

## Retrospective Study

## Role of serological rapid antibody test in the management of possible COVID-19 cases

Fatma Yıldırım, Pinar Yıldız Gulhan, Özlem Ercen Diken, Aylin Capraz, Meltem Şimsek, Berna Botan Yıldırım, Muhammet Ridvan Taysi, Sakine Yılmaz Ozturk, Nurcan Demirtas, Julide Ergil, Adem Dirican, Tugce Uzar, Irem Karaman, Sevket Ozkaya

**ORCID number:** Fatma Yıldırım 0000-0001-8410-8016; Pinar Yıldız Gulhan 0000-0002-5347-2365; Özlem Ercen Diken 0000-0001-8388-9500; Aylin Capraz 0000-0002-9195-7398; Meltem Şimsek 0000-0001-8044-9737; Berna Botan Yıldırım 0000-0001-7730-1379; Muhammet Ridvan Taysi 0000-0002-2609-264X; Sakine Yılmaz Ozturk 0000-0002-7444-1883; Nurcan Demirtas 0000-0001-5215-6945; Julide Ergil 0000-0002-4580-7866; Adem Dirican 0000-0001-7180-8478; Tugce Uzar 0000-0003-4225-0991; Irem Karaman 0000-0001-7559-9095; Sevket Ozkaya 0000-0002-8697-4919.

**Author contributions:** Yıldırım F, Gulhan PY, Diken ÖE, Capraz A, Şimsek M, Yıldırım BB, Taysi MR, Ozturk SY, Demirtas N, Ergil J, Dirican A, and Ozkaya S collected and analyzed the data and wrote the first draft of the manuscript; Uzar T and Karaman I reviewed the literature and wrote the second draft of the manuscript; All authors contributed equally and approved the final version of the manuscript.

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**Fatma Yıldırım**, Department of Pulmonary and Critical Care Medicine, University of Health Sciences Diskapi Yıldırım Beyazıt Research and Education Hospital, Ankara 06110, Turkey

**Pinar Yıldız Gulhan**, Department of Pulmonary Medicine, Düzce University, Faculty of Medicine, Düzce 81100, Turkey

**Özlem Ercen Diken**, Department of Chest Diseases, Adana Research and Education Hospital, University of Health Sciences, Adana 01230, Turkey

**Aylin Capraz**, Department of Pulmonary Medicine, Amasya University Sabuncuoglu Serefeddin Research and Education Hospital, Amasya 05200, Turkey

**Meltem Şimsek**, Medical Intensive Care Unit, University of Health Sciences Diskapi Yıldırım Beyazıt Research and Education Hospital, Ankara 06110, Turkey

**Berna Botan Yıldırım**, Department of Pulmonology, Research and Education Hospital of Baskent University, Konya 42030, Turkey

**Muhammet Ridvan Taysi**, Department of Infectious and Clinical Microbiology, University of Health Sciences Diskapi Yıldırım Beyazıt Research and Education Hospital, Ankara 06110, Turkey

**Sakine Yılmaz Ozturk**, Department of Pulmonary Medicine, Vezirkopru State Hospital, Samsun 55090, Turkey

**Nurcan Demirtas**, Department of Pulmonary Medicine, Kumluca State Hospital, Antalya 07070, Turkey

**Julide Ergil**, Department of Anaesthesiology and Reanimation, Diskapi Yıldırım Beyazıt Research and Education Hospital, University of Health Sciences, Ankara 06110, Turkey

**Adem Dirican**, Department of Pulmonary Medicine, Samsun Medicalpark Hospital, Samsun 55090, Turkey

**Tugce Uzar, Irem Karaman**, Medical Student/Intern, Bahcesehir University Faculty of Medicine, Istanbul 34734, Turkey

**Sevket Ozkaya**, Department of Pulmonary Medicine, Bahcesehir University, Faculty of Medicine, Istanbul 34734, Turkey

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**Corresponding author:** Sevket Ozkaya, MD, Associate Professor, Doctor, Department of Pulmonary Medicine, Bahcesehir University, Faculty of Medicine, Sahrayı Cedit District, Batman Street, No. 66, 34734 Kadıköy, Istanbul 34734, Turkey. [ozkayasevket@yahoo.com](mailto:ozkayasevket@yahoo.com)

## Abstract

### BACKGROUND

Although the detection of viral particles by reverse transcription polymerase chain reaction (RT-PCR) is the gold standard diagnostic test for coronavirus disease 2019 (COVID-19), the false-negative results constitute a big challenge.

