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Research Article

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THE POSITIVITY RATE OF COVID-19 PCR TEST PERFORMED FOR SCREENING BEFORE THYROID FINE NEEDLE ASPIRATION BIOPSY

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome. Coronavirus 2 (SARS-CoV-2) is spreading rapidly around the world. Asymptomatic infection is highly contagious, potentially leading to viral spread. We aimed to determine the rate of patients positive for COVID-19 PCR performed for safety measures before thyroid fine-needle aspiration biopsy (FNAB).

Materials and Methods: The patients applied to Ankara City Hospital, Endocrinology and Metabolism Clinics between 15.03.2020 and 15.08.2020 and underwent routine COVID-19 PCR test before FNAB were evaluated retrospectively. Age, gender, history of hypertension and Type 2 Diabetes Mellitus (T2DM), use of levothyroxine (LT4) or antithyroid drug, 25-hydroxyvitamin D3 [25(OH)D3], TSH, freeT3 (fT3), free (fT4) levels, FNAB results were obtained from the records.

Results: Asymptomatic COVID-19 infection was detected in 29 (2.43%) of 1195 patients who underwent FNAB. There was no statistically significant difference between patients with COVID-19 PCR test positive asymptomatic and negative patients in terms of age, gender, median values of 25(OH)D3, TSH, fT3, fT4, the ratio of hypertension and T2DM.

Conclusion: The healthcare professionals work devotedly against COVID-19 infection, demonstrating a great example of struggle worldwide. FNAB is an invasive procedure requiring close contact. It should be known by the clinician that COVID-19 infection is associated with a high risk of transmission in asymptomatic patients. The rate of 2.43% in the population cannot be underestimated and indicates the importance of the use of personal protective equipment and taking infection prevention measures.

Keywords: SARS-CoV-2, COVID-19, asymptomatic infection, FNAB, screening.

Introduction

COVID-19, which emerged on 12 December 2019, spread rapidly and became the cause of the pandemic. From then until January 2022, there were over 340 million cases and over 5 million deaths of COVID-19. SARS-CoV-2 is the etiological agent in this pandemic disease, an enveloped, positive-sense, single-stranded RNA virus. COVID-19 infection presents with clinical symptoms ranging from asymptomatic infection to mild upper respiratory tract disease and severe interstitial pneumonia, and it may cause mortality in some patients. COVID-19 is a life-threatening condition with the highest infection rate and a long and slow incubation period.[1-2] The source of the massive community spread of SARS-CoV-2 is rapid viral spread, particularly by asymptomatic or pre-symptomatic carriers. Nasopharyngeal and oropharyngeal sampling is considered the gold standard method in diagnosing upper respiratory tract infections. RT-PCR is the most widely used test to diagnose COVID-19.[3] Thyroid nodules are a common clinical problem. Ultrasound-guided FNAB is the most accurate and essential method for detecting malignancy and monitoring thyroid nodules.[4]

Materials and Methods

Patients who applied to our Endocrinology and Metabolism Clinics between March 2020 and August 2020 for multinodular goiter (MNG), nodular goiter (NG), papillary thyroid cancer (PTC), follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), noninvasive follicular thyroid neoplasms (NIFTP), operated recurrent MNG who underwent FNAB and who underwent routine COVID-19 PCR test for screening beforehand were retrospectively analyzed. During the study, all patients were tested within 72 hours before their planned FNAB. Real-time reverse transcription-quantitative PCR (RT-qPCR) testing analysis was performed from upper respiratory tract, nasopharyngeal and oropharyngeal swab samples. Patients' COVID PCR test results, age, gender, autoimmunity status (antithyroid peroxidase, antithyroglobulin, thyrotropin receptor antibody), history of hypertension, T2DM, and TSH, fT3, fT4, 25(OH)D3 levels, FNAB results were noted from the records. FNAB has been reported by the Bethesda System for Reporting Thyroid Cytopathology; a sampled nodule is classified as Bethesda I: Nondiagnostic, Bethesda II: Benign, Bethesda III- follicular lesion of undetermined significance (FLUS) or atypia of undetermined significance (AUS), Bethesda IV: Follicular neoplasm or suspicious for a follicular neoplasm, Bethesda V: Suspicious for malignancy, and Bethesda VI: Malignant.

