Turk Thorac J 2021; 22(3): 247-250 DOI: 10.5152/TurkThoracJ.2021.20284

Original Article

Clinical Outcome of PCR-Negative COVID-19 Patients: A Retrospective Study

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Cite this article as: Sayiner A, Sezai Tasbakan M, Ergan B, *et al*. Clinical outcome of PCR-negative COVID-19 patients: A retrospective study. *Turk Thorac J.* 2021; 22(3): 247-250.

Abstract

OBJECTIVE: To evaluate the clinical features and outcomes of patients who were admitted with a diagnosis of coronavirus disease 2019 (COVID-19) but who were not confirmed with polymerase chain reaction (PCR) positivity.

MATERIAL AND METHODS: This is a retrospective analysis of all patients admitted to two tertiary care centers between March 15 and May 15, 2020, with a diagnosis of COVID-19. From a common database prepared for COVID-19, we retrieved the relevant data and compared the clinical findings and outcomes of PCR-positive patients with those of PCR-negative cases who had been diagnosed on the basis of typical clinical and radiographic findings.

RESULTS: A total of 349 patients were included in the analysis, of which 126 (36.1%) were PCR-negative. PCR-negative patients were younger (54.6 ± 20.8 vs. 60.8 ± 18.9 years, $P = .009$) but were similar to PCR-positive patients in terms of demographics, comorbidities, and presenting symptoms. They had higher lymphocyte counts (1519 ± 868 vs. 1331 ± 737/mm^3, $P = .02$) and less frequently presented with bilateral radiographic findings (68.3% vs. 79.4%, $P = .046$) than PCR-positive patients. Besides, they had less severe disease and better clinical outcomes regarding admission to the intensive care unit (9.6% vs. 20.6%, $P = .023$), oxygen therapy (21.4% vs. 43.5%, $P < .001$), ventilatory support (3.2% vs. 11.2%, $P = .03$) and length of hospital stay (5.0 ± 5.0 vs. 9.7 ± 5.9 days, $P < .001$).

CONCLUSION: This study confirms that about one-third of the COVID-19 patients are PCR-negative and diagnosed based on clinical and radiographic findings. These patients have a more favorable clinical course, shorter hospital stays, and are less frequently admitted to the intensive care unit.

KEYWORDS: COVID-19, diagnosis, polymerase chain reaction, outcome
Received: *November 19, 2020* ***Accepted:*** *April 1, 2021*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) poses a critical problem to the clinicians in that the golden standard for the diagnosis, reverse transcriptase-polymerase chain reaction (RT-PCR), has a relatively low diagnostic yield (63% in nasopharyngeal swabs).[1] Thus, the physicians treat a group of patients who are present with clinical and radiographic features suggestive of COVID-19 but who are polymerase chain reaction (PCR)-negative. Several guidelines recommend such patients be managed similarly to the PCR-positive patients.[2,3] On the other hand, studies reporting on the clinical features of COVID-19 patients have only included PCR-confirmed cases.[4-6] This is an underrepresentation of real life. This study, thus, aimed to determine whether PCR-negative patients have similar clinical features to PCR-positive patients, that is, whether the clinical diagnosis is valid and to compare the clinical outcomes of these two groups of patients (i.e., to evaluate whether this clinical approach to management is associated with any adverse outcomes).

MATERIAL AND METHODS

All patients admitted to two university hospitals with a diagnosis of COVID-19 pneumonia were included in this retrospective analysis. The diagnosis was either confirmed with PCR or when PCR was negative. It was clinically made based on the presence of relevant symptoms and radiographic findings suggestive of COVID-19 (predominantly peripheral ground-glass opacities at lower lung zones). The latter patients were managed similarly to the definite cases, as per the national guideline.[7] Treatments were given at the discretion of the attending physicians and included hydroxychloroquine and/or favipiravir or supportive care.

The primary endpoint was admission to the intensive care unit. The secondary endpoints were in-hospital mortality and the length of hospital stay. Besides, we also examined other clinically relevant endpoints, namely time to defervescence,

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need for anticoagulant and anti-inflammatory treatments (systemic steroids, tocilizumab), and need for supplemental oxygen and mechanical ventilation.

All relevant demographic, clinical, laboratory, radiographic (computerized tomography—CT—of the chest was performed in all patients) findings, and data on clinical course and outcome were recorded in a database and retrieved and analyzed in order to find answers to specific clinical problems related to COVID-19. For this study, comparisons were made between PCR-positive and -negative patients.

