	49.2 ± 22.8	51.6 ± 23.7	45.0 ± 20.5	0.005^a
CRP, median (IQR), mg/l	47.6 (21.8–83.4)	46.0 (20.0–85.0)	49.7 (25.0–75.8)	0.66
Anti-TPO positivity (<i>n</i> = 311), <i>n</i> (%)	42/311 (13.5)	33/205 (16.1)	9/106 (8.5)	0.06
Anti-Tg positivity (<i>n</i> = 237), <i>n</i> (%)	36/237 (15.2)	20/154 (13.0)	16/83 (19.3)	0.19

Anti-TPO anti-thyroid peroxidase antibody, *Anti-Tg* anti-thyroglobulin antibody, *COVID-19* the coronavirus disease 2019, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *fT3* free-triiodothyronine, *fT4* free-thyroxine, *IQR* interquartile range, *TSH* thyroid-stimulating hormone, *SAT* subacute thyroiditis, *SD* standard deviation

^aStatistically significant (*p* < 0.05)

experienced in using the Hitachi® HI VISION Preirus unit (Hitachi, Tokyo, Japan) with a 13 MHz linear array transducer. The volume of the thyroid gland was calculated using the ellipsoid formula of (length (cm) × width (cm) × thickness (cm) × π/6).

Statistical analysis

Statistical analysis was performed using SPSS software (version 23.0, SPSS, IBM Corporation, NY, USA). Data distribution was assessed with the Kolmogorov–Smirnov test. Data with normal distribution were presented using mean ± standard deviation values, while those with non-normal distribution were reported using median with interquartile range values. Continuous variables with normal distribution were compared using the independent samples *t* test, and those with non-normal distribution with the Mann–Whitney *U* test. Categorical variables were expressed as frequencies and percentages (%) and compared using the χ^2 test. The χ^2 test was also used to compare the ratios of newly-diagnosed SAT/total patients over the years. Poisson regression analysis was performed to examine the

seasonal distribution of the SAT cases. A value of *p* < 0.05 was accepted as the level of statistical significance.

Results

Characteristics of study population

From January 2018 to December 2021, a total of 432 newly-diagnosed SAT patients in our clinic were included in the final analyses. The mean age of the patients was 43.5 ± 9.8 years and the female:male ratio was 3:1. Bilateral involvement of the disease was observed on the thyroid US at the rate of 66.4%. At the time of diagnosis, 346 (77.8%) patients were hyperthyroid. Anti-TPO antibodies were observed in 13.5% of 311 patients with data, and anti-Tg antibodies were observed in 15.2% of 237 patients with data. The detailed laboratory findings of the study population are presented in Table 1. Of the 409 patients with available treatment data, 236 (57.7%) received corticosteroid only, 146 (35.7%) received non-steroidal anti-inflammatory drugs (NSAIDs) only, and 27 (6.6%) received NSAIDs plus corticosteroid therapy (Table 2).

Table 2 Treatment modalities and follow-up parameters of the study population

Variables	Available data analyses	Pre-COVID-19 pandemic SAT	COVID-19 pandemic SAT	<i>p</i> value
Treatment modality, <i>n</i> (%)	409/432 (94.7)	252/272 (92.6)	157/160 (98.1)	0.86
NSAIDs	146/409 (35.7)	88/252 (34.9)	58/157 (36.9)	
Corticosteroids	236/409 (57.7)	148/252 (58.7)	88/157 (56.1)	
NSAIDs plus corticosteroids	27/409 (6.6)	16/252 (6.4)	11/157 (7.0)	
Patients with ≥ 3 months follow-up, <i>n</i> (%)	315/432 (72.9)	204/272 (75.0)	111/160 (69.4)	0.20
Follow-up time of these patients (<i>n</i> = 315), median (IQR), months	10.0 (6.0–24.0)	19.0 (6.0–29.0)	6.0 (4.0–10.0)	0.001^a
Recurrent disease, <i>n</i> (%)	32/315 (10.1)	20/204 (9.8)	12/111 (10.8)	0.77
Time of recurrence, median (IQR), days	52.5 (30.0–104.0)	60.0 (31.0–100.7)	37.5 (28.5–134.2)	0.83
Patients with ≥ 6 months follow-up, <i>n</i> (%)	253/432 (58.6)	173/272 (63.6)	80/160 (50.0)	0.006^a
Follow-up time of these patients (<i>n</i> = 253), median (IQR), months	14.0 (7.0–26.0)	23.0 (10.0–31.0)	8.0 (6.0–11.7)	0.001^a
Permanent hypothyroidism, <i>n</i> (%)	43/253 (17.0)	31/173 (17.9)	12/80 (15.0)	0.56
LT replacement dose, median (IQR), mcg/week	350.0 (175.0–525.0)	350.0 (200.0–525.0)	350.0 (175.0–506.2)	0.42

