



Beyond Acute COVID-19: Investigating the Incidence of Subacute Thyroiditis in Long COVID-19 in Korea

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Background: The correlation between acute coronavirus disease 2019 (COVID-19) and subacute thyroiditis (SAT) has not been clearly investigated in “long COVID” patients. We aimed to investigate the incidence of SAT during convalescence and after the acute phase of COVID-19, comparing with that of the general population.

Methods: Data from a total of 422,779 COVID-19 patients and a control group of 2,113,895 individuals were analyzed. The index date was defined as the date 3 months after confirmation of COVID-19. The incidence rate (IR) of SAT and hazard ratios (HRs) were calculated per 100,000 persons. Subgroup analysis included analysis of HRs 90–179 and 180 days post-COVID-19 diagnosis; and additional analysis was conducted according to hospitalization status, sex, and age group.

Results: The IR of SAT was 17.28 per 100,000 persons (95% confidence interval [CI], 12.56 to 23.20) in the COVID-19 group and 8.63 (95% CI, 6.37 to 11.45) in the control group. The HR of COVID-19 patients was 1.76 (95% CI, 1.01 to 3.06; $P=0.045$). The HR of SAT was 1.39 (95% CI, 0.82 to 2.34; $P=0.220$) up to 6 months after the index date and 2.30 (95% CI, 1.60 to 3.30; $P<0.001$) beyond 6 months. The HR for SAT among COVID-19 patients was 2.00 (95% CI, 1.41 to 2.83) in hospitalized patients and 1.76 (95% CI, 1.01 to 3.06) in non-hospitalized patients compared to the control group. The IR of SAT was 27.09 (95% CI, 20.04 to 35.82) for females and 6.47 (95% CI, 3.34 to 11.30) for males. In the 19 to 64 age group, the IR of SAT was 18.19 (95% CI, 13.70 to 23.67), while the IR was 9.18 (95% CI, 7.72 to 10.84) in the 65 to 69 age group.

Conclusion: SAT could be a potential long-term complication of COVID-19. Long-term surveillance for thyroid dysfunction is needed especially in hospitalized, female and young-aged subjects.

Keywords: COVID-19; Thyroiditis; Subacute; Post-acute COVID-19 syndrome

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been impacting global health since first scientifically described in December 2019 and was classified as a pandemic by the World Health Organization (WHO) in March 2020. However, as coronavirus disease 2019 (COVID-19) has transitioned to an endemic disease in some regions, its impact on global health is constantly evolving [1].

SARS-CoV-2 infects the host's cells through the angiotensin-converting enzyme 2 (ACE2) receptor by binding of the SARS-CoV-2 spike or S protein to the ACE2 receptor [2,3]. Viral RNA has been found in serum, urine, and fecal samples of infected COVID-19 patients, suggesting that SARS-CoV-2 could have a systemic effect on multiple organs with ACE2 expression and could result in multi-systemic failure [4]. In particular, high ACE expression levels have been detected in the thyroid gland [5,6]. Triiodothyronine and thyroxine are correlated with serum ACE2 levels and are crucial for adaptive immune response [7]. Several hypotheses that contribute to the increased risk of inflammatory thyroidal disease in COVID-19 patients have been suggested. One is the destruction of follicular cells by autoimmune and/or viral thyroiditis [8]. A second is the initiation of a cytokine storm from the increased production of proinflammatory cytokine such as interleukin-6 and tumor necrosis factor causing thyroid hyperfunction [9]. Although the correlation between subacute thyroiditis (SAT) and viral infection has been well-established, the mechanism, pathogenesis, and consequences of thyroid involvement in COVID-19 patients are not clearly understood. Moreover, previous studies have only focused on new-onset SAT during the acute phase of COVID-19 [7,9-11].

Approximately 10% of COVID-19 patients have reported prolonged symptoms beyond 4 weeks after diagnosis, known as "long COVID" [12,13] or "post-COVID conditions" according to the Centers for Disease Control and Prevention [14]. Previous research has reported that 1.9% of patients with normal thyroid function progressed to thyroiditis during convalescence [15]. In terms of long COVID, considering the possibility of late-onset thyroiditis after a longer period following diagnosis of COVID-19 is important. Long COVID was defined as the persistence of symptoms and signs after 12 weeks following COVID-19 diagnosis by the Korea Disease Control and Prevention and the Korean Society of Infectious Diseases [16]. Therefore, we aimed to establish the nationwide incidence of SAT during convalescence and after the acute phase of COVID-19 and to compare this incidence to that of the general population, thereby deter-

mining whether post-COVID-19 SAT presents a public health burden.

