Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

The correlation between combined nasal and throat swab and chest CT findings in the diagnosis of COVID 19

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ARTICLE INFO

Keywords:
COVID-19; combined nasal & throat swab; RT-PCR; chest CT.

Received: Apr 20, 2021
Accepted: Jul 30, 2021
Available Online: Feb, 15, 2022
DOI:10.5455/annalsmedres.2021.04.353

Abstract

Aim: COVID-19 has spread rapidly, caused a pandemic and become a serious public health problem all over the world. The aim of the study is to investigate whether reverse transcriptase-polymerase chain reaction (RT-PCR) method, the most commonly used method for the diagnosis of COVID-19, correlate with the chest CT findings.

Material and Methods: The file records of the patients with COVID-19 and suspected COVID-19 were examined retrospectively between 11 March and 30 August 2020 after the approval of the local ethics committee. Patient files were divided into 2 groups. RT-PCR negative patients were in group 1 and RT-PCR positive patients were in group 2. Combined nose and throat swab (CNTS) was used for swab sampling.

Results: Of the 492 patients included in the study, 277 were men and 215 were women, with an average age of 57.45 ± 19.83. While there were 81 (29.2%) patients with chest CT findings compatible with COVID-19 in the first group, there were 80 (37.2%) patients in the second group. While the number of patients whose chest CT findings were incompatible with COVID-19 was 196 (70.8%) in group 1, it was 135 (62.8%) in group 2. There was a poor agreement between chest CT and RT-PCR in diagnosing COVID-19 (p = 0.062).

Conclusion: To diagnose the disease is the most important step in treatment management. Especially in patients with incompatible RT-RCR and chest CT, the diagnosis should be strengthened by evaluating the laboratory findings and clinical symptoms of the patient.

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Intoduction

In the diagnosis of the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), reverse transcriptase –polymerase chain reaction (RT-PCR) is used for the detection of the viral RNA particles. Various body fluids obtained from nasopharyngeal and oropharyngeal swabs as well as sputum, tracheal aspirate and bronchoalveolar lavage (BAL) are used for RT-PCR. In different studies, RT-PCR positivity rate of nasopharyngeal samples is 40-63%, while this rate is 32-61% oropharyngeal samples (1, 2). As it's easy to access to the nose and the throat, it's often preferred to take the swabs from these areas. However, both low positivity and high false negativity rates may require repeated tests. Although the rate of the positive results of the tracheal aspirate and the BAL is higher, their use is limited due to the difficulty of sampling. In our country, routine sampling is done as combined nose and throat sample (CNTS) since the onset of the pandemic. In addition to the sampling location, various factors are also important, such as the experience of the sampler, the conditions of sample handling and storage, the time of sample collection and the risk of contamination. In order to obtain positive RT-PCR, the incubation period of the disease should also be considered.

Chest computed tomography (CT) is used to evaluate the grade and the extension of the viral pneumonia by COVID-19 (3). Chest CT reveals typical radiological features, including single or multiple ground-glass opacities, multifocal patchy consolidation, and/or interstitial changes with a peripheral distribution. Typical radiological findings were also observed in patients with negative RT-PCR results, but clinical symptoms compatible with COVID-19 (3-6).

Various hematological parameters such as complete blood count, lymphocyte and platelet counts, IL-6, ferritin, lactate dehydrogenase (LDH) and d-dimer are used in diagnosis in COVID-19 (7, 8). LDH and d-dimer elevation and lymphopenia are important in diagnosis of COVID-19 and they are associated with poor prognosis (8, 9). Especially in RT-PCR negative COVID-19 patients with the presence of clinical findings, these parameters support the diagnosis of COVID-19.

The aim of our study is to compare the compatibility of chest CT findings with RT-PCR results of the patients with COVID-19 that treated in our hospital.