### AIM

To examine a group of patients diagnosed and treated as possible COVID-19 pneumonia whose multiple nasopharyngeal swab samples were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by RT-PCR but then serological immunoglobulin M/immunoglobulin G (IgM/IgG) antibody against SARS-CoV-2 were detected by rapid antibody test.

### METHODS

Eighty possible COVID-19 patients who had at least two negative consecutive COVID-19 RT-PCR test and were subjected to serological rapid antibody test were evaluated in this study.

### RESULTS

The specific serological total IgM/IgG antibody against SARS-CoV-2 was detected in twenty-two patients. The mean age of this patient group was  $63.2 \pm 13.1$ -years-old with a male/female ratio of 11/11. Cough was the most common symptom (90.9%). The most common presenting chest computed tomography findings were bilateral ground glass opacities (77.2%) and alveolar consolidations (50.1%). The mean duration of time from appearance of first symptoms to hospital admission, to hospital admission, to treatment duration and to serological positivity were 8.6 d, 11.2 d, 7.9 d, and 24 d, respectively. Compared with reference laboratory values, serologically positive patients have shown increased levels of acute phase reactants, such as C-reactive protein, ferritin, and procalcitonin and higher inflammatory markers, such as erythrocyte sedimentation rate, lactate dehydrogenase enzyme, and fibrin end-products, such as D-dimer. A left shift on white blood cell differential was observed with increased neutrophil counts and decreased lymphocytes.

### CONCLUSION

Our study demonstrated the feasibility of a COVID-19 diagnosis based on rapid antibody test in the cases of patients whose RT-PCR samples were negative. Detection of antibodies against SARS-CoV-2 with rapid antibody test should be included in the diagnostic algorithm in patients with possible COVID-19 pneumonia.

**Key Words:** COVID-19; Rapid antibody test; Reverse transcription polymerase chain reaction; High resolution computed tomography; Serology; Pneumonia

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**Core Tip:** This is the first clinical retrospective study in Turkey that reports the features of the patients that were diagnosed and treated as possible coronavirus disease 2019 (COVID-19) cases whose multiple nasopharyngeal swab samples were negative by reverse transcription polymerase chain reaction (RT-PCR) but serological immunoglobulin M/immunoglobulin G antibody against severe acute respiratory syndrome coronavirus 2 was detected by a rapid antibody test. Our study demonstrated the feasibility of COVID-19 diagnosis based on rapid antibody tests in the cases of patients whose RT-PCR samples were negative. An effective diagnosis for COVID-19 is likely to require a hybrid strategy of PCR and serologic testing with the radiological

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## INTRODUCTION

The coronavirus disease-2019 (COVID-19) is a unique pneumonia caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that typically causes various degrees of respiratory disease[1]. Currently, the entire world is battling COVID-19 pneumonia, which can be lethal in high-risk patient groups. Although a COVID-19 diagnosis is generally based on clinical, laboratory, and radiological features of the patients, the gold standard test for diagnosis is the real time reverse transcription polymerase chain reaction (RT-PCR) assay from respiratory samples[2,3]. However, several studies have indicated the concerns regarding the sensitivity of RT-PCR tests[4, 5]. False negative results are thought to originate from several technical issues, including the high variability of RT-PCR tests, low nasopharyngeal viral load, manual mistakes performing the test, inappropriate collection and transportation of samples, and timing of specimen in relation to onset of symptoms, whereas false positive results are rarely seen[4].

Rapid antibody card tests can produce results in as short as fifteen minutes by detecting immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies produced against SARS-CoV-2, and they have been approved in Europe, as well as in China. Although the specificity of these tests is lower than with PCR, in some cases they can aid in the diagnosis of possible COVID-19 patients. In this retrospective study; we aimed to investigate whether these rapid antibody tests would be useful in the diagnostic challenge faced in suspected, possible COVID-19 pneumonia patients whose PCR tests were negative but has radiologically and clinically features that are consistent with COVID-19 pneumonia.

## MATERIALS AND METHODS

We retrospectively evaluated the clinical characteristics, laboratory results, and radiological features of 80 possible COVID-19 patients with multiple negative RT-PCR tests and reported the characteristics of 22 serologically positive COVID-19 patients.

