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Evaluation of hospitalized patients with a possible diagnosis of COVID-19

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The study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/14).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The definitive diagnosis of COVID-19 disease is made by demonstrating the presence of SARS-CoV-2 in nasopharyngeal swab samples. In patients who present with COVID-19-like symptoms but are found to be PCR negative, lung tomography, physical examination, and specific laboratory findings can guide diagnosis and treatment. This study aims to retrospectively evaluate the clinical, laboratory, and radiological findings of patients who presented with Covid-19-like symptoms. but were found to be PCR negative.

Methods: This study was planned as a retrospective cohort study. Patients hospitalized in the pandemic service of Afyonkarahisar Health Sciences University between 19 March and 30 September 2020 - who were PCR negative and defined as possible cases through diagnosis, treatment, and follow-up guidelines of the Republic of Turkey Ministry of Health, were included. Of these patients, those without radiological pulmonary involvement were defined as group A, and those with radiological pulmonary involvement were defined as group B. Clinical and laboratory findings of both groups were evaluated and compared.

Results: In the lung tomographic examination of 238 patients in the study, 16.4% in group A without radiological lung findings and 83.6% in group B with signs of inflammation were identified. While common complaints were high fever and diarrhea in group A, cough and shortness of breath were significantly higher in group B. The most common comorbidities in both groups were hypertension and diabetes, respectively, while hypertension was found to be significantly higher in group B. There was no mortality in any patient without lung involvement, but there was no significant difference between groups in terms of mortality.

Conclusion: These techniques can be used in PCR-negative patients presenting with COVID-19, for an estimation of patients with a severe prognosis with pulmonary tomography findings, symptoms, laboratory results, and accompanying disease at the time of admission. Determining parameters that identify at-risk patients during the early period may contribute to improving patient management and the appropriate use of limited resources.

Keywords: COVID-19 pandemic, Diagnosis, SARS-CoV-2 virus

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Introduction

Coronavirus-related disease (COVID-19), a new beta coronavirus caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), having spread all over the world, causing a pandemic shortly after the first cases were seen in China in December 2019. The disease can cause different clinical pictures, ranging from mild upper respiratory tract infection to severe pneumonia, multi-organ failure, and thromboembolic complications [1]. The worldwide method for definitive diagnosis of COVID-19 is to assess for the presence of SARS-CoV-2 in nasopharyngeal swab samples by the reverse-transcribed polymerase chain reaction (RT-PCR) method. Sputum, tracheal aspirate, and bronchoalveolar lavage samples are used in cases with pneumonia from the second week of infection [2]. Although RT-PCR is a precise method, its sensitivity decreases when viral load in samples is low [2, 3].

Computed tomography (CT) is an essential diagnostic criterion as well as for follow-up of the disease, especially in RT-PCR negative patients, who typically present a bilateral ground-glass view in lower zones with multiple foci and peripheral or subpleural patch-like consolidation areas [3-5].

Determining parameters affecting the clinical course of PCR-negative patients with COVID-19 findings may contribute to reducing mortality rates by guiding clinicians in follow-up and treatment of patients. Retrospective evaluation of those who could not be diagnosed microbiologically, but were accepted as possible COVID-19 with clinical and non-specific laboratory tests; we aimed to investigate whether a difference exists between clinical and laboratory findings, and prognosis between patients with and without pulmonary involvement.

Materials and methods

This retrospective cohort study was conducted in the pandemic clinic of Afyonkarahisar Health Sciences University Medical Faculty Hospital between 19 March 2020 and 30 September 2020. All hospitalized patients defined as possible cases per COVID-19 diagnosis, treatment, and follow-up guides of the Republic of Turkey Ministry of Health, but RT-PCR did not detect SARS-CoV-2 in nasopharyngeal swab samples, were included in the study [6]. Our study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/14).

The following criteria were used to define COVID-19, as its clinical picture could not be explained by another cause or disease, including:

A: At least one symptom of fever, cough, shortness of breath, sore throat, headache, muscle aches, loss of taste and smell, or diarrhea.

