Relationship Between the Nasopharyngeal Swab Sampling Method, Nasal Obstruction, and SARS-Cov-2 Positivity

Dogan Cakan*, Zeliha Kubra Cakan**, Semih Usaklioglu***, Yetkin Zeki Yilmaz*, Omer Uysal****, Hasan Ahmet Ozdogan*

*Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Otorhinolaryngology, Istanbul, Turkey

**Eyupsultan State Hospital, Clinic of Internal Medicine Istanbul, Turkey

***University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Otorhinolaryngology, Istanbul, Turkey

****Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Biostatistics, Istanbul, Turkey

─────────────────────── **Abstract** ───────────────────────

Aim: We think that the nasopharyngeal swab sample should be taken bilaterally to improve the sensitivity of the real-time-reverse transcriptase-polymerase chain reaction (RT-PCR) test since there may be pathologies that cause nasal obstruction, such as nasal septum deviation (NSD). In this context, we investigated the effect of the nasopharyngeal swab sampling method and the presence of nasal obstruction on the detection of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).

Methods: This prospective clinical study was conducted from March 2021 to January 2022. Forty-four hospitalized patients with NSD were included in the study group, and 44 hospitalized patients without NSD were included in the control group. The results of the RT-PCR test studied with a unilateral nasopharyngeal swab sample taken during hospitalization and the RT-PCR test studied with a bilateral nasopharyngeal swab sample taken on the 2nd day of hospitalization and the visual analog scale (VAS) scores showing the patients' pain during the first sampling were determined.

Results: In the first test, 23 (52.3%) patients in the study group and 32 (72.7%) patients in the control group were evaluated as SARS-CoV-2 positive. The first test sensitivity was significantly higher in the control group (p=0.048). The VAS score was significantly higher in the study group (p=0.00008). In the second test, 35 (79.5%) patients in the study group and 37 (84.1%) patients in the control group were evaluated as SARS-CoV-2 positive. The sensitivity increases in the study group and in the population were statistically significant (p=0.007 and p=0.004, respectively). The consistency of the first and second test results increased in patients without NSD and in patients with low VAS scores [odds ratio (OR)=3.779; p=0.001, OR=2.572; p=0.005, respectively].

Conclusion: Nasopharyngeal swab sampling may be affected by nasal congestion and the sampling method. To avoid this, it may be more appropriate to take a nasopharyngeal swab sample through the bilateral nasal cavity.

Keywords: COVID-19 testing, SARS-CoV-2, reverse transcriptase polymerase chain reaction, specimen handling/methods nasal obstruction

Introduction

The causative virus of coronavirus disease-2019 (COVID-19), the first pandemic since the 1918 influenza pandemic (1918-1920), is severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1,2). The most important step in the fight against this disease is to identify patients with SARS-CoV-2 quickly and accurately, especially asymptomatic patients, and to ensure their isolation (3). The reverse transcriptase-polymerase chain reaction (RT-PCR) is the most commonly used diagnostic method for detecting SARS-CoV-2 infection, which can be performed on different specimens (4). The samples can be obtained from the upper airways such as nasopharyngeal (NP) swabs, oropharyngeal (OP) swabs, and a combination

of OP and NP (naso/OP) swabs, the lower respiratory tract such as bronchoalveolar lavage, the gastrointestinal tract such as anal swabs, or directly from specimens such as tears, saliva, sputum, and feces (4). Despite all these methods, the naso/OP swab is used as the gold standard for detecting the virus (5). Although RT-PCR with a naso/OP swab sample is the most commonly used test for the identification of COVID-19, it has low sensitivity, ranging from 37% to 71% (6-8). This sensitivity, which decreases due to external factors such as improper sampling technique, the way the sample is transported and stored, and the characteristics of the kit used, is higher in chest computed tomography (CT), 70-93%, and artificial intelligence-supported programs, 80.5-98.7% (4,6,9). Additionally, different methods for collecting naso/OP swab samples have been described. For example, there are different recommendations regarding the use of the nasal cavity unilaterally or bilaterally for the NP swab sample (10-12). Nasal septum deviation (NSD) is a common reason for nasal obstruction. Although the prevalence of this pathology, which narrows the nasal passage and prevents access to the nasopharynx, depends on various factors such as gender and age, it was found to be 46.56% in Turkey (13). We think that the NP swab sample should be taken bilaterally to improve the sensitivity of the RT-PCR test since there may be pathologies that cause nasal obstruction, such as NSD. This study determines the relationship between RT-PCR test results of unilaterally or bilaterally taken naso/OP swab samples and the presence of NSD.

