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Clinical Research Article

Thyroid Incidentalomas in Hospitalized Patients With COVID-19: A Single-Center Retrospective Analysis

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Abstract

Context: During the COVID-19 pandemic, both people with underlying diseases and previously healthy people were infected with SARS-CoV-2. In our institute, most hospitalized patients underwent chest computed tomography (CT) to evaluate pulmonary involvement and complication of COVID-19. There are currently limited data regarding thyroid CT incidentalomas in healthy people.

Objective: We aimed to investigate the prevalence and predictors of thyroid incidentalomas among hospitalized patients with COVID-19.

Methods: A single-center retrospective study included hospitalized patients aged ≥15 years with COVID-19 who underwent chest CT during April 2020 and October 2021. Thyroid incidentalomas were reviewed and identified by an experienced radiologist. Logistic regression analysis was used to determine predictors for thyroid incidentalomas.

Results: In the 1326 patients (mean age 49.4 years and 55.3% female) that were included, the prevalence of thyroid incidentalomas was 20.2%. Patients with thyroid incidentalomas were older (59.6 years vs 46.8 years, $P < .001$) and more often female than those without incidentalomas (63.4% vs 53.2%, $P = .003$). On multivariate analysis, only female sex (OR 1.56; 95% CI 1.17-2.07) and older age (OR 1.04; 95% CI 1.03-1.05) were significantly associated with thyroid incidentalomas.

Conclusion: In COVID-19 patients, the prevalence of thyroid incidentalomas identified on chest CT was higher (20.2%) than in previous studies in the general population (<1% to 16.8%). Female sex and older age were independent factors associated with thyroid incidentalomas.

Key Words: adult, diagnostic imaging, elderly, neoplasm, COVID-19, SARS-CoV-2, thyroid nodule

Abbreviations: 18F-FDG, fluorine-18 fluorodeoxyglucose; ACE2, angiotensin-converting enzyme 2; AP, anteroposterior; BMI, body mass index; CT, computed tomography; FPG, fasting plasma glucose; PET, positron emission tomography; T, transverse; TMPRSS2, transmembrane serine protease type 2; US, ultrasound.

Thyroid incidentaloma refers to an asymptomatic thyroid nodule serendipitously discovered during the investigation of an unrelated condition to thyroid disease. Thyroid incidentalomas are increasing due to the widespread use of high-resolution imaging studies. Thyroid incidentalomas in adults are very common with the prevalence ranging from 5% to 67% depending on the imaging methods used [1]. The prevalence of thyroid incidentalomas reported is up to 67% on ultrasound (US) [2], up to 25% for contrast-enhanced chest computed tomography (CT) examinations [3], 16% to 18% for neck CT and magnetic resonance scans [4-6], and 1% to 2% for fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scans [7-9]. Females, increasing age, and possibly obesity seem to increase the prevalence of thyroid nodules [10-12].

At the end of 2019, the emergence and rapid spread of Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic. SARS-CoV-2 utilizes its surface spike protein to specifically recognize the host cell surface angiotensin-converting enzyme 2 (ACE2) receptor facilitating viral entry and replication [13]. The host cell proteases, mainly transmembrane serine protease type 2 (TMPRSS2) cleavage the spike protein that is necessary for its binding to the ACE2 receptor [14]. Both the receptor bindings with membrane-bound ACE2 and TMPRSS2 are necessary for the entrance of the virus to the host cell [13, 14]. Several studies have demonstrated extensive ACE2 expression in various endocrine tissues including the hypothalamus, pituitary, thyroid, adrenal, pancreas, testis, ovaries, and adipose tissue [15]. Thyroid tissue has a high mRNA expression of ACE2 and TMPRSS2 regardless of sex [15-17]. This evidence suggests that the thyroid gland may be a vulnerable target for SARS-CoV-2 infection. COVID-19 infection can induce exaggerated systemic inflammatory immune responses in the thyroid gland [18], and severe thyroid follicular cell injury has been described in SARS-CoV infection [19]. Thyroid involvement in COVID-19 may present with euthyroid sick syndrome, subacute thyroiditis, Graves disease, Hashimoto thyroiditis, postpartum thyroiditis, and silent thyroiditis, but