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Material and Methods

The retrospective study was initiated after the approval of the local ethics committee (No: 2020-36). The file records of the patients with COVID-19 and suspected COVID-19 were examined between 11 March and 30 August 2020. The swab samples, blood parameters, demographics, comorbid diseases, prognoses and chest CT data of the patients were accessed through the file recording system. The number of samples, the day and the sampling time of the RT-PCR positive patients were also recorded. All patients with COVID-19 and suspected COVID-19 were included in the study if they had a chest CT. The patients without chest CT and under 18 years old were excluded from the study. Patient files were divided into 2 groups as RT-PCR negative (group 1) and RT-PCR positive (group 2). Chest CT findings of the patients in both groups were evaluated and those who had findings compatible with COVID-19 and those who did not have findings compatible with COVID-19 were recorded. As reported in the literature, if chest CT findings were classified as COVID-19 Reporting and Data System (CORADS) 4 and 5, it was accepted COVID-19, and if chest CT findings were classified as CORADS 1, 2 and 3, it was considered incompatible with COVID-19 (10). Comorbid diseases of the patients were classified as hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), asthma and/or chronic obstructive pulmonary disease (COPD), psychiatric diseases, malignancy and others. While taking the CNTS, the oropharyngeal sample is taken by rubbing a swab on both tonsils and the pharyngeal wall, then the same swab is entered through the nostril to reach the nasopharynx and touched for 5-10 seconds and sample collection is completed. Samples taken from the patients are placed in a 5 ml container and delivered to the laboratory. Materials are stored at 2 to 8 ℃ until they are delivered to the laboratory. The levels of SARS-CoV-2 RNA are detected by quantitative RT-PCR using a Rotor-Gene Q Real-time PCR instrument (Qiagen, Hilden, Germany).

Statistical Analysis:

Statistical analysis was performed via the Statistical Package for the Social Sciences program (SPSS for Windows, Version 25.0, Chicago, IL, USA). Results were presented as frequencies and percentages. The Chi-square test was used to compare categorical variables. Cohen's kappa analysis was used to evaluate the agreement between the RT-PCR result and the CT findings. $p<0.05$ was considered sufficient for statistical significance.

Results

Four hundred ninety two COVID-19 or suspected COVID-19 patients from March 11 to August 30, 2020 were included in the study. Two hundred seventy seven of the patients were male and 215 of them were female and the mean age was 57.45 ± 19.83. There were 215 patients in the first group and 277 patients in the second group. While there were 81 (29.2%) patients with chest CT findings compatible with COVID-19 in the first group, there were 80 (37.2%) patients in the second group. While the number of patients whose chest CT findings were incompatible with COVID-19 was 196 (70.8%) in group 1, it was 135 (62.8%) in group 2. There was a poor agreement between chest CT and RT-PCR in diagnosing COVID-19 ($p = 0.062$) (table 1).

The comorbid diseases of the patients were, HT in 198 patients (125 RT-PCR negative, 73 RT-PCR positive), CAD in 146 patients (91 RT-PCR negative, 55 RT-PCR positive), DM in 83 patients (49 RT-PCR negative, 34 RT-PCR positive), asthma and/or COPD in 62 patients (43 RT-PCR negative, 19 RT-PCR positive), psychiatric disease in 55 patients (36 RT-PCR negative, 19 RT-PCR positive) and malignancy in 17 patients (11 RT-PCR negative, 6 RT-PCR positive). Different diseases detected in 93 patients and they were mentioned as the other group. When the relationships between these comorbid diseases and CT findings were examined, no statistically significant difference was found (Table 2). In the RT-PCR positive 212 patients, 183 of them were found positive in the first sample, 24 of them were found positive in the second sample and 5 of them were found positive in the third sample.

Table 1. Agreement between CT and RT-PCR in diagnosing COVID-19. There was a poor agreement between CT and RT-PCR in diagnosing COVID-19

	PCR result				
	Negative	Positive	Total	*Kappa	p
Typical CT findings					
Negative	196	135	331	0.082	0.062
Positive	81	80	161		
Total	277	215	492		

* Cohen's kappa coefficient.