Statistical analysis

The continuous variables were presented as median (minimum-maximum), and the categorical variables were presented as number and percentage. Normality analyzes of continuous variables were performed with the Kolmogorov-Smirnov Goodness of Fit Test. The data analysis that did not fit the normal distribution between

the two groups was performed with the Mann-Whitney U-test. Chi-square test and Fisher's exact test were used to compare categorical data. Analyzes were performed with IBM SPSS Package Program version 22.0 (IBM Corporation, Armonk, NY, USA). A p-value of < 0.05 was considered statistically significant.

Results

Asymptomatic COVID-19 infection was detected in 29 (2.43%) of 1195 patients who underwent FNAB. While the median age of asymptomatic patients was 53 (23-80) years, others were 50 (20-88) years. Female patients were in the majority in both groups. Although autoimmunity rates were higher in COVID-19 PCR positive asymptomatic patients (44.82%) than in patients with negative COVID-19 PCR (36.10%), the difference was not statistically significant (p=0.335). The mean 25(OH)D3 level of asymptomatic patients was 21.5 ng/ml. No statistically significant difference was found between patients with positive and negative COVID-19 PCR test in terms of age, gender, median values of 25(OH)D3, TSH, fT3, fT4, rates of hypertension, and T2DM (Table 1).

Table 1. The comparison of clinical and biochemical features of patients with COVID-19 PCR positive asymptomatic and negative patients

	COVID-19 PCR negative (n=1166)	**COVID-19 PCR positive asymptomatic (n=29)**	***p***
Age (years) [median (min-max)]	50 (20-88)	53 (23-80)	0.579*
Gender (n,%)			
female	898 (77.01)	22 (75.86)	0.826**
male	268 (23.80)	7 (24.13)	
25(OH)D3 (ng/ml) [median(min-max)]	18 (4-80)	21.5 (7-46)	0.168*
TSH (mU/L) [median (min-max)]	1.32 (0.1-48)	1.36 (0-17)	0.709*
fT3 (ng/L) [median (min-max)]	1.19 (0.3-2.29)	1.23 (1-2.04)	0.198*
fT4 (ng/dl) [median (min-max)]	3.22 (1-33.30)	3.30 (2-5)	0.166*
Autoimmunity (n,%)			
Negative	745 (66.16)	16 (55.17)	0.335**
Positive	421 (36.10)	13 (44.82)	
Hypertension (n,%)			
No	869 (74.52)	23 (79.31)	0.669**
Yes	297 (25.47)	6 (20.68)	
Type 2 Diabetes Mellitus (n,%)			
No	934 (80.10)	25 (86.20)	0.636**
Yes	232 (19.89)	4 (13.79)	

* Mann-Whitney U-test
** Fisher's exact test

The distribution of the clinical diagnoses of the patients in both groups is shown in Table 2. Among COVID-19 PCR-negative patients, 58% were euthyroid MNG, 7.4% were PTC, in COVID-19 PCR-positive asymptomatic patients, 58.6% were euthyroid MNG, 17.2% were PTC. MNG subtypes are shown in figure 1. 22.5% of COVID-19 PCR negative patients were using levothyroxine, 6.7% were using thyromazole, 20.7% of PCR positive

asymptomatic patients were using levothyroxine, and 10.3% were using thyromazole (Table 3). FNAB results of COVID-19 PCR positive asymptomatic patients and negative patients are indicated in the graphics (Figure 2-Figure 3).

