European Review for Medical and Pharmacological Sciences 2021; 25: 4149-4155

Analysis of the involvement of the thyroid gland using computed tomography in patients with suspected SARS-CoV-2 infection: a retrospective study

Y. AKKOYUNLU[1], B. KALAYCIOGLU[2], I. YURTSEVER[3], A. EREN[4], M. BAYRAM[5], A. MERT[6], M.E. AKKOYUNLU[5]

[1]Infectious Diseases and Clinical Microbiology, Bezmialem Vakif University, Istanbul, Turkey
[2]Department of Radiology, Seka Hospital, Kocaeli, Turkey
[3]Department of Radiology, Bezmialem Vakif University, Istanbul, Turkey
[4]Department of Radiology, Medipol Mega University, Istanbul, Turkey
[5]Department of Pulmonary Medicine, Medipol Mega University, Istanbul, Turkey
[6]Department of Internal Medicine, Medipol Mega University, Istanbul, Turkey

Abstract. – OBJECTIVE: SARS-CoV-2 primarily infects the respiratory tract and leads to severe pneumonia by binding to the ACE-2 receptor. The virus can also interact with ACE-2 receptors expressed in other tissues as in thyroid. This study predicted the complications involving the thyroid in patients with suspected SARS-CoV-2.

PATIENTS AND METHODS: Patients with suspected SARS-CoV-2 infection between March 11, 2020-May 31, 2020 were retrospectively evaluated. Sixty-nine patients who were radiologically diagnosed as COVID-19 according to thoracic CT and had previously performed thoracic CT before November 2019 were included in the study according to the exclusion and inclusion criteria. Age and gender-matched controls (No. 69) were selected with normal thoracic CT whose PCR tests were also negative. Thyroid densities of participants were calculated and compared from the previous and current thoracic CTs. Results were also compared with the control group.

RESULTS: Participants were composed of 69 patients (39 male, mean age 64.35 years). Thyroid densities were significantly decreased from 89HU to 76HU for whole gland, from 88HU to 76HU for right lobes and from 87.5HU to 75.5HU for left lobes at current thoracic CTs performed during COVID-19 (*p*<0.001, *p*<0.001, *p*<0.001 respectively). The decrease in densities of the whole thyroid gland, both left and right lobes, was correlated with mortality (*p*<0.001). The changes in thyroid densities were not correlated with age nor gender. The decreases in HU values of thyroid densities for whole gland, left and right lobes, were correlated with mortality (*p*<0.001, *p*<0.001, and *p*<0.001 respectively).

CONCLUSIONS: COVID-19 is a multi-systemic disease that threatens vital organs, including the thyroid. Future studies are needed to investigate the association between SARS-CoV-2 and other complications.

Key Words:
SARS-CoV-2, Thyroid, Computed tomography, COVID-19.

Introduction

COVID-19 was declared a pandemic on March 11, 2020 by the WHO; the disease is acted by Coronavirus-2 (SARS-CoV-2) and results in severe acute respiratory syndrome[1]. The virus primarily infects the respiratory tract and leads to severe pneumonia by binding to the angiotensin-converting enzyme-2 (ACE-2) receptor[2]. Apart from those expressed in pneumocytes, the virus can also interact with ACE-2 receptors expressed in other tissues[3]. Similar to that in the small intestine, testis, kidneys, heart, and adipose tissue, the thyroid gland also has an increased expression of ACE-2 receptors[2]. Particularly, it was shown that mRNA encoding for the ACE-2 receptor was also expressed in thyroid follicular cells, a major entry point for SARS-CoV-2[4].

Most respiratory infections are frequently held liable for being a major environmental factor implicated in subacute thyroiditis and autoimmune thyroid diseases. It can also precipitate thyroid storm, which is a life-threatening exacerbation of

Corresponding Author: Yasemin Akkoyunlu, MD; e-mail: yaseminakkoyunlu@gmail.com

hyperthyroidism characterized by multiorgan failure[5,6]. Besides causing subacute thyroiditis, viruses can directly harm the thyroid tissue, as in the case of thyroiditis associated with SARS-CoV-2[7]. Data on SARS-CoV-2 infection and its possible long-term complications are limited. Therefore, this study aimed to predict the complications involving the thyroid gland in patients with suspected SARS-CoV-2 infection. Scientists are trying to predict them with what we had got from SARS experience. The SARS virus was pathologically shown to damage follicular cells by destroying follicular epithelium and desquamating epithelial cells into the follicular lumen[8]. A postmortem COVID-19 study[9] showed chronic inflammation of the thyroid with follicular and epithelial cell disruption in two (22%) of nine patients.

