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Delayed Follow-up Visits and Thyrotropin Among Patients With Levothyroxine During the COVID-19 Pandemic

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Abbreviations: aRR, adjusted risk ratio; fT4, free thyroxine; TSH, thyrotropin.

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Abstract

Context: The indirect effects of the COVID-19 pandemic on clinical practice have received great attention, but evidence regarding thyroid disease management is lacking.

Objective: We aimed to investigate the association between delayed follow-up visits during the pandemic and their serum thyrotropin (TSH) levels among patients being treated with levothyroxine.

Methods: This study included 25 361 patients who made a follow-up visit as scheduled (n = 9063) or a delayed follow-up visit (< 30 d, n = 10 909; ≥ 30 d, n = 5389) during the pandemic (after April 2020) in Japan. We employed modified Poisson models to estimate the adjusted risk ratio (aRR) of TSH greater than 4.5 mIU/L and greater than 10 mIU/L during the pandemic according to the 3 types of follow-up visit group (ie, as scheduled, delayed < 30 d, and delayed ≥ 30 d). The models included age, sex, city of residence, TSH levels, underlying thyroid disease, dose of levothyroxine, and duration of levothyroxine prescriptions.

Results: The mean age was 52.8 years and women were 88%. Patients who were older and had a higher dose or longer duration of levothyroxine prescriptions were more likely to make a delayed follow-up visit during the pandemic. Changes in TSH were larger among the delayed-visit groups than the scheduled-visit group. We found increased risks of elevated TSH levels during the pandemic among the delayed visit groups, particularly

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those with delayed visit of 30 or more days (TSH > 4.5 mIU/L, aRR [95% CI] = 1.72 [1.60-1.85]; and TSH > 10 mIU/L, aRR [95% CI] = 2.38 [2.16-2.62]).
Conclusion: A delayed follow-up visit during the COVID-19 pandemic was associated with less well-controlled TSH among patients with levothyroxine.

Key Words: delayed follow-up, levothyroxine, TSH, COVID-19, pandemic

Since the first cases of COVID-19, which is caused by SARS-CoV-2, was reported in December 2019, COVID-19 has become a global pandemic. As of August 4, 2021, nearly 200 million people worldwide had been infected by SARS-CoV-2, and more than 4.2 million people had died of COVID-19 [1]. Although the literature on COVID-19 patients (eg, clinical characteristics, risk factors, and treatment) has been increasing, the indirect effects of the COVID-19 pandemic on clinical practice regarding non–COVID-19 patients remain unclear. In view of the rapid change in health care services [2] and the increased mental health problems [3] related to treatment adherence [4] in 2020, there is a need to evaluate the extent to which the pandemic has affected health care use and disease control among non–COVID-19 patients.

Levothyroxine, a medication used to treat both overt and subclinical hypothyroidism, has been commonly prescribed worldwide [5, 6]. Ample evidence has shown that, if untreated or uncontrolled, such hypothyroid status increases the risk of long-term adverse health outcomes (eg, cardiovascular disease and death) [7-11]. Recent reports in the literature have suggested a possible link between COVID-19 and thyroid disorders, such as subacute thyroiditis related to SARS-CoV-2 [12] and severe complications due to SARS-CoV-2 in uncontrolled thyrotoxicosis [13]. Furthermore, given the limited resources and accessibility of the health care system during the pandemic, thyroid disorders including hypothyroidism may not be as closely controlled and managed as expected before the pandemic. However, evidence based on individual-level data has thus far been lacking about whether and the extent to which the pandemic has influenced the clinical management of patients being treated with levothyroxine.

To fill this knowledge gap, using individual-level data on more than 25 000 patients being treated with levothyroxine at Ito Hospital–one of the largest hospitals in Japan that specialize in thyroid disorders–before the pandemic, we identified patients' characteristics associated with delayed follow-up visits during the pandemic since April 2020. Then, we aimed to investigate the association between delayed follow-up visits and control of thyroid function, particularly serum thyrotropin (TSH) levels.

