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Is Polymerase Chain Reaction Positivity More Common in Patients with COVID-19 Pneumonia with Fever?

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Keywords
COVID-19 · Fever · Polymerase chain reaction · Sensitivity · Specificity

Abstract

Introduction: There is conflicting data about the rate of fever at admission and during hospitalization in COVID-19 pneumonia. We analyzed the rate of fever in our patients to find the diagnostic value of fever and to predict PCR status in COVID-19. ***Methods:*** It was a retrospective cross-sectional study conducted in the Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, which was a tertiary chest diseases pandemic hospital in İzmir. We included 389 patients hospitalized for COVID-19 and analyzed them according to PCR status and presence of fever. Fever was defined as temperature over 38°C. ***Results:*** Thirty-eight percentage of our patients complained of fever before admission. However, when they were admitted, only 13.6% of them had objective high fever. 26.5% had high fever during hospital stay. PCR-positive patients had less comorbidity. More of PCR-positive patients had fever in the course of hospitalization and their length of hospital stay was longer and mortality was higher. Although we expected to find a high sensitivity, the sensitivity of high fever in our settings was low. Sensitivity, specificity, positive, and negative predictive values of high fever at admission in predicting the positivity of the PCR test were 16.9%, 90.6%, 69.8%, and 45.8%, respectively. Sensitivity, specificity, positive, and negative predictive values of high fever during hospitalization to predict the positivity of PCR test were 36.1%, 85.9%, 76.7%, and 51.0%, respectively. ***Conclusion:*** 13.6% of our COVID-19 patients had objective high fever at admission. 26.5% had high fever during hospital stay. PCR-positive patients had less comorbidity. More PCR-positive patients had fever in the course of hospitalization and their length of hospital stay was longer and mortality was higher. Although we expected to find a high sensitivity, the sensitivity of high fever in our settings was lower than expected. Temperatures <38°C at admission and during hospitalization determine 90.6% and 85.9% of the PCR-negative patients, respectively. These high specificity values imply that if the PCR test is negative, the patient's temperature is more likely to be lower than 38°C.

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Introduction

COVID-19 emerged in China, in December 2019, and the WHO announced it as a pandemic on March 11, 2020 [1]. First confirmed case of COVID-19 in Turkey was reported on the same day [2].

Cough, myalgias, and headache are the most common reported symptoms among patients with symptomatic COVID-19. Pneumonia is the most frequent manifestation, and patients have fever, cough, dyspnea, and bilateral pulmonary infiltrates. But these symptoms and signs can be seen in pneumonias other than COVID-19 [1].

Fever is a common symptom which is monitored very often in everyday practice for COVID-19. It is necessary to have more information about fever and its diagnostic value. There is conflicting data about the rate of fever at admission and in hospital. Early studies from China report fever in 43.8% of patients at admission but 88.7% of them have fever during hospitalization [3]. A study from New York reports the rate of fever at triage to be 30.7% [4]. The incidence of fever differs due to the group of patients studied.

It is necessary to use some clinical features to predict PCR-positive COVID-19 patients in places with limited facilities or in patient triage. Fever may be an easy tool which helps us to predict PCR positivity of COVID-19 suspected patients. We examined the rate of fever in our patients and diagnostic value of high fever (≥38°C) to predict PCR positivity.

Materials and Methods

The study was a retrospective cross-sectional study. It was conducted in the Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, which was a tertiary chest diseases pandemic hospital in Izmir, Turkey. We included all patients who were hospitalized for COVID-19 pneumonia and severe acute respiratory infection. They were treated for COVID-19 pneumonia according to the National COVID-19 Treatment Guideline which was compatible with the WHO COVID-19 guidelines [1, 2].

Study Population

We studied consecutive 389 patients with COVID-19 pneumonia who were internalized in all of our pandemics clinics in 11 March–15 May 2020 period. We used the same COVID-19 case definitions and hospitalization criteria WHO proposed [1, 2]. Thorax CT was used as a diagnostic tool in PCR-negative patients.

Laboratory Testing Methods

PCR Testing: Respiratory (oropharingeal and/or nasal) swabs of all patients were analyzed in Public Health Department Microbiology Reference Laboratories for COVID-19. Verification of COVID-19 was done by nucleic acid amplification test which was real-time polimerase chain reaction (rRT- PCR) test and specific sequences were determined. Results were reported as "positive" if COVID-19 sequence was confirmed. If first PCR test was negative, serial tests were taken 24 h apart (total of three swabs).