Radiological evaluation of the thyroid gland includes ultrasound (US), nuclear scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI)[10]. The US is often the first procedure used in the diagnostic evaluation of thyroid nodules because it is simple, has a low cost, can help distinguish between nodules, such as cyctic-solid or benign- malignant, and has no radiation. CT and MRI are used for the structural assessment of a nodular-enlarged thyroid gland, a thyroid mass, or the differentiation of a thyroid mass from an adjoining neck mass. In contrast, nuclear medicine studies are used to assess the function of the thyroid gland and nodules[10]. The iodine content of the thyroid acts as a contrast agent and allows excellent visualization of the normal thyroid tissue with CT. Moreover, the normal thyroid gland has high density values, reflected by a homogenous increase in density on CT images; this is due to the metabolism, storage, and active uptake of iodine[11]. When the iodine content of the thyroid diminishes, as seen in thyroiditis, the density decreases to that of other soft tissues.

Recently, some studies[12,13] were published investigating thyroid hormone levels, but till date there are no studies on radiological evaluation of thyroid tissue during COVID-19 course. Therefore, the study is the first one investigating thyroid tissue changes by CT without contrast material due to SARS-CoV-2 infection.

Patients and Methods

Study Population

Patients admitted to Seka Hospital, Medipol Mega University Teaching Hospital, and Bezmialem Vakıf University, with the suspicion of clinical COVID-19 between March 11, 2020 and May 31, 2020, were retrospectively evaluated. In this study, we included 3259 patients with typical thoracic CT findings such as bilateral “patchy” and “confluent, bandlike” ground glass opacity or consolidation in peripheral and mid-to-lower lung zones; they were radiologically diagnosed as patients with COVID-19 according to the multinational consensus of Fleischner Society Smith DL[14-16]. Among them, we further selected 201 patients who had previously undergone thoracic CT before November 2019, the date in which SARS-CoV-2 was firstly described. Previous and current CTs were performed using the same CT machine for inclusion in the study. Moreover, 23 patients were excluded because of previous thyroid disorders. A total of 109 cases were excluded because contrast CT imaging was used to measure thyroid density and yielded low image qualities. The grading of lung involvement was performed according to related references[14-16]. According to both inclusion and exclusion criteria, 69 patients were enrolled in this study (Figure 1). We compared the thyroid density (TD) in both previous and current thoracic CTs. Age and gender matched controls (No. 69) were also selected with normal thoracic CT whose PCR tests were negative. Thyroid densities of participants were also compared with the control group.