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Table 1. Baseline characteristics of participants

Characteristics	Total n = 1326	Thyroid incidentaloma n = 268	No thyroid incidentaloma n = 1058	*P* value
Age, years	49.4 ± 18.5 (range 15-97)	59.6 ± 18.4 (range 19-97)	46.8 ± 17.7 (range 15-96)	<.001
Female, n (%)	733 (55.3)	170 (63.4)	563 (53.2)	.003
Body mass index, kg/m^2	27.1 ± 6.7	26.0 ± 5.7	27.3 ± 6.8	.001
History of radiation, n (%)	9 (0.7)	1 (0.4)	8 (0.8)	.500
Hypertension, n (%)	481 (36.3)	136 (50.7)	345 (32.6)	<.001
Diabetes mellitus, n (%)	347 (26.2)	97 (36.2)	250 (23.6)	<.001
Dyslipidemia, n (%)	419 (31.6)	115 (42.9)	304 (28.7)	<.001
FPG[a], mg/dL	119.0 ± 56.9	125.0 ± 62.1	117.6 ± 55.4	.101
HbA1c[b], %	6.2 ± 1.6	6.4 ± 1.6	6.2 ± 1.7	.077
Triglyceride[c], mg/dL	113 (85, 151)	113 (83, 151)	112 (86, 151)	.880
HDL[c], mg/dL	44.5 ± 14.4	45.2 ± 15.1	44.3 ± 14.2	.370
LDL[d], mg/dL	114.0 ± 38.8	108.7 ± 44.4	115.3 ± 37.2	.017
Total cholesterol[c], mg/dL	175.3 ± 42.4	171.8 ± 47.1	176.1 ± 41.1	.160
TSH[e], mIU/L	0.5 (0.2, 1.0)	0.4 (0.1, 0.8)	0.6 (0.3, 1.1)	.170
FT3[f], pg/mL	1.5 ± 0.6	1.4 ± 0.6	1.5 ± 0.6	.390
FT4[g], ng/dL	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	.490

Abbreviations: FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; HbA1c, hemoglobin A1C; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TSH, thyroid-stimulating hormone.
Data availability for evaluation: [a]n = 1159; [b]n = 1304; [c]n = 1219; [d]n = 1220; [e]n = 94; [f]n = 81; [g]n = 90

little is known about SARS-CoV-2 and its oncogenic potential in the thyroid gland [20]. To date, there are limited data about thyroid incidentalomas among patients with COVID-19 [21-23].

People of all ages including healthy people can be infected by SARS-CoV-2, largely depending on their high risk of exposure. Individuals infected with COVID-19 have a wide spectrum of symptoms ranging from mild symptoms to critical illness. At the beginning of the COVID-19 pandemic, most hospitalized patients with COVID-19 had pulmonary involvement and underwent CT. Prior to the COVID-19 pandemic, chest CTs were usually performed in older adults due to their illness. There are still gaps in the literature regarding the prevalence of thyroid incidentalomas in the younger population. Although thyroid cancer screening is not recommended in asymptomatic persons [24], thyroid ultrasonography is frequently used in health check-up programs. In healthy subjects who underwent voluntary cancer screening, the prevalence of thyroid incidentaloma identified by ^{18}F-FDG PET was 1.2% to 3% [25, 26]. However, there are no data on thyroid incidentaloma identified by CT chest in healthy subjects. We aimed to investigate the prevalence of thyroid incidentalomas and associated factors among hospitalized patients with COVID-19.

Materials and Methods

Study Population and Design

This was a retrospective cohort study using electronic medical record data of all hospitalized COVID-19 patients aged ≥15 years who underwent chest CT with or without contrast at the Chakri Naruebodindra Medical Institute between April 2020 and October 2021. In Thailand, the first wave of COVID-19 began in March 2020. In response to the rapidly increased number of individuals infected with COVID-19, our institute was the referral center for patients with COVID-19. The study was approved by the Institutional Review Board, and the need to obtain informed patient consent was waived due to the retrospective study design.