Table 2. Comparison of CT findings in terms of co-morbidities

		Typical CT findings					
		Negative		Positive			
		n	%	n	%	χ^2	p
Hypertension	No	206	62.2	88	54.7	2.586	0.108
	Yes	125	37.8	73	45.3		
Diabetes Mellitus	No	282	85.2	127	78.9	3.079	0.079
	Yes	49	14.8	34	21.1		
COPD	No	288	87.0	142	88.2	0.139	0.709
	Yes	43	13.0	19	11.8		
CAD	No	240	72.5	106	65.8	2.308	0.129
	Yes	36	10.9	19	11.8		
Malignancy	No	320	96.7	155	96.3	0.053	0.818
	Yes	11	3.3	6	3.7		
Other	No	268	81.0	131	81.4	0.011	0.915
	Yes	63	19.0	30	18.6		

Discussion

Various diagnostic tools have been used for the diagnosis of COVID-19 such as RT-PCR, chest CT, antigen-antibody tests and hematological parameters since the beginning of the pandemic. Among these, RT-PCR analysis of various body fluids such as oropharyngeal swab, nasopharyngeal swab and tracheal aspirate is widely accepted, since sampling is easy and non-invasive (11). However, tracheal aspirate intake is a more invasive procedure and creates intense aerosol content, so it is

not preferred as it puts healthcare professionals and the patient under various risks (12). It has been reported that changes in lung of the patients may ocur very early, even before RT-PCR positivity (5). The effectiveness of nasopharyngeal, oropharyngeal or CNTS samples depends on various factors such as the timing of swab collection, the method of taking the samples, the ability to obtain sufficient material, whether the cold chain rules are followed during transportation and the storage of the appropriate material in the appropriate container. In addition, taking samples during the period when viral load is highest in the upper respiratory tract may increase the success rate of RT-PCR results. The sampler should know the oropharyngeal and nasal anatomy for appropriate sampling and should have sufficient training on this subject. Like other samples taken from the upper respiratory tract, swabs for COVID-19 should have kept in flocked non-toxic synthetic fibers such as polyester as well as synthetic nylon handles and universal transport medium and transport via under refrigerated conditions (13).

It is reported that the disease has an incubation period of 2-12 days (average 5.1 days) from the time of transmission, and the viral load in the upper respiratory tract reaches the highest level on the 5th or 6th days after the symptoms of COVID-19 disease (14-18). During this period, the rate of positive RT-PCR results of samples taken from the upper respiratory tract is high. When the patients have the main symptoms of the disease, but negative RT-PCR result, an interval of 24-96 hours may be required for repeating RT-PCR (19). In some patients, the disease progresses asymptomatic and RT-PCR positivity is detected incidentally. Studies have reported a wide range of asymptomatic patients between 1.2% and 50.9% (20-24). In the asymptomatic patient group, if laboratory and chest CT findings suggest COVID-19, a swab can be taken after 24 or 48 hours again. Mohammedi et al. reported that the estimated percentage of positive tests were 75% (95% CI: 60–88%) between days 0–7, 35% (95% CI: 27–43%) between days 8–14 and 12% (95% CI: 2–25%) after 14 days from symptom onset, for oropharyngeal swab sampling (25). In this case, timing of the swab is another matter of discussion.

Low viral load in the early stages of the disease, false negative results and technical problems are among the reasons for not detecting positivity in RT-PCR. Huang et al. reported that they detected positivity in the third sample after 2 consecutive negative results from an infected patient (6). Similarly, Xie et al. reported that the first sample results of 5 infected patients were negative or weakly positive (5). Işıkbay et al. reported the false negative RT-PCR rate below 1% after the 4th sample in regions with high disease burden, and the false positive rate as 2.7% after the 4th sample (26). In case of the negative control result of RT-PCR in patients whose symptoms do not regress after treatment, false negativity should not be ignored. In our study, the first RT-PCR samples of 29 patients were negative, then, positive results were obtained after repeated sampling.