Table 2. Distribution of clinical diagnoses of patients with COVID-19 PCR positive asymptomatic and negative patients

Clinical Diagnoses (n,%)		
	COVID-19 PCR negative (n=1166)	**COVID-19 PCR positive asymptomatic (n=29)**
MNG	1012 (86,79)	23 (79,31)
NG	22 (1,88)	1 (3,44)
PTC	86 (7,37)	5 (17,24)
MTC	2 (0,17)	0 (0,0)
FTC	1 (0,08)	0 (0,0)
NIFTP	1 (0,08)	0 (0,0)
Operated recurrent MNG	42 (3,60)	0 (0,0)

* Chi-square test

Table 3. Patients' thyroid drug use status

Thyroid medication (n,%)	**COVID-19 PCR negative (n=1166)**	**COVID-19 PCR positive (n=29)**	***p***
No medications	822 (70,6)	20 (69,0)	0.884*
Levothyroxine (LT4)	262 (22,5)	6 (20,7)	
Propylthiouracil (PTU)	2 (0,2)	0 (0,0)	
Methimazole (MMI)	78 (6,7)	3 (10,3)	

* Chi-square test

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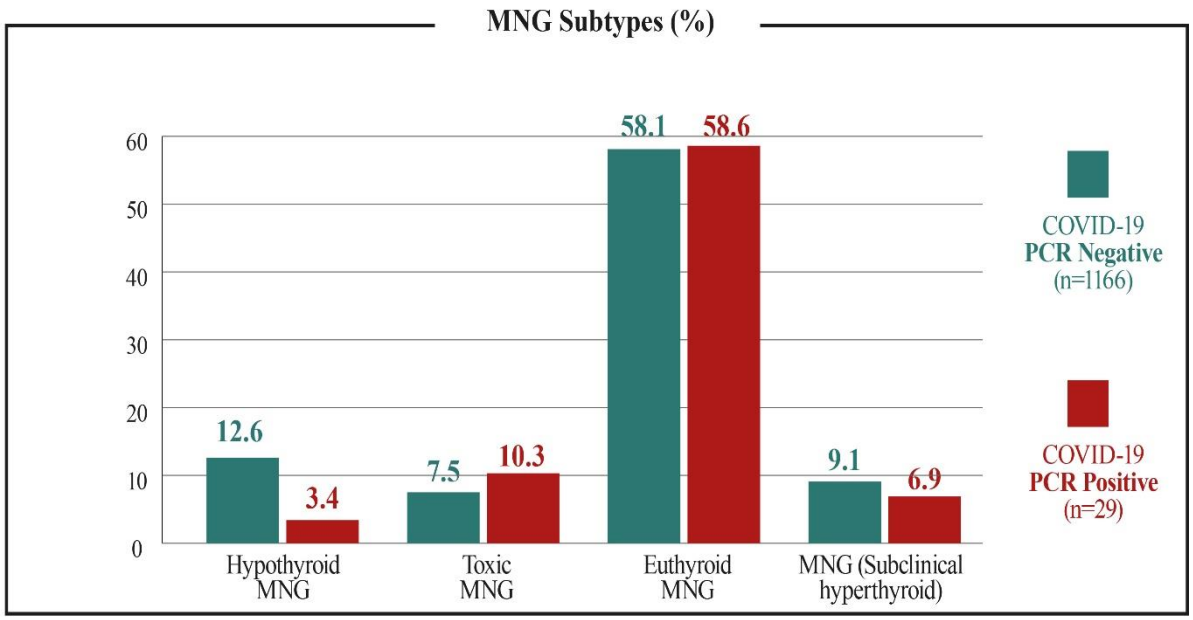

Figure 1. The patients with MNG were clinically grouped as hypothyroid MNG, toxic MNG, euthyroid MNG, MNG with subclinical hyperthyroid