COVID-19 the coronavirus disease 2019, IQR interquartile range, LT levothyroxine, NSAID non-steroidal anti-inflammatory drugs, SAT subacute thyroiditis, SD standard deviation

^aStatistically significant ($p < 0.05$)

Incidence of SAT

The rates of newly-diagnosed SAT/total number of patients in our outpatient clinic were 129/94,776 (0.136%) in 2018, 133/104,764 (0.127%) in 2019, 84/53,282 (0.157%) in 2020, and 86/75,364 (0.114%) in 2021, respectively (Fig. 1). There was observed to be no statistically significant difference in the incidence of SAT in our clinic between these years ($p = 0.19$). When adjustments were made for March 2020, when the COVID-19 pandemic was declared official in Turkey, the incidence of SAT in our clinic was 234/179,642 (0.130%) in the 22-month period before the pandemic, and 160/108,587 (0.147%) in the 22-month period during the pandemic ($p = 0.23$).

Seasonal variation of SAT

While 244 (56.5%) of the study population were diagnosed with SAT in the autumn-winter seasons, 188 (43.5%) were diagnosed in the spring-summer seasons. In 2018 and 2019 ($n = 262$), a significant seasonal clustering was detected in newly-diagnosed SAT cases in the autumn (35.1%) ($p < 0.001$), and a significant clustering was detected in winter (33.0%) in 2020 and 2021 ($n = 170$) ($p < 0.001$). There was a significant shift in the diagnosis of SAT from autumn to winter in the last 2 years ($p = 0.017$) (Table 3). The factor causing this divergence was determined to be the SAT frequency that increased in December during the pandemic period compared to the previous period (15.3% vs. 6.1%, $p < 0.001$) (Fig. 2). The number of monthly SAT patients in the pandemic period and the number of confirmed COVID-19 cases in Turkey in the same period were

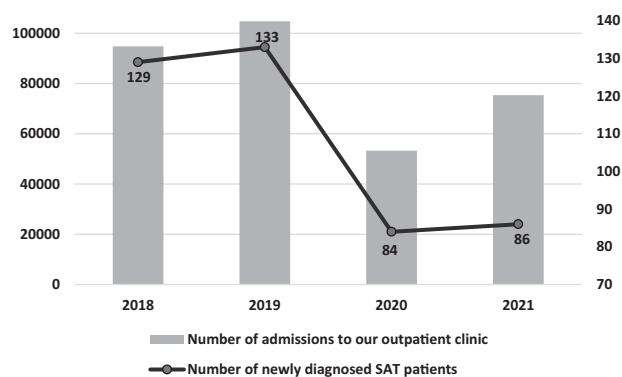


Fig. 1 The graph depicts the admissions to our outpatient clinic (gray columns) and newly diagnosed SAT cases (black line) in 2018 and 2021. The decrease in SAT cases followed the reduction in the number of patient admissions with the pandemic. SAT subacute thyroiditis

compared. It was observed that the peaks in SAT cases overlapped with the COVID-19 case peaks in Turkey (Fig. 3). The SAT cases were observed to continue to follow the confirmed COVID-19 case peaks after February 2021, when mass vaccination started in Turkey (Fig. 3).

