Clinical and Experimental Health Sciences

Evaluation of Laboratory Results with Data from Bio-Speedy Respiratory Panel 2 in Nasopharyngeal Swab Specimens of COVID-19-Suspected Patients Having PCR(-) Results

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ABSTRACT

Objective: The distinction between COVID-19 and other respiratory infections can be difficult during the flu and winter seasons. The aim of this study is to detect bacterial/viral microorganisms in nasopharyngeal swab samples and to evaluate routine laboratory results of patients with PCR (-) but suspected covid 19.

Methods: Between 1 July 2021 and 31 December 2021, 78 patients who were hospitalized and followed up in the suspected Covid service were included in the study. The patients were divided into two groups as those with and without growth on the respiratory panel. Laboratory, demographic and radiological data were compared between groups.

Results: C-reactive protein (CRP) and ferritin levels were found to be statistically significantly higher in the group with growth on the respiratory panel compared to the group without growth (p= .05, p= .041, respectively). Reproduction was detected in nasopharyngeal swab samples taken in 56.4% of the patients. More than half of the patients were radiologically defined as CO-RADS 3.

Conclusion: It should not be forgotten that other respiratory viral and bacterial infections that mimic the COVID-19 clinic are also commonly observed during this period.

Keywords: SARS CoV-2, nasopharyngeal/throat swab, PCR, flu season

1 .INTRODUCTION

The cause of a serious respiratory disease epidemic that occurred in Wuhan City of China in December 2019 is the new type of coronavirus named as "novel coronavirus-2019" by the World Health Organization (WHO) (1,2). The coronaviruses that can cause disease in humans are as follows: SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), MERS-CoV, SARS-CoV HCoV-NL63, HCoV-OC43, HCoV-HKU1, and HCoV 229E (3,4). Intense symptoms associated with SARS-CoV-2 infection are shortness of breath, cough, fatigue, fever and muscle aches. (5-7). Similar symptoms can be seen in infections associated with different viruses such as influenza A, influenza B, parainfluenza A, parainfluenza B, and RSV. The distinction between COVID-19 and other respiratory viral infections can be difficult during the flu and winter seasons (8). The clinical course of most COVID-19 patients is mild. However, it may have a more severe course, especially in elderly people and those with comorbidities such as coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), hypertension (HT), and diabetes mellitus (DM) (2,9).

Early identification of the SARS CoV-2 virus is very important to prevent the progression of clinical pathologies caused by this virus. Polymerase chain reaction (PCR) is a laboratory method with high sensitivity and specificity used for rapid detection of some viral and bacterial microorganisms (10,11). In viruses other than SARS CoV-2, clinical pictures such as upper respiratory tract infection, pneumonia, and unilateral or bilateral ground-glass and patchy consolidated lesion-like radiological appearance can be observed. Therefore, many 'suspicious' cases have been reported with computed tomography (CT) images of the thorax according to the CO-RADS classification, showing the clinical features of COVID-19 with RT-PCR (-) (12).

Our aim in this study is to detect bacterial/viral microorganisms in nasopharyngeal swab samples and to evaluate routine laboratory results of patients with PCR (-) but suspected covid 19, especially during the flu season.

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2. METHODS

Ethical approval was obtained from the Faculty of Medicine of Harran University (Approval number: 22/01/07, Approval date: 10.01.2022) and all participants gave their written informed consents.

Between 1 July 2021 and 31 December 2021, 100 patients who were hospitalized and followed up in the suspected Covid service were analyzed retrospectively. All patients over 18 years of age, who had a COVID 19 PCR test (-), whose Chest Computer Tomography (CT) report was interpreted as CO-RADS 3, CO-RADS 4 or CO-RADS 5, and patients whose respiratory panel was studied with nasopharyngeal swap were included in the study. Patients under 18 years of age, whose Chest CT report was interpreted as CO-RADS 1 and CO-RADS 2, and patients whose respiratory panel was not studied with nasopharyngeal swap were excluded from the study. According to these criteria, 10 patients who did not have nasopharyngeal swabs, 8 patients whose registered laboratory data could not be accessed, and 4 patients who did not have Chest CT images and reports were excluded from the study (Figure 1). Information such as patients' age, sex, comorbidity status as well as hemogram, biochemistry and coagulation results were obtained from all patients on the first day of hospitalization. Chest CT reports and nasopharyngeal swab results were obtained from the recorded data.