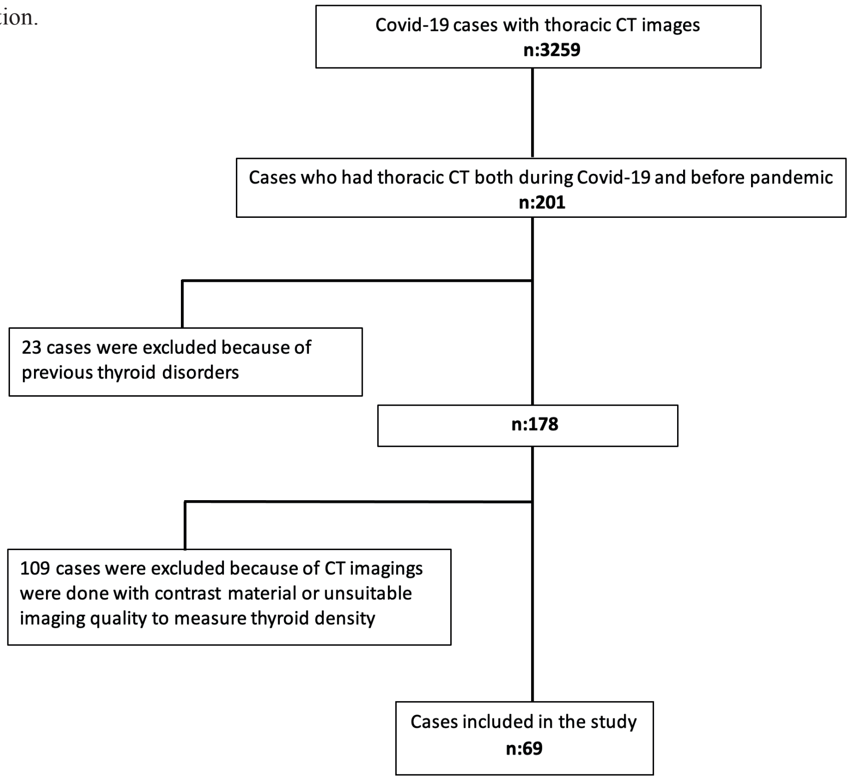
Radiologic Evaluation

All scans were performed with the patients in the supine position. During end-inspiration without intravenous contrast, chest CT was performed cranio-caudally from the level above the sternoclavicular joint to the diaphragm. Moreover, CT images were obtained using a 64-slice multidetector-row CT scanner (Aquilion CX; Toshiba Medical Systems, Japan) at Bezmialem, a 128-slice multidetector-row CT scanner (GE Healthcare, Chicago, Illinois, United States) at SEKA, and a 256-slice multidetector-row CT scanner (ICT-256 Philips Healthcare, Amsterdam, Netherlands) at the Medipol hospitals. The Hounsfield unit (HU) of the TD was calculated using the same radiologist.

CT Parameters

Parameters and calibration were as follows: 1 mm collimation, 1.25 pitch, 0.5 seconds rotation time, 3 mm reconstructed section thickness, 3 mm intersection gap with a matrix of 512 mm × 512 mm, 120 kV tube voltage, and 250 mA tube

Figure 1. Flow chart of the case selection.



current-time product. All images were obtained using a standard dose protocol without intravenous contrast media. The lung window setting had a window level and width of -500 HU and 1400 HU, respectively.

Image Interpretation

Reviewers were blinded from the clinical and laboratory information. All CT images were reviewed independently by the Food and Drug Administration (FDA)-approved OsiriX 11.0 Dicom viewer (Pixmeo, Bernex, Switzerland). Moreover, CT data were further reviewed on a PACS system (FUJIFILM Medical Systems, Lexington, Massachusetts, USA). The three reviewers evaluated both axial reconstructions and coronally reformatted images.

Statistical Analysis

Descriptive statistics were presented as median, mean, standard deviation, and range. The Kolmogorov-Smirnov test was used to assess the normality. Ordinal or non-normal distribution measurements were evaluated using the Wilcoxon test within groups and overall sample comparisons; the Mann-Whitney test was used in comparisons between subgroups. The quantitative data with a normal distribution were compared using a paired *t*-test within the group and a *t*-test for independent groups among subgroups. Analyses were performed using SPSS 20.0 (SPSS, Corp., Armonk, NY, USA). In all tests, a *p*-value of 0.05 was deemed significant.

The study design was approved by the Ethical Committee of Medipol University (505-6.26.2020) and the study protocols were compliant of the ethical standards.

Results

In this study, 69 patients were included; 39 of whom were male. The mean age was 64.35 (±12.76) years. Whole TDs were significantly decreased in the thoracic CTs performed when they were COVID-19-classified ($p<0.001$). This significant difference was detected twice: when comparing with previous thoracic CTs and also comparing with control group. During the anatomical evaluation of the lobar densities of the thyroid gland, significant decreases in HU values were detected in both the right ($p<0.001$) and left ($p<0.001$) lobes, separately (Table I). Additionally, comparative results of the TDs taken before and after the onset of COVID-19 are depicted in Figure 2. The decreasing levels of TDs were

Table I. Comparison of thyroid densities (TD) measured at thoracic CTs: current (group 1), previous (Group 2) and control group (Group 3) as Hounsfield Unit (HU).

Thyroid part	Group-1 TD (HU) mean (%25/%75)	Group-2 TD (HU) mean (%25/%75)	Group-3 TD (HU) mean (%25/%75)
Whole gland	76 (63.5-91.3)	89* (76,5-103,8)	88.5* (77-102.5)
Right lobe	76 (60-92.8)	88* (76.5-103.8)	86* (74,5-102)
Left lobe	75.5 (62.5-91.8)	87.5* (77.3-103.8)	85.5* (75.8-102)

*$p < 0.05$ when compared with group 1.

grouped as follows: high, >30%; moderate, 20%-30%; and mild, 10%-20%. As a result, 11 (15.9%), 8 (11.6%), and 18 (26.1%) patients showed mildly, moderately, and highly decreased HU values, respectively. Furthermore, there were no significant associations between HU values and gender (p = 0.117), age (p = 0.973), and grade of lung involvement (p = 0.27).