Before and during the COVID-19 pandemic

The patients were separated into two groups as pre-COVID-19 pandemic SAT (pre-pandemic SAT) ($n = 272$) and COVID-19 pandemic SAT (pandemic SAT) ($n = 160$) based on March 2020 (Table 1). The mean ages of the two groups were similar, and there was an increase in the frequency of male patients in the pandemic SAT group ($p = 0.005$). The two groups were similar in terms of disease involvement and thyroid volumes.

Table 3 Seasonal distribution of the study population over 2-year periods

Variables	All patients (n = 432)	Patients diagnosed in 2018–2019 years (n = 262)	Patients diagnosed in 2020–2021 years (n = 170)	p value
Season, n (%)				0.017^a
Spring	104 (24.1)	65 (24.8)	39 (22.9)	
Summer	84 (19.4)	53 (20.2)	31 (18.2)	
Autumn	136 (31.5)	92 (35.1)	44 (25.9)	
Winter	108 (25.0)	52 (19.9)	56 (33.0)	

^aStatistically significant ($p < 0.05$)

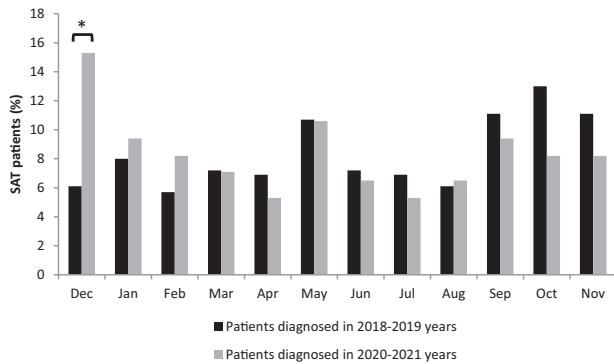


Fig. 2 Monthly distribution of SAT frequency between the pre-pandemic 2-year period (2018–2019) (black columns) and the subsequent period (2020–2021) (gray columns). Particularly in the COVID-19 pandemic, the serious divergence experienced due to the increased SAT cases in December draws attention. COVID-19 the coronavirus disease 2019, SAT subacute thyroiditis. *Statistically significant ($p < 0.05$)

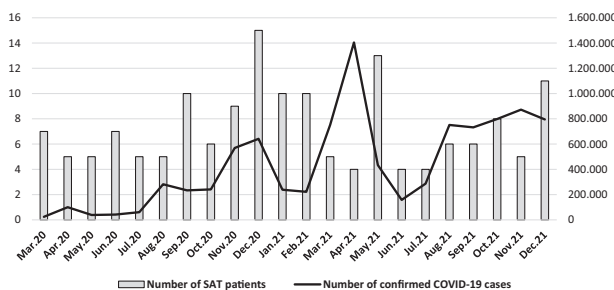


Fig. 3 Monthly distribution graph of SAT cases (gray columns) and confirmed COVID-19 cases (black curve) in the pandemic. SAT case increases in December 2020, May 2021, and December 2021 appear to overlap with COVID-19 case peaks. COVID-19 the coronavirus disease 2019, SAT subacute thyroiditis

At the time of diagnosis, overt hyperthyroidism was significantly more common in the pandemic SAT group than in the pre-pandemic SAT group (71.2% vs. 62.8%, $p = 0.029$). The median fT4 values were significantly higher in the pandemic SAT group (2.20 (1.62–3.03) vs. 1.88 (1.22–2.72), $p = 0.001$). While the CRP values of the two groups were comparable, the ESR at the time of diagnosis was higher in the pre-pandemic SAT group ($p = 0.005$). There was no difference between the groups in terms of thyroid autoantibody positivity at the time of diagnosis (Table 1). Both groups were similar in terms of treatment modalities ($p = 0.86$) (Table 2).