A total of 1566 chest CT studies were eligible for inclusion in this study. After reviews of electronic medical records, we excluded 240 patients with pre-existing thyroid diseases (n = 49), invisible thyroid gland on chest CT (n = 6), and duplicated studies (n = 185). For participants who underwent both noncontrast and contrast-enhanced chest CT, only contrast chest CT was selected for analysis.

Chest CT Scans

All images were obtained with a uCT 530 CT scanner (United Imaging Healthcare, China). Imaging parameters included 120 kVp, automatic mAs, 1-mm section thickness, 1.1250 pitch, 0.5 s rotation time, and slice collimation 0.55 mm × 40. CT imaging data sets were reviewed by a blinded experienced radiologist (P.H.). The following characteristics of thyroid incidentalomas were collected: number, size, homogeneity, calcification, and density. For participants with multiple thyroid incidentalomas, only the largest nodules were characterized.

Baseline Characteristics

Basic demographic data such as age, sex, body weight, height, history of neck radiation, and underlying diseases were included. The laboratory results including fasting plasma glucose (FPG), hemoglobin A1C (HbA1c), lipid profile, and thyroid function tests were also collected.

Statistical Analysis

Categorical variables are presented as frequency and percentage. Continuous variables which were normally distributed are presented as mean and SD, and variables with non-normal distribution are presented as median and interquartile range (IQR). Student's t-test or quantile regression was used to calculate differences in continuous variables. Chi-squared test or Fisher's exact test, where appropriate, was used to calculate differences in categorical variables. Simple and multiple logistic regressions were performed to assess the correlation between the associated factors and the presence of thyroid incidentalomas. The correlation is presented as OR and 95% CI. Statistical analyses were performed using STATA version 17.0 (StataCorp LLC, College Station, TX). $P < .05$ was considered to be statistically significant.

Results

Baseline Characteristics and Prevalence

A total of 1326 chest CT imaging (1181 CTs with contrast and 145 CTs without contrast) were included in the study. The mean age of the patients was 49.4± 18.5 years and 733 (55.3%) were female. The mean body mass index (BMI) was 27.1± 6.7 kg/m^2. The demographic data of the 2 groups (CT with and without thyroid incidentaloma) are shown in Table 1.

The prevalence of thyroid incidentaloma detected in chest CT was 20.2% (268/1326). Thyroid incidentaloma was found on chest CT with contrast more than without contrast (37.9%, 55/145 vs 18%, 213/1181, $P < .001$).

Characteristics of Incidentalomas

About half of the incidentalomas (52.6%) were solitary nodules. The median anteroposterior (AP) and transverse (T) diameter were 0.6 cm (0.4, 1.0) and 0.6 cm (0.4, 1.0), respectively. Median attenuation was 65.5 Hounsfield unit (41.5, 94.0). Over 80% of thyroid incidentalomas were homogeneous (83.2%) and had no calcifications (80.6%). More detailed CT characteristics of thyroid incidentaloma are shown in Table 2.

Factors Associated With Thyroid Incidentalomas

A univariate analysis was used to assess the association between participants' baseline characteristics and the presence of thyroid incidentalomas. Factors including age, sex, BMI, hypertension, diabetes mellitus, and dyslipidemia were significantly associated with thyroid incidentalomas (Table 3). Other laboratory investigations including FPG, HbA1c, lipid profile, and thyroid function tests showed no significant association with thyroid incidentalomas.

A multivariate analysis was performed to determine the variables that were independently associated with the prevalence of thyroid incidentalomas. Female sex and increased age were the only 2 factors significantly associated with thyroid incidentalomas. The prevalence of thyroid incidentalomas was increased by 4% in every 1-year increase in age (OR 1.04, 95% CI 1.03-1.05, $P < .001$). Females had a 1.56 times higher probability of developing thyroid incidentalomas than males (OR 1.56, 95% CI 1.17-2.07, $P = .003$).