Materials and Methods

Ethical Standards

This clinical study was conducted on subjects who applied to Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine from March 2021 to January 2022 with the approval of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision date/number: 09.07.2020/604.01.02). All subjects signed an informed consent form.

Populations, Inclusion, and Exclusion Criteria

All subjects of this study applied to the Emergency (ER) of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine. The hospitalized patients, according to the criteria in the COVID-19 guideline of the Turkish Ministry of Health (TMH) (the patients with poor prognostic criteria (blood lymphocyte count <800/µl or C-reactive protein >10 mg/L x upper limit of normal value or ferritin >500 ng/mL or D-Dimer >1000 ng/mL) in blood tests, bilateral diffuse involvement (>50%) in lung imaging, respiratory rate >24/min, and/or SpO2 <93% in room air (12) were

included in this study. The patients were on day 5 of COVID-19 symptoms and their clinic and chest CTs were compatible with COVID-19 (CO-RADS 4, high risk; 5, very high risk; 6, proven) (14). The naso/OP swab samples were taken through the right nasal cavity on the day of hospitalization. All patients signed an informed consent form. Group 1 consisted of subjects with a right deviated nasal septum and group 2 consisted of subjects without NSD.

The subjects under the age of 18 and over 80 years old, with a history of respiratory tract surgery or respiratory tract infection in the last 3 months, immunodeficiency, chronic lung disease, having a lack of mental capacity, having a prominent inferior turbinate (covering more than 2/3 of the nasal passage on anterior rhinoscopy), having a chest CT in COVID-19 Reporting and Data System (CO-RADS) category 0-3, smokers, and those who did not accept participating were excluded from the study. Additionally, patients with a deviated nasal septum to the left were excluded from the study (15).

Sample Size and Sampling Technique

The minimum subject number was estimated on the basis of the study by Yilmaz et al. (16). The minimum sample size with a 95% confidence interval and 5% tolerable error assumptions was 88. A stratified sampling method was used in this study. Patients admitted to the COVID-19 clinic were separated into subgroups according to the presence of NSD. The patients who had any exclusion criteria for the study were excluded from the subgroups. Among the patients in each stratum, 88 patients were randomly selected to be included in the study and control groups in equal numbers.

Procedures and Data Collection

Day 0: Detailed anamnesis of the patients who were transferred from the emergency room to the COVID-19 service was taken and the treatments (enoxaparin 1x4000 anti-Xa IU/0.4 mL, Favipiravir 2x1600 mg loading dose on the first day + 2x600 mg maintenance dose for four days) were arranged (13). It was determined how the swab sample was taken for the RT-PCR test. The patient's pain score during the swab test procedure was determined using the visual analog scale (VAS). The patients were asked to score their pain from 0 (no pain) to 10 (worst pain) (13). RT-PCR test results were recorded.

Day 2: The bilateral nasal cavity was evaluated with a nasal speculum by an expert otolaryngologist. Secondly, swab samples were taken from the patients. The second swab samplings of the patients were performed by another, same-expert, with 10 years of experience as an otolaryngologist, to ensure standardization and to avoid BIAS.