Table 1. Demographic data and clinical characteristics (*n* = 389)

Age, years (mean ± SD)	52.1±15.2
Gender	
Female, *n* (%)	165 (42)
Male, *n* (%)	224 (58)
Comorbidity, *n* (%)	193 (49.6)
Smoking history (*n* = 299), *n* (%)	
Nonsmoker	174 (58.2)
Ex-smoker	74 (24.7)
Smoker	51 (17.1)
Fever complaint before admission, *n* (%)	
Yes	148 (38.0)
No	241 (62.0)
Fever at triage, *n* (%)	
Yes	53 (13.6)
No	336 (86.4)
Fever during hospitalization, *n* (%)	
Yes	103 (26.5)
No	286 (73.5)
Course of fever during hospitalization, *n* (%)	
(at admission/in hospital)	
Fever (–)/fever (–)	286 (73.5)
Fever (–)/fever (+)	50 (12.9)
Fever (+)/fever (+)	26 (6.7)
Fever (+)/fever (–)	27 (6.9)
COVID-19 PCR status, *n* (%)	
Negative	170 (43.7)
Positive	219 (56.3)
C-reactive protein	16.6 (0.0–377.5)
Chest X-ray, *n* (%)	
Normal	122 (31.4)
Unilateral lesion	94 (24.2)
Bilateral lesion	173 (44.5)
Positive CT findings (*n* = 378)	362 (95.8)
Mean length of hospital stay,	
days (mean ± SD)	8.9±0.4
Outcome, *n* (%)	
Survival	370 (95.1)
Mortality	19 (4.9)
Leukocyte, *n*	7,594.3 (2,600–31,900)
Neutrophil, *n*	5,485.2 (400–30,300)
Neutrophil, %	69.4 (26.3–98.1)
Lymphocyte, *n*	1,385.0 (100–9,600)
Lymphocyte, %	21.0 (1.2–55.8)
Monocyte, *n*	634.1 (0–8,600)
Monocyte, %	8.2 (0.5–24.8)
Hemoglobin, g/dL	13.2 (7.8–17.7)
Platelets	253,172.2 (45,000–840,000)

PCR, polymerase chain reaction; CT, computerized tomography.

Table 2. Comparison of demographic and clinical parameters depending on PCR status

	PCR negative (n = 170)	PCR positive (n = 219)	p value
Age, years (mean±SD)	53.8±15.7	50.8±14.7	0.051
Gender, *n* (%)			
Male	99 (58.2)	125 (57.1)	0.819
Female	71 (41.8)	94 (42.9)	
Comorbidity, *n* (%)	99 (60.0)	94 (43.3)	0.001
Fever complaint before admission, *n* (%)			
Yes	63 (37.1)	85 (38.8)	0.724
No	107 (62.9)	134 (61.2)	
Fever at triage, *n* (%)			
Yes	16 (9.4)	37 (16.9)	0.033
No	154 (90.6)	182 (83.1)	
Fever during hospitalization, *n* (%)			
Yes	24 (14.1)	79 (36.1)	<0.001
No	146 (85.9)	140 (63.9)	
Course of fever during hospitalization, *n* (%) (at admission/in the hospital)			
Fever (–)/fever (–)	146 (51.0)	140 (49.0)	<0.001
Fever (–)/fever (+)	8 (16.0)	42 (84.0)	
Fever (+)/fever (+)	5 (19.2)	21 (80.8)	
Fever (+)/fever (–)	11 (40.7)	16 (59.3)	
C-reactive protein	5.0 (0.03–377.5)	3.9 (0.0–340.5)	0.235
Chest X-ray, *n* (%)			
Normal	46 (27.1)	76 (34.7)	0.175
Unilateral	40 (23.5)	54 (24.7)	
Bilateral	84 (49.4)	89 (40.6)	
Positive CT findings (n = 378)	168 (99.4)	194 (92.8)	0.002
Length of hospital stay, days	5 (1–38)	8 (1–53)	<0.001
Outcome			
Survival	167 (98.2)	203 (92.7)	0.012
Mortality	3 (1.8)	16 (7.3)	
Leukocyte	7,900 (2,700–30,900)	5,800 (2,600–31,900)	<0.001
Neutrophil	5,300 (400–30,300)	3,800 (1,100–28,000)	<0.001
Neutrophil, %	7.0 (26.3–98.1)	69.1 (34.5–96.2)	0.011
Lymphocyte	1,400 (200–9,600)	1,100 (100–5,500)	0.006
Lymphocyte, %	18.4 (1.2–44.0)	21.3 (2.7–55.8)	0.062
Monocyte	600 (100–4,000)	500 (0–8,600)	0.007
Monocyte, %	7.4 (0.7–16.4)	8.2 (0.5–24.8)	0.017
Hemoglobin	13.1 (7.8–17.7)	13.3 (8.1–17.3)	0.198
Platelets	261,000 (81,000–688,000)	209,000 (45,000–840,000)	<0.001

PCR, polymerase chain reaction; CT, computerized tomography.

