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MINIREVIEWS

Antenatal corticosteroids in COVID-19 perspective

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Abstract

The aim of this manuscript is to discuss the practice of antenatal corticosteroids administration for fetal maturation in severe acute respiratory syndrome coronavirus 2 positive pregnant women. Recent high-quality evidence supports the use of dexamethasone in the treatment of hospitalized patients with coronavirus disease 2019 (COVID-19). Randomized disease outcome data have identified an association between disease stage and treatment outcome. In contrast to patients with more severe forms who benefit from dexamethasone, patients with mild disease do not appear to improve and may even be harmed by this treatment. Therefore, indiscriminate usage of fluorinated corticosteroids for fetal maturation, regardless of disease trajectory, is unadvisable. Obstetrical care needs to be adjusted during the COVID-19 pandemic with careful attention paid to candidate selection and risk stratification.

Key Words: Antenatal corticosteroids; COVID-19; Dexamethasone; Pregnancy; SARS-CoV-2; Preterm delivery

Core Tip: Evidence from the randomized evaluation of coronavirus disease 2019 therapy trial supports the use of dexamethasone in the setting of maternal respiratory disease requiring either invasive mechanical ventilation or oxygen alone but not for patients receiving no respiratory support. Dexamethasone will have the added benefit of promoting fetal maturity at < 34 wk gestation in cases at risk for preterm delivery. Fetal indications for antenatal corticosteroids should be limited to obstetrical indications resulting in a high probability of preterm delivery and indiscriminate usage of fluorinated corticosteroids for fetal maturation, regardless of disease stage, is unadvisable.

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INTRODUCTION

Early in the pandemic, the use of corticosteroids as a means of immune-modulatory therapy among patients with coronavirus disease 2019 (COVID-19) was considered relatively contraindicated based on limited data suggesting adverse outcomes in the previous coronavirus outbreaks (severe acute respiratory syndrome coronavirus 1 and Middle East respiratory syndrome coronavirus)[1]. This position was supported by a 2019 meta-analysis of 6548 patients with influenza pneumonia, demonstrating that the use of corticosteroids was associated with increased mortality and duration of intensive care unit stay[2].

Notwithstanding such concerns, during the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, methylprednisolone, and less frequently dexamethasone (DXM), have been used globally in as great as 50% of patients with COVID-19[3].A resultant systematic review on the role of corticosteroids in the management of COVID-19 identified 5 studies (4 retrospective and 1 prospective study) with mixed findings: 3 studies have shown benefit, while 2 studies failed to demonstrate benefit with one suggesting harm from a sub-study[3].

Renewed interest in the use of corticosteroid adjunct therapy in COVID-19 followed the recent publication of the randomized evaluation of COVID-19 therapy (RECOVERY) trial, which presented preliminary compelling evidence of benefit with the use of DXM[4]. The American College of Obstetricians and Gynecologists (ACOG) and several other national and international organizations shortly thereafter reversed their initial recommendations, now prioritizing DXM as the steroid of choice in pregnant women with COVID-19. It is worth shining a light on the RECOVERY trial with a critical lens at the available data emerging from it.

BENEFICIAL EFFECT OF CORTICOSTEROIDS IS DEPENDENT ON PATIENT SELECTION

The RECOVERY trial, which is still ongoing in the United Kingdom, is an open-label, multi-center, randomized controlled study, with several arms. The study design is pragmatic, and allows for the potential differentiation between several therapeutic agents (DXM, hydroxychloroquine, lopinavir-ritonavir, azithromycin, tocilizumab, and convalescent plasma) in hospitalized patients with COVID-19. In the arm assigned to DXM treatment (6 mg daily, orally or intravenously for 10 days, or until hospital discharge), a total of 2104 patients were randomized to receive the corticosteroid and they were compared with 4324 patients randomized to the standard of care. The primary outcome (28-d mortality) was significantly reduced from 25.7% to 22.9% (rate ratio 0.83, 95%CI: 0.75-0.93; $P < 0.001$). The therapeutic effect was directly proportional to the severity of illness. In patients receiving mechanical ventilation, mortality was reduced by about one third (29.3% *vs* 41.4%; rate ratio 0.64; 95%CI: 0.51-0.81) while in those receiving oxygen without invasive mechanical ventilation, the reduction in mortality was about one fifth (23.3% *vs* 26.2%; rate ratio 0.82; 95%CI: 0.72-0.94). A striking finding occurred among patients who did not require any respiratory support to maintain adequate oxygen saturation at the time of randomization; among them, mortality was 17.8% with DXM *vs* 14.0% without DXM (non-significant difference with a rate ratio 1.19; 95%CI: 0.91-1.55). Other small observational studies have also shown a lack of benefit with corticosteroids among patients with mild COVID-19[5], and we believe that the trend towards harm with the absence of benefit warrants ongoing consideration and caution with use. Specifically, while we concur that the RECOVERY trial supports the use of DXM among hospitalized COVID-19 patients with moderate to severe respiratory disease (*i.e.*, requiring mechanical ventilation or oxygen therapy), inferring benefit in the absence of harm for patients with mild or asymptomatic disease would be premature. Our perspective is shared by the authors of the RECOVERY trial themselves, as they stated that "It is likely that the beneficial effect of glucocorticoids…is dependent on a selection of the right dose, at the right time, in the