METHODS

Data collection

This population-based retrospective and cross-sectional study used data from the Health Insurance Review and Assessment (HIRA) claims database, which contains information on individuals who underwent SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction testing of nasal or pharyngeal swabs in accordance with WHO guidelines. The participants with COVID-19 infection between January 2020 and September 2021 in the National Health Insurance Service and Korea Disease Control and Prevention Agency databases were included. The HIRA database is a comprehensive healthcare dataset that is managed by the Korean government and encompasses nearly 100% of the country's population. The database includes information on the beneficiaries' demographic characteristics, healthcare utilization history based on the International Classification of Diseases 10th Revision (ICD-10), and hospitalization and outpatient care prescriptions.

Study population

COVID-19 patients were defined by ICD-10 codes U18 (provisional assignment of new diseases of uncertain etiology or emergency use), U07.1 (COVID-19), B34.2 (coronavirus infection, unspecified site), and B97.2 (coronavirus as the cause of diseases classified to other chapters). A total of 432,795 patients with COVID-19, ranging in age from 19 to 89 years, were enrolled in the study. Out of these, 25,386 subjects were excluded based on the following criteria: patients who received a steroid prescription for SAT as a diagnosis within the past year before the index date, subjects who died before the index date, subjects who underwent thyroidectomy (as indicated by HIRA procedure codes P4561, P4552, P4554, P4551, and P4553) and individual who had a presence of autoimmune thyroiditis (ICD-10 code, E06.3). The index date was defined as the date 3 months after confirmation of COVID-19. We matched COVID-19 patients with a control group of 2,037,135 individuals in a 1:5 ratio based on age and sex. Ultimately, data from a total of 407,427 COVID-19 patients and 2,037,135 control subjects were analyzed, and these subjects were followed from baseline to April 30, 2022. This study complied with the ethical standards of the Declaration of Helsinki (IRB approval No. 2022-081). The protocol using secondary data received approval from the Eunpyeong St. Mary's

Hospital Institutional Review Board of Catholic Medical Center, Catholic University of Korea (IRB approval No. PC20ZASI0091). The requirement for written informed consent was waived due to the use of previously collected and anonymized data.

Definition of outcomes

In our study, we evaluated the incidence of SAT, which was defined as the presence of ICD-10 code E061 (SAT) at least one time during the study period. To identify cases of SAT, we selected patients who had both the E061 code and a prescription for corticosteroids concurrently.

Statistical analysis

Baseline characteristics are presented as the mean \pm standard deviation, median (interquartile range), or number (%). The incidence rate (IR) of SAT was calculated as the number of events divided by the total follow-up duration (person-years) and standardized the rate per 100,000 person-years, and the 95% confidence interval (CI) and *P* value were calculated using a Poisson approximation. The risk ratio of COVID-19 patients is presented as hazard ratios (HRs) with 95% CIs using Cox proportional hazards models for matched data compared to the control group. In subanalysis, the HR for COVID-19 was evaluated according to hospitalized patients and non-hospitalized status, gender and age with the control group as reference. All tests were two-sided and a *P* value <0.05 was considered statistically significant. All statistical analyses were performed using the R program version 4.1.1 (R Development Core Team, Vienna, Austria).

RESULTS

Baseline characteristics in COVID-19 and the control group

A total of 244,562 subjects were analyzed. The mean age of all study subjects during the follow-up period was 46.3 ± 17.4 years. Of the analyzed subject data, 50.4% of subjects were male. The mean follow-up time from the index date after COVID-19 was 10.8 ± 5.6 months. Table 1 presents the baseline characteristics of COVID-19 patients and the control group after 1:5 matching.