Nasopharyngeal swabs were obtained from all patients for RT-PCR analysis. Up to a total of three samples were analyzed at least 24 hours apart when the first sample was negative. Severe acute respiratory syndrome coronavirus 2 ribonucleic acid (SARS-CoV-2 RNA) was detected by a commercial quantitative reverse transcription PCR (RT-qPCR) assay provided by the Ministry of Health.

The database included parameters involving radiographic findings obtained from chest X-ray and/or CT scan. For practical reasons, the recorded findings were limited to a qualitative assessment of the images that is, unilateral versus bilateral involvement and presence of consolidation, patchy infiltrates, and ground-glass opacities.

As arterial blood gas analysis was not performed in all patients, oxygen saturation measured with pulse oximetry (SpO_2) was recorded. In order to correct for the supplemental oxygen, SpO_2/FiO_2 was used for analysis.

The study was approved by the local ethics committee (approval number: 20-5T/48).

Statistical Analysis

The Statistical Package for Social Sciences version 20.0 software (IBM Corp.; Armonk, NY, USA). Categorical variables are reported as frequency and percentages and continuous variables as mean ± standard deviation (SD). Means for continuous variables were compared using *t*-test for independent groups when the data were normally distributed; otherwise, the Mann–Whitney *U*-test was used, and the chi-square test was used for categorical variables. We considered $P < .05$ as statistically significant.

RESULTS

The hospital records of 395 patients admitted for COVID-19 between March 15 and May 15, 2020 were retrospectively evaluated. Forty-six patients had missing data in the records and were excluded. Of the remaining 349 patients (mean age 58.5 ± 19.8 years, 177 females), 223 (63.9%) and 126 (36.1%) had PCR-positive and -negative disease, respectively.

Table 1. Laboratory and Radiographic Findings at Admission

	PCR-Positive ($n = 223$)	PCR-Negative ($n = 126$)	*P*
Lymphocyte count/mm^3	1331 ± 737	1519 ± 868	.02
CRP, mg/dL	56.2 ± 58.0	69.9 ± 79.5	.28
Ferritin, µg/L	451 ± 727	236 ± 250	.08
D-dimer, µg/mL FEU	1270 ± 2823	1945 ± 5186	.28
LDH, U/L	295 ± 180	276 ± 126	.90
Creatinine, mg/dL	1.00 ± 0.70	1.04 ± 0.73	.98
AST, U/L	38.5 ± 61.3	35.2 ± 30.2	.39
ALT, U/L	30.3 ± 33.9	32.3 ± 37.2	.44
SpO_2/FiO_2	412.3 ± 83.1	425.1 ± 71.5	.07
HRCT findings			
Bilateral involvement, *n* (%)	177 (79.4)	86 (68.3)	.046
Ground glass opacities, *n* (%)	192 (86.1)	109 (86.5)	.92
Consolidation, *n* (%)	94 (42.2)	54 (42.9)	.68
Patchy infiltrates, *n* (%)	34 (15.2)	14 (11.1)	.51

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; HRCT, high-resolution computed tomography; LDH, lactate dehydrogenase; PCT, procalcitonin; SpO_2, oxygen saturation as measured by pulse oximetry.

Regarding the clinical presentation, PCR-negative patients were younger (54.6 ± 20.8 vs. 60.8 ± 18.9 years, $P = .009$) but were otherwise similar to PCR-positive patients in terms of gender, smoking history, presence of comorbidities (54.0% vs. 65.9%, $P = .064$), and immunosuppression (10.3% vs. 6.7%, $P = .47$). They also presented with similar symptoms, and the duration of symptoms prior to admission was similar (5.4 ± 4.9 vs. 6.6 ± 8.4 days, $P = .50$). On the other hand, they had less severe disease with higher lymphocyte counts and less frequently presented with bilateral radiographic involvement (Table 1). The ferritin and O_2sat/FiO_2 levels also tended to be lower but did not reach significance.

With regards to clinical outcomes, there was a significant difference in the primary endpoint, namely PCR-negative patients were less likely to be admitted to the intensive care unit. They also had a shorter length of hospital stay but no difference in the rates of in-hospital mortality was detected. All clinical outcomes are shown in Table 2.

Main Points

- One-third of the COVID-19 patients are PCR-negative and diagnosed based on clinical and radiographic findings.
- They have less severe disease than PCR-positive patients.
- These patients have a more favorable clinical outcome.