Methods

The naso/OP swab samples were taken in the ER by the same internal medicine specialist in accordance with the TMH guidelines (the sampling was performed first from the oropharynx and afterward from the nasopharynx with the same tool). Afterward, the swab samples were placed in a transfer container (Bio-Speedy-vNAT, Bioeksen, Turkey). The capped containers were transferred to the public health laboratory at temperatures ranging between 2 °C and 8 °C. Patients who were transferred to the COVID-19 service, whose NP swabs were taken unilaterally through the right nasal cavity and whose RT-PCR test did not result, were included in the study. Before the second swab sampling, nasal cavities were examined with a speculum (Hartmann nasal speculum; catalog number, 400500; Karl Storz SE & Co. KG, Germany). The inferior turbinates were evaluated and the patients whose inferior turbinate obstructed more than 2/3 of the nasal passage were excluded from the study. Nasal examinations were repeated 5 minutes after nasal administration of xylometazoline (Otrivine®; GlaxoSmithKline, UK). Patients whose nasal septum was deviated to the right and more than 1/3 of the right nasal passage was obstructed due to the septum deviation were included in group 1. The second swab samples were taken first from the oropharynx, afterward through the left nasal cavity, and then through the right nasal cavity by reaching the nasopharynx by the same person. The storage and transfer procedures were performed in the same manner as for the first swab applications.

Computed Tomography

Chest CT images were obtained using the same device (Siemens SOMATOM Scope 16, Siemens Healthineers, Erlangen, Germany). Parenchymal infiltrates were evaluated with high-resolution reconstruction images of 1-mm section thickness. Chest CT has a sensitivity of 70-93% and a specificity of 93-100% in distinguishing COVID-19 pneumonia (6). Although there are different classifications such as the British Society of Thoracic Imaging and the CO-RADS, CO-RADS is most commonly used for radiological evaluation of COVID-19 (6). There are 7 categories in CO-RADS. CO-RADS 0 technically indicates an inadequate review, while categories 1 to 6 describe an increased risk of COVID-19 (CO-RADS 1, very low risk; CO-RADS 6, definitive diagnosis) (7,14,15). High-resolution thin-section, non-contrast chest tomography was categorized according to the CO-RADS classification by the same expert, with 12 years of experience as a radiologist.

RT-PCR Test

The samples kept for at least 30 min were analyzed with the RT-PCR kit (Bio-Speedy DoubleGeneRT-qPCR, Bioeksen, Turkey). The presence of viruses in the samples passed through various stages was detected by the real-time PCR analyzer (Rotor-Gene Q, Qiagen, Germany). Samples with a cycle threshold value of less than 38 were considered positive for COVID-19.

Statistical Analysis

The minimal subject was estimated using the G*Power program (17). Statistical analysis was performed using the SPSS 21.0 program (IBM, USA). The normal distribution and homogeneity of data were analyzed with the Kolmogorov-Smirnov test and Levene's test, respectively. The Pearson chi-square test, the independent-samples t-test, and the Mann-Whitney U tests were used for statistical comparisons. A binary logistic regression analysis was performed to examine the association between the resulting variables. The level of significance was determined as a p-value<0.05.

Results

A total of 88 subjects, 53 (60.2%) males and 35 (39.8%) females, were included in this study. Group 1 consisted of 26 (59.1%) male and 18 (40.9%) female subjects. Group 2 consisted of 27 (61.4%) male and 17 (38.6%) female subjects. The groups were statistically similar in terms of the gender distribution (pearson chi-square test, the value=0.047 and p=0.828; p>0.05). The mean age of the subjects was 54.06+15.28 (minimum: 21-maximum: 80) years. The mean ages were 54.27±15.49 years in group 1 and 51.84±15.14 years in group 2. No significant difference was detected between the groups according to patient age (independent samples t-test, p=0.790; p>0.05). All subjects were discharged from the hospital after treatment.

The first RT-PCR test results are given in Table 1. In the comparison of the test results, the positivity rate (sensitivity) of the first RT-PCR test was significantly higher in group 2 (p=0.048; p<0.05) (Table 1).