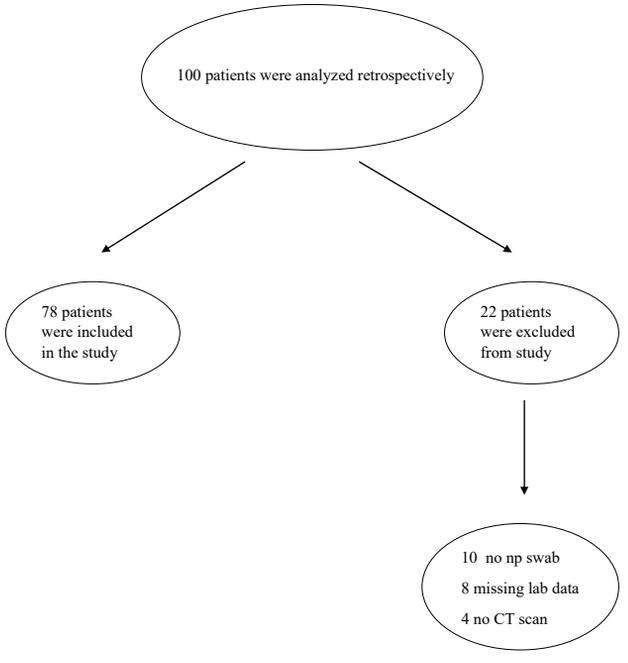

Figure 1. *Distribution of patients*

Chest CT images of the patients were reported by experienced radiologists according to the CO-RADS classification. CO-RADS is a classification developed by the Dutch Society of Radiology to determine the level of suspicion for COVID-19 pneumonia and is consistent with the consensus statement recommended by the RNSA (13,14). The classification was defined in 5 levels: Normal: 1 **negative**; not atypical for COVID-19 signs of infection: 2 Low (***atypical***); consistent with COVID-19 and other infections: 3 Equivocal/unsure (***indeterminate-lower likelihood***); Suspicious for COVID-19: 4 High (***indeterminate –high likelihoo***d); Typical for COVID-19: 5 Very high (***typical***).

Nasopharyngeal swab samples were taken from all patients by experienced healthcare personnel under sterile conditions. Bio-speedy Respiratory RT-qPCR MX-24S Panel is used for evaluation of nasopharyngeal swap samples (Table 1). It is used for rapid and accurate diagnosis of 24 respiratory tract pathogens (as viral and bacterial agents) from clinical samples with multiplex polymerase chain reaction. The kit is applied to nucleic acid isolates obtained from nasopharyngeal swab, bronchoalveolar lavage, oropharyngeal swab and nasopharyngeal aspirate samples. Rapid diagnosis with the kit is performed by one-step reverse transcription (RT) and real-time PCR (qPCR / RT-qPCR) targeting genomic RNA and DNA regions specific to the target agent. LoD values were determined as copies/mL. Transport is provided with a vNat Transfer tube (BS-NA513s-100 or Bio-Speedy vNat Transfer Tube BS-NA-513-100). Swab samples were collected using dacron or polyester swabs. The samples were transported to the laboratory and stored at 2-8°C. The RT-qPCR Application Protocol has been programmed by the manufacturer and is run on the appropriate Bio-Rad CFX96 device. Program t includes the steps of reverse transcription, Pre-incubation and Growth (denaturation, binding-elongation and fluorescence reading). Test results are interpreted by microbiologists according to the shape of the amplification curves.

The patients were divided into two groups as those with and without growth on the respiratory panel. Laboratory, demographic and radiological data were compared between groups. In addition, microorganisms grown in the respiratory panel were compared based on the radiological classification. Nasopharyngeal swab respiratory panel results of all patients included in the study were expressed as numerical and percentage values.