Prevalence by Age and Gender

The prevalence of thyroid incidentalomas classified in each decade of life and gender are shown in Table 4. Both males and females had a higher prevalence of thyroid incidentalomas in older age. Due to the small number of participants in the nonagenarian (4 females and 2 males), the true prevalence of thyroid incidentalomas in this age group could not be precisely estimated. Among participants aged less than 30 years, the prevalence of thyroid incidentalomas was 9.8%. After matching with the same age period (Table 4 and Fig. 1), the prevalence of thyroid incidentaloma in males was comparable with females aged 15-19 years (7.7% vs 7.7%) and higher than female participants aged 20-29 years (12.8% vs 8.2%).

Discussion

Our study is the first dedicated review of CT scans for thyroid incidentalomas in patients with COVID-19. The prevalence of thyroid incidentalomas was 20.2% in hospitalized patients with COVID-19 who underwent chest CT for investigation of pulmonary and other COVID-19-related complications. Most thyroid lesions detected on CT were small size and had no calcification. From multivariate analysis, female sex and increased age were independent factors associated with the presence of thyroid incidentalomas. The prevalence of thyroid incidentaloma significantly increased with age for CT chest scans with and without contrast.

Previous studies revealed a wide range of prevalence of thyroid incidentalomas detected from CT scans, varying from <1% to 16% [4, 5, 27-29]. The higher prevalence is due to the dedicated imaging reviews of thyroid lesions [4, 5], similar to our study. In contrast, the larger database studies (~100

Table 2. Computed tomography characteristics of thyroid incidentaloma

Characteristics	n = 268
Solitary lesion, n (%)	141 (52.6)
Anteroposterior diameter, cm	0.6 (0.4, 1.0)
Transverse diameter, cm	0.6 (0.4,1.0)
Anteroposterior/transverse ratio	1.1 ± 0.4
Density, HU	65.5 (41.5, 94.0)
Homogeneous density, n (%)	223 (83.2)
Calcification, no. (%)	52 (19.4)

Abbreviation: HU, Hounsfield unit.

Table 3. Correlation between variables and the presence of thyroid incidentalomas

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years	1.04 (1.03, 1.05)	<.001	1.04 (1.03, 1.05)	<.001
Female	1.53 (1.16, 2.01)	.002	1.56 (1.17, 2.07)	.003
BMI, kg/m^2	0.97 (0.95, 0.99)	.003		
Hypertension	2.13 (1.62, 2.79)	<.001		
Diabetes mellitus	1.83 (1.38, 2.44)	<.001		
Dyslipidemia	1.86 (1.41, 2.46)	<.001		

Abbreviations: BMI, body mass index.

Table 4. Prevalence of thyroid incidentalomas classified in each decade of life and gender

	Number of thyroid incidentaloma (% prevalence)									*P*-value
	Age, years									
	15-19	20-29	30-39	40-49	50-59	60-69	70-79	80–89	≥90	
All chest CT (n = 1326)										
All	2/26 (7.7%)	23/228 (10.1%)	22/195 (11.3%)	25/206 (12.1%)	50/251 (19.9%)	56/198 (28.3%)	53/146 (36.3%)	33/70 (47.1%)	4/6 (66.7%)	<.001
Female	1/13 (7.7%)	11/134 (8.2%)	14/106 (13.2%)	18/110 (16.4%)	34/146 (23.3%)	31/97 (32.0%)	29/76 (38.2%)	28/47 (59.6%)	4/4 (100.0%)	<.001
Male	1/13 (7.7%)	12/94 (12.8%)	8/89 (9.0%)	7/96 (7.3%)	16/105 (15.2%)	25/101 (24.8%)	24/70 (34.3%)	5/23 (21.7%)	0/2 (0.0%)	<.001
Chest CT without contrast (n = 1181)										
All	2/26 (7.7%)	23/226 (10.2%)	22/191 (11.5%)	21/185 (11.4%)	43/213 (20.2%)	39/164 (23.8%)	35/111 (31.5%)	25/60 (41.7%)	3/5 (60.0%)	<.001
Female	1/13 (7.7%)	11/132 (8.3%)	14/104 (13.5%)	16/99 (16.2%)	30/134 (22.4%)	25/84 (29.8%)	21/63 (33.3%)	21/40 (52.5%)	3/3 (100.0%)	<.001
Male	1/13 (7.7%)	12/94 (12.8%)	8/87 (9.2%)	5/86 (5.8%)	13/79 (16.5%)	14/80 (17.5%)	14/48 (29.2%)	4/20 (20.0%)	0/2 (0.0%)	.019
Chest CT with contrast (n = 145)										
All	–	0/2 (0.0%)	0/4 (0.0%)	4/21 (19.0%)	7/38 (18.4%)	17/34 (50.0%)	18/35 (51.4%)	8/10 (80.0%)	1/1 (100.0%)	<.001
Female	–	0/2 (0.0%)	0/2 (0.0%)	2/11 (18.2%)	4/12 (33.3%)	6/13 (46.2%)	8/13 (61.5%)	7/7 (100.0%)	1/1 (100.0%)	0.005
Male	–	–	0/2 (0.0%)	2/10 (20%)	3/26 (11.5%)	11/21 (52.4%)	10/22 (45.5%)	1/3 (33.3%)	–	.018