Recurrent disease

When 315 patients (72.9%) with at least 3 months of follow-up data were evaluated, 32 patients (10.1%) had recurrent disease. Relapses occurred at a median of 52.5 (30.0–104.0) days after the patients’ last healthy visit. The number of patients with a follow-up of 3 months or longer in the pre-pandemic and pandemic SAT groups was similar. There was no difference between the groups in terms of recurrence rates and recurrence times ($p > 0.05$) (Table 2).

Permanent hypothyroidism

When 253 patients (58.6%) with at least 6 months of follow-up data were evaluated, permanent hypothyroidism was detected in 43 patients (17.0%). In the pre-pandemic SAT group, the number of patients with follow up of 6 months or longer was higher and the follow-up period of the patients was longer than that of the other group ($p < 0.001$) (Table 2). There was no difference between the groups in terms of the frequency of permanent hypothyroidism and LT replacement dose ($p > 0.05$).

Discussion

The possible relationship between COVID-19 and SAT became one of the hot topics in the Endocrinology community during the pandemic. Some cases of SAT have been reported following COVID-19 infection and its vaccination, including in our clinic [12–17]. The high expression of the angiotensin-converting enzyme-2 (ACE2) receptor used by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter the cell in thyroid follicular cells suggests that COVID-19 may directly cause inflammation in thyroid cells [19–21]. The finding of SARS-CoV-2 antigens in the thyroid gland showing the histopathological features of SAT in a post-mortem examination also strengthens this hypothesis [22]. However, considering that SAT often develops following viral infections, the molecular mimicry hypothesis also comes to the fore. The high similarity of the spike proteins of SARS-CoV-2 to

mammalian peptides (e.g., thyroid peroxidase peptides) may explain the cases of SAT following COVID-19 infection and its vaccination [23, 24]. Although the relationship between COVID-19 and SAT, which mainly relies on case reports along with a few mechanistic studies, is still debatable, mounting case reports have necessitated evaluating a possible change in the incidence of SAT. Therefore, in the present study, it was investigated whether there was a change in the incidence and characteristics of SAT by comparing the pre-pandemic and pandemic periods.

Two recent studies with a very limited SAT population were conducted to address the incidence and characteristics of SAT during the pandemic [25, 26]. Pirola et al. compared 10 SAT patients in a 7-month period of the pandemic with the previous periods and found no difference in the incidence of SAT [25]. Brancatella et al. compared 46 newly-diagnosed SAT patients in 2020 with previous periods and found that newly-diagnosed SAT cases were comparable between years [26]. In the current study, 160 SAT cases during the 2-year pandemic period were examined and there was observed to be no increase in the number of newly-diagnosed SAT cases compared to previous years. In the previous study of our clinic, a temporal relationship with the vaccination was observed in 29.1% of SAT cases in the 10-month period following the COVID-19 vaccination in 2021 [16]. The present study showed that there was also no change in the incidence of SAT in the months corresponding to this period (February to October) compared to previous years (Fig. 3). Recently, SAT cases developing after COVID-19 vaccination or infection have been associated with predisposed individuals homozygous for HLA-B*35 and HLA-C*04 alleles [27, 28]. From this perspective, it is understandable that the number of new cases remains stable, considering that SARS-CoV-2 only triggers the development of SAT in genetically susceptible individuals. Moreover, the decrease in other virus infections due to social isolation and the use of face masks during the pandemic may have prevented a possible increase in SAT cases [29].

The seasonal clustering of SAT is a controversial issue. There is a limited number of studies based on regional observations in Italy and Japan showing that SAT cases peak in the summer and early autumn (June to November) [5, 6, 30]. Conversely, two studies conducted in Finland and Israel found no seasonal variation in SAT frequency [31, 32]. In the current study, clustering of SAT cases was observed in the autumn during the 2-year pre-pandemic period. This cluster can be associated with viral respiratory tract infection epidemics in Turkey that started in autumn and increased toward winter [29, 33]. During the pandemic, the autumn clustering was determined to shift significantly toward winter with the contribution of SAT cases that increased particularly in December (Fig. 2). In addition, it was observed that the confirmed COVID-19 case peaks in Turkey overlapped with the SAT case peaks in both