B: The presence of at least one symptom or finding of fever, cough, shortness of breath, sore throat, headache, muscle aches, loss of taste and smell, or diarrhea.

C: At least one of the signs and symptoms of fever and severe acute respiratory tract infection (cough and respiratory distress), and the presence of a hospitalization requirement, with Severe Acute Respiratory Infections-Severe Acute Respiratory Infections (SARI; fever, cough and dyspnea, tachypnea, hypoxemia, hypotension, common radiological findings with lung imaging, and a need for hospitalization due to changes in consciousness with acute respiratory tract infection that had developed in the last 14 days).

D: A combination of at least two of the findings or symptoms of fever, cough, shortness of breath, sore throat, headache, muscle aches, loss of taste and smell, or diarrhea [6].

The demographic findings of patients included in the study, whether they had suspicious contact, complaints at admission (fever, cough, shortness of breath, diarrhea), chest CT findings, hematological and biochemical blood findings, length of stay in the service, treatment responses, and prognoses were all assessed. Patient data were obtained from the hospital's automation system of file information.

Patients included in the study were also classified as to whether they had lung involvement or not. Patients without lung involvement were classified as group A, and those with lung involvement as group B. Those patients in group B were evaluated as mild/moderate (group B1), severe (group B2), and critical (group B3), using these criteria. Mild/moderate: patients with a cough, shortness of breath, tachypnea (SS: 24-30/min), hypoxia (Spo_2: 90 - 94%), fever, ground glass appearance in lower zones of lung CT. Severe patients: frequent cough and shortness of breath, tachypnea (SD > 30/min), hypoxia (Spo2 < 90%), high fever, diffuse bilateral involvement in lung CT. Critical patients: those who need mechanical ventilation, for organ dysfunction, sepsis, septic shock, and acute respiratory distress syndrome [7].

The pulmonary CT findings of patients were evaluated by dividing them into two groups, as typical involvement and atypical involvement in COVID-19. Criteria for typical involvement included peripheral bilateral ground-glass opacities with or without consolidation or visible intralobular infiltration, round morphology of multifocal ground-glass opacities with or without consolidation, or visible intralobular infiltration, an inverted halo sign, or other signs of organized pneumonia. Patients who did not meet these criteria but had signs of inflammation of lung CT were evaluated as having atypical radiological involvement [8].

Patients' clinical findings, treatment responses, and prognoses were compared based on clinical classification at the end of the study.

Statistical analysis

The IBM-SPSS Statistics v. 22 program was used for statistical analysis. Frequencies and percentages were given for categorical data, and median (minimum-maximum) values were given for quantitative data. Pearson and Fisher chi-square tests were used to evaluate the differences between categorical variables. $P < 0.05$ was considered significant.

Results

A total of 238 possible COVID-19 cases were hospitalized and followed in our pandemic service between March 19 and September 30, 2020. Of PCR negative patients, 129 (54.2%) were male and 109 (45.8%) were female.

Thirty-nine (16.4%) of 238 patients in the study were in group A, and 199 (83.6%) were in group B. Of patients in group B, 173 (86.9%) were classified as B1, 16 (8%) as B2, and 10 (5.1%) as B3. The mean age of group A was 54.49 (18.53), while the mean age of group B was 57.43 (18.45) There was no significant difference between the two groups in terms of age and gender ($P = 0.250$, $P = 0.689$). The demographic findings and admission symptoms of patients are based in groups and shown in Table 1.

High fever, malaise, and diarrhea were common symptoms at admission in group A, with cough, fever, and shortness of breath in group B. Eighteen patients had a family history of high-risk contact with patients with definitive diagnosis of COVID-19 (Table 1). When all patients were examined, the most common comorbidities were hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and malignancy (29.8%, 20.2%, 12.2%, and 10.1%). It was observed that 4.2% with hypertension, 10.3% with COPD, and 20.8% with malignancy took a critical course. When group B patients were evaluated, hypertension (P = 0.017) and COPD (P = 0.016) were more common in group B2, and malignancy (P = 0.001) and heart failure (P = 0.032) in group B3. When patient laboratory parameters were examined, leukocyte count and neutrophil/lymphocyte ratio was significantly higher in group A, while lymphocyte count, ferritin, creatinine, LDH, and troponin levels were significantly higher in group B. Patient laboratory findings at admission are shown in Table 2.