2.1. Statistical Analysis

SPSS (version 22.0) was used for all analyses. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Continuous measurements are presented as mean ± standard deviation (SD) if normally distributed, median (25-75 quartile range) if not, and categorical variables are presented as numbers (%). Student's t test was used to compare normally distributed data, and Mann-Whitney U test was used to compare not normally distributed data. Categorical data were expressed in numbers (percentage) and compared using the Chi-square test. A p value of < 0.05 was considered statistically significant.

Table 1. *Bio-speedy respiratory rt-qpcr mx-24s panel targets*

Sars-Cov-2-Nucleocapsid gene	Legionella pneumophila	Human Coronavirus 229E	Parainfluenza 1
Influenza-B	Mycoplasma pneumoniae	Human Coronavirus NL63	Parainfluenza 2
Influenza-A	Chlamydophila pneumonia	HumanCoronavirus HKU1	Parainfluenza 3
Human Bocavirus	Haemophilus influenzae	Human Coronavirus OC43	Parainfluenza 4
Human Parechovirus	Bordetella pertussis	Respiratory syncytial virus A	H.Metapneumovirus
H.Enterovirus/Human Rhinovirus Set 2	Streptococcus pneumoniae	Respiratory syncytial virus B	H.Enterovirus/Human Rhinovirus Set 1adenovirus

Table 2. *Comparison of demographic and comorbidity data in the between groups*

	Respiratory panel reproduction (-) (n=34)	**Respiratory panel reproduction** (+) (n=44)	p
Age, years	68.0 (54.7-78.0)	69.5 (52.0-78.0)	0.876
Gender, f/m	18/16	22/22	0.797
DM, %	7 (20.5)	12 (27.2)	0.495
HT, %	11 (32.3)	10 (22.7)	0.342
CAD, %	15 (44.1)	13 (29.5)	0.183
SVD, %	5 (14.7)	6 (13.6)	0.893
CKF, %	3 (8.8)	6 (13.6)	0.530
COPD, %	5 (14.7)	9 (20.4)	0.546
Malignancy, %	1 (2.9)	1 (2.3)	0.853

DM, diabetes mellitus; HT, hypertension; CAD, coronary arterial diseases; SVD, cerebrovascular diseases; CKF, chronic kidney failure; COPD, chronic obstructive pulmonary disease.

Table 3. *Laboratory and radiological data of patients*

	Respiratory panel reproduction (-) (n=34)	**Respiratory panel reproduction (+)** (n=44)	p
Glucose, mg/dL	143.5 (120.5-239.0)	138.5 (110.0-178.7)	0.182
Urea, mg/dl	48.6 (33.0-76.8)	47.5 (30.5-70.5)	0.668
Creatine, mg/ dL	0.9 (0.7-1.4)	0.9 (0.6-1.1)	0.203
Albumin, g/ dL	3.5 (2.7-4.0)	3.2 (2.6-3.9)	0.212
AST, U/L	20.0 (10.0-35.6)	13.5 (8.9-26.7)	0.173
ALT, U/L	25.5 (17.5-35.5)	22.0 (13.1-35.7)	0.316
T.bilirubin, mg/ dL	0.5 (0.3-0.8)	0.4 (0.2-0.6)	0.185
Sodium, mg/ dL	137.7 ± 4.7	139.0 ± 7.4	0.372
Potassium, mg/ dL	4.5 ± 0.8	4.3 ± 0.6	0.395
Calcium, mg/ dL	8.3 ± 0.7	8.2 ± 0.6	0.666
LDH, U/L	223.0 (184.2-339.5)	194.0 (167.7-426.7)	0.692
CRP, mg/dl	103.0 (34.7-220.7)	64.5 (116.7-426.7)	**0.05**
WBC, x10^3/mL	10.8 (8.0-14.3)	9.9 (6.0-14.8)	0.261
Neutrophil, x10^3/mL	8.7 (6.3-11.4)	8.5 (4.2-11.8)	0.288
Lymphocite, x10^3/mL	(0.6-1.4)	1.0 (0.6-1.9)	0.653
Platelet, x10^3/mL	228.5 (190.0-289.2)	228.0 (165.2-287.7)	0.860
MPV, fL	10.5 ± 0.9	10.2 ± 1.1	0.201
MCV, fL	87.4 ± 8.3	87.8 ± 11.5	0.862
RDW, %	15.2 ± 2.7	15.5 ± 2.1	0.586
Procalcitonin, ng/ml	0.2 (0.06-0.8)	0.1 (0.01-0.5)	0.612
Ferritin, mg/L	323.0 (92.0-496.0)	452.0 (180.5-857.0)	**0.041**
D-dimer, ng/ mL	0.8 (0.5-2.2)	1.9 (0.6-4.1)	0.109
CORADS, % *Uncertain (corads 3)* *High suspect (corads 4)* *Very high suspicious (corads 5)*	 16 (47) 9 (26.5) 9 (26.5)	 27 (61.3) 11 (25) 6 (13.6)	0.306