right patient"[4].Other guiding entities have reiterated this point, including the expert consensus opinion of the Chinese Thoracic Society that stated: "Corticosteroid treatment is a double-edged sword…we oppose liberal use of corticosteroids"[6].The take-home message from the frontlines is that appropriate and judicious patient selection for potential benefit is key[4],and that corticosteroids should not be administered indiscriminately[7] nor in the outpatient setting[8].

Recognizing that every day brings better understanding of the biologic underpinnings to COVID-19, it is generally accepted that while the viral dynamics are predictable, there is marked heterogeneity among patients as to if and when they will experience clinical disease[9]. Administering DXM during early phases of disease hallmarked by viral replication may actually impair the host's functional immune response, including dampening of innate immunity, disrupting T-cell dependent initiation of humoral immunity and inhibiting requisite cognate interactions with antigen presenting cells[9,10].The net effect of disrupting initiation of functional immunity includes the potential to not only increase the circulating viral load and promote transmissibility, but also hindrance of crucial interactions within the immune system necessary for the production of lasting immunity (inclusive of the production of neutralizing antibodies, critical for immunity on re-exposure). This is not merely a theoretical consideration, as early corticosteroid administration was shown to delay viral clearance and result in higher plasma viral loads in the SARS epidemic[11].

With respect to disease severity and clinical heterogeneity, we know that COVID-19 not only presents with cardiopulmonary symptoms ranging from mild to severe but, in a subgroup of patients, is also associated with systemic autoimmune inflammation as evidenced by elevated inflammatory markers (C-reactive protein, ferritin, D-dimer, IL-1, IL-2, IL-6, IL-7, tumor necrosis factor α, granulocyte-macrophage colony-stimulating factor, macrophage inflammatory protein 1-α; the so-called "cytokine storm")[12].This dysregulated systemic inflammation is thought to be a key contributor to the COVID-19-associated fatality rate and will typically lag behind active viral replication[13].In contrast to periods with high viral replication, it is both logical and evidence-based to anticipate that corticosteroids would be of benefit amongst this subset of patients in their course of clinically evident disease. For the better part of 6 decades we have understood that corticosteroids downregulate proinflammatory cytokine transcription, consequently preventing an over-extended cytokine response and accelerating the resolution of pulmonary and systemic inflammation[14,15].

In keeping with the RECOVERY findings, DXM, a widely available and inexpensive therapeutic agent, is recommended by the World Health Organization for the treatment of patients with severe and critical COVID-19, but not in the treatment of patients with non-severe COVID-19 (www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline). Similarly, the National Institutes of Health in the US recommend against using DXM in patients with COVID-19 who do not require supplemental oxygen (www.covid19treatmentguidelines.nih.gov).

BENEFICIAL EFFECT OF CORTICOSTEROIDS IS DEPENDENT ON THE DOSE

An emerging and common pattern arising from the aggregated analysis of the experience with the use of corticosteroids in the management of COVID-19 patients is the potential for benefit with low dose corticosteroids when compared to high dose protocols[3].It is considered that a low dose of corticosteroids should not exceed 1 mg/kg per day of methylprednisolone or equivalent (Table 1). The dose of DXM used in the RECOVERY trial (6mg daily) was carefully selected to be in the low dosage range. Although high doses may exert a more rapid anti-inflammatory effect, the associated risks of secondary infections, hyperglycemia, or psychosis are also increased. High dose corticosteroids concomitantly increase the neutrophil/lymphocyte ratio and D-dimer levels. The WAYFARER Study has identified an increased risk of thromboembolism with high doses of corticosteroids, a very concerning trend since COVID-19 itself may increase the risk of coagulopathy[16].