Favipiravir was given to 36.9% of patients, and hydroxychloroquine was given to 61.7%, low molecular weight heparin to 47%, and steroids to 1.2%. Eleven patients (4.6%) required oxygen at discharge. While 10 patients (4.2%) whose oxygen requirement was above 5 L/min were group B patients, 92.3% of group A patients were followed without oxygen. Those without pneumonic involvement and 30% of critically ill patients were discharged in recovery status, but 5.8% of patients and 80% of those critically ill were transferred to the intensive care unit (ICU) (Table 3).

While no patients in group A faced mortality, its mean in group B was 5%. When patients in group B were evaluated, mortality was significantly higher (B1 P = 0.001, B2 P = 0.023, B3 P < 0.001): it was also significantly higher in patients receiving hydroxychloroquine in group B (P = 0.001). The rates of intensive care admission and mortality were higher in group B, but this difference was not statistically significant.

Table 1: Demographic findings and complaints at admission by group

Results	Group A	Group B n (%)				*P*-value *
	n (%)	B1	B2	B3	Total	
Gender						
F	19 (48.7%)	80 (46.2%)	8 (50%)	2 (20%)	90 (45.2%)	0.689
M	20 (51.3%)	93 (53.8%)	8 (50%)	8 (80%)	109 (54.7%)	
Fever	23 (59%)	70 (40.5%)	5 (31.2%)	5 (50%)	80 (40.2%)	0.030
Cough	13 (33.3%)	120 (69.4%)	9 (56.2%)	6 (60%)	135 (67.8%)	<0.001
Throat ache	7 (17.2%)	20 (11.6%)	1 (6.2%)	2 (20%)	23 (11.5%)	0.292†
Shortness of breath	3 (7.7%)	57 (32.9%)	12 (75%)	7 (70%)	76 (38.1%)	<0.001
Headache	5 (12.8%)	21 (12.1%)	1 (6.2%)	0 (0%)	22 (11.0%)	0.783†
Myalgia	12 (30.8%)	53 (30.6%)	4 (25%)	1 (10%)	58 (29.1%)	0.839
Abdominal ache	2 (5.1%)	12 (7%)	1 (6.2%)	0 (0%)	13 (6.5%)	1.000†
Diarrhea	14 (35.9%)	9 (5.2%)	1 (6.2%)	0 (0%)	10 (5.0%)	<0.001
Nausea-Vomiting	7 (17.9%)	28 (16.2%)	0 (0%)	0 (0%)	28 (14.0%)	0.532
Malaise	16 (41%)	67 (38.7%)	4 (25%)	2 (20%)	73 (36.6%)	0.608
Hypertension	5 (12.8%)	54 (31.2%)	9 (56.2%)	3 (30%)	66 (33.1%)	0.011
Heart failure	1 (2.5%)	13 (7.5%)	3 (18.7%)	3 (30%)	19 (9.5%)	0.353
COPD	3 (7.7%)	18 (10.4%)	5 (31.2%)	3 (30%)	26 (13.0%)	0.433†
Malignancy	2 (5.1%)	14 (8.1%)	3 (18.8%)	5 (50%)	22 (11.0%)	0.386†
Smoking	5 (12.8%)	5 (2.9%)	0 (0%)	0 (0%)	5 (2.5%)	0.012†
Renal failure	0 (0%)	5 (2.9%)	1 (6.2%)	1 (10%)	7 (3.5%)	0.603
Diabetes	4 (10.3%)	38 (22%)	5 (31.2%)	1 (10%)	44 (22.1%)	0.092
Liver insufficiency	1 (2.6%)	1 (0.6%)	0 (0%)	0 (0%)	1 (0.5%)	0.301†
Contact history	3 (7.7%)	13 (7.5%)	0 (0%)	2 (20%)	15 (7.3%)	1.000†