Materials and Methods

Data Sources and Study Population

We retrieved data on patients aged 20 years or older who made a follow-up visit between April 2020 and August 2020 and were treated with levothyroxine at Ito Hospital. Across a total of 25 361 patients, 9063 patients made a follow-up visit as scheduled, 10 909 patients made a delayed (< 30 d) follow-up visit, and 5389 patients made a delayed (≥ 30 d) follow-up visit. The scheduled follow-up date was estimated by the duration (No. of d) of levothyroxine prescription at the last visit before April 2020. Although we introduced telemedicine consultations in March 2020 (one time per patient allowed) in response to the announcement of the Ministry of Health, Labor and Welfare in Japan, our study did not include patients who used the telemedicine option because thyroid hormone levels (ie, primary outcomes of our study) were not measured during virtual care. All patients provided informed written consent on their visits at clinic. This specific research was approved by the institutional review board of our hospital (No. 305).

Measurements

Patients' age, sex, city of residence (Tokyo [the city where the clinic is located] or not), the primary underlying thyroid diseases (Hashimoto disease, Basedow disease, thyroid cancer, and others/unlabeled), and medications (names, doses, and days) at the last visit before April 2020 were obtained from electronic medical records. TSH and free thyroxine (fT4) were measured at both the last visit before April 2020 and the first follow-up visit in 2020 with a commercial rapid electrochemiluminescence immunoassay kit (ECLusys TSH and ECLusys fT4; Roche Diagnostics GmbH). The reference range of each thyroid function measurement was as follows: TSH, 0.2 to 4.5 mIU/L and fT4, 0.8 to 1.6 ng/dL.

Statistical Analysis

First, after describing the monthly trends in the aggregated numbers of follow-up visits to the clinic between 2019 and 2020 among patients being treated with levothyroxine, we described the demographic characteristics of patients

in each type of follow-up visit (ie, as scheduled, delayed < 30 d, and delayed ≥ 30 d). Then, we employed modified Poisson regression models to estimate the adjusted risk ratio (aRR) of delayed (< 30 d and ≥ 30 d, respectively) follow-up visits in 2020 according to the patients' characteristics, including age, sex, city of residence, TSH levels (< 0.2, 0.2-4.5, or > 4.5 mIU/L), underlying thyroid diseases, dose of levothyroxine (< 25 µg, 25-< 50 µg, 50-< 100 µg, or ≥ 100 µg), and duration of levothyroxine prescription (≤ 120 d or 120-≤ 180 d), at the last visit before April 2020.

Second, we calculated adjusted TSH levels at the last visit before April 2020 and the first visit after April 2020 and adjusted change in TSH according to each type of follow-up visit group by using the margins command in Stata after fitting multivariable linear regression models [14]. The models were adjusted for age, sex, city of residence, TSH levels, underlying thyroid diseases, dose of levothyroxine, and duration of levothyroxine prescriptions, at the last visit before April 2020. To account for the right-skewed distribution of TSH, we reanalyzed the data using negative binomial regression models instead of linear regression models. We also estimated adjusted fT4 levels at the last visit before April 2020 and the first visit after April 2020, and adjusted changes in fT4 using our main models.

Third, we described a prevalence of TSH greater than 4.5 mIU/L and greater than 10 mIU/L at the last visit before April 2020 and the first visit after April 2020 according to each type of follow-up visit. We employed modified Poisson regression models to estimate the aRR of TSH greater than 4.5 mIU/L and greater than 10 mIU/L at the first visit after April 2020 among the delayed follow-up visit groups compared with the scheduled follow-up visit group.

To assess whether the association between delayed follow-up visits and elevated TSH levels during the pandemic varies by demographic characteristics, we also stratified the analysis by age (≤ 50 y, > 50 y), sex (male, female), and underlying diseases (Hashimoto disease, Basedow disease, thyroid cancer, and others/unlabeled).