DISCUSSION

This study showed that PCR-negative patients who were admitted to the hospital with a clinical diagnosis of COVID-19 pneumonia had similar clinical features but better outcomes compared with PCR-positive patients. This may have two explanations. First, PCR-negative patients may actually

Table 2. Clinical Outcome of the Patients

	PCR-Positive (*n* = 223)	PCR-Negative (*n* = 126)	*P*
Time to defervescence, days	4.3 ± 3.3	1.9 ± 1.6	.02
Tocilizumab treatment, *n* (%)	19 (8.5)	0	.003
Anticoagulant treatment, *n* (%)	136 (61.0)	52 (41.3)	.001
Systemic glucocorticoid treatment, *n* (%)	21 (9.4)	11 (8.7)	.93
Admission to the ICU, *n* (%)	46 (20.6)	12 (9.6)	.023
Supplemental oxygen, *n* (%)*	97 (43.5)	27 (21.4)	<.001
Non-invasive ventilation, *n* (%)**	25 (11.2)	4 (3.2)	.03
Invasive ventilation, *n* (%)	25 (11.2)	10 (7.9)	.59
Length of hospital stay, days	9.7 ± 5.9	5.0 ± 5.0	<.001
In-hospital mortality, *n* (%)	27 (12.1)	13 (10.3)	.83

*This refers to the need for supplemental oxygen any time during the hospitalization. The numbers include the patients who also required invasive and/or non-invasive ventilation.
**Patients requiring non-invasive ventilation first, who then had to be intubated and received invasive ventilation, were counted as "invasive ventilation" only.

have been infected with other respiratory viruses with similar clinical presentations. Unfortunately, due to the pandemic, the microbiology laboratories had to concentrate their efforts on the diagnosis of SARS-CoV-2 infection and to temporarily stop testing for other respiratory viruses. However, because the study period witnessed the peak of COVID-19 activity and the clinical findings were highly suggestive, the probability of COVID-19 was high. Besides, the clinical and radiographic findings were similar to previous reports of PCR-confirmed COVID-19 cases,[4-6,8,9] whereas there is no evidence that significant differences exist in high-resolution computed tomography (HRCT) findings between COVID-19 patients and those infected with other respiratory viruses.[10]

The more likely explanation is possibly related to the viral load. A low viral load is associated with a lower likelihood of the PCR test to identify the pathogen and a weaker inflammatory reaction with lower levels of serum biomarkers. A lower rate of viral replication and a weak inflammatory response would be expected to result in milder disease, which, in turn, is expected to be associated with better clinical outcomes.[11]

The main limitation of the study is that PCR negativity may have just been due to inappropriate sampling, problems in transferring to the laboratory, and low sensitivity of the RT-PCR kit.[12] This, however, is unlikely to have altered the findings, as up to three consecutive samples were analyzed with PCR if the first nasopharyngeal swab sample was found to be negative. Besides, these technical issues would not explain the differences in clinical outcomes between the two groups.

This study thus confirms previous observations that there are a substantial group of clinically diagnosed PCR-negative COVID-19 patients. The findings also indicate that PCR (–) unconfirmed patients have a more favorable clinical course and outcome. Thus, in circumstances where the microbiologic diagnosis is not made, management based on a clinical diagnosis of COVID-19 does not lead to any concerning adverse outcomes.

Ethics Committee Approval: This study was approved by Ethics committee of Ege University, (Approval No: 20-5T/48).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – A.S., B.E., O.K; Design – A.S., B.E., O.K., R.S.; Supervision – A.S., B.E., O.K.; Materials – A.S., R.S.; Data Collection and/or Processing – A.S., A.S., B.E., O.K., M.S.T., S.O., S.E., Y.S., P.K.E., O.K.B., M.H.O.; Analysis and/or Interpretation – M.S.T. A.S., A.S., B.E., O.K., O.K.B., M.H.O.; Literature Search – A.S., S.O., S.E., Y.S., P.K.E.; Writing Manuscript – A.S.; Critical Review – A.S., M.S.T., B.E., O.K., A.S., R.S.

Acknowledgments: Thank you for their contributions. İzmir COVID Study Group: Aylin O. Alpaydın, Fırat Bayraktar, Caner Çavdar, Gürsel Cok, Münevver Erdinc, Özlem Göksel, Tuncay Göksel, Alev Gurgun, Ziya Kuruuzum, Nesrin Mogulkoc, Can Sevinc, Gökcen O. Simsek, Müjde Soytürk, Kemal C. Tertemiz.

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

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

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