BENEFICIAL EFFECT OF CORTICOSTEROIDS IN PREGNANCY

In the RECOVERY trial, a small number of pregnant women were enrolled, but instead

Table 1 Synthetic corticosteroids – comparative chart

Compound	Equivalent dose	Anti-inflammatory activity	Mineralocorticoid activity
Dexamethasone	0.8 mg	25	0
Betamethasone	0.8 mg	25	0
Cortisone	25 mg	0.8	0.8
Hydrocortisone	20 mg	1	1
Prednisone	5 mg	4	0.6
Prednisolone	5 mg	4	0.6
Methylprednisolone	4 mg	5	0.25

of DXM they received either prednisolone or hydrocortisone at an equivalent dosage. Prednisolone, which is inactivated by placental 17alpha-hydroxylase, as well as hydrocortisone which is rapidly inactivated by fetal enzymes, are not expected to have fetal effects and the treatment was intended exclusively for maternal benefit. Only 6 pregnant women were such treated and their number is too small to allow for valid interpretations. With the same goal, of limiting the fetal exposure, methylprednisolone, which has very limited transplacental passage, has been recommended by some to replace at least partially the DXM in the treatment of pregnant women[17].The use of methylprednisolone in COVID-19 has been studied in several small controlled trials, with a mixture of positive and negative results[18-21].Given that the sample size of many of these trials was insufficient to assess efficacy, it is reasonable to conclude that the evidence to support the use of methylprednisolone is not as robust as that demonstrated for DXM. The effectiveness of methylprednisolone or lack thereof has not been established yet and several randomized trials are currently underway or in development. Moreover, DXM may be preferable to methylprednisolone because of its higher anti-inflammatory properties and lower mineralocorticoid activity (Table 1), being therefore less likely to cause sodium and fluid retention, a concern in these critically ill patients.

The RECOVERY trial did not address the administration of antenatal corticosteroids for the purpose of fetal maturation among pregnant women with COVID-19 and it is our opinion that ACOG (www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics) and a number of other guiding bodies did not exercise sufficient caution when extrapolating the results of the RECOVERY trial to the pregnant population. Evidence from the RECOVERY trial supports the use of DXM in the setting of maternal respiratory disease, and will have the added benefit of promotion of fetal maturity at < 34 wk gestation in cases at risk for preterm delivery. Even in cases not expected to deliver prematurely, given the potential benefit of decreased maternal mortality, it is ethically acceptable to expose the fetus to a short course of low-dose DXM. In consideration here, however, is the maternal risk of morbidity and death following corticosteroid exposure in asymptomatic or mild COVID-19 cases. Indeed, the great majority of pregnant women infected with SARS-CoV-2 are not candidates for DXM by virtue of failing to meet RECOVERY criteria[22]. In a single institution study from the United States, 95% of pregnant women infected with SARS-CoV-2 remained asymptomatic or had mild disease[23].The use of antenatal corticosteroids for fetal benefit should be judiciously considered and weighed against any potential harm to the pregnant patient based on her clinical status. It has been said that in a pandemic-adjusted clinical practice, the decisions must be precisely delineated based on level of risk rather than a reflexive "one size fits all" approach[24].

CONCLUSION

Based on the above evidence and considerations, with regard to the administration of antenatal corticosteroids for fetal maturation in SARS-CoV-2 infected pregnant women, we urge consideration of the following.

The safety signal of possibly increased mortality elicited in the RECOVERY trial among patients with mild COVID-19 receiving DXM should not discourage the appropriate use of a single course of fluorinated corticosteroids (betamethasone 12 mg

daily for 2 d or dexamethasone 4 doses of 6 mg 12 h apart) for mothers with impending (within 7 d) anticipated delivery at 24 to 34 wk. The fetal indications for antenatal corticosteroids should be limited to obstetrical indications resulting in a high probability of preterm delivery. Unfortunately, the track record of antenatal corticosteroids utilization in clinical practice is inviting concern. There is a tendency to give out antenatal corticosteroids more than it is truly necessary and several studies have reported on how poorly antenatal corticosteroids are timed; 30 to 80% of women receiving them for threatened preterm birth deliver at or after 34 wk[25]. A rigorous application of the existent guidelines is necessary, promoting minimally necessary exposure and elimination of indiscriminate usage.