The second RT-PCR test results are given in Table 2. In the comparison of the test results, no significant difference was found between the groups in terms of sensitivity of the second RT-PCR test (p=0.58; p>0.05) (Table 2). The mean VAS scores were 5.07±0.27 (median=5, minimum: 2 -maximum: 9) for group 1 and 3.66±0.18 (median=4, minimum: 2-maximum: 6) for group 2. The VAS score was significantly higher in group 1 (p=0.00008; p<0.05) (Figure 1). The comparison of RT-PCR test results with unilateral samples (first RT-PCR test) and RT-PCR test results with bilateral samples (second RT-PCR test), is given in Table 3. When all patients included in the study were examined as a single group (single group), the sensitivity of the first RT-PCR test was 63.5% and the sensitivity of the second RT-PCR test was 81.2%. The sensitivity

Table 1. Evaluation of RT-PCR results of unilateral swab samples

Patient groups	SARS-CoV-2 + n (%)	SARS-CoV-2- n (%)	p
Group 1 (n=44)	23 (52.3%)	21 (47.7%)	0.048*
Group 2 (n=44)	32 (72.7%)	12 (27.3%)	

*Pearson chi-square test, value: 3,927; df: 1, p<0.05.
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

Table 2. Evaluation of RT-PCR results of bilateral swab samples

Patient groups	SARS-CoV-2 + n (%)	SARS-CoV-2- n (%)	p
Group 1 (n=44)	35 (79.5%)	9 (20.5%)	0.580*
Group 2 (n=44)	37 (84.1%)	7 (15.9%)	

*Pearson chi-square test, value: 0.306; df: 1, p>0.05.
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

Table 3. The comparison of test results

Patients	Swap sampling	SARS-CoV-2 + n (%)	SARS-CoV-2- n (%)	p	Kappa (κ) value
Group 1 (n=44)	Unilateral	23 (52.3%)	21 (47.7%)	0.007*	0.439
	Bilateral	35 (79.5%)	9 (20.5%)		
Group 2 (n=44)	Unilateral	32 (72.7%)	12 (27.3%)	0.195	0.671
	Bilateral	37 (84.1%)	7 (15.9%)		
All patients (n=88)	Unilateral	55 (63.5%)	33 (37.5%)	0.004*	0.541
	Bilateral	72 (81.2%)	16 (18.2%)		

*Pearson chi-square test, p<0.05.
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

increases in group 1 and in the single group were statistically significant (the value=7,283; df: 1; p=0.007, and the value=8,173; df: 1; p=0.004, respectively). In the evaluation of test agreements, a moderate agreement was found in group 1 test results [kappa (κ) value=0.439], a substantial agreement was found in group 2 test results (κ value=0.671), and a moderate agreement was found in the single group results (κ value=0.541) (Cohen's kappa statistic, p<0.001) (Table 3). When the relationship between positive RT-PCR test results obtained using both methods and the patient's age, gender, presence of septum deviation, and VAS score was examined, it was found that the consistency of test results increased in patients without septum deviation and in patients with low VAS scores [Binary logistic regression, odd ratio (OR)=3,779; p=0.001, OR=2,572; p=0.005, respectively] (Table 4).

Discussion

Although several methods have been used in COVID-19 diagnosis, the RT-PCR test is used routinely (18). The sample required for this test is most often taken from both the oropharynx and nasopharynx with the swab technique (3-5). There are different techniques and recommendations for the naso/OP swab method, which is applied millions of times every day around the world (1-4,19). Due to the swab sampling technique and features

of the RT-PCR test, different sensitivity and specificity rates for detecting SARS-CoV-2 have been reported in the literature (2,5,9,12,20,21). In this study, the sensitivity of the RT-PCR test, which was performed with a unilateral naso/OP swab sample, in subjects with NSD was significantly lower than in subjects without NSD, and the pain felt by the patients during the swab sampling was significantly higher in subjects with NSD (p<0.05). When the NP swab sample is taken through the bilateral nasal cavity, it increases the RT-PCR test sensitivity. Additionally, there was low agreement between the RT-PCR test sensitivity studied with a unilateral NP swab sample and the RT-PCR test sensitivity studied with a bilateral NP swab sample in the entire population, particularly in people with NSD. This agreement was higher in patients with low-pain VAS scores.