December 2020–2021 and May 2021 (Fig. 3). Likewise, Brancatella et al. revealed that while the cases in the pre-pandemic period clustered in the 3rd quarter of the year, the cluster shifted to the 2nd and 4th quarters of the year with the pandemic, and the SAT case peaks during the pandemic coincided with the COVID-19 case peaks [26]. These data suggest that SARS-CoV-2 infection may have an impact on SAT distribution during the pandemic. In addition, the reduction in the epidemic of other upper respiratory viral agents due to measures during the pandemic could also be another potential factor of the seasonal shift. Overall, this result once again highlights the close relationship between SAT and viral infections.

It has been well documented that SAT frequently affects females more than males. Interestingly, while the female: male ratio was classically 4:1 in the pre-pandemic SAT cohort, it decreased to 2:1 in the pandemic SAT group. The present study is the first to demonstrate such an observation. Although gender has been reported to not significantly contribute to the risk of COVID-19 infection, male gender has been shown to be a risk factor for more severe COVID-19 [34]. In a study examining SAT in intensive care patients during the pandemic, Muller et al. found that 9 of 14 patients with thyrotoxicosis were male [35]. Li et al. detected high ACE2 expression in the thyroid and lungs and found that ACE2 expression in the thyroid and lungs was positively correlated in males and negatively in females after CD8+ T cell, interferon, and B cell enrichment methods [19]. In the light of these studies, the fact that ACE2 expression is higher in males than in females during active infection may explain the increase in the number of male SAT cases during the pandemic. However, it should be taken into account that the SAT during the pandemic is not only caused by COVID-19 or its vaccination. In addition, the lack of data on the COVID-19 history of the cases in the current study also limits the ability to make definite conclusions based on the increasing number of male cases. Therefore, this result needs to be supported by further larger, multicentric, observational and advanced molecular studies.

Brancatella et al. found that SAT cases in 2020 had higher ft4, ESR, CRP, and thyroglobulin levels and a higher incidence of hypothyroidism during the follow-up compared to previous years [26]. Therefore, the authors speculated that SAT may be more severe during the pandemic. Similarly, in the current study, overt hyperthyroidism was more common in the pandemic SAT group compared to the other group, and in parallel with this, ft4 levels at the time of diagnosis were higher. However, unlike the previous study, CRP levels at diagnosis were similar in the two groups, while ESR levels were interestingly higher in the pre-pandemic SAT group. In addition, in the current study, recurrence and persistent hypothyroidism frequencies were found to be 10.1% and 17.0%, respectively, in line with the literature [3, 31, 36, 37].

These two important follow-up parameters showing the course of the disease had a similar distribution in the pre-pandemic and pandemic SAT groups. So, the current study results demonstrate that the SAT during the pandemic was no more severe than normal. This discrepancy between the two studies may be explained both by the fact that the current study was conducted in a much larger SAT population and had relatively longer follow-up data. Moreover, clinical and ultrasonographic findings at the time of diagnosis and laboratory findings can sometimes differ in SAT [38]. Thus, the time between the onset of the symptoms and the presentation of the patients may affect the laboratory findings at the time of diagnosis. However, the time of onset of symptoms is highly subjective data, and the lack of data in the current study prevented comparisons in this regard. Nevertheless, during the COVID-19 pandemic, increased patient awareness and the easy confusion of SAT with upper respiratory tract infections may have resulted in earlier patient admissions. Therefore, the fT4 elevation in the pandemic SAT group can be attributed to the fact that the presentation rate was higher in the initial thyrotoxic phase rather than the severity of the disease. This claim is supported by the absence of difference between the groups in terms of both treatment modalities and follow-up parameters in the current study.

The single-center and retrospective nature of the study, as well as possible cross-country and regional variations, limit the generalizability of the incidence data, so it is crucial to check the current results with general population-based multicenter studies. In addition, due to the higher number of patients in the pandemic SAT group who have not yet completed the required follow-up time, it may be wrong to make definite conclusions in terms of permanent hypothyroidism. Nevertheless, the case population in this study can be considered substantial for a rare disease such as SAT. The fact that the region where our clinic is located is endemic in terms of SAT (>100 cases per year) and that it is the second province in Turkey with the highest incidence of COVID-19 cases increases the reliability of the results of the study.