Sensitivity Analyses

We conducted the following 3 sensitivity analyses. First, to assess the sensitivity of our results to the cutoff points for dichotomizing patient group with delayed follow-up visit (ie, 1 mo, or 30 d), we reconducted the analysis using the median value (ie, 16 d) to categorize the patients with delayed follow-up visit into 2 groups. Second, to evaluate whether these findings are observed in general or specific to the pandemic, we examined the change in TSH according to each type of follow-up visit group during both prepandemic and pandemic periods. In this analysis, we restricted patients to those who visited the hospital during the first quarter (January-March) and extracted their follow-up visits during the second quarter (April-June) for both years to minimize the possible influence by seasonal differences. Last, to balance the covariates between the scheduled visit group and delayed visit group, we employed nearest-neighbor one-to-one propensity score matching without replacement. All statistical analyses were performed using Stata software version 15 (StataCorp).

Results

Between 2019 and 2020, we found a statistically significant decrease in the average number (per month) of follow-up visits to the clinic among patients being treated with levothyroxine (11 502 in 2019 vs 9577 in 2020 including telemedicine; 17% decline; $P < .001$). The average number of telemedicine use during March 2020 to August 2020 was 1466 per month.

Across a total of 25 361 patients who made a scheduled or delayed follow-up visits, the mean (SD) age was 52.8 (15.2) years; women were 88%. Baseline characteristics in each group are shown in Table 1. The multivariable modified Poisson regression models showed the increased risk of the delayed follow-up visits during the pandemic among older patients and patients taking a higher dose or a longer duration of levothyroxine prescriptions before April 2020 (Table 2).

In the entire cohort, TSH levels decreased during the pandemic (mean [95% CI], 3.13 [3.04-3.22] mIU/L before April 2020, and 2.55 [2.47-2.63] mIU/L after April 2020; $P = .001$). Although there was not a statistically significant difference in adjusted TSH levels across the scheduled or delayed follow-up visit groups before the pandemic, we found the larger adjusted TSH levels during the pandemic among patients who made a delayed follow-up visit compared with those who made a scheduled follow-up visit (Table 3). The decrease in TSH levels during the pandemic was smaller among patients who made a delayed follow-up visit (< 30 d, –0.52 [95% CI, –0.66 to –0.38]; and ≥ 30 d, –0.15 [95% CI, –0.36 to 0.06]) than those who made a scheduled follow-up visit (–0.88 [95% CI, –1.04 to –0.73]) (see Table 3). The findings were consistent when using negative binomial regression models instead of linear regression models (Supplementary Table S1) [15]. We also found a larger reduction in fT4 levels among patients who made a delayed (< 30 d or ≥ 30 d) follow-up visit than those who made a follow-up visit as scheduled (Supplementary Table S2) [15].

In the multivariable modified Poisson regression models, we found a statistically significant association of delayed follow-up visit with increased risks of TSH greater than

Table 1. Demographic characteristics among patients being treated with levothyroxine according to whether they made a scheduled or delayed follow-up visit during April 2020 to August 2020

Variables[a]	Patients who made a follow-up visit as scheduled during Apr 2020 to Aug 2020 (n = 9063)	Patients who made a delayed (< 30 d) follow-up visit during Apr 2020 to Aug 2020 (n = 10 909)	Patients who made a delayed (≥ 30 d) follow-up visit during Apr 2020 to Aug 2020 (n = 5389)
Age, y	51.1 ± 14.8	53.8 ± 15.2	53.7 ± 15.8
Sex			
Male	1034 (11.4)	1485 (13.6)	588 (10.9)
Female	8029 (88.6)	9424 (86.4)	4801 (89.1)
City of residence			
Tokyo	4745 (52.4)	5681 (52.1)	2650 (49.2)
Outside Tokyo	4318 (47.6)	5228 (47.9)	2739 (50.8)
TSH at last visit before pandemic(at baseline), mIU/L			
< 0.2	1062 (11.9)	1266 (11.8)	621 (11.8)
0.2-4.5	6182 (69.4)	7822 (72.7)	3834 (72.6)
> 4.5	1661 (18.7)	1668 (15.5)	826 (15.6)
Underlying thyroid diseases			
Hashimoto disease	3118 (34.4)	3808 (34.9)	2073 (38.5)
Basedow disease	2358 (26.0)	2678 (24.6)	1299 (24.1)
Thyroid cancer	1738 (19.2)	2241 (20.6)	1121 (20.8)
Others/ Unlabeled	1849 (20.4)	2180 (20.0)	896 (16.6)
Dose of levothyroxine at last visit before pandemic (at baseline), μg			
< 25	2577 (28.4)	2620 (24.0)	1284 (23.8)
25-< 50	2944 (32.5)	3685 (33.8)	1766 (32.8)
50-< 100	1822 (20.1)	2234 (20.5)	1201 (22.3)
≥ 100	1720 (19.0)	2370 (21.7)	1138 (21.1)
Duration of levothyroxine prescriptions at last visit before pandemic (at baseline), d			
≤ 120	3816 (42.1)	3542 (32.5)	1846 (34.3)
121-≤ 180	5247 (57.9)	7367 (67.5)	3543 (65.8)