Real-time SARS-CoV-2 Reverse Transcription-Polymerase Chain Reaction (RT-PCR) tests were positive in 30.4% (21/69) of the patients. Moreover, thyroid densities of both PCR-positive cases (right p: 0.05, left p: 0.02, bilateral p: 0.02) and PCR-negative cases (right p<0.001, left p<0.001, bilateral p<0.001) significantly decreased (Table II). The overall mortality rate was at 26% (n = 18). Associated decreases in the HU values of TDs in both the left and right lobes of the thyroid gland, with relation to the mortality rate, were also significant (p<0.001, p<0.001, and p<0.001, respectively).

Discussion

In our study, suspected patients with COVID-19 showed significant thoracic CT changes in the densities of their thyroid tissue during their infective states as compared to prior their infection. Results showed that the iodine content in thyroid tissues decreased, thereby suggesting thyroiditis. Two possible mechanisms might be responsible for these changes: (a) the direct viral effect and (b) the indirect effect of various proinflammatory cytokines caused by the infection[13]. However, this is different from subacute thyroiditis. Subacute thyroiditis is precipitated by autoimmune mechanisms mostly triggered by viral infections; it develops approximately 4-6 weeks after infection[5,6]. However, silent thyroiditis was also shown to occur during active SARS-CoV-2 infection, indicating a nonpost-infectious disorder. This supported the hypothesis of a direct viral effect. Moreover, parafollicular and follicular epithelial cells, might be injured by apoptosis, disrupting the follicle as demonstrated previously with SARS-CoV-2[8,12,17].

In our study, a minimum decrease of 10% in TDs was detected in more than half of the patients. The result agreed with a previous study[13] on thyroid functions in which thyrotropin (TSH) levels were lower in 56% of patients. A decrease in TD was also detected in patients from all three centers when evaluated separately. Therefore, it may not be an incidental finding. Furthermore,

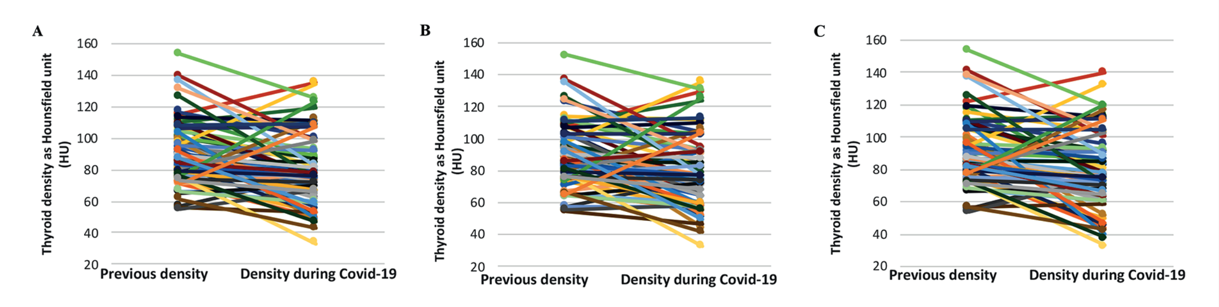


Figure 2. A, Comparison of whole thyroid densities at previous and current thoracic CTs during COVID-19. **B,** Comparison of the density of right lobe of the thyroid at previous and current thoracic CTs. **C,** Comparison of the density of left lobe of the thyroid at previous and current thoracic CTs.

Table II. Comparison of thyroid densities (TDs) as Hounsfield Unit (HU) of COVID-19 patients according to PCR results.