Incidence of SAT according to COVID-19 infection during the study period

During the follow-up period, the IR of SAT demonstrated different patterns in COVID-19 patients compared to the control group. A total of 220 SAT events occurred in the entire cohort during 2,205,713 person-years of follow-up and resulted in an IR of 9.97 (95% CI, 8.70 to 11.38). The mean of age was 46.5 years. The

Table 1. Baseline Characteristics of Subject with COVID-19 and without COVID-19

Clinical parameter	Total (n=2,444,562)	After 1:5 matching	
		COVID-19 (n=407,427)	Control (n=2,037,135)
Sex			
Male	1,259,382 (51.5)	209,897 (51.5)	1,049,485 (51.5)
Female	1,185,180 (48.5)	197,530 (48.5)	987,650 (48.5)
Age, yr	46.3 \pm 17.4	46.3 \pm 17.4	46.3 \pm 17.4
19–29	538,620 (22.0)	87,770 (22.0)	448,850 (22.0)
30–39	435,096 (17.8)	72,516 (17.8)	362,580 (17.8)
40–49	440,970 (18.0)	73,495 (18.0)	367,475 (18.0)
50–59	435,432 (18.0)	72,572 (17.8)	362,860 (17.8)
60–69	323,118 (13.2)	53,853 (13.2)	269,265 (13.2)
70–89	271,326 (11.1)	45,221 (11.1)	226,105 (11.1)
Follow-up, mo	10.8 \pm 5.6	10.8 \pm 5.7	10.8 \pm 5.6

Values are expressed as number (%) or mean \pm standard error. COVID-19, coronavirus disease 2019.

events of SAT were 87.6% in women and 12.4% in men (Table 2).

In COVID-19 patients, 61 cases of SAT were reported during 366,346 person-years of follow-up, resulting in an IR of 16.65 (95% CI, 12.74 to 2.59). The IR in the general population was 9.97 (95% CI, 8.70 to 11.38). COVID-19 patients had a significantly higher IR compared to the control group with a HR of 1.93 (95% CI, 1.43 to 2.59; *P* <0.01).

The cumulative incidence of SAT was higher in the COVID-19 group compared to the control group over a 2-year period. The HR for COVID-19 was 1.39 (95% CI, 0.82 to 2.34; *P*=0.220) at 90 to 179 days after diagnosis and increased to 2.30 (95% CI, 1.60 to 3.30; *P* <0.001) after 180 days compared to the control group. During the period of 560 days following COVID-19 diagnosis, the IR of SAT was found to be 5.05 (95% CI, 1.89 to 13.45; *P*=0.001) (Fig. 1).

The incidence of SAT according to different parameters

Table 3 shows the incidence of SAT according to severity of COVID-19, sex, and age. In subanalysis, hospitalized patients with COVID-19 had an IR for SAT of 17.28 (95% CI, 12.56 to 23.20), and those without COVID-19 had IR of 15.21 (95% CI, 8.86 to 24.35). The HR in hospitalized patients for COVID-19 was 2.00 (95% CI, 1.41 to 2.83; *P* <0.001). In the outpatient clinic, the HR with 95% CI for COVID-19 was 1.76 (95% CI, 1.01 to 3.06; *P*=0.153). The IR of SAT was 27.09 (95% CI, 20.04 to 35.82) for females and 6.47 (95% CI, 3.34 to 11.30) for males.

Table 2. Incidence of Subacute Thyroiditis according to COVID-19 Infection

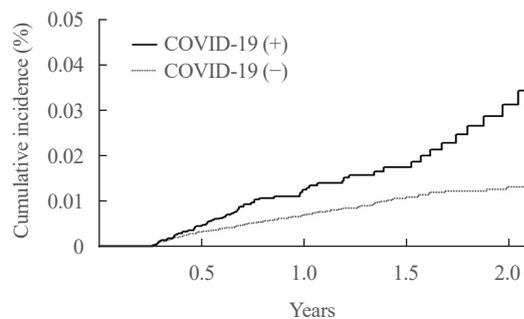
Variable	Total	COVID-19	Control	P value
No. of cases	220	61	159	
Person-years of follow-up	2,205,713	366,346	1,839,367	
Incidence /100,000 person-yr	9.97 (8.70–11.38)	16.65 (12.74–2.59)	8.64 (7.35–10.10)	
HR		1.93 (1.43–2.59)	Reference	<0.001
Sex				0.082
Male	31 (14.1)	12 (19.7)	19 (11.9)	
Female	189 (85.9)	49 (80.3)	140 (88.1)	
Age, yr				0.827
19–64	189 (88.9)	54 (88.5)	135 (84.9)	
65–89	31 (14.1)	7 (11.5)	24 (15.1)	

Values are expressed as HR (95% confidence interval) or number (%).
 COVID-19, coronavirus disease 2019; HR, hazard ratio.