*The sum of group A and group B were compared. †Fisher's Exact Test

Table 2: Laboratory findings by groups

Parameters, (reference range)	Group A Median (Min-Max)	Group B n (%) B1 Median (Min-Max)	B2 Median (Min-Max)	B3 Median (Min-Max)	Total Median (Min-Max)	*P*-value *
WBC†	9,720 (2,280-18,000)	7,560 (700-35,750)	8,950 (4,390-29,010)	10,745 (3,400-24,060)	8,215 (700-35,750)	0.005
LYM†	970 (110-2,990)	1,300 (60-5,200)	1,100 (90-2,500)	465 (80-2,620)	1,245 (60-5,200)	0.048
N/L†	8.4 (1.54-123.91)	4.00 (0.70-47.96)	6.31 (2.08-116.56)	15.28 (2.17-137.75)	4.4 (0.70-137.75)	0.004
PLT†	237,000 (79,000-402,000)	213,000 (22,000-537,000)	210,000 (120,000-417,000)	195,000 (9,000-337,000)	218,500 (9,000-537,000)	0.571
CRP†	4.2 (0.1-17.0)	4.4 (0.0-41.9)	8.9 (1.5-37.2)	13.2 (0.80-31.3)	5 (0.0-41.9)	0.131
DD†	0.48 (0.00-77.28)	0.49 (0.00-7.74)	0.61 (0.10-1.96)	1.42 (0.20-8.77)	0.52 (0.0-8.77)	0.743
FERR†	104 (7-826)	245.2 (6-8,069)	490.35 (86.48-1,226)	745.9 (6.10-3,018)	224 (6-8,069)	<0.001
AST†	21 (10-155)	26 (8-271)	29.9 (13-103)	29 (14-50)	26 (8-271)	0.074
ALT†	17 (5-79)	20 (2-496)	17 (4-47)	30 (6-48)	20 (2-496)	0.145
Creatinine†	0.76 (0.37-1.60)	0.84 (0.37-7)	1.02 (0.32-2.90)	0.78 (0.49-8.28)	0.82 (0.32-8.28)	0.014
LDH†	199.5 (132-497)	249 (120-779)	278 (149-758)	256.5 (158-842)	245 (120-842)	<0.001
Troponin†	0.003 (0.00-0.04)	0.007 (0.00-0.25)	0.016 (0.00-1.75)	0.012 (0.01-0.04)	0.007 (0.00-1.75)	<0.001
Procalcitonin†	0.16 (0.02-6.40)	0.078 (0.00-17.90)	0.082 (0.06-8.04)	0.217 (0.06-24.58)	0.069 (0.00-24.58)	0.006

* The sum of group A and B were compared. † WBC: Leukocyte count (4000–1000 /µL), LYM: Lymphocyte (1200 – 4000 /µL), N/L: Neutrophil/Lymphocyte ratio, PLT: Platelet (160,000 – 370,000 /µL), CRP: C-Reactive Protein (0 – 0.5 mg/dL), DD: D-dimer (0 – 0.5 µg FEU/mL), FERR: Ferritin (30 – 400 ng/mL), AST: Aspartate amino transferase (5 - 40 U/L), ALT: Alanine aminotransferase (5 – 41 U/L), Creatinine (0.5 – 1.2), LDH: Lactate dehydrogenase (135-225 U/L), Troponin (0-0 -- 014 ng/mL), Procalcitonin (0.005 – 2 ng/mL)