Abbreviation: TSH, thyrotropin.
[a]Data are presented as mean ± SD for continuous variables, and number (%) for categorical variables.

4.5 mIU/L (delayed < 30 d, aRR [95% CI] = 1.13 [1.05-1.21]; delayed ≥ 30 days, aRR [95% CI] = 1.72 [1.60-1.85]) and TSH greater than 10 mIU/L (delayed < 30 d, aRR [95% CI] = 1.17 [1.06-1.29]; delayed ≥ 30 d, aRR [95% CI] = 2.38 [2.16-2.62]) during the pandemic (Fig. 1, Table 4).

When stratified by age, we found a stronger association between delayed follow-up visit and elevated TSH levels during the pandemic among younger adults aged 50 years or younger than older adults older than 50 (Table 5). However, we did not find a difference in the magnitude of the association by sex and underlying diseases (Supplementary Tables S3 and S4) [15].

Sensitivity Analyses

We found consistent results when we dichotomized patients who made a delayed follow-up visit using median value of 16 days (Supplementary Table S5) [15]. When we compared the change in TSH according to whether patients made a scheduled or delayed follow-up visit between 2019 and 2020, we found a smaller or no improvement among patients who made a delayed (≥ 30 d) follow-up visit than those who made a scheduled follow-up visit in 2020, but this association was not observed in 2019 (ie, even patients who made a delayed follow-up visit showed a decrease in TSH levels at their follow-up visit in 2019; Supplementary Table S6) [15]. In the propensity score matching analyses, covariates were well balanced between the scheduled-visit group and delayed-visit group (Supplementary Table S7) [15] and patients with a delayed follow-up visit were more likely to show elevated TSH levels during the pandemic (Supplementary Table S8) [15].

Discussion

In this large cohort study in Japan, we found that the number of follow-up visits among patients being treated

Table 2. Risk ratio of a delayed follow-up visit during April 2020 to August 2020 according to baseline characteristics among patients being treated with levothyroxine

Variables	Adjusted risk ratio (95% CI) of delayed (< 30 d) follow-up visits (vs scheduled visits) during Apr 2020 to Aug 2020[a]	*P*	Adjusted risk ratio (95% CI) of delayed (≥ 30 d) follow-up visits (vs scheduled visits) during Apr 2020 to Aug 2020[a]	*P*
Age (per 20 y)	1.07 (1.05-1.10)	< .001	1.10 (1.08-1.14)	< .001
Sex				
Male	Reference	–	Reference	–
Female	0.94 (0.88-0.99)	.02	1.06 (0.99-1.13)	.08
City of residence				
Tokyo	Reference	–	Reference	–
Outside Tokyo	0.99 (0.95-1.03)	.61	1.07 (1.03-1.11)	< .001
TSH at last visit before pandemic, mIU/L				
< 0.2	0.96 (0.90-1.02)	.20	0.96 (0.90-1.02)	.18
0.2-4.5	Reference	–	Reference	–
> 4.5	0.90 (0.86-0.95)	< .001	0.87 (0.83-0.92)	< .001
Underlying thyroid diseases				
Hashimoto disease	Reference	–	Reference	–
Basedow disease	0.97 (0.92-1.02)	.21	0.90 (0.86-0.95)	< .001
Thyroid cancer	0.97 (0.91-1.02)	.22	0.92 (0.87-0.97)	.003
Others/ Unlabeled	1.03 (0.98-1.09)	.22	0.85 (0.81-0.90)	< .001
Dose of levothyroxine at last visit before pandemic, μg				
< 25	Reference	–	Reference	–
25-< 50	1.07 (1.02-1.13)	.01	1.10 (1.04-1.16)	< .001
50-< 100	1.06 (1.00-1.13)	.04	1.17 (1.10-1.23)	< .001
≥ 100	1.11 (1.05-1.18)	.001	1.16 (1.09-1.23)	< .001
Duration of levothyroxine prescriptions at last visit before pandemic, d				
≤ 120	Reference	–	Reference	–
121-≤ 180	1.15 (1.10-1.20)	< .001	1.13 (1.08-1.18)	< .001