ALT*, alanine aminotransferase;* ***AST****, aspartate aminotransferase;* ***LDH****, lactat dehydrogenase;* ***CRP****, C-reactive protein;* ***WBC****, white blood cell;* ***MCV****, mean corpuscular volume;* ***MPV****, mean platelet volume;* ***RDW****, red cell distribution width;* ***CO-RADS****, COVID-19 Reporting and Data System.*

Table 4. *Respiratory panel results of nasopharyngeal swab samples*

RESPIRATORY PANEL	PATIENTS (n=78)
Reproductive *Non-reproductive*	44 (56.4) 34 (43.6)
SARS CoV 2, %	3 (3.8)
Influenza A, %	8 (10.3)
Coronavirus HKU1, %	1 (1.3)
Coronavirus OC43, %	3 (3.8)
Parainfluenza, %	8 (10.3)
Haemophilus influenzae, %	15 (19.2)
Streptococcus pneumonia, %	16 (20.5)
Respiratory syncytial virus, %	4 (5.1)
Pseudomonas spp, %	1 (1.3)
Rhinovirus, %	2 (2.6)

3. RESULTS

A total of 78 patients consisting of 40 women and 38 men were included in the study. Demographic and comorbidity data between the groups were compared in Table 2. There was no significant difference between the two groups in terms of age and sex. The most common comorbidities were coronary arterial disease (CAD), hypertension (HT) and diabetes mellitus (DM), respectively.

Table 3 shows the laboratory and radiological data of two groups. C-reactive protein (CRP) and ferritin levels were found to be statistically significantly higher in the group with growth on the respiratory panel compared to the group without growth (p= .05, p= .041, respectively). More than half of the patients were radiologically defined as CO-RADS 3.

SARS CoV-2 was detected in the second nasopharyngeal swab sample in three patients (3.8%). Reproduction was detected in nasopharyngeal swab samples taken in 56.4% of the patients. In the remaining patients, the most frequently detected microorganisms were *streptococcus pneumonia* (20.5%), *hemophilus influenza* (19.2%), *parainfluenza* (10.3%) and *influenza A* (10.3%), respectively (Table 4).

Nasopharyngeal swab results are compared according to the radiological classification of the patients. There was growth in nasopharyngeal swab samples at a rate of 62.7% in the CO-RADS 3 (n=43) group, 55% in the CO-RADS 4 (n=20) group, and 40% in the CO-RADS 5 (n=15) group. SARS CoV-2 growth occurred in only one patient in each of the three groups. Among the microorganisms that grow in all groups, the most frequently detected *Streptococcus pneumonia*, *Hemophilus influenzae*, *İnfluenza A*, respectively.

4. DISCUSSION

In this study, different viral and bacterial microorganisms were determined in repeated PCR examinations conducted via nasopharyngeal swabs from COVID-19 infection-suspected patients with PCR (-) results during the flu season. The clinical picture of the COVID-19 infection, which has caused a pandemic all over the world for about two years, can imitate those of different viral and bacterial infections, especially during the seasonal flu period. Usually during the winter months, the variation patterns peak in most of the viruses, causing epidemics (15). The best-known respiratory viruses are *parainfluenza 1, parainfluenza 2, parainfluenza 3, adenovirus, rhinovirus, influenza A, influenza B, respiratory syncytial virus, coronavirus, human metapneumovirus,* and *human bocavirus* (16,17). Furthermore, viral infections can damage the respiratory epithelium, facilitating the development of bacterial infections. Some laboratory parameters play a role in the clinical diagnosis and follow-up of many viral and bacterial infections, including SARS CoV-2 (2,18,19). CRP and ferritin are the most important acute phase reactants. Ferritin and CRP levels are increased in acute or chronic inflammatory diseases characterized by tissue damage and repair (20). In many studies, it has been shown that there is a significant increase in serum ferritin and CRP levels in bacterial and viral infections (21-23). CRP and ferritin levels were found to be significantly higher in our patients with growth on the respiratory panel. Also, many studies have shown that patients with viral and bacterial pneumonia have common comorbidities, similar to patient with COVID-19. The most common comorbidities are HT, DM, Congestive heart failure (CHF) and COPD (24-26). Similarly, in our study, the most common comorbidities in patients with growth on the respiratory panel were CAD, HT, and DM.