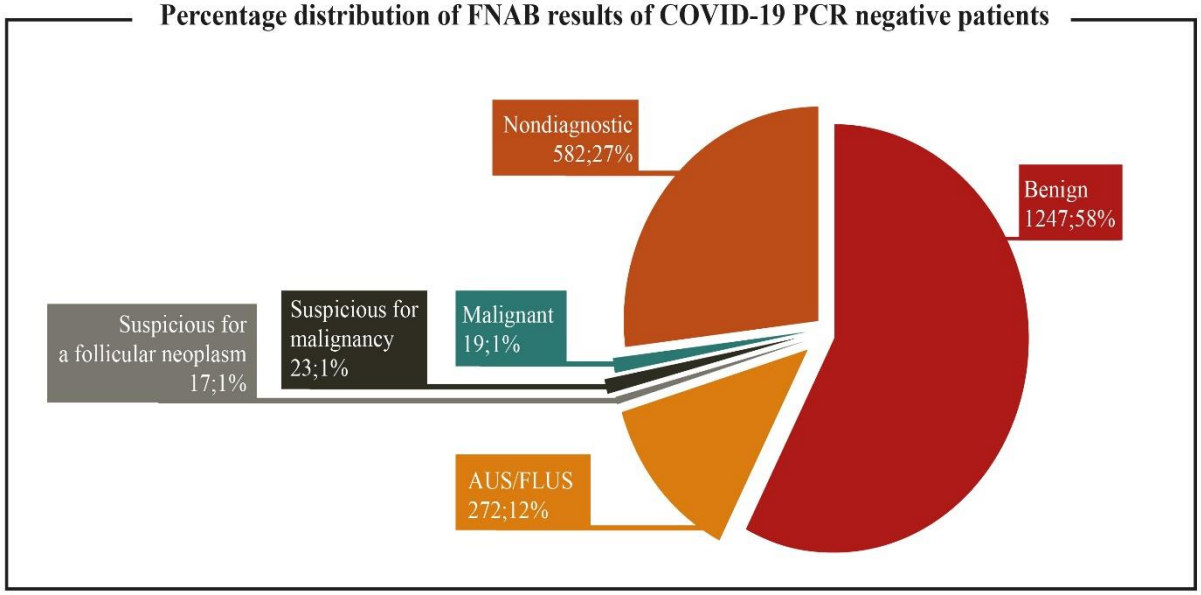

Figure 2. Results of 2160 nodules fine-needle aspiration biopsies, obtained from 1166 patients with COVID-19 PCR negative according to the Bethesda system. (The frequency of each Bethesda class was as follows: Bethesda I: 27%, Bethesda II: 58%, Bethesda III: 12%, Bethesda IV: 1%, Bethesda V: 1%, Bethesda VI: 1%)