"Fever" was defined as temperature ≥38°C. We measured temperatures by using infrared thermometers (Model QN-100 MCM Healthcare) and recorded temperatures at admission and during hospital stay. We recorded the highest fever measures of each day.

Inclusion Criteria and Analyzed Criteria

All patients were over 18 years old. Demographic data, highest temperature measurements of each day, PCR results, comorbidities, total duration of hospital stay, and in-hospital mortality were recorded in a standardized database. Temperature values at admission and during hospital stay were recorded. Fever values before admission were not recorded as they were not measured by the same thermometer and the expressed values would not be reliable.

Statistical Analysis

Analyses were done with SPSS software version 25.5 (IBM, Armonk, NY, USA). Shapiro-Wilk and Kolmogorov-Smirnov normality tests were used to check whether continuous variables show normal distribution or not. When comparing PCR-negative and PCR-positive patients, the Mann-Whitney U test was used to compare parameters that were not normally distributed, and Student's t test was used to compare the normally distributed variables and χ^2 and Fisher's exact test were used for comparison of categorical

Table 3. Risk of PCR positivity of patients with high fever at admission and during hospitalization

	OR	95% CI	*p* value	Sensitivity	Specificity	PPV	NPV
Fever at admission, %							
Fever (+) versus fever (–)	1.95	1.05–3.65	0.033	16.9	90.6	69.8	45.8
Fever during hospital stay, %							
Fever (+) versus fever (–)	3.43	2.06–5.73	<0.001	36.1	85.9	76.7	51.0

data. Results were given as median (min-max), mean ± SD, number, and percentage (%). Sensitivity, specificity, positive, and negative predictive values of high fever was calculated using SPSS cross-tabulation formulas to predict the positivity of the PCR test of COVID-19. Results were given as mean median (min-max), number, and percentage (%). p value <0.05 was considered statistically significant. The study was approved by the Scientific Research and Thesis Evaluation Board of Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital (EPK No.: 12.06.2020/10/20).

Results

389 patients were hospitalized in the wards with COVID-19 pneumonia. Their demographic data and clinical characteristics were presented in Table 1. Mean age of the patients was 52.1 ± 15.2 years. Fifty-eight percent of the patients were men and about half of the patients (49.6%) had a comorbidity. 38% of the patients reported fever complaint before admission; however, only 13.6% had measured temperature over 38°C. 103 (26.5%) patients had fever during hospitalization. 219 (56.3%) patients were PCR positive. 170 (43.7%) were PCR negative and they were diagnosed by clinical and radiological features. Patients with COVID-19 pneumonia were compared according to their PCR status and their characteristics were presented in Table 2.

Temperature characteristics of the patients were examined according to their PCR status and were presented in Table 2. The complaint of fever before admission to the hospital did not differ between PCR-negative (number of patients: 63, percentage: 37.1%) and PCR-positive (number of patients: 85, percentage 38.8%) patients ($p = 0.72$). Fever rate was higher (number of patients: 37, percentage 16.9%) in PCR-positive patients in triage (number of PCR-negative patients: 16, percentage 9.4%) ($p = 0.033$). A higher rate of fever was detected in PCR-positive patients (number of patients: 79, percentage 36.1%) during hospitalization (number of PCR-negative patients: 24, percentage 14.1%) ($p < 0.001$). PCR positivity was higher in patients with fever at admission and during hospitalization. The risks of PCR positivity of patients with high fever at admission and during hospitalization are presented in Table 3.

Fever at Admission

Sensitivity, specificity, positive predictive, and negative predictive values of high fever at admission in predicting the positivity of the PCR test were 16.9%, 90.6%, 69.8%, and 45.8%, respectively (Table 3). The patients with high fever at admission had the odds of having PCR-positive results 1.95 times (OR = 1.95; 95% CI: 1.05–3.65; $p = 0.033$) more when compared with the patients without fever (Table 3).