Table 4. The evaluation of study parameters with test result positivity

Parameters	p	OR
Gender	0.078	0.472
Age	0.117	0.958
Nasal septum deviation	0.001	3,779
VAS score	0.005	2,572

Binary logistic regression, Constant significance of model p=0.005 correct classification 85%.
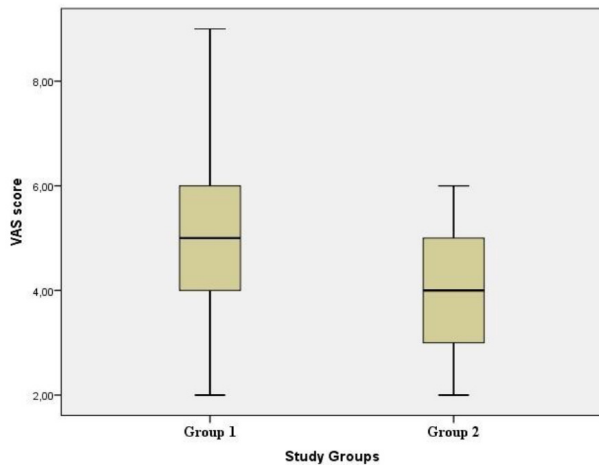VAS: Visual analog scale, OR: Odds ratio

Figure 1. Evaluation of visual analogue scale (VAS) scores in the study groups with box plots (median, interquartile range, 5th and 95th percentiles)

There are different recommendations for taking a NP swab sample for the RT-PCR test, which is defined as the gold standard method in SARS-CoV-2 detection (5). Although there are opinions stating that it is sufficient to reach the nasopharynx from the unilateral nasal cavity and take a swab, some institutions recommend reaching the nasopharynx separately from the bilateral nasal cavity and taking a sample (10-12). In the COVID-19 guidelines of TMH, samples can be taken from both nostrils, but if the swab is saturated with enough liquid in the first application, it is not necessary to take a swab from both sides (12). Additionally, in the same guideline, it is requested to question whether there is any problem (deviation, polyp, bleeding tendency, etc.) related to the nasal passage. The Center for Disease Control and Preventions guidelines offer the same recommendations, but how to behave in such a situation is not specified in either of the guidelines (12,22). Although there are many reasons in the literature to reduce the sensitivity of the RT-PCR test, we did not encounter any study examining the relationship between NSD and SARS-CoV-2 RT-PCR test results in our literature review. Based on this information, we hypothesized that a unilateral NP swab sample for the RT-PCR test is not sufficient, especially in patients with NSD, and that swab samples should be taken from both nasal cavities separately by reaching the nasopharynx order to obtain higher test sensitivity. To ensure optimal standardization and avoid BIAS in our study, we determined the exclusion criteria and ensured that the samples were collected by the same specialists. Patients who were radiologically and clinically compatible with COVID-19 and had an indication for hospitalization were included in the study because they might have a higher viral load and the second RT-PCR test could be performed more easily (23). Because the