Nasopharyngeal swab RT-PCR result is used as the gold standard method in the diagnosis of COVID-19 disease. Although the sensitivity of the RT-PCR test is 89% and the specificity is 100%, the test result may be (-) due to different reasons (delays before arrival at the laboratory or poor storage conditions, lack of standardization for sample collection, use of insufficiently validated assays, insufficient viral samples and load, presence of mutations that escape PCR inhibitors etc.) (27). In one study, it was emphasized that up to 54% of COVID-19 patients had a false-negative RT-PCR result at baseline, and therefore, RT-PCR tests should be repeated in these patients with suspected SARS-CoV-2 infection (28). In our study, SARS CoV-2 was detected only in 3.8% (n=3) of the patients in the PCR analysis of the nasopharyngeal swab samples taken for the second time. We can say that the reason for this low value in our study is the infections caused by other respiratory viral and bacterial factors related to the winter and flu seasons.

The most common symptoms in SARS-CoV-2 pneumonia are shortness of breath, cough, fatigue, fever and muscle aches (5-7). While the most common symptoms associated with bacterial pneumonias are cough, sputum, and chest pain; In viral pneumonias, fever, myalgia, cough and shortness of breath are more prominent (29). Both bacterial and viral microorganisms were grown in the nasopharyngeal swap swab samples of the patients in our study. The most frequently observed ones were *Streptococcus pneumonia*, *Hemophilus influenzae*, *Influenza A* and *Parainfluenza 3*, respectively.

Similar to literature data, the main symptoms seen in study patients were fever, cough, dyspnea, and myalgia.

Chest CT is a routinely used test for the diagnosis of pneumonia. Therefore, it has been stated that it can also be used for the diagnosis of COVID-19 (30). The most common CT abnormalities observed in COVID-19 patients are ground-glass opacities (GGO), consolidation, and interlobular septal thickening (31,32). While some studies stated that COVID-19 patients had high and/or very high probability radiological findings in Chest CT scans, other studies emphasized that they might have similar radiological findings with different viral pneumonias, and therefore Chest CT scans were considered to have low specificity (33). Therefore, in this period when we are in the process of pandemic, nasopharyngeal/throat swab examination should be performed in patients with Chest CT that is radiologically interpreted as CO-RADS ≥ 3 during the flu season and winter months (34). In our study, different viral and bacterial microorganisms other than SARS CoV-2 were detected in the nasopharyngeal/throat swab sample of more than half of the patients. Chest CT of these patients commonly had GGO and consolidation appearances.

In this study conducted during the pandemic, we showed that lower respiratory tract infection caused by different viral and bacterial agents is similar to COVID-19 infection in terms of both radiological, clinical and laboratory features.

There are some limitations of our study. In this single-center and retrospective study, the absence of cases under the age of 18, the insufficiency of long-term follow-up information of the patients and the lack of recorded information about the time between the onset of symptoms and the application of the respiratory panel test are the limitations of our study.

5. CONCLUSION

Especially during the flu season, the nasopharyngeal swab respiratory panel test is an important diagnostic test recommended for COVID-19-suspected patients with a PCR (-) result. It should not be forgotten that other respiratory tract viral and bacterial infections are also commonly observed during this period.

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Research idea: IH, LK
Design of the study: IH
Acquisition of data for the study: IH, FG
Analysis of data for the study: IH
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Drafting the manuscript: IH, FG
Revising it critically for important intellectual content: IH, LK
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