In conclusion, although SAT cases have been reported during or after COVID-19 infection and after COVID-19 vaccination, there was no increase in SAT cases in the pandemic compared to previous years. Moreover, no significant change in the clinical course of SAT was experienced during the pandemic. However, it was observed that SAT cases, which had previously clustered in autumn in our region, shifted to winter in parallel with the local COVID-19 case peaks with the pandemic. In addition, unlike in previous years, there was an increase in SAT cases in males, where COVID-19 was more severe than in females during the pandemic. These results highlight the possible relationship between SARS-CoV-2 and SAT. More importantly, even if there was a change in the etiology of SAT with the pandemic,

it can be understood that this did not have a negative effect on the incidence and clinical course of the disease.

Author contributions H.B., M.E.S., and M.C. conceptualized and designed the article. H.B., M.C., S.K., S.H., A.C. and U.G. collected and interpreted the data. H.B. and M.C. performed the statistical analysis. H.B. wrote the first draft of the manuscript. M.E.S., I.O.U., O.O., M.K., B.U., and E.C. reviewed and supervised the manuscript critically. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital (Date: 18.04.2022/No:135/01).

References

1. A.A. Alfadda, R.M. Sallam, G.E. Elawad, H. Aldhukair, M.M. Alyahya, Subacute thyroiditis: clinical presentation and long term outcome. *Int. J. Endocrinol.* **2014**, 794943 (2014). <https://doi.org/10.1155/2014/794943>
2. M.H. Samuels, Subacute, silent, and postpartum thyroiditis. *Med. Clin. North Am.* **96**, 223–233 (2012). <https://doi.org/10.1016/j.mcna.2012.01.003>
3. V. Fatourehchi, J.P. Aniszewski, G.Z.E. Fatourehchi, E.J. Atkinson, S.J. Jacobsen, Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. *J. Clin. Endocrinol. Metab.* **88**, 2100–2105 (2003). <https://doi.org/10.1210/jc.2002-021799>
4. C. Cappelli, I. Pirola, E. Gandossi, A.M. Formenti, B. Agosti, M. Castellano, Ultrasound findings of subacute thyroiditis: a single institution retrospective review. *Acta Radio.* **55**, 429–433 (2014). <https://doi.org/10.1177/0284185113498721>
5. E. Martino, L. Buratti, L. Bartalena et al. High prevalence of subacute thyroiditis during summer season in Italy. *J. Endocrinol. Invest.* **10**, 321–323 (1987). <https://doi.org/10.1007/BF03348138>
6. E. Nishihara, H. Ohye, N. Amino et al. Clinical characteristics of 852 patients with subacute thyroiditis before treatment. *Intern. Med.* **47**, 725–729 (2008). <https://doi.org/10.2169/internalmedicine.47.0740>
7. G. Dimos, G. Pappas, N. Akritidis, Subacute thyroiditis in the course of novel H1N1 influenza infection. *Endocrine* **37**, 440–441 (2010). <https://doi.org/10.1007/s12020-010-9327-3>
8. R. Desailoud, D. Hober, Viruses and thyroiditis: an update. *Virology* **6**, 5 (2009). <https://doi.org/10.1186/1743-422X-6-5>
9. Š. Nyulassy, P. Hnilica, M. Buc, M. Guman, V. Hirschova, J. Stefanovic, Subacute (de Quervain's) thyroiditis: association with HLA-Bw35 antigen and abnormalities of the complement system, immunoglobulins and other serum proteins. *J. Clin. Endocrinol. Metab.* **45**, 270–274 (1977). <https://doi.org/10.1210/jcem-45-2-270>
10. M. Stasiak, B. Tymoniuk, R. Michalak, B. Stasiak, M.L. Kowalski, A. Lewiński, Subacute thyroiditis is associated with HLA-B* 18: 01,-DRB1* 01 and-C* 04: 01—the significance of the new molecular background. *J. Clin. Med.* **9**, 534 (2020). <https://doi.org/10.3390/jcm9020534>