Fever during Hospitalization

Sensitivity, specificity, positive predictive, and negative predictive values of high fever during hospitalization in predicting the positivity of the PCR test were 36.1%, 85.9%, 76.7%, and 51.0%, respectively (Table 3). The patients with high fever during hospitalization had the odds of having PCR-positive results 3.43 times (OR = 3.43; 95% CI: 2.06–5.73; $p < 0.001$) more when compared with the patients without fever (Table 3).

Discussion

Although 38% of our COVID-19 pneumonia patients complained of fever, only 13.6% of them had objective high fever at admission. 26.5% of our patients had high fever during hospitalization. Sensitivity, specificity, positive predictive, and negative predictive values of high fever at admission in predicting the positivity of PCR test were 16.9%, 90.6%, 69.8%, and 45.8%, respectively. Sensitivity, specificity, positive predictive, and negative predictive values of high fever during hospitalization period in predicting the positivity of PCR test were 36.1%, 85.9%, 76.7%, and 51.0%, respectively. These high specificity values imply that if the PCR test was negative, the patient's temperature was more

likely to be lower than 38°C. The patients with high fever at admission and during hospitalization had the odds of having PCR-positive results 1.95 and 3.43 times more, respectively, when compared with the patients without fever. However, sensitivity of high fever was low. PCR-positive patients had less comorbidity. More PCR-positive patients had fever in the course of hospitalization and their length of hospital stay was longer and mortality was higher.

The critical clinical presentation of COVID-19 is pneumonia. It usually presents with fever, cough, and dyspnea. Fever is found in various ratios in different studies. Notably, fever is not a universal finding on presentation, even among hospitalized cohorts. First case series from China report that almost all patients (respectively, 98% and 98.6%) report fever but only measured high fever over 38°C is seen in 20% [5, 6]. Fever is reported in 43.6% at admission and in 88.7% during hospitalization [5, 6]. A study from New York shows that 30.7% of patients at triage report fever; and another study from Detroit show that 68% of patients who admit to hospital and are hospitalized have fever [4, 7]. In a case surveillance study from the USA, 43% have subjective or measured fever over 38°C [8]. In UK, fever is reported in 71.6% of inpatients [9]. The differences in the rates of fever may be due to several reasons. Each of these studies gives the rates in different patient groups and there is limited information about the fever measurements of these patients. In our study, 38% of our patients complained of fever before admission. This value is similar to the case surveillance study from the USA [8]. Only 13.6% of our patients had measured high fever at admission. Even during hospital stay, only 26.5% of our patients had high fever. These values were much lower than previous studies. In previous studies, data may have been recorded on the basis of patients' statements. The difference may be due to over-reporting of fever by the patients or due to sub febrile fever (lower than 38°C). Another reason of high rate seen in some studies may be due to the high fever limit being determined as 37.5°C.

There are various reasons of fever in COVID-19. Some patients with severe COVID-19 develop exuberant inflammatory response during the course of the disease. These patients have persistent fevers, and elevations in inflammatory markers such as D-dimer and ferritin and proinflammatory cytokines. This clinical course and laboratory abnormalities have been associated with critical and fatal disease [5, 10]. These features are linked to cytokine release syndrome, but proinflammatory cytokines in COVID-19 are lower than levels seen in sepsis. Patients with cytokine storm usually need intensive care. Our study group consisted of COVID-19 patients hospitalized in patient wards, and patients in intensive care unit were not included. As duration of hospital stay increases, the risk of hospital-acquired secondary infections may increase. Although data are limited, secondary infections are not common in COVID-19 pneumonia [11, 12]. Only 8% of the patients with COVID-19 pneumonia are reported to have bacterial or fungal coinfections. In one prospective study from Italy with COVID-19 patients on mechanical ventilation, 28% have probable aspergillosis [13]. This probable diagnosis is based on serum or bronchoalveolar lavage galactomannan levels, growth of *Aspergillus* on BAL cultures, or a cavitary infiltrate without other cause. Also cases of mucormycosis are reported from India [14]. Overall prevalence of mucormycosis patients is reported to be 0.27%. Our patients were moderate patients and mucormycosis usually occur in patients hospitalized for a longer duration (mean 15.6 days). The mean hospital stay of our patients was 8.9 days.