Abbreviation: TSH, thyrotropin.
[a]Modified Poisson regression model was employed to estimate the risk ratio of delayed follow-up visit in 2020. The model included age, sex, city of residence, TSH levels, underlying thyroid diseases, dose of levothyroxine, and duration of levothyroxine prescriptions at the last visit before the pandemic.

Table 3. Adjusted thyrotropin levels before and during the pandemic according to whether patients made a scheduled or a delayed follow-up visit during April 2020 to August 2020

Outcomes	Patients who made a follow-up visit as scheduled during Apr 2020 to Aug 2020	Patients who made a delayed (< 30 d) follow-up visit during Apr 2020 to Aug 2020	Patients who made a delayed (≥ 30 d) follow-up visit during Apr 2020 to Aug 2020
Adjusted TSH at last visit before pandemic (95% CI)[a]	3.15 (3.03 to 3.28)	3.02 (2.90 to 3.13)	3.37 (3.20 to 3.53)
P	–	.12	.05
Adjusted TSH at first visit during pandemic (95% CI)[a]	2.29 (2.17 to 2.42)	2.48 (2.36 to 2.59)	3.18 (3.01 to 3.35)
P	–	.03	< .001
Adjusted change in TSH before and during pandemic (95% CI)[a]	–0.88 (–1.04 to –0.73)	–0.52 (–0.66 to –0.38)	–0.15 (–0.36 to 0.06)
P	–	.001	< .001

Abbreviation: TSH, thyrotropin.
[a]Multivariable linear regression model was employed to estimate adjusted TSH levels. The model included age, sex, city of residence, TSH levels, underlying thyroid diseases, dose of levothyroxine, and duration of levothyroxine prescriptions at the last visit before the pandemic.

levels, underlying thyroid diseases, dose of levothyroxine, and duration of levothyroxine prescriptions at the last visit before the pandemic.