SARS-CoV-2 viral load peaked on day 5 after that symptom onset, patients on day 5 of COVID-19 symptoms were included in our study (20). The second swab sampling was taken on the 7th day of the disease since the higher viral load persisted in the samples taken from the upper respiratory tract during the first 7 days of the disease (3). We performed a nasal examination with and without a decongestant to leave NSD as the only pathology causing nasal obstruction. In this study, the sensitivity of the RT-PCR test performed using a unilateral swab sample was significantly lower in subjects with NSD than in subjects without NSD. Additionally, this difference disappeared in the RT-PCR test performed using a bilateral swab sample. In group 1, the sensitivity of the RT-PCR test studied from a unilateral swab sample was 52.3%, while the sensitivity of the RT-PCR test studied from a bilateral swab sample increased to 79.5%. In group 2, the sensitivity increased from 79.5% to 84.1%. Additionally, the pain felt during swab sampling was significantly higher in patients with NSD. Discordance between the first (unilateral) and second (bilateral) RT-PCR test sensitivities exists in the entire population, particularly in patients with a septal deviation. Additionally, this inconsistency is also present in patients with high-pain-related VAS scores. Therefore, swab samples should be taken by entering the bilateral nasal cavity in the whole population, particularly in patients who feel excessive pain during NP swab sampling and have a history of NSD.

Study Limitations

There are some limitations to this study, which examines a subject that has not been addressed in the literature before. The first limitation is that we determined the subjects we defined as COVID-19 patients in our study according to their clinical symptoms and chest CT scans (24). Although the sensitivity and specificity of radiology are higher than RT-PCR, both the symptoms on the list of WHO for COVID-19 and the findings used for CO-RADS can also be observed in other viral types of pneumonia (6,12,25). The second limitation is that RT-PCR tests were performed in a different center, even though it was an approved center by the TMH. Accordingly, we cannot exclude human-induced errors during the transfer process or RT-PCR test run. Another limitation is that the first and second swab samples are taken by different doctors. If the first swab samples were also taken by the otorhinolaryngologist, they might have a higher sensitivity rate because of their better command of nasal anatomy. Another limitation is that we only perform nasal examinations with anterior rhinoscopic evaluation since the endoscopic examination is not recommended under pandemic conditions (26). Therefore, we may have miscalculated the amount of nasal obstruction and overlooked other pathologies that

may cause nasal obstruction (27). The final limitation is that we used a subjective test to assess the pain felt by patients during swab sampling. Despite all the limitations of the study, our study is the first study examining the relationship between RT-PCR test results, the way NP swab samples were obtained (unilateral or bilateral), and the presence of NSD in the patient.

Conclusion

Nasopharyngeal swab sampling used to obtain the sample required for RT-PCR testing may be affected by pathology that narrows the nasal passage. The NSD, which is one of the most common causes of nasal obstruction, may be one of these reasons. Patients with NSD experience more pain when taking a NP swab sample. To avoid the effects of nasal obstruction on the RT-PCR test, NP swab sampling should be performed by entering from both nasal cavities, particularly in patients who feel a lot pain during the swab sampling and have a history of NSD.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision date/number: 09.07.2020/604.01.02).

Informed Consent: All subjects signed an informed consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.C., Z.K.C., H.A.O., Concept: S.U., Y.Z.Y., Design: D.C., S.U., Y.Z.Y., Data Collection and/or Processing: D.C., Z.K.C., H.A.O., Analysis and/or Interpretation: O.U., Literature Research: Z.K.C., S.U., Y.Z.Y., H.A.O., Writing: D.C., Z.K.C., O.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Şahin AR, Koçyiğit BF, Aksu E, et al. Multisystemic Long-Term Sequelae of Covid-19: A Review Based on the Current Literature Over a Year of Pandemic Experience. EJMO 2021;5:6-19.

2. Mawaddah A, Gendeh HS, Lum SG, Marina MB. Upper respiratory tract sampling in COVID-19. Malays J Pathol 2020;42:23-35.

3. Wu J, Liu J, Zhao X, et al. Clinical Characteristics of Imported Cases of Coronavirus Disease 2019 (COVID-19) in Jiangsu Province: A Multicenter Descriptive Study. Clin Infect Dis 2020;71:706-12.

4. Huang S, Yang J, Fong S, Zhao Q. Artificial intelligence in the diagnosis of COVID-19: challenges and perspectives. Int J Biol Sci 2021;17:1581-7.

5. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323:1843-4.