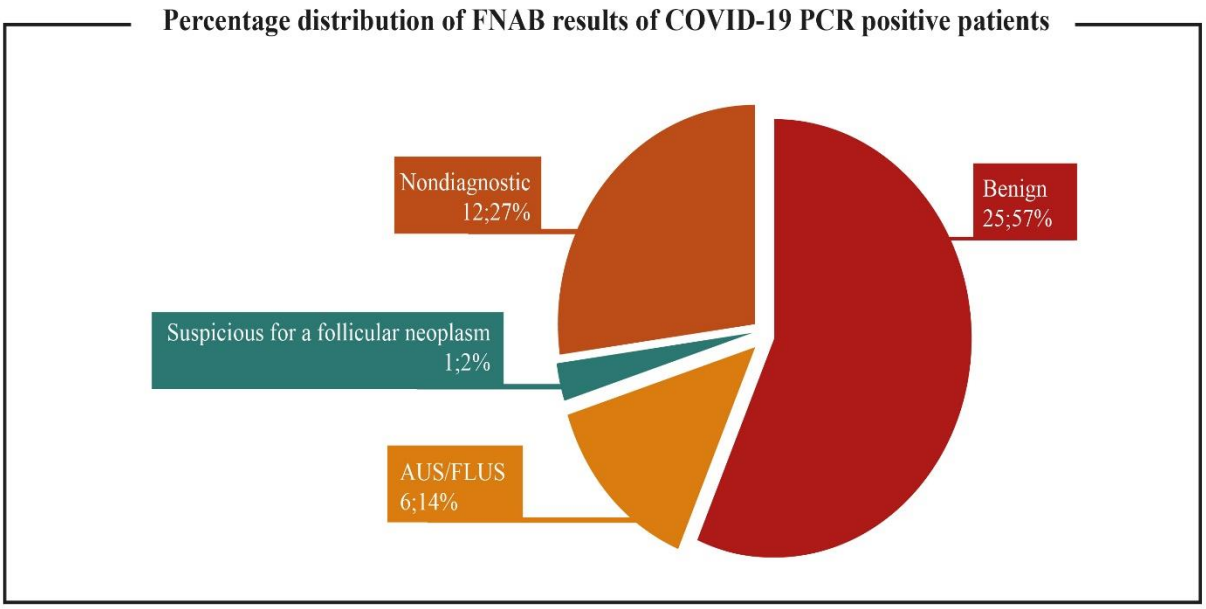

Figure 3. Results of 44 nodules fine-needle aspiration biopsies, obtained from 29 patients with COVID-19 PCR positive according to the Bethesda system. (The frequency of each Bethesda class was as follows: Bethesda I: 27%, Bethesda II: 57%, Bethesda III: 14%, Bethesda IV: 2%, Bethesda V: 0%, Bethesda VI: 0%)

Discussion

Our study found the rate of asymptomatic COVID-19 infection as 2.43% in 1195 patients for whom FNAB was planned. FNAB is an invasive procedure requiring close contact, and sometimes the contact time is prolonged depending on the number of nodules. The clinician should know that COVID-19 infection is associated with a high risk of transmission in asymptomatic patients, and this risk is also high in the early stages of the disease. Healthcare workers worldwide are working with great devotion against the COVID-19 infection and displaying a great example of struggle, which brings with it the risk of infection. In SARS-CoV infection, the transmission of infection to healthcare workers by infected patients is very common (33%-42%).[5] SARS-CoV-2 genome sequences have 79.5% similarity to the SARS-CoV genome sequence. The difference of COVID-19 from other coronavirus infections is that it has a less severe course but has a higher transmission rate.[6] Compared to asymptomatic patients with influenza, asymptomatic individuals with influenza had a shorter viral spread and lower viral load in their secretions.

Contrary to influenza, in a study, asymptomatic COVID-19 infection was defined as the achilles tendon of pandemic control to emphasize the importance of asymptomatic infection control.[7] Li et al.'s study, which compared patients with mild symptoms and asymptomatics in a cabin hospital in Wuhan, found that 74

(29.4%) patients in a total of 252 were asymptomatic. They detected pneumonia on CT imaging of 36 asymptomatic patients. This study found that the median transmission duration was seven days in asymptomatic and mildly symptomatic patients. This study, which showed that asymptomatic patients have the same risk of transmission as symptomatic patients, emphasizes the importance of quarantining asymptomatic individuals in disease control.[8] Han et al. in the study, asymptomatic and symptomatic patients with COVID-19 infection were compared, and it was found that asymptomatic patients had faster virus turnover, higher numbers of lymphocytes, T cells, B cells and natural killer cells, and low IgM, low LDH levels, and normal liver function tests. These results show that viral clearance is faster in asymptomatic patients because the viral load was determined at the same rate in both groups. The incubation period for COVID-19 infection can be up to 29 days.[9] The clinician should consider that COVID-19 infection is associated with a high risk of transmission in asymptomatic patients and only in patients with atypical presentations such as headache and fatigue, and this risk is at the same level in the early stages of the disease.[10] In a meta-analysis of 41 studies with 50.155 confirmed COVID-19 patients, the percentage of asymptomatic infection was 15.6%.[11] In a study, the prevalence of asymptomatic patients and the rate of COVID-19 asymptomatic infection in the cancer population was extremely low (4%).[12] The asymptomatic COVID-19 infection rate in pregnant women, a specific group, was determined as 5%.[13] A study carried out in the Obstetrics and Gynecology Department of Ankara City Hospital found that 3 (1.4%) of 206 pregnant women had asymptomatic PCR positive COVID-19 infection. These asymptomatic PCR-positive pregnancies were high-risk pregnancies.[14] In various studies, the rate of asymptomatic COVID-19 infection varies between 0.6-35.5%, although it varies by region. It has been determined that the rate of asymptomatic infection is low in China.[15] The rate of 2.43% in the population can not be underestimated and indicates the importance of using personal protective equipment and taking infection prevention measures for healthcare workers.