Table 3: Treatment and prognosis

	Group A	Group B n (%)				*P*-value *
	n (%)	B1	B2	B3	Total	
Hydroxychloroquine	34 (87.2%)	96 (55.5%)	9 (56.2%)	8 (80%)	113 (56.7%)	<0.001
Favipiravir	1 (2.6%)	73 (42.2%)	8 (50%)	6 (60%)	87 (43.7%)	<0.001
Heparin	17 (43.6%)	82 (47.4%)	8 (50%)	10 (100%)	95 (47.7%)	0.635
Steroid	0 (0%)	1 (0.6%)	2 (12.5%)	0 (0%)	3 (1.5%)	1.000†
Oxygen-free follow-up	36 (92.3%)	111 (64.1%)	0 (0%)	0 (0%)	111 (55.7%)	<0.001
Oxygen < 3 L/min	2 (5.2%)	50 (28.9%)	1 (6.2%)	1 (10%)	52 (26.2%)	0.004
Oxygen 3-5 L/min	1 (2.5%)	10 (5.7%)	10 (62.5%)	6 (60%)	26 (13.1%)	0.092†
Oxygen > 5 L/min	0 (0%)	2 (1.1%)	5 (31.3%)	3 (30%)	10 (5.0%)	0.375†
Recovery	39 (100%)	168 (97.1%)	10 (62.5%)	3 (30%)	181 (90.9%)	0.050†
Transfer to ICU	0 (0%)	5 (2.9%)	1 (6.2%)	8 (80%)	14 (7.0%)	0.135†
ICU or Deceased	0 (0%)	2 (1.2%)	0 (0%)	5 (50%)	7 (3.5%)	0.603†
Mortality	0 (0%)	2 (1.2%)	3 (18.8%)	5 (50%)	10 (5.0%)	0.375†
O^2 requirement at discharge	1 (2.6%)	8 (4.6%)	1 (6.2%)	1 (10%)	10 (5.0%)	1.000†

*The sum of groups A and group B were compared. †Fisher's Exact Test

Discussion

The first case was seen in our country on March 19, 2020, but the number of cases increased rapidly, as patients admitted to hospitals were evaluated in accord with the COVID-19 guidelines prepared by the Ministry of Health, and upper respiratory tract samples were taken from patients with possible criteria for a preliminary diagnosis of COVID-19 and RT-PCR positive cases were evaluated, a definitive diagnosis made, and treatment started. Cases not found to be RT-PCR positive were managed with clinical, laboratory, and lung imaging, and in cases of high clinical suspicion, the patient was accepted as having COVID-19 and treated.

Definitive diagnosis of COVID-19 is made by RT-PCR tests of respiratory tract samples, especially in patients who develop pneumonia, as lower respiratory tract samples are more useful in diagnosis. The sensitivity of PCR tests decreases to 50-70% due to low viral load, problems in transfer of respiratory tract samples, and inappropriate sample collection [2]. Therefore, patients' symptoms, physical examination, and imaging findings should be considered when guiding treatment in patients for whom COVID-19 cannot be excluded.

Symptoms at admission are important during the pandemic period. In a study conducted by Rona et al. in our country, 338 RT-PCR negative patients followed with a preliminary diagnosis of COVID-19 were evaluated for cough, fever, and dyspnea (58.87%, 40.82%, 39.34%, respectively) were the most common presenting symptoms [9]. In our study, common symptoms were cough, fever, malaise, and shortness of breath. Fever and diarrhea were more common in group A without lung involvement on CT, and cough and shortness of breath were significantly higher in group B patients, along with CT findings.

Knowing potential risk factors that predict the course of the disease is crucial for patient triage, treatment management, mortality and morbidity prediction, and determining the need for intensive care. Preexisting cardiovascular disease, chronic renal failure, chronic lung diseases (especially COPD), diabetes mellitus, hypertension, immune suppression, and obesity predispose patients to a more severe clinical course and an increased risk of intubation and death [10, 11]. In a study of 35,583 patients with at least one comorbid disease in Mexico, obesity, diabetes, and hypertension were reported as risk factors for being infected and developing severe disease [12]. In our study, hypertension was more common in group B, but no difference was observed between groups A and B for other comorbidities. When group B was evaluated within itself, it was found that patients with heart failure and malignancy were significantly higher in the critically ill group. These findings confirm the literature data.