### Patient Selection

In Turkey, rapid antibody test kits for COVID-19 were become commercially available at the beginning of April 2020. Symptomatic RT-PCR-negative patients who were suspected to be infected with SARS-CoV-2 based on epidemiological history, laboratory results, and positive radiological findings were included in the study. Until September 2020, we were able to test 80 suspected RT-PCR negative possible COVID-19 patients; 22 serologically positive cases were detected. All patients had a contact history and most patients had a history of a family member who tested positive with RT-PCR for COVID-19 disease. All COVID-19 antibody test positive cases had fever and at least one respiratory system symptom such as cough, dyspnea, or sputum. Herein, we introduced features of 22 serologically positive COVID-19 cases. High resolution computed tomography (HRCT) was used for the radiological assessment. In patients with possible COVID-19 pneumonia, ground-glass formation and/or consolidative opacities distributed usually bilateral, peripheral, and mostly basal, were considered as positive HRCT findings. The patients with negative RT-PCR tests were tested for specific antibodies against SARS-CoV-2 following the COVID-19 treatment, which was in average 24 d after the initiation of symptoms.

### COVID-19 IgM/IgG rapid antibody test

Samples were taken from the patients with oro-nasopharyngeal and nasal swabs and analyzed by RT-PCR. The humoral responses against SARS-CoV-2 were tested with rapid card test with blood samples of patients. The blood taken from the patient was dropped on this rapid card test and the total antibody response (either IgM or IgG) was analyzed. The clinical samples were anonymized and used in accordance with local ethical guidelines. Total antibody levels against SARS-CoV-2 were noted. We used the Colloidal Gold SARS-CoV-2 IgG/IgM Rapid Test (Beijing Hotgen Biotech Co., Ltd), which is a lateral flow chromatographic immunoassay detecting total antibodies produced against the SARS-CoV-2. The anti-SARS-CoV-2 virus IgM, if present in the specimen, will bind to the SARS-CoV-2 conjugates. The immuno-complex is then captured by the anti-human IgM line, forming a burgundy colored M Line, indicating a SARS-CoV-2 virus IgM positive test result.

### Statistical analysis

Mean and standard deviations were given for normally distributed metric variables. Frequencies and percentages were given for non-metric variables.

## RESULTS

The demographic and clinical characteristics of 22 serologically positive RT-PCR negative COVID-19 patients were shown in [Table 1](#). Each of these patients had at least two consecutive negative PCR tests, taken at a minimum of 2 d apart. The mean age was  $63.2 \pm 13.1$ -years-old and male to female ratio was 11/11. The mean duration of time from appearance of first symptoms to hospital admission, to hospital admission, to treatment duration and to serological positivity were  $8.6 \pm 7.2$ ,  $11.2 \pm 5.4$ ,  $7.9 \pm 3.2$  and  $24 \pm 17$  d, respectively.

The radiological findings and drug regimens were shown in [Table 2](#). The radiological findings, such as bilateral reticular and ground-glass opacities were demonstrated in [Figures 1-5](#). Also, dense consolidations were noted in [Figures 3 and 5](#). The bilateral fibroreticular infiltrates with crazy-paving patterns are shown in [Figure 6](#). Hydroxychloroquine and/or azithromycin and/or favipiravir therapy was initiated by the consensus of infectious disease specialists and pulmonologists according to the clinical, laboratory, and radiological findings of the patients. The selection of the drug regimen was made based on the clinical evaluation of each patient.

The laboratory results of the patients were given in [Table 3](#). Compared with reference laboratory values, serologically positive patients have shown increased levels of acute phase reactants such as C-reactive protein, ferritin, and procalcitonin, higher inflammatory markers, such as erythrocyte sedimentation rate, lactate dehydrogenase enzyme, and fibrin end-products, such as D-dimer. A left shift on white blood cell differential observed with increased neutrophil counts and decreased lymphocytes.