	PCR + cases			PCR- cases		
Thyroid part	**Previous TD mean (HU) (%25/%75)**	**Current TD mean (HU) (%25/%75)**	***p*-value**	**Previous TD mean (HU) (%25/%75)**	**Current TD mean (HU) (%25/%75)**	***p*-value**
Whole gland	79.5 (74.7-90.2)	75 (55.7-90.2)	**0.02**	94 (82-106.5)	76.5 (67-92)	**0.00**
Right lobe	81 (76-91)	76 (58- 91.5)	0.05	94 (82-107)	76 (64-93)	**0.00**
Left lobe	80 (72-92)	72 (54-96)	**0.02**	93 (80-109)	78 (69-92)	**0.00**

the results were not associated with the level of lung involvement. This suggests that the cause of thyroid involvement is different from the cause of the disease severity. However, this was not supported by the finding that the involvement of the thyroid was associated with mortality. It may have also been due to the small number of cases. A previous study[18] revealed that thyroid diseases were associated with an increased risk of severe COVID-19 infection.

Although thyroid diseases were more common in women[19], the change in density values in patients with COVID-19 was not associated with both sex and age[11]; this coincided with our results. We selected previous thoracic CT images and designated them as the control of the same cases; we consider this point the strength of our study. We excluded the confounders by comparing the cases amongst themselves.

Recent clinical studies[12,13,19] have shown that thyrotoxicosis and COVID-19 were associated. However, according to our knowledge, there is no radiological study showing the involvement of the thyroid. COVID-19 is a droplet infection; strict precautions must be taken in all healthcare settings. Furthermore, it was difficult to perform US and nuclear medicine imaging during active infection due to high infectivity rates. However, due to lung involvements, thoracic CT has been selected as the imaging method for almost all patients; thoracic CT is not the first imaging choice to evaluate thyroid tissue because of radiation.

Limitations include the retrospective nature and the relatively small size of this study. We could not correlate these results with thyroid function tests, thyroid US, and histopathological findings. In addition, the number of cases may be relatively small. Moreover, the CT devices were different in three centers; previous and subsequent imaging of all included patients was performed using the same device. The high mean age of our study population may be due to the inclusion criteria of having previous chest CT. Older patients were more often evaluated with chest CT because chronic lung diseases were especially seen in the elderly.

Other limitations include the study population and their COVID-19 status. The population was not completely composed of confirmed COVID-19 cases. SARS-CoV-2 PCR tests were positive only in 30.4% (n = 21) of cases. Although nucleic acid testing is accepted as the gold standard for the diagnosis of COVID-19, current tests may deliver false-negative results. The positive predictive (PPV) and negative predictive values (NPV) of RT-PCR were estimated to range from 57.7%-93.5% and from 96.1%-99.6% at different prevalence levels, respectively[20]. In addition, different RT-PCR test kits from different companies have different PPV and NPV[21]. Concerning the typical clinical findings, CT imaging can be used for making the clinical diagnosis of COVID-19, despite negative nucleic acid test results[22]. In the study we compared thyroid densities of patients with previous thyroid densities of themselves and also a control group whose thoracic CT were normal and PCR test results were negative. The results of thyroid densities were similar in both control group as shown in Table I. So, the decrease in TDs during COVID-19 shows the real impact of COVID-19 on the thyroid gland.

According to the WHO situation report as of December 15, 2020, the overall case fatality rate of COVID-19 was 2.21[23]. In our study, the mortality rate was 26%, which was much higher than the mortality rate of 2.7% in the general population of Turkey[24]. It was thought to be due to the case selection; our cases were all symptomatic with pneumonia and followed up at inpatient clinics. The mortality rate was also associated with a decrease in thyroid density.

Conclusions

COVID-19 is a multi-systemic disease that threatens vital organs, including the thyroid. Future clinical studies are needed to investigate the association between SARS-CoV-2 and other long-term complications.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

Disclosure Statements

No competing financial interests.