11. World Health Organization. WHO Coronavirus (COVID 19) Dashboard. (2022). <https://covid19.who.int/>
12. Y. Zhao, X. Wu, Influence of COVID-19 vaccines on endocrine system. *Endocrine* (2022). <https://doi.org/10.1007/s12020-022-03119-3>
13. A. Brancatella, D. Ricci, D. Cappellani et al. Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection? Insights from a case series. *J. Clin. Endocrinol. Metab.* **105**, e3742–e3746 (2020). <https://doi.org/10.1210/clinem/dgaa537>
14. S. Sohrabpour, F. Heidari, E. Karimi, R. Ansari, A. Tajdini, F. Heidari, Subacute thyroiditis in COVID-19 patients. *Eur. Thyroid J.* **9**, 321–323 (2021). <https://doi.org/10.1159/000511707>
15. M. Popescu, A. Ghemigian, C.M. Vasile, A. Costache, M. Carsote, A.E. Ghenea, The new entity of subacute thyroiditis amid the COVID-19 Pandemic: from infection to vaccine. *Diagnostics* **12**, 960 (2022). <https://doi.org/10.3390/diagnostics12040960>
16. H. Bostan, S. Kayihan, M. Calapkulu et al. Evaluation of the diagnostic features and clinical course of COVID-19 vaccine-associated subacute thyroiditis. *Hormones* (2022). <https://doi.org/10.1007/s42000-022-00380-z>
17. Ö. Topaloğlu, S. Tekin, S.N. Topaloğlu, T. Bayraktaroglu, Differences in clinical aspects between subacute thyroiditis associated with COVID-19 vaccines and classical subacute thyroiditis. *Horm. Metab. Res.* **54**, 380–388 (2022). <https://doi.org/10.1055/a-1840-4374>
18. D.S. Ross, H.B. Burch, D.S. Cooper et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid* **26**, 1343–1421 (2016). <https://doi.org/10.1089/thy.2016.0229>
19. M.-Y. Li, L. Li, Y. Zhang, X.-S. Wang, Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect. Dis. Poverty* **9**, 45 (2020). <https://doi.org/10.1186/s40249-020-00662-x>
20. M. Rotondi, F. Coperchini, G. Ricci et al. Detection of SARS-CoV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. *J. Endocrinol. Invest.* **44**, 1085–1090 (2021). <https://doi.org/10.1007/s40618-020-01436-w>
21. F. Coperchini, G. Ricci, L. Croce et al. Modulation of ACE-2 mRNA by inflammatory cytokines in human thyroid cells: a pilot study. *Endocrine* **74**, 638–645 (2021). <https://doi.org/10.1007/s12020-021-02807-w>
22. H. Jakovac, A. Ferenčić, C. Stemberger, B.M. Vitezić, D. Cuculić, Detection of Sars-Cov-2 antigens in thyroid gland showing histopathological features of subacute thyroiditis. *Eur. Thyroid J.* **11**, e220005 (2022). <https://doi.org/10.1530/ETJ-22-0005>
23. D. Kanduc, Y. Shoenfeld, Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. *Immunol. Res.* **68**, 310–313 (2020). <https://doi.org/10.1007/s12026-020-09152-6>
24. A. Vojdani, E. Vojdani, D. Kharrazian, Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. *Front. Immunol.* **11**, 617089 (2021). <https://doi.org/10.3389/fimmu.2020.617089>
25. I. Pirola, E. Gandossi, M. Rotondi et al. Incidence of De Quervain's thyroiditis during the COVID-19 pandemic in an area heavily affected by Sars-CoV-2 infection. *Endocrine* **74**, 215–218 (2021). <https://doi.org/10.1007/s12020-021-02841-8>
26. A. Brancatella, N. Viola, G. Rutigliano, D. Sgrò, F. Santini, F. Latrofa, Subacute thyroiditis during the SARS-CoV-2 pandemic. *J. Endocr. Soc.* **5**, bvab130 (2021). <https://doi.org/10.1210/jendso/bvab130>