## DISCUSSION

In patients with possible COVID-19 pneumonia, rapid identification, isolation, and treatment of infected individuals will be a key step to prevent onward community transmission. Currently, COVID-19 diagnosis is made by the direct detection of SARS-CoV-2, supported by clinical, laboratory and radiological features of the suspected patients. According to the first COVID-19 case series by [Bai \*et al\*\[4\]](#); the sensitivity of CT was estimated to be 97% compared to PCR tests, which had 71% sensitivity[4]. [Ai \*et al\*\[5\]](#) also reported as the sensitivity of RT-PCR assays to be in the range of 60% to 70% [5]. Here, our results supported that chest CT results were more sensitive than RT-PCR results to suspect from a possible COVID-19 diagnosis.

It was suggested that PCR-negative cases with positive CT findings and high clinical suspicion may benefit from repeated RT-PCR testing[6]. [Shi \*et al\*\[7\]](#) reported that COVID-19 pneumonia might manifest with chest CT imaging abnormalities, even in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground glass opacities that progressed to, or coexisted with, consolidations within 1-3 wk[7]. Another study with 1099 patients from China revealed that 56% of patients had ground-glass opacities, but no radiological findings were reported in 18% of COVID-

**Table 1 Demographic and clinical characteristics of serologically positive reverse transcription polymerase chain reaction negative coronavirus disease 2019 patients**

	<i>n</i> (%)
Age in yr	
mean ± SD	63.2 ± 13.1
Gender	
Male/Female	11/11
Symptoms, <i>n</i> (%)	
Cough	20 (90.9)
Dyspnea	14 (63.6)
Fever	10 (45.4)
Chest pain	8 (36.3)
Duration in d, mean ± SD	
From first symptom to admission	8.6 ± 7.2
Hospital stay	11.2 ± 5.4
From symptoms to antibody test	24 ± 17
Drug treatment	7.9 ± 3.2

**Table 2 Radiological findings and drug regimens of serologically positive reverse transcription polymerase chain reaction negative coronavirus disease 2019 patients**

	<i>n</i> (%)
Radiology	
GGO	17 (77.2)
Consolidation	11 (50)
Nodular infiltrates	4 (18.1)
Fibroreticular infiltrates	3 (5.9)
Drug regimens	
HCQ+Azithromycine + Favipravir	11 (50)
HCQ+Azithromycine	7 (31.8)
Favipravir	4 (18.1)

GGO: Ground-Glass Opacities; HCQ: Hydroxychloroquine.

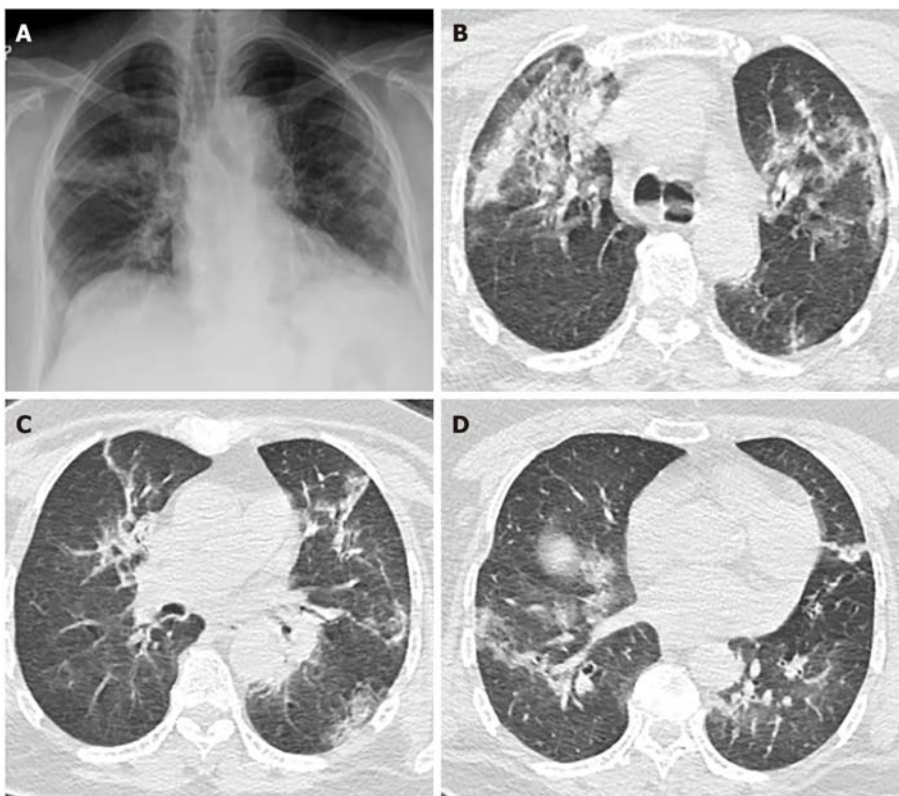
19 cases. Although bilateral and peripheral ground-glass opacities constitute the most typical CT findings, they were not specific for the COVID-19 disease[8,9]. Since radiological evaluation of the thorax is often the key diagnostic element in patients with possible COVID-19 pneumonia, like in our present study, the patients with positive CT findings but negative RT-PCR results should be isolated and re-evaluated [9,10]. Combined assessment of imaging features with clinical and laboratory findings is key to facilitate an early diagnosis of COVID-19. Therefore, we suggest that in RT-PCR-negative cases, radiological diagnosis should be supported with specific antibody detection. Our study demonstrated that the diagnosis of COVID-19 should be confirmed by rapid antibody test at least 5 d after the treatment of RT-PCR negative patients with typical CT findings.