References

1) Mongioi LM, Barbagallo F, Condorelli RA, Cannarella R, Aversa A, La Vignera S, Calogero AE. Possible long-term endocrine-metabolic complications in COVID-19: lesson from the SARS model. Endocrine 2020; 68: 467-470.
2) Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020; 9: 45.
3) Pal R, Banerjee M. COVID-19, and the endocrine system: exploring the unexplored. J Endocrinol Invest 2020; 43: 1027-1031.
4) Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST, Villani L, Magri F, Latrofa F, Chiovato L. Detection of SARS-COV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. J Endocrinol Invest 2020: 1-6.
5) Bartalena L, Chiovato L, Marcocci C, Vitti P, Piantanida E, Tanda ML. Management of Graves' hyperthyroidism and orbitopathy in time of COVID-19 pandemic. J Endocrinol Invest 2020; 43: 1149-1151.
6) Desailloud R, Hober D. Viruses and thyroiditis: an update. Virol J 2009; 6: 5.
7) Asfuroglu Kalkan E, Ates I. A case of subacute thyroiditis associated with COVID-19 infection. J Endocrinol Invest 2020; 43: 1173-1174.
8) Wei L, Sun S, Xu CH, Zhang J, Xu Y, Zhu H, Peh SC, Korteweg C, McNutt MA, Gu J. Pathology of the thyroid in severe acute respiratory syndrome. Hum Pathol 2007; 38: 95-102.
9) Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, Thursz M, Manousou P, Corbett R, Goldin R, Al-Sarraj S, Abdolrasouli A, Swann OC, Baillon L, Penn R, Barclay WS, Viola P, Osborn M. Histopathological findings, and viral tropism in UK patients with severe fatal COVID-19: a postmortem study. Lancet Microbe 2020; 1: e245-e253.
10) Weber AL, Randolph G, Aksoy FG. The thyroid and parathyroid glands. CT and MRI and correlation with pathology and clinical findings. Radiol Clin North Am 2000; 38: 1105-1129.
11) Larger PH, Jennings AS, Gordon LF, Coleman BG, Axel L, Kressel HY, Baron RL. Computed tomography findings in clinically healthy and unhealthy thyroid patients. J Comput Tomogr 1985; 9: 111-117.
12) Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. Eur J Endocrinol 2020; 183: 381-387.
13) Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. Thyroid 2021; 31: 8-11.
14) Xu YH, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, Dong L, Ma X, Zhang HJ, Gao BL. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. J Infect 2020; 80: 394-400.
15) Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, Panebianco V, Andreoli C, Colaiacomo MC, Zingaropoli MA, Ciardi MR, Mastroianni CM, Pugliese F, Alessandri F, Turriziani O, Ricci P, Catalano C. Chest CT score in patients with COVID-19: correlation with disease severity and short-term prognosis. Eur Radiol 2020; 30: 6808-6817.
16) Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus 2019 (COVID-19) imaging reporting and data system (COVID-RADS) and common lexicon: a proposal based on the imaging data of 37 studies. Eur Radiol 2020; 30: 4930- 4942.
17) Agarwal S, Agarwal SK. Endocrine changes in patients with SARS-CoV-2 and lessons from SARS-CoV. Postgrad Med J 2020; 96: 412-416.
18) Hariyanto TI, Kurniawan A. Thyroid disease is associated with severe coronavirus 2019 (COVID-19) infection. Diabetes Metab Syndr 2020; 14: 1429-1430.
19) Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, Ferrante E, Orsi E, Rei V, Longari V, Cuzzocrea M, Bandera A, Lazzaroni E, Dolci A, Ceriotti F, Re TE, Gori A, Aro-

sio M, Salvi M. SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol 2020; 8: 739-741.

20) Jarrom D, Elston L, Washington J, Prettyjohns M, Cann K, Myles S, Groves P. Effectiveness of tests to detect SARS-CoV-2 virus, and antibodies against SARS-CoV-2, to inform COVID-19 diagnosis: a rapid systematic review. BMJ Evid Based Med 2020 Oct 1;bmjebm-2020-111511.

21) Lu Y, Li L, Ren S, Liu X, Zhang L, Li W, Yu H. Comparison of the diagnostic efficacy between two PCR test kits for SARS-CoV-2 nucleic acid detection. J Clin Lab Anal 2020; 34: e23554.

22) Li B, Li X, Wang Y, Han Y, Wang Y, Wang C, Zhang G, Jin J, Jia H, Fan F, Ma W, Liu H, Zhou Y. Diagnostic value, and key features of computed tomography in Coronavirus 2019. Emerg Microbes Infect 2020; 9: 787-793.

23) World Health Organization. COVID-19 Weekly epidemiological update - December 15, 2020: World Health Organization; 2020 [cited 2020 18 Dec]. Available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.

24) Si S, DheIr H, ToCoGlu A, Bekta SM, SB AC, Gen CA, Mutlu F, M KO, Erdem AF, Karabay O. Characteristics and mortality determinants of patients with COVID-19 undergoing hemodialysis. Turk J Med Sci 2020. doi: 10.3906/sag-2006-54. Online ahead of print.