It is stated that the neutrophil-lymphocyte ratio (NLR), LDH, d-dimer, CRP, fibrinogen, and ferritin can be used in the early period to predict the severity of infection and prognosis at the first admission for SARS-CoV-2 infection [13, 14]. In the study conducted by Baştuğ et al., increases in d-dimer, NLR, and CRP were reported as the strongest laboratory predictors of severe prognosis [15]. When group A and B patients were compared in our study, ferritin, creatinine, LDH, and troponin values were significantly higher in group B patients with CT involvement. Yet, further studies will determine prognostic laboratory parameters related to the severity of the disease with COVID-19 and use them for triage at the time of admission.

The treatment of our patients was arranged in line with treatment recommendations of the Ministry of Health of the Republic of Turkey COVID-19 guidelines. In our study, 147 (61.7%) patients received hydroxychloroquine (87.2% and 47.4% in groups A and B, respectively), 88 (36.9%) patients received favipiravir (2.6% and 36.5% in groups A and B, respectively), and 112 (47%) patients received anticoagulant therapy (A and B groups; 43.6%, 42%, respectively). Although hydroxychloroquine, favipiravir, remdesivir, ivermectin, steroids, lopinavir/ritonavir, and immune plasma treatment are approaches used in the treatment of COVID-19 so far, there is an urgent need for effective and specific antiviral treatment against it [16, 17]. Hydroxychloroquine is not recommended for treating COVID-19 inpatients, but the hydroxychloroquine-azithromycin combination has been widely used in the first months of the pandemic as an attractive option for the immunomodulatory and antiviral effects of both drugs. However, hydroxychloroquine is not a preferred agent in daily practice, since patients treated with hydroxychloroquine were noted to have an increased intubation probability, increased QT prolongation due to combined use with azithromycin, and sudden cardiac death risks [7, 18]. Given the update of May 5, 2021, hydroxychloroquine treatment was removed from the Ministry of Health guidelines, although due to its possible side effects, its use was avoided in treating severe patients in our service prior to this date and favipiravir was preferred. In a multicenter randomized study, 96 patients using favipiravir and chloroquine were evaluated. In two groups who did not differ significantly for comorbidities, it was found that the hospital stay and need for mechanical ventilation were shorter in those on favipiravir [19]. In our study, it is notable that mortality rate was higher in patients receiving hydroxychloroquine in group B compared to other group B patients.

SARS-CoV-2 causes multi-organ failure by creating respiratory, gastrointestinal, cardiovascular, nephrological, and central nervous system involvement. In the patients, it is imperative to provide supportive treatment, such as hemodynamic support, IV fluid replacement, vasoactive agents, respiratory support, and adequate mechanical ventilation as necessary [20]. Hypoxia is a leading cause of multiple organ damage and death in COVID-19 patients [21]. In our study, 92.3% of group A patients and 64.1% of group B patients were followed without oxygen, while patients needing more oxygen than 5 L/min were in group B.

In a meta-analysis evaluating the COVID-19 mortality rates, overall mortality coincided with the rate we obtained: 4.9% in the U.S., 4.7% in Iran, and 4.3% in Brazil, while it was 1.4% in Russia, 3.02% in India, 13.9% in England, and 14.5% in Italy [22]. These rates, which vary by country, can be explained by the quality of the health service provided and differences in patients' clinical picture in the study. CT findings showing diffuse lung involvement were associated with increased mortality in the literature [10]. In our study, the rate of mortality among all patients was 4.2%. There was no statistically significant difference between A and B groups regarding mortality, yet all

of those who developed mortality were in group B with lung involvement, and mortality rates increased in tandem with increase in disease severity.

Limitations

An important limitation of this study is that we did not investigate SARS-CoV-2 in lower respiratory tract samples with the RT-PCR method. Another limitation is that we could not show microbiological evidence for other respiratory tract infectious agents. It will be informative to investigate these findings in other studies.

Conclusions

Determining the parameters predicting the clinical course in COVID-19 patients is important in assessing appropriate treatment and intensive care needs and using limited resources correctly. Although the clinical prognosis is better in PCR-negative patients with COVID-19-with findings but none in lung tomography, symptoms and lab findings at admission, accompanying comorbidities are striking as they guide the clinical approach for patients.

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