27. M. Stasiak, K. Zawadzka-Starczewska, A. Lewiński, Clinical manifestation of subacute thyroiditis triggered by SARS-CoV-2 infection can be HLA-dependent. *Viruses* **13**, 2447 (2021). <https://doi.org/10.3390/v13122447>
28. S.N. Şendur, F. Özmen, S.H. Oğuz et al. Association of human leukocyte antigen genotypes with severe acute respiratory syndrome coronavirus 2 vaccine-induced subacute thyroiditis. *Thyroid* **32**, 640–647 (2022). <https://doi.org/10.1089/thy.2022.0010>
29. H. Agca, H. Akalin, I. Saglik, M. Hacimustafaoglu, S. Celebi, B. Ener, Changing epidemiology of influenza and other respiratory viruses in the first year of COVID-19 pandemic. *J. Infect. Public Health* **14**, 1186–1190 (2021). <https://doi.org/10.1016/j.jiph.2021.08.004>
30. S. Saito, T. Sakurada, M. Yamamoto, T. Yamaguchi, K. Yoshida, Subacute thyroiditis: observations on 98 cases for the last 14 years. *Tohoku J. Exp. Med.* **113**, 141–147 (1974). <https://doi.org/10.1620/tjem.113.141>
31. C. Benbassat, D. Olchovsky, G. Tsvetov, I. Shimon, Subacute thyroiditis: clinical characteristics and treatment outcome in fifty-six consecutive patients diagnosed between 1999 and 2005. *J. Endocrinol. Invest.* **30**, 631–635 (2007). <https://doi.org/10.1007/BF03347442>
32. H. Oksa, P. Jarvenpaa, L. Metsahonkala, A. Pasternack, P. Leinikki, No seasonal distribution in subacute de Quervain's thyroiditis in Finland. *J. Endocrinol. Invest.* **12**, 495 (1989). <https://doi.org/10.1007/BF03350743>
33. A. Altay-Kocak, S. Sarzhanova, A. Tapisiz, M. Dizbay, A. Basustaoglu, G. Bozdayi, Retrospective evaluation of viral respiratory tract infections in a university hospital in Ankara, Turkey (2016–2019). *J. Infect. Dev. Ctries.* **16**, 857–863 (2022). <https://doi.org/10.3855/jidc.14427>
34. T. Meister, H. Pisarev, R. Kolde et al. Clinical characteristics and risk factors for COVID-19 infection and disease severity: a nationwide observational study in Estonia. *PLoS ONE* **17**, e0270192 (2022). <https://doi.org/10.1371/journal.pone.0270192>
35. I. Muller, D. Cannavaro, D. Dazzi et al. SARS-CoV-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol.* **8**, 739–741 (2020). [https://doi.org/10.1016/S2213-8587\(20\)30266-7](https://doi.org/10.1016/S2213-8587(20)30266-7)
36. J. Sato, T. Uchida, K. Komiya et al. Comparison of the therapeutic effects of prednisolone and nonsteroidal anti-inflammatory drugs in patients with subacute thyroiditis. *Endocrine* **55**, 209–214 (2017). <https://doi.org/10.1007/s12020-016-1122-3>
37. M.E. Sencar, M. Calapkulu, D. Sakiz et al. An evaluation of the results of the steroid and non-steroidal anti-inflammatory drug treatments in subacute thyroiditis in relation to persistent hypothyroidism and recurrence. *Sci. Rep.* **9**, 16899 (2019). <https://doi.org/10.1038/s41598-019-53475-w>
38. T. Tachibana, Y. Orita, Y. Ogawara et al. Time-lag between symptom onset and laboratory findings in patients with subacute thyroiditis. *Auris Nasus Larynx* **41**, 369–372 (2014). <https://doi.org/10.1016/j.anl.2013.11.003>

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