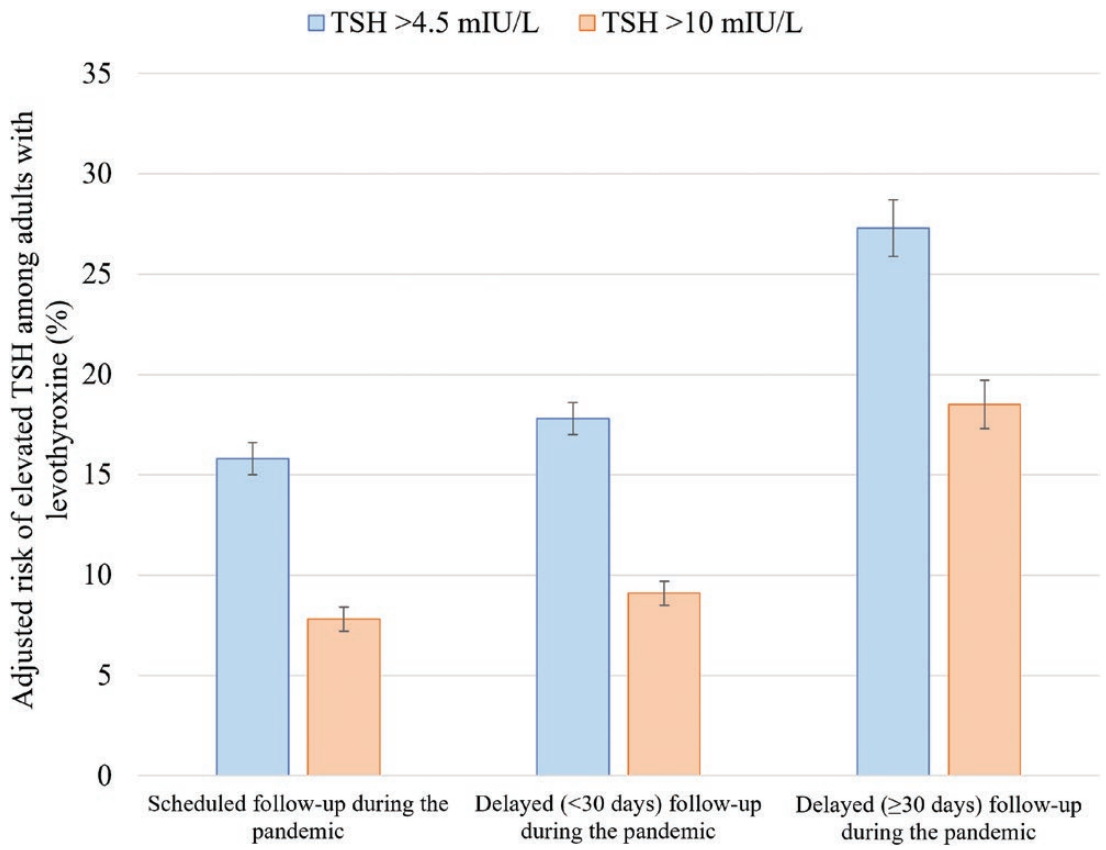

Figure 1. Adjusted risk of elevated thyrotropin (TSH > 4.5 mIU/L and > 10 mIU/L) at the first visit after April 2020 according to whether patients made a scheduled or a delayed follow-up visit during April 2020 to August 2020. Adjusted risk ratios of TSH greater than 4.5 mIU/L or greater than 10 mIU/L according to whether patients made a scheduled or a delayed follow-up visit during April 2020 to August 2020 are shown in Table 4.

Table 4. Risk ratio of thyrotropin greater than 4.5 mIU/L or greater than 10 mIU/L according to whether patients made a scheduled or a delayed follow-up visit during April 2020 to August 2020

Variables	No. of patients with TSH > 4.5 mIU/L/total No. of patients at first visit during pandemic (%)	**Adjusted risk ratio of TSH > 4.5 mIU/L at first visit during pandemic (95% CI)**[a]	*P*	No. of patients with TSH > 10 mIU/L/total No. of patients at first visit during pandemic (%)	**Adjusted risk ratio of TSH > 10 mIU/L at first visit during pandemic (95% CI)**[a]	*P*
Scheduled follow-up during pandemic	1466/9063 (16.2)	Reference	–	718/9063 (7.9)	Reference	–
Delayed (< 30 d) follow-up visits during pandemic	1931/10 909 (17.7)	1.13 (1.05 to 1.21)	.001	993/10 909 (9.1)	1.17 (1.06 to 1.29)	.002
Delayed (≥ 30 d) follow-up visits during pandemic	1451/5389 (26.9)	1.72 (1.60 to 1.85)	< .001	987/5389 (18.3)	2.38 (2.16 to 2.62)	< .001

Abbreviation: TSH, thyrotropin.

[a]Modified Poisson regression model was employed to estimate the risk ratio of TSH > 4.5 mIU/L or >10 mIU/L in 2020. The model included age, sex, city of residence, TSH levels, underlying thyroid diseases, dose of levothyroxine, and duration of levothyroxine prescriptions at the last visit before the pandemic.

with levothyroxine has decreased since the COVID-19 pandemic developed in 2020. Patients with a higher dose and a longer duration of levothyroxine prescription before the pandemic were more likely to make a delayed follow-up visit during the pandemic. Patients who made a delayed follow-up visit showed less well-controlled thyroid

Table 5. Risk ratio of thyrotropin greater than 4.5 mIU/L or greater than 10 mIU/L according to whether patients made a scheduled or a delayed follow-up visit during April 2020 to August 2020 stratified by age