Abbreviation: CT, computed tomography.

000 imaging studies) identified thyroid incidentaloma with a <1% reported rate due to routine radiology reports in clinical practice [27, 29]. The different rate of incidental detection of a thyroid nodule is 10% when comparing routine reports and dedicated reviews [29]. In clinical practice, thyroid incidentaloma was reported less in the impression section than the findings section of the radiology report, leading to fewer further diagnostic work-ups [30]. This is predominantly influenced by the American College of Radiology's recommendations [31]. The 3-tiered system, which categorizes patients based on CT and magnetic resonance imaging findings, suspicious imaging features (suspicious lymph nodes, local invasion, PET-avid nodule), thyroid nodule size ≥15 mm, and patient age ≥35 years, could reduce unnecessary diagnostic work-up of thyroid incidentaloma without missed malignancies [30, 32]. These recommendations are against the American Thyroid Association guidelines that recommend using US for all thyroid nodules seen on CT scans [24].

Thyroid incidentalomas are commonly detected during the interpretation of CT chest examinations. Thyroid nodules can be easily detected even without contrast because the normal thyroid gland has a high CT attenuation value due to its high iodine content [33]. While US is the preferred imaging modality for thyroid evaluation due to superior spatial resolution, there is no reliable CT finding to distinguish benign from malignant lesions [34].

Cystic lesions, lobulated/irregular margins, absence of halo, and microcalcifications can be better seen on US than CT. Previous studies showed CT findings matched US findings in only 53% to 57.4% of patients, and CT missed other thyroid nodules or multinodularity in 40% to 40.7% of patients [5, 34]. CT also underestimates the size of thyroid nodules compared with US [35, 36]. Thyroid incidentalomas detected on CT may be difficult to characterize because the CT chest scan was not performed specifically with the intention of assessing the thyroid gland, and the entire gland may not be fully visualized. CT artifacts from high contrast material in the subclavian veins may obscure or simulate pathology [37]. In our study, the size of most nodules was <1 cm with an AP/T ratio of 1.1, and around 80% had no calcification. The attenuation value was 65.5 Hounsfield units. Despite no reliable CT findings to predict malignancy, Yoon et al reported that malignant lesions frequently demonstrated calcifications, AP/T ratio >1, and attenuation values >130 Hounsfield units on contrast-enhanced CT [5]. Small (<1 cm) thyroid incidentalomas have a high probability of being benign [34].

Patient age is considered to be an important clinical risk factor in the management of thyroid incidentalomas [31]. In our study, the prevalence of thyroid incidentalomas in young patients with COVID-19 (<30 years) was 9.8%. Previous studies reported a higher rate of malignancy in patients aged ≤35 years who had a thyroid incidentaloma detected on CT [6, 34]. According to the American College of Radiology's recommendations, further evaluation with US for patients ≤35 years with a nodule measuring ≥1 cm is suggested due to the high prevalence of malignant lesions [31].