Contrary to the well justified, standard of care use of antenatal corticosteroids for infants delivered at 24 to 34 wk, when the anticipated benefits of antenatal corticosteroids are minimal, potential maternal adverse effects become a highly relevant concern and assuming the risk of corticosteroids administration in asymptomatic or mild COVID-19 cases is no longer warranted. Rescue corticosteroid courses are not advisable and the administration of antenatal corticosteroids after 34 wk (late preterm) may be associated with an unfavorable risk/benefit ratio. The late preterm administration of corticosteroids does not reduce neonatal mortality, overall RDS, NICU admissions or need for mechanical ventilation[26].The benefit is primarily a reduction in transient tachypnea of the newborn, a typically mild and self-limited condition. Such a modest benefit pales when weighed against maternal risks. After 34 wk, the risk of antenatal corticosteroids administered to the SARS-CoV-2 positive mothers with asymptomatic or mild disease, in our opinion, outweighs the expected modest benefit to the neonate.

The decision to use (or not use) antenatal corticosteroids is best made in consultation with a multidisciplinary team that includes maternal fetal medicine and intensive care specialists who consider the phase of the disease and the potential for maternal harm. Corticosteroids should be used prudently and withheld when maternal comorbidities pose increased risk. One such example is heart failure secondary to ischemia, where corticosteroids should be avoided since they may potentiate infarction[27].

As on so many other times before in obstetrics, our decisions have to be based on extrapolation of data from non-pregnant populations. It is hoped that in the future, pregnant and lactating women will be included in therapeutic clinical trials of COVID-19. Moreover, recognition of the further disproportionality of underserved populations and the impact of social determinants of health on both acquisition and severity of disease should prompt ardent efforts at recruiting and retaining underserved populations of reproductive age and pregnant or lactating women.

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ORIGINAL ARTICLE

Retrospective Study

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

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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± 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

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 ± 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 ± 7.2, 11.2 ± 5.4, 7.9 ± 3.2 and 24 ± 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 azithromycine 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

	***n* (%)**
Agein yr	
mean ± SD	63.2 ± 13.1
Gender	
Male/Female	11/11
Symptoms, *n* (%)	
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 regiments of serologically positive reverse transcription polymerase chain reaction negative coronavirus disease 2019 patients

	***n* (%)**
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 ± SD
ESR in mm/h	68.5 ± 41.7
LDH in U/L	362 ± 152
CRP in mg/L	95 ± 101
Ferritinin µg/L	778 ± 684
WBCs	8621 ± 3549
Lymphocytes, *n* (%)	1430 ± 530
Lymphocytes, *n* (%)	22 ± 10.8
Neutrophils, *n* (%)	5390 ± 2450
Neutrophils as %	70.5 ± 12.3
D-Dimer in mg/L	1875 ± 2757
Procalcitonin in mg/L	0.15 ± 0.03

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

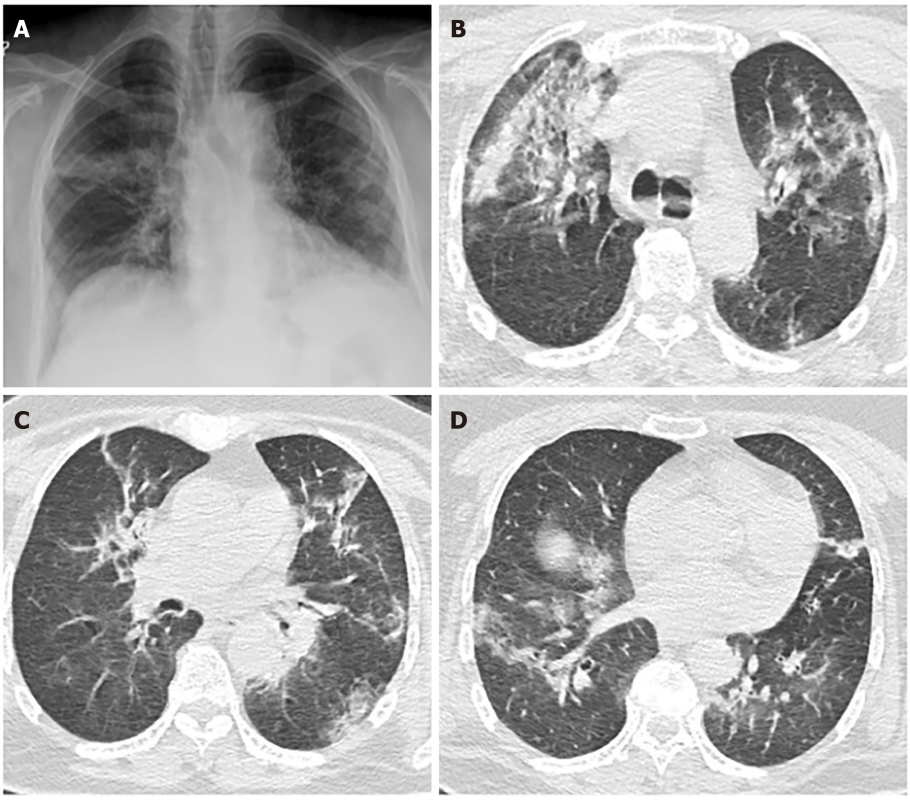

Figure 1 Example of the radiological images of a patient whose multiple reverse transcription polymerase chain reaction were negative but serological immunoglobulin M/immunoglobulin G against severe acute respiratory syndrome coronavirus 2 positive. A: Chest radiograph of coronavirus disease 2019 (COVID-19) 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