SARS-CoV-2 can be detected in different tissues and body fluids. In our study, the nasopharyngeal and nasal swabs samples taken from the patients were utilized and assessed by RT-PCR test. In a study on 1070 specimens collected from 205 patients with COVID-19, bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%),

**Table 3** The laboratory parameters of serologically positive reverse transcription polymerase chain reaction negative coronavirus disease 2019 patients

Value	mean $\pm$ SD
ESR in mm/h	68.5 $\pm$ 41.7
LDH in U/L	362 $\pm$ 152
CRP in mg/L	95 $\pm$ 101
Ferritinin $\mu$ g/L	778 $\pm$ 684
WBCs	8621 $\pm$ 3549
Lymphocytes, <i>n</i> (%)	1430 $\pm$ 530
Lymphocytes, <i>n</i> (%)	22 $\pm$ 10.8
Neutrophils, <i>n</i> (%)	5390 $\pm$ 2450
Neutrophils as %	70.5 $\pm$ 12.3
D-Dimer in mg/L	1875 $\pm$ 2757
Procalcitonin in mg/L	0.15 $\pm$ 0.03

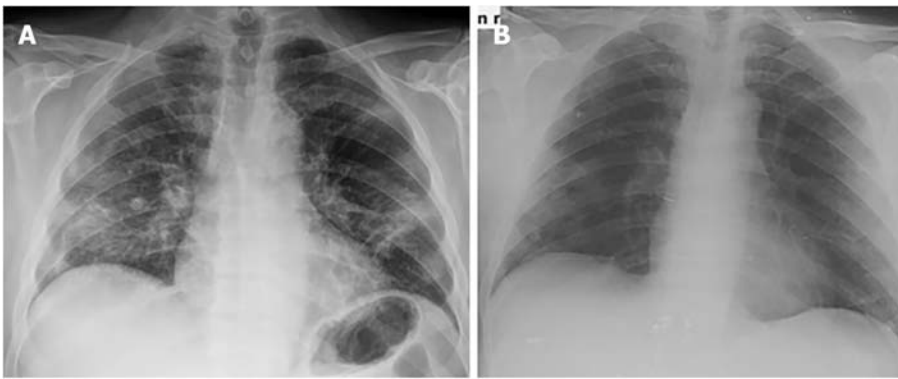
CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; WBCs:White blood cells.