To the best of our knowledge, there is no evidence yet associating SARS-CoV-2 with the development or alteration of a thyroid nodule. However, US changes in the echostructure and increased size of benign thyroid nodules after COVID-19 infection have been preliminarily reported [38]. In our study, the prevalence of thyroid incidentalomas detected on CT was higher than in previous reports (20.2% vs

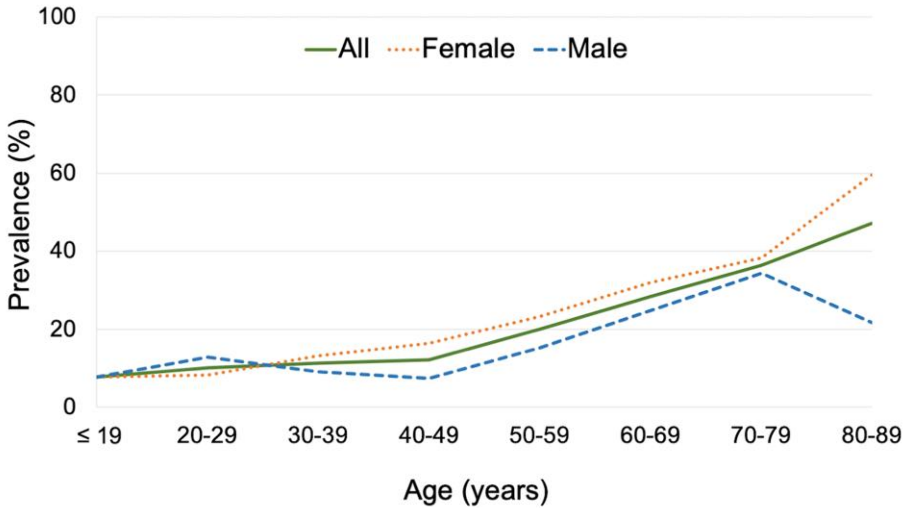

Figure 1. Prevalence of thyroid incidentalomas in each decade of life.

~16%) [4, 5]. The higher prevalence of thyroid incidentalomas in patients with COVID-19 could be due to the following reasons: (1) a dedicated review of thyroid incidentaloma, (2) thinner CT slide thickness (1 mm vs 3-5 mm in the previous studies [4, 5], and (3) potential mechanisms of thyroid nodule formation caused by SARS-CoV-2 infection.

The strength of this study is the wide range of the study population, from 15 to 97 years. About one-third of participants in this study (33.86%) were aged under 40 years. Thyroid incidentalomas are usually described in people undergoing imaging studies due to nonthyroid-related health conditions. Our study population might represent the prevalence of thyroid incidentalomas in assumedly healthy people who are not normally seeking medical care. To date, our study is the first and largest study reporting prevalence of thyroid incidentalomas in patients with COVID-19. We acknowledge several limitations of our study. First, this was a retrospective study at a single center. Second, we also did not further evaluate for thyroid incidentalomas via US or fine-needle aspiration biopsy because our participants with COVID-19 were referred to primary care physicians after discharge from the hospital. The rate of malignancy remained undetermined.

Conclusions

The prevalence of thyroid incidentalomas identified on chest CT scans was 20.2% in patients with COVID-19. The prevalence in our study was higher than in previous studies (<1% to 16.8%). The increased prevalence of thyroid incidentalomas was associated with female sex and increased age.

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Author Contributions

M.J., S.T., P.H., and C.S. designed the study. M.J., S.T., P.H., and W.B. were responsible for data collection. M.J., S.T., P.H., and W.B. conducted statistical analyses, interpreted the initial results, and drafted the manuscript. S.S. and C.S. contributed to discussion and revised the manuscript. All authors participated in the data interpretation, contributed to the manuscript writing with important intellectual content, and approved the final version of the manuscript.

Disclosures

The authors have nothing to disclose.

Data Availability

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

Ethics Approval

The study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (ethics approval number: MURA2021/981).

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