6. Pekçevik Y, Belet Ü. Patient Management in the Radiology Department, the Role of Chest Imaging During the SARS-CoV-2 Pandemic and Chest CT Findings Related to COVID-19 Pneumonia. J Tepecik Educ Res Hosp 2020;30:195-212.

7. Wang X, Tan L, Wang X, et al. Comparison of nasopharyngeal and oropharyngeal swabs for SARS-CoV-2 detection in 353 patients received tests with both specimens simultaneously. Int J Infect Dis 2020;94:107-9.

8. Penha D, Pinto EG, Matos F, et al. CO-RADS: Coronavirus Classification Review. J Clin Imaging Sci 2021;11:9.

9. Poggiali E, Vercelli A, Vadacca GB, et al. Negative nasopharyngeal swabs in COVID-19 pneumonia: the experience of an Italian Emergengy Department (Piacenza) during the first month of the Italian epidemic. Acta Biomed 2020;91:e2020024.

10. Public Health Laboratory Network. PHLN guidance on laboratory testing for SARS-CoV-2 (the virus that causes COVID-19), version 1.16.Updated 28 January 2022. https://www.health.gov.au/resources/publications/phln-guidance-on-laboratory-testing-for-sars-cov-2-the-virus-that-causes-covid-19

11. Ahmadzadeh M, Vahidi H, Mahboubi A, Hajifathaliha F, Nematollahi L, Mohit E. Different Respiratory Samples for COVID-19 Detection by Standard and Direct Quantitative RT-PCR: A Literature Review. Iran J Pharm Res 2021;20:285-99.

12. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü COVID-19 Rehberi. https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html (visited February 14, 2022).

13. Salihoglu M, Cekin E, Altundag A, Cesmeci E. Examination versus subjective nasal obstruction in the evaluation of the nasal septal deviation. Rhinology 2014;52:122-6.

14. Majumder J, Minko T. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. AAPS J 2021;23:14.

15. Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. Radiology 2020;296:E97-104.

16. Yilmaz YZ, Yilmaz BB, Ozdemir YE, et al. Effects of hypertonic alkaline nasal irrigation on COVID-19. Laryngoscope Investig Otolaryngol 2021;6:1240–7.

17. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.

18. Filchakova O, Dossym D, Ilyas A, Kuanysheva T, Abdizhamil A, Bukasov R. Review of COVID-19 testing and diagnostic methods. Talanta 2022;244:123409.

19. Dhanani R, Wasif M, Pasha HA, et al. COVID-19: Implications, Reactions and Future Directions. Turk Arch Otorhinolaryngol 2020;58:122-6.

20. https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html (visited February 14, 2022).

21. Moreira VM, Mascarenhas P, Machado V, et al. Diagnosis of SARS-Cov-2 Infection by RT-PCR Using Specimens Other Than Naso- and Oropharyngeal Swabs: A Systematic Review and Meta-Analysis. Diagnostics (Basel) 2021;11:363.

22. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465-9.

23. Lee MJ. Quantifying SARS-CoV-2 viral load: current status and future prospects. Expert Rev Mol Diagn 2021;21:1017-23.

24. Amanollahi A, Sotoodeh Ghorbani S, Basir Ghafouri H, Afrashteh S, Hashemi Nazari SS. Which criteria were used to describe patients with COVID-19? A systematic review and meta analysis of clinical, laboratory, and imaging features. Med J Islam Repub Iran 2021;35:112.

25. Liu G, Chen Y, Runa A, Liu J. Diagnostic performance of CO-RADS for COVID-19: a systematic review and meta-analysis. Eur Radiol 2022;32:4414-26.

26. Kapoor S, Gupta A, Saidha PK. Ear, Nose, and Throat Practice Guidelines: An Update for COVID-19. Int Arch Otorhinolaryngol 2021;25:e621-7.

27. Hsu DW, Suh JD. Anatomy and Physiology of Nasal Obstruction. Otolaryngol Clin North Am 2018;51:853-65.