Although oropharyngeal sampling can be done easily, the rate of RT-PCR positivity is low. Yang et al. reported the positivity rate of RT-PCR between 42.9% and 61.1% in oropharyngeal samples, while Wang et al. reported this rate as 32% (1, 27). Taking oropharyngeal samples from some patients may be difficult due to the gag reflex. It is recommended to apply the swab to different areas of the oropharynx for 10 seconds and repeat it several times when necessary (28). In order to get the reliable results, the experience of the sampler, patient's compliance and the stage of the disease are important. The clearance of the oral cavity by the saliva and elimination of the virus from the oropharynx during eating may be among the reasons for the low rate of RT-PCR positive results from oropharynx samples. RT-PCR positivity may continue for weeks even when, after remission of symptoms (29). If the patient's two RT-PCR results that performed in every 24 hours are negative, isolation will no longer be required. It was reported that the nasopharyngeal samples have higher positive RT-PCR rate (53.6% to 63%) than oropharyngeal samples (1, 27, 30).

There are some difficulties and risks in nasopharyngeal sampling such as anatomical obstacles (such as concha hypertrophy, nasal septum deviation) and high aerosolization for healthcare professionals. In addition to that sneezing during sampling can complicate this process. Li et al. stated that RT-PCR test results of pharyngeal swab samples are variable and should not be considered as the only indicator for diagnosis, treatment, isolation, recovery / discharge and transfer for patients with COVID-19 (31).

CNTS has been used as a sampling method since the pandemic started in our country. To obtain the viral particles in both the oropharynx and the nasopharynx in the sames swab may increase the RT-PCT positivity rate. Regardless to SARS-CoV-2, CNTS increases the diagnostic yield of respiratory viruses (32). In contrast, it was reported in another study that CNTS yield a similar sensitivity to detect SARS-CoV-2 nasopharyngeal swabs (33). LeBlanc et al. reported that samples taken from both oropharynx and anterior nares can be an alternative to samples taken from the nasopharynx (34). However, considering the mucociliary activity in the nasal cavity, it should not be ignored that samples taken from the posterior of the nasal cavity may yield more positive results.

Other samples may be preferred in patients who do not have positive results from all upper respiratory tract samples. RT-PCR is the most important marker in diagnosis, according to the current diagnostic and treatment guidelines, chest CT findings are important for the diagnosis of the disease at the early stages. However, in our study, it was found that RT-PCR results and chest CT findings did not correlate. Since the typical chest CT findings for COVID-19 are advanced stages of the disease, negative RT-PCR at this stage may not indicate that the patient is not COVID-19. It should be considered that there may be false negative and false positive results in RT-PCR. In our study, the first RT-PCR results were negative, but the repeated samples of them were positive in a small number of patients, as well. Although all swab samples were taken by trained doctors, individual differences in sampling may be one of the limitations of this study. In addition, not knowing the time difference between sampling time and the onset of symptoms is another limitation of the study. Our other limitation does not know the time of onset of symptoms while taking samples from the patients. In future researches, the chest CT classification may be used for staging.

In conclusion, how and by whom the swab was taken, which sample was taken at what stage of the disease, and the storage and transportation conditions of the samples are extremely important for the diagnosis of COVID-19. It may not be sufficient to diagnose only by the RT-PCR positive or negative results or only the chest CT findings. While there are findings compatible with COVID-19 in chest CT, the reason for the negative detection of RT-PCR may be that the viral load in the lung is

higher than that in the upper respiratory tract in the advanced stages of the disease. With a similar theory, while RT-PCR is positive, the absence of COVID-19 findings in chest CT may be that the viral load in the lung is lower than that in the upper respiratory tract in the early period of the disease. In addition, it should not be ignored that CNTS may show false negativity in both theories. Improper clinical sampling, variation in detection rate from different manufacturers and immature development of nucleic acid detection technology are the other subjects. Examination of laboratory values and chest CT findings may be important in the diagnosis and treatment management of RT-PCR negative patients, especially in the early stage of the disease. Multi-center studies can be planned in the future and they may support our study.

Ethics approval:

Onyedi Eylül University local ethical approval number 2020-36. The manuscript has been read and approved by the all authors. The manuscript was not presented as part at a meeting or an organization. All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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