Outcomes	**Adjusted risk ratio of TSH > 4.5 mIU/L at first visit during pandemic (95% CI)[a]**	
	Age ≤ 50 y (n = 12 265)	**Age > 50 y (n = 13 096)**
Scheduled follow-up during pandemic	Reference	Reference
Delayed (< 30 d) follow-up visits during pandemic	1.22 (1.10-1.36) *P* for interaction = .02	1.06 (0.97-1.16)
Delayed (≥ 30 d) follow-up visits during pandemic	1.91 (1.71-2.14) *P* for interaction = .003	1.57 (1.42-1.73)
Outcomes	**Adjusted risk ratio of TSH > 10 mIU/L at first visit during pandemic (95% CI)[a]**	
	Age ≤ 50 y (n = 12 265)	**Age > 50 y (n = 13 096)**
Scheduled follow-up during pandemic	Reference	Reference
Delayed (< 30 d) follow-up visits during pandemic	1.35 (1.16-1.56) *P* for interaction = .02	1.04 (0.92-1.19)
Delayed (≥ 30 d) follow-up visits during pandemic	2.67 (2.30-3.10) *P* for interaction = .02	2.12 (1.87-2.42)

Abbreviation: TSH, thyrotropin.

[a]Modified Poisson regression model was employed to estimate the risk ratio of TSH greater than 4.5 mIU/L or greater than 10 mIU/L in 2020. The model included sex, city of residence, TSH levels, underlying thyroid diseases, dose of levothyroxine, and duration of levothyroxine prescriptions at the last visit before the pandemic. *P* for interaction was assessed by inserting multiplicative interaction term between age (≤ 50 y, and > 50 y) and follow-up visit (scheduled, delayed < 30 d, and delayed ≥ 30 d).

hormone levels (ie, elevated TSH levels, decreased fT4 levels, and increased risk of TSH > 4.5 mIU/L and TSH > 10 mIU/L) than those who made a follow-up visit as scheduled during the pandemic. These findings should raise concern about the potentially harmful effect of the pandemic on thyroid function control among patients being treated with levothyroxine.

To the best of our knowledge, this is the first and largest study to describe the change in thyroid hormone levels among patients being treated with levothyroxine during the pandemic. A clinical practice guideline for the management of thyroid disorders was recently published in response to the COVID-19 pandemic [13]. The guideline made some suggestions for maintaining the quality of care for thyroid disorder patients during the pandemic and their possible limitations: i) telephone and video consultations; ii) remote monitoring services; iii) face-to-face appointments for a certain group of patients, for example, patients with newly diagnosed or uncontrolled thyroid eye disease, patients with enlarging goiters and symptoms of obstruction, and patients without the expected response to treatment; and iv) satellite blood-testing services [13]. Although a preexisting autoimmune or nonautoimmune thyroid disorder alone may not be a risk factor for SARS-CoV-2 infection or severity of COVID-19 [12, 16, 17], many thyroid disorder patients have other chronic diseases such as diabetes and dyslipidemia that can be risk factors for COVID-19 severity [18]. Given our findings of the increased risk of delayed follow-up visits among patients with a higher dose or longer duration of levothyroxine prescriptions and the deteriorating trends in TSH levels among patients who made a delayed follow-up visit, careful monitoring with adequate prescription amounts and refills to cover needs would be important to control TSH levels for such patients during the pandemic. Future studies are needed to understand whether the observed change in TSH control during the pandemic has a clinically significant influence on long-term adverse health outcomes at the population level.

Our findings may at least partially be explained by decreased treatment adherence or no longer having access to treatment. The COVID-19 pandemic has inflicted huge damage on economies around the world, and that has resulted in an increase in the numbers of unemployed and the numbers of people who have lost their health insurance [19, 20]. Such adverse effects of the pandemic might have led to a decrease in the treatment adherence rates by shifting more costs onto patients. In Japan, the first COVID-19 case was reported in mid-January 2020, and nearly 1 million cases had been reported as of August 4, 2021 [1]. A nationwide state of emergency was declared from April to late May 2020 that called for noncompulsory restrictions on people's behavior to control the pandemic's trajectory [21]. This political decision might have had the unfortunate consequence unrelated to COVID-19 of limiting the

accessibility of health care facilities for routine care and medication management, for example, reduced contact with clinicians and possibly restricted pharmacy access are automatically enforced if the prescription expires for some patients. Moreover, we found a stronger association between delayed follow-up visit and elevated TSH levels among younger adults than older adults. Given the strong association between the COVID-19 pandemic and deteriorated mental health [3, 22], particularly among young adults [23], it may also have increased the risk of delaying follow-up visits and decreased treatment adherence [4]. Since levothyroxine has consistently been one of the medications commonly prescribed worldwide [5, 6], these potentially harmful effects of the pandemic on the clinical management of patients being treated with levothyroxine should be recognized and further evaluated.