COVID-19 is diagnosed primarily by detection of severe acute respiratory syndrome coronavirus (SARS-CoV-2) RNA by nucleic acid amplification tests from upper respiratory tract [1]. Nucleic acid amplification tests are highly specific [15, 16]. Although PCR tests have high sensitivity in ideal setting, their clinical performance is variable. False-positive results are rare but have been reported [17]. False negative tests are more common; false-negative rates ranges from 5 to 40% [18, 19]. In clinical reality, false negative test rates are decreased by serial testing in COVID-19 probable cases. Sensitivity of testing depends on the type and quality of the specimen, the site of specimen collection, the viral load, the phase of illness at the time of testing, and the type of assay. Our swabs were taken from oropharynx and nasopharynx; but the intolerance of the patient and technical problems might result in false-negative results. In acute and/or convalescence phase of the disease, the detection rate of virus in the upper respiratory tract is higher, while the virus can be found at a lower rate in the upper respiratory tract as the disease progresses. Since we did not have records about how many days the patients had had complaints, it was not clear at what stage the disease was. Respiratory swabs of all of our patients were analyzed in Izmir Tepecik Hospital Public Health Department Microbiology Reference Laboratory, which was a reference laboratory with nationally accepted standards.

Although the PCR method used to diagnose COVID-19 has some shortcomings, it is still accepted as the gold standard diagnostic test. Our aim was to find the diagnostic value of fever to predict PCR status in COVID-19. We used of RT-PCR as the reference standard test and assessed the performance of high fever in the diagnosis of

COVID-19. Our analysis showed that the sensitivity of fever to predict PCR positivity of COVID-19 patients was very low, both in triage and in hospital (16.9% and 36.1%, respectively). Also, specificity of fever to predict the PCR positivity of COVID-19 patients was high, both in triage and in hospital (90.6% and 85.9%, respectively). This was thought to be due to the high false-negative rate of the PCR test. False-negative rate of PCR testing might be high due to the technical and other problems mentioned above, at the beginning of the pandemic. As PCR testing false-negative rate increased, sensitivity decreased and specificity increased. Similarly, fever might be affected by many factors as mentioned before and its false negative rate might increase. Depending on this situation, specificity values were found to be remarkably high. Having temperature lower than 38°C at admission or during hospitalization determined 90.6% and 85.9% of the PCR-negative patients. These high specificity values imply that if the PCR test is negative, the patient's temperature is more likely to be normal. Although sensitivity of fever was low, when compared with the patients without fever, we found that the patients with high fever at admission and during hospitalization have the odds of having PCR-positive results 1.95 and 3.43 times more, respectively.

Our study had some limitations. This is a single-center retrospective study, but we included all patients with COVID-19 who were hospitalized in the wards in 11 March–15 May 2020 period. Also, our center is a specific pulmonary diseases hospital in the Aegean region. Second, it was a retrospective noninterventional study; therefore, some of the laboratory data were absent in some of the patients. However, PCR status and temperature measurements were complete.

Conclusion

In conclusion, our study shows that, in 11 March–15 May 2020 period, only 13.6% of patients with COVID-19 have objective high fever at admission. 26.5% of all patients have high fever during hospital stay. The patients with high fever at admission and during hospitalization have the odds of having PCR-positive results 1.95 and 3.43 times more, respectively, when compared with the patients without fever. PCR-positive patients have less comorbidity. More PCR-positive patients have fever in the course of hospitalization and their length of hospital stay is longer and mortality is higher. Although we expect to find a high sensitivity, the sensitivity of high fever in our settings is low. Temperatures lower than 38°C at admission and in hospital determine 90.6% and 85.9% of the PCR-negative patients, respectively. These high specificity values imply that if the PCR test is negative, the patient's temperature is more likely to be lower than 38°C.

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Statement of Ethics

The study was approved by the Scientific Research and Thesis Evaluation Board of Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital (EPK no: 12.06.2020/10/20). Written informed consent was not requested by the Scientific Research and Thesis Evaluation Board of Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital since it was a retrospective data search study and confidentiality of patient data was ensured. Patients data privacy was ensured, de-identified data was used. EMR system safety and security were ensured.

Conflict of Interest Statement

The authors declare that they do not have any financial and nonfinancial aspects to disclose regarding conflict of interest with respect to this manuscript.

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Author Contributions

Dr. E.C. contributed to tools, data management and analysis, and writing manuscript. Dr. A.M. contributed to tools, data analysis, and writing manuscript. Dr. A.K.Ç. contributed to writing manuscript. Dr. A.B and Dr N.K. contributed to data analysis. Dr. G.B. contributed to data analysis and writing manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author E.C. upon reasonable request.

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