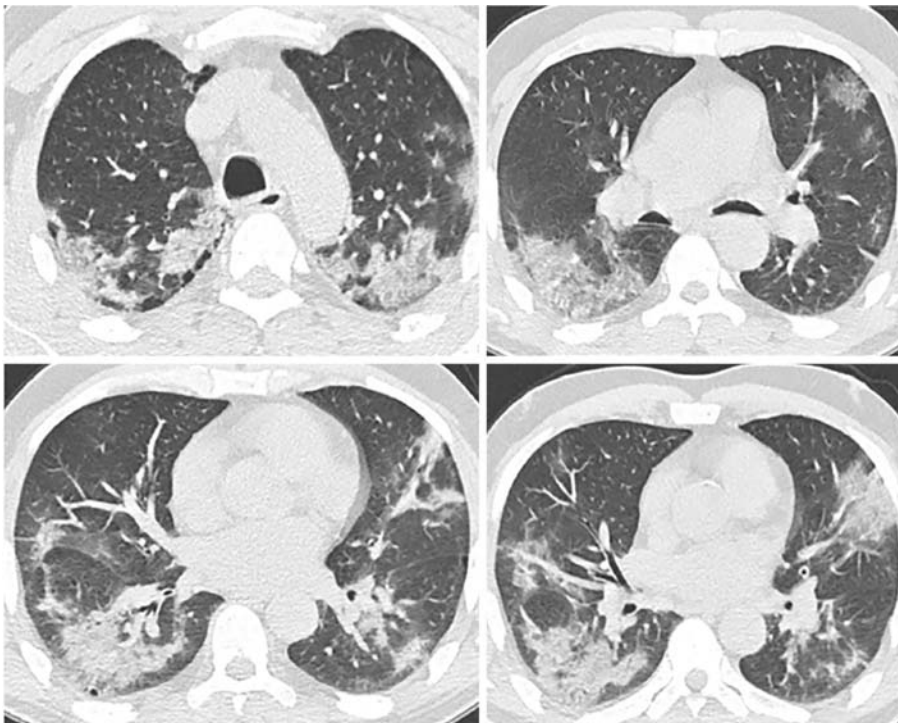
**Figure 1** Example of the radiological images of a patient whose multiple reverse transcription polymerase chain reaction were negative but serological immunoglobulin M/immunoglobulin G against severe acute respiratory syndrome coronavirus 2 positive. A: Chest radiograph of coronavirus disease 2019 (COVID-19) patient showing the bilateral infiltrates; B-D: High resolution computed tomography images showing the bilateral reticular and ground-glass opacities of COVID-19 patient.

fibro-bronchoscopy brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%). None of the 72 urine specimens tested positive[9]. That study by Ding *et al*[9] supported that sensitivity of nasal and nasopharyngeal swabs for PCR tests remained questionable.

The first comprehensive study on the host humoral response against SARS-CoV-2 has shown that serological response can aid in the diagnosis of COVID-19, including



**Figure 2** Example of the radiological images of a patient whose multiple reverse transcription polymerase chain reaction were negative but serological immunoglobulin M/immunoglobulin G against severe acute respiratory syndrome coronavirus 2 positive. A: Chest x-ray of the coronavirus disease 2019 (COVID-19) patient showing the bilateral infiltrates before treatment; B: Chest x-ray of the COVID-19 patient showing reduced bilateral infiltrates after treatment.



**Figure 3** High resolution computed tomography images of coronavirus disease 2019 patient showing the bilateral ground-glass opacities and consolidations.

those subclinical cases. In that study, IgA, IgM, and IgG response using an ELISA-based assay on the recombinant viral nucleocapsid protein was analyzed in 208 plasma samples from 82 confirmed and 58 probable cases[11,12]. The median duration of IgM and IgA antibody detection were 5 d (IQR 3-6), while IgG was detected on day 14 (IQR 10-18) after symptom onset, with a positive rate of 85.4%, 92.7% and 77.9% respectively. It was shown that detection efficiency by IgM ELISA was higher than that of PCR after 5.5 d of onset of symptoms. In another study of 173 patients, the seroconversion rates (median time) for IgM and IgG were 82.7% (12 d) and 64.7% (14 d), respectively. Our study also reported the mean duration of time from appearance of first symptoms to hospital admission, to hospital admission, to treatment duration and to serological positivity were  $8.6 \pm 7.2$ ,  $11.2 \pm 5.4$ ,  $7.9 \pm 3.2$  and  $24 \pm 17$  d, respectively. It was also reported that a higher titer of antibody was independently associated with severe course of diseases[13]. Since our study included only RT-PCR-negative serologically positive COVID-19 patients who were diagnosed and treated based on radiological and clinical findings, we were unable to compare the severity of RT-PCR-positive and RT-PCR-negative COVID-19 patients.



Figure 4 High resolution computed tomography images showing the bilateral patchy ground-glass opacities in a coronavirus disease 2019 patient.