Table 3. The Incidence of Subacute Thyroiditis according to Parameters

Variable	No.	COVID-19 IR	Control IR	HR	P value
Severity of COVID-19					
Non-hospitalization	690,690	15.21 (8.86–24.35)	8.63 (6.37–11.45)	1.76 (1.01–3.06)	0.045
Hospitalization	1,777,380	17.28 (12.56–23.20)	8.65 (7.11–10.42)	2.00 (1.41–2.83)	<0.001
Sex					
Male	1,259,382	6.47 (3.34–11.30)	1.82 (1.06–2.92)	3.54 (1.69–7.42)	0.001
Female	1,185,180	27.09 (20.04–35.82)	15.65 (13.18–18.45)	1.73 (1.25–2.39)	0.001
Age, yr					
19–64	2,039,592	18.19 (13.70–23.67)	9.18 (7.72–10.84)	1.98 (1.45–2.71)	<0.001
65–89	404,970	9.39 (3.45–20.43)	6.14 (3.75–9.49)	1.52 (0.61–3.79)	0.368

Values are expressed as IR per 100,000 patient-years (95% confidence interval [CI]) or HR (95% CI). P values are also provided for each category.
 COVID-19, coronavirus disease 2019; IR, incidence rate; HR, hazard ratio.



Years	0	0.5	1.0	1.5	2.0
COVID-19 (+)	407,427	404,742	216,124	81,878	35,305
COVID-19 (-)	2,037,135	2,027,926	1,086,212	414,060	178,049

Fig. 1. The cumulative incidence of subacute thyroiditis in coronavirus disease 2019 (COVID-19) patients and general population.

However, the HR for SAT in females was 1.73 (95% CI, 1.25 to 2.39; $P=0.001$) and 3.54 (95% CI, 1.69 to 7.42; $P=0.001$) in males. The IR of SAT was 18.19 (95% CI, 13.70 to 23.67) in the 19 to 64 age group, while the IR was 9.39 (95% CI, 3.45 to 20.43) in the 65 to 89 age group. The HR of SAT was 1.98 (95% CI, 1.45 to 2.71; $P<0.01$) in younger patients and 1.52 (95% CI, 0.61 to 3.79; $P=0.368$) in the older group.

DISCUSSION

COVID-19 has been associated with a spectrum of prolonged health sequelae, including respiratory and cardiovascular domains [17–19]. Previous studies reported that long COVID affects long-term morbidity and mortality [20,21]. Therefore, our study aimed

to investigate the association between COVID-19 and the incidence of SAT during the post-acute phase for COVID-19. Our results showed a significantly higher IR of SAT in COVID-19 patients compared to the control group, with a HR of 1.93. The IR of SAT showed no significant difference during the first 6 months following the index date. However, from 6 months onward, the IR increased two-fold. These results suggest the potential long-term impact of COVID-19 on thyroid function and long-term surveillance of COVID-19-related health outcomes is required.

The IR of SAT during the pandemic era has been reported to range from 7.3 to 11.4 per 100,000 person-years in various studies [22-24]. Our study found that the IR of SAT in the general population was 8.64. This is consistent with previous research that reported an IR of 8.3 [22]. In COVID-19 infection, the IR of SAT was 16.82, 1.93-fold higher than in the control group. This finding is consistent with previous studies that also reported an increased risk of SAT in COVID-19 infection. Muller et al. [25] found a higher prevalence of SAT in hospitalized COVID-19 patients compared to non-COVID-19 patient. However, this study only included hospitalized patients and did not include a control group from the general population. In contrast, our study included a control group from the general population. A recent systematic review and meta-analysis found that COVID-19 infection was associated with a significantly increased risk of SAT, with a pooled odds ratio of 2.90 (95% CI, 2.15 to 3.92) [26]. Lui et al. [27] reported a lower prevalence of SAT (13.9%) in patients with mild COVID-19, which is similar to that observed in non-COVID-19 controls. However, this study only included patients with mild COVID-19, and thus the prevalence of SAT in severe COVID-19 cases remains unclear. These studies had small sample sizes.