Significant destruction of thyroid follicular and parafollicular cells was observed in autopsies of patients with SARS, but no virus was detected in the thyroid. Studies have shown that thyroid dysfunction is not permanent.[16-17] Chang C. et al., in their study, 1811 FNAB cases between 2019-2020 and 1567 FNAB cases between 2020-2021 were screened. While a decrease was detected in FNAB cases in the pandemic, it was observed that the rate of atypical, suspicious and malignant cases decreased by only 5%. It was observed that the abnormal case rate was maintained before and during the pandemic.[18] In our study, there were 1195 FNAB cases within six months from the onset of the pandemic in our clinic. Nowadays, the number of FNAB performed in our clinic is 900 per month. When we compare it with the first period of the pandemic, there is an increase in monthly biopsies. With the recent emergence of the omicron variant, the number of asymptomatic cases seen in the last month has reached 30 patients. Although there is an increase in the number of patients undergoing a biopsy, there is also an increase in the number of asymptomatic patients. The fact that the number of asymptomatic patients seen in the last month and the number of asymptomatic patients seen in the first six months of the pandemic is approximately the same, indicates the high transmission rate of the omicron variant.

SARS-CoV-2 enters the host cell via ACE2 and TMPRSS2 receptors. These receptors are highly expressed in the thyroid gland. Thyrotoxicosis negatively affects the clinic of COVID-19 infection. Thyrotoxic patients with COVID-19 developed atrial fibrillation (32%) and thromboembolic events (16%).[19] Our study found that asymptomatic COVID-19 infection can also be detected in thyrotoxic patients under medical treatment. Thyroid hormones play essential roles in innate and adaptive immunity.[20] In a meta-analysis that included 21 studies and a total of 31339 patients, it was found that thyroid abnormalities and hypothyroidism were associated with worsening COVID-19, the age of the patient was important, but there was no such relationship in hyperthyroidism.[21] There are no data to suggest that patients with autoimmune thyroid disease are at higher risk for COVID-19. Treatment of asymptomatic or mildly symptomatic patients should be continued in the same dose.[22] In a systematic review of seven studies to evaluate the prevalence of thyroid dysfunction in COVID-19 patients, including 1237 COVID-19 patients, there was heterogeneity between studies, most COVID-19 patients were euthyroid, and there was a positive correlation between thyroid dysfunction and clinical severity of COVID-19.[23] In our study, there was no difference between the two groups in terms of TSH, fT4, fT3 values, and these values were within normal limits. We found that the most common diagnosis of our patients was euthyroid MNG.

This is the first study in the literature to determine the risk of asymptomatic COVID-19 infection in the group of patients scheduled for FNAB due to a thyroid nodule. The patient group planned for FNAB with a thyroid nodule is a specific but common population. It is an important study in which the rate of asymptomatic COVID-19 patients, the demographic characteristics, clinical and laboratory findings, and FNAB results are determined cross-sectionally in these days when the pandemic continues and the number of cases increases. Asymptomatic patients carry a risk of transmission for both healthcare workers and the community, and protocols are needed to manage asymptomatic patients to control the pandemic.

Ethical Considerations: Our cross-sectional study protocol was approved by the Ethics Committee of Ankara City Hospital (Signature number: E1-20-1106).

Conflict of Interest: The authors declare no conflict of interest.

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