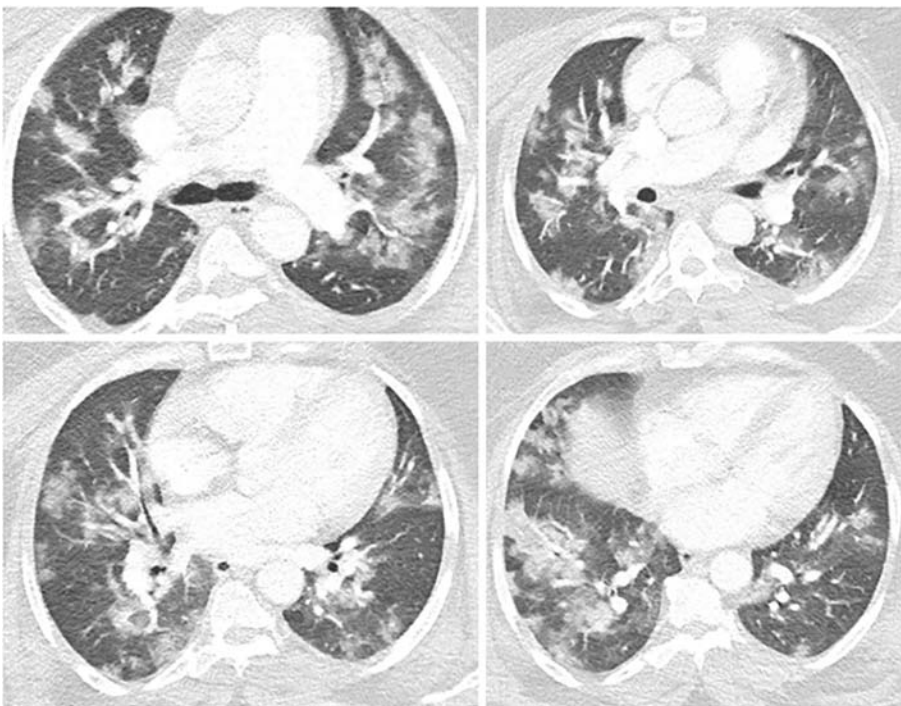
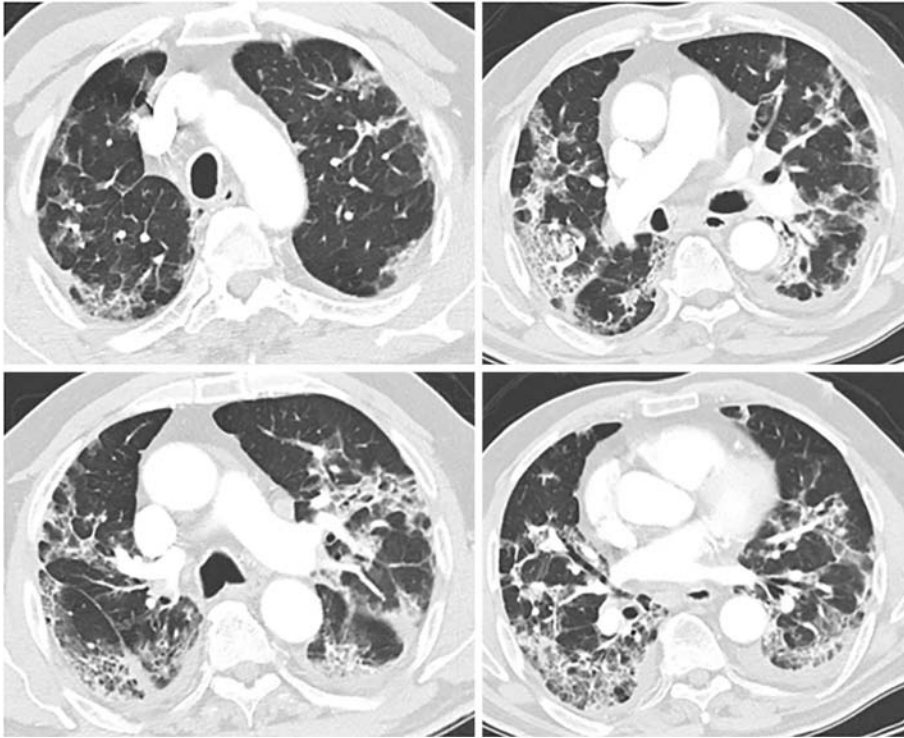


Figure 5 High resolution computed tomography images in a severe coronavirus disease 2019 patient showing the bilateral patchy ground-glass opacities with consolidations.