Although our hospital began providing telemedicine in March 2020, the present study did not include patients who used telemedicine because their thyroid hormone levels were not measured during the virtual care. Thus, our findings do not apply to patients who had already started receiving their routine care by telemedicine [24]. Despite the rise in telemedicine as a replacement for the outpatient clinic during the COVID-19 pandemic, the environment (eg, remote monitoring system and satellite blood-testing services) for conducting telemedicine is still not sufficient in most areas of Japan. Moreover, evidence remains lacking as to whether such virtual care eventually improves the long-term health outcomes and quality of care for thyroid disorder patients. Future studies are warranted to evaluate the trends in thyroid hormone levels among patients being treated with levothyroxine during virtual care.

A major strength of our study is its large sample size and analysis of individual-level data at different time points before and during the pandemic (ie, in 2019 and 2020). This strength enabled us to assess the change in serum TSH levels as well as fT4 levels. Our focus on change in thyroid hormone levels among patients being treated with levothyroxine has unique clinical implications, because hypothyroid status is mostly affected by the treatment, whereas other noncommunicable diseases are easily affected by a higher-dimensional set of external factors that are also related to the COVID-19 pandemic, including exercise and diet. For example, a growing body of literature has shown the substantial reduction of physical activity levels during the pandemic, raising a concern about its health consequences such as diabetes and depression [25, 26]. Unlike thyroid hormone levels as shown in the present study, it is challenging to disentangle the possible influence of the pandemic on the management of these diseases into i) the pathway mediated through changes in health care delivery (eg, out of medications due to delayed follow-up visits) and ii) the pathway mediated through changes in behaviors (eg, reduced physical activity levels).

Our study also had several limitations. A major limitation was its generalizability: that is, since our study was based on a single institution that specializes in thyroid disorders, the results are not generalizable to other hospitals or medical settings (eg, primary care physicians' clinics, emergency departments). They may also not be generalizable to other countries, particularly because of the differences in the epidemiology of COVID-19 infection and its complications and differences in policy (eg, lockdown, stay-at-home orders, and financial support). This study focused on the difference in thyroid hormone levels before and during the pandemic, thus our findings do not apply to patients who did not visit the hospital and have thyroid hormone measurements taken after April 2020. In addition, we used information on the number of days of levothyroxine prescription to calculate the expected follow-up visit date, but some patients might have visited later because they had some amount of medications leftover. Such exposure misclassification would be overcome in a future prospective study with detailed information on the number of medications leftover with a valid reporting system. We also did not have information on COVID-19 infection, which limited the interpretation as to why patients delayed their follow-up visits during the pandemic. Last, we cannot rule out the possibility of unmeasured confounding due to the lack of information on comorbidities such as chronic diseases, changes in body weight, correct absorption of levothyroxine, and use of other medications in proximity to thyroxine. Given the huge worldwide strain on health systems imposed by the pandemic [27], larger multicenter studies are needed to validate our findings, increase generalizability (to other populations and other diseases) with assessment of heterogeneity across countries and regions, and identify the underlying mechanisms of our findings, including health care use, changes in lifestyle, and treatment adherence during the pandemic.

In conclusion, our study showed that there was a group of patients being treated with levothyroxine who are likely to delay their follow-up visits during the COVID-19 pandemic, and patients who made a delayed follow-up visit showed less well-controlled thyroid hormone levels at their follow-up visits than those who made a follow-up visit as scheduled. Our findings highlight the importance of careful monitoring of patients being treated with levothyroxine during the pandemic. Ensuring adequate prescriptions amounts, health care accessibility, and opportunities for biochemical testing would be critical to managing such patients during and after the COVID-19 pandemic.

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