The IR for SAT in females with COVID-19 was 27.09 per 100,000 person-years and the IR in females without COVID-19, with same age distribution as COVID-19 patients, was 15.61 per 100,000 person-years. This showed that females had 11.44 more cases per 100,000 person-years. This figure in males with COVID-19 was 3.54 per 100,000 person-years. This trend is consistent with previous studies that reported a higher prevalence of SAT in females (75% to 80%) [28,29]. A recent study suggests that sex differences in immune responses and the presence of multiple immune-related genes on the X-chromosome may explain the higher prevalence of immune diseases in females [30]. However, our findings indicated that male gender is more correlated to developing SAT after COVID-19 infection. Thus, the biological mechanism underlying the observed sex

differences in the incidence of SAT remains unclear. Additionally, the HR of SAT was 1.98 in younger patients (19 to 64 years) and 1.52 in elderly patients (65 to 89 years). This finding could be explained by age-related changes in the immune system, resulting in a decreased immune response to infections in the elderly population. In contrast, a more robust immune response to infections is preserved in younger patients and it leads to increase the risk of SAT following COVID-19 [31]. Another plausible mechanism for the higher incidence of SAT in young age could be attributed to the higher expression of ACE2 [32]. The increased expression of ACE2 in younger age groups may render the thyroid gland more susceptible to viral entry. This heightened susceptibility could potentially lead to viral infection, subsequent inflammation, and the development of SAT. However, age-related differences in SAT incidence following COVID-19 has not been clearly documented.

Our study found the incidence of SAT was approximately two-fold higher in the COVID-19 group after 6 months following infection compared to the control group. However, there was no significant difference in the incidence between the COVID-19 group and the control group within the period of 90 to 179 days. Regarding the relationship between SAT and long COVID, there is limited research. A majority of previous studies has focused on the acute phase of COVID-19 within 8 to 12 weeks [10,11,18,23,27]. A recent study from Hong Kong reported that there were no significant differences between patients with and without long COVID at 6 months. This included consideration of disease COVID-19 severity at baseline [33]. However, the size of the severe COVID-19 group in that study was relatively small. The underlying mechanisms of SAT in long COVID patients are not yet fully established. Previous studies have reported rates of up to 33% for thyroid dysfunction and 20% for autoimmune thyroiditis in patients treated with interferon beta-1b [34,35]. One plausible mechanism is that the treatment using interferon therapy in COVID-19 patients may directly affect the thyroid gland and on iodine organification, leading to inflammation and subsequent damage to the thyroid cells during the post-acute phase [36]. Another possibility is that chronic exposure to interferon may trigger autoimmune reactions or disrupt the normal functioning of the immune system, potentially leading to thyroid-related complications. Another possibility is that unwanted autoimmune reaction [37]. These mechanisms may contribute to the development of SAT in long COVID patients. However, we encountered challenges in obtaining data for the study period due to the delayed availability of billing data retrieval.

To the best of our knowledge, this is the first study to investi-

gate the incidence of SAT in long COVID cases. This study is based on a large sample size from a nationally representative database. Thus the results should reflect clinical practice experience. Second, the use of a 1:5 matching strategy of COVID-19 patients to the general population enhances the reliability of our results and minimize selection bias. Despite these strengths, our study had several limitations. First, the database of claims data we used did not provide detailed clinical information on COVID-19 patients, such as disease severity, biochemistry such as thyroid function and thyroid antibody test results, treatment of COVID-19 or vaccination. Therefore, the causal relationship between COVID-19 and SAT could not be assessed due to the study design. Second, the accuracy of our findings is reliant on the quality and completeness of the HIRA database, which may contain inaccuracies or missing information. Finally, we cannot completely rule out the possibility of misclassification bias, as the identification of SAT was based on ICD-10 codes. The operational definition of SAT did not include the erythrocyte sedimentation rate (ESR), which is crucial maker for SAT. By not incorporating ESR into definition, some cases could be missed or misclassified. However, we took measures to ensure consistency in conditions for both the patient and control groups to enhance the reliability of our study.

In conclusion, our findings showed that SAT could be a potential long-term complication of COVID-19. These findings suggest the importance of long-term surveillance of COVID-19 patients, especially focusing on monitoring for signs of thyroid dysfunction. Further research is needed to investigate the underlying mechanisms and to prove the causality between long COVID-19 and SAT.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: J.L. Acquisition, analysis, or interpretation of data: J.L., G.H.S., K.S. Drafting the work or revising: J.L., G.H.S. Final approval of the manuscript: J.L., G.H.S., K.S.

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