To date, several population-based studies demonstrated false-negative RT-PCR is a particular concern in the diagnosis of COVID-19. Baron *et al*[14] reported that among COVID-19 patients, the ratio of false-negative RT-PCR results was 18% compared to a negative serology ratio of 4% [14]. West *et al*[15] clearly stated that the variety in the test performance and diagnostic validity of different methods have not been well investigated, which raises concern for generating a false sense of security[15]. As Benoit[16] suggested, a multi-step strategy to limit the likelihood of COVID-19 patients to be labeled incorrectly as negative should be applied, which includes RT-



**Figure 6** High resolution computed tomography images of a severe coronavirus disease 2019 patient showing the bilateral fibroreticular infiltrates with crazy-paving pattern.

PCR tests, serological testing, and clinical and radiological findings of the patients[16]. It should be noted that RT-PCR tests alone to define COVID-19 negative cohorts are not valid and likely to produce biased results based on many concerns regarding the sensitivity of RT-PCR assays.

Our study has several limitations, including low sample size and follow-up for serology results due to its retrospective nature; however, ideal research conditions are often difficult to be established during a pandemic situation. Also, the comparison of laboratory and radiological findings between patients who demonstrated a seroconversion and those who did not could better reveal the differences and may give information about the severity of the disease course. In addition, this study did not differentiate the serological results in terms of specific IgM and IgG against SARS-CoV-2.

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## CONCLUSION

In conclusion, our study remarks the feasibility of total antibody testing by a rapid card test in the diagnosis of suspected PCR-negative COVID-19 patients who are likely to have false negative results or viral clearance of the upper respiratory tract. Even though there is no specific treatment for COVID-19, it is highly important to confirm the diagnosis of highly suspected cases to prevent further transmission and to prevent long-term complications. We suggest that detection of antibodies against SARS-CoV-2 with rapid-card test should be included in the diagnostic algorithm in PCR-negative patients with COVID-19 pneumonia. An effective diagnosis is likely to require a hybrid strategy of PCR and serologic testing with radiological demonstration.

## ARTICLE HIGHLIGHTS

### **Research background**

Novel coronavirus disease (COVID-19) is unique pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that typically causes various degrees of respiratory disease. Currently, the entire world is battling COVID-19 pneumonia, which can be lethal in high-risk patient groups. Although COVID-19

diagnosis is generally made based on clinical, laboratory, and radiological features of the patients, the most common standard of care for diagnosis is the reverse transcription polymerase chain reaction (RT-PCR) assay.

### **Research motivation**

Several studies have indicated concerns regarding the sensitivity of RT-PCR tests, and an alternative rapid test is required to confirm the diagnosis by RT-PCR test.

### **Research objectives**

In this study; we aimed to investigate whether rapid antibody tests would be useful in the diagnostic challenge faced in suspected COVID-19 patients whose PCR tests were negative but has radiologically and clinically consistent features with COVID-19.

### **Research methods**

Eighty suspected COVID-19 patients who had at least two negative consecutive COVID-19 PCR tests and were subjected to serological rapid antibody tests were evaluated. The clinical and laboratory characteristics of serologically positive RT-PCR negative COVID-19 patients were presented in this study.

### **Research results**

The specific serological total immunoglobulin M/immunoglobulin G antibody against SARS-CoV-2 was detected in 22 patients. The most common presenting chest computed tomography findings were bilateral ground glass opacities (77.2%) and alveolar consolidations (50.09%). The mean duration of time from appearance of first symptoms to hospital admission, to hospital admission, to treatment duration and to serological positivity were 8.6, 11.2, 7.9, and 24 d, respectively. Compared with reference laboratory values, serologically positive patients have shown increased levels of acute phase reactants such as C-reactive protein, ferritin, and procalcitonin, higher inflammatory markers, such as erythrocyte sedimentation rate, lactate dehydrogenase enzyme, and fibrin end-products, such as D-dimer. A left shift on white blood cell differential was observed with increased neutrophil counts and decreased lymphocytes.

### **Research conclusions**

Rapid serological card tests can be a feasible alternative in the diagnosis and treatment algorithm of suspected COVID-19 cases.

### **Research perspectives**

An effective diagnosis for COVID-19 is likely to require a hybrid strategy of PCR and serologic testing with radiological demonstration.

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