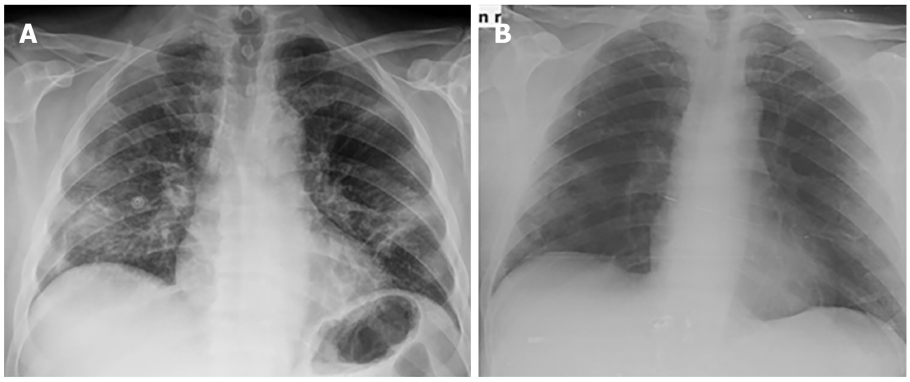

Figure 2 Example of the radiological images of a patient whose multiple reverse transcription polymerase chain reaction were negative but serological immunoglobulin M/immunoglobulin G against severe acute respiratory syndrome coronavirus 2 positive. A: Chest x-ray of the coronavirus disease 2019 (COVID-19)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

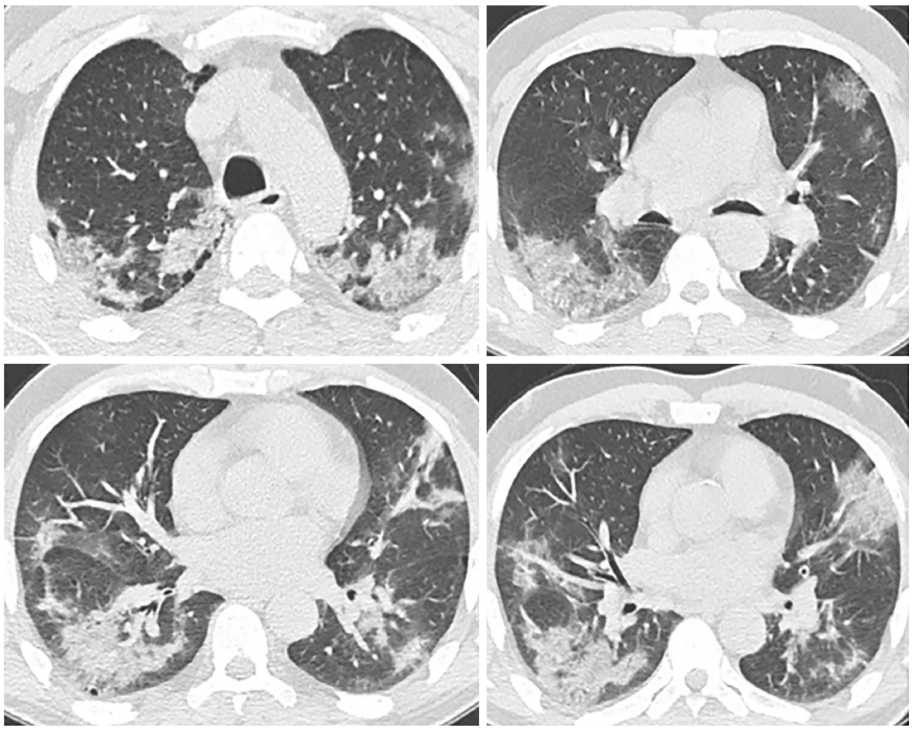

Figure 3 High resolution computed tomography images of coronavirus disease 2019 patient showing the bilateral ground-glass opacities and consolidations.

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 ± 7.2, 11.2 ± 5.4, 7.9 ± 3.2 and 24 ± 17 d, respectively. It was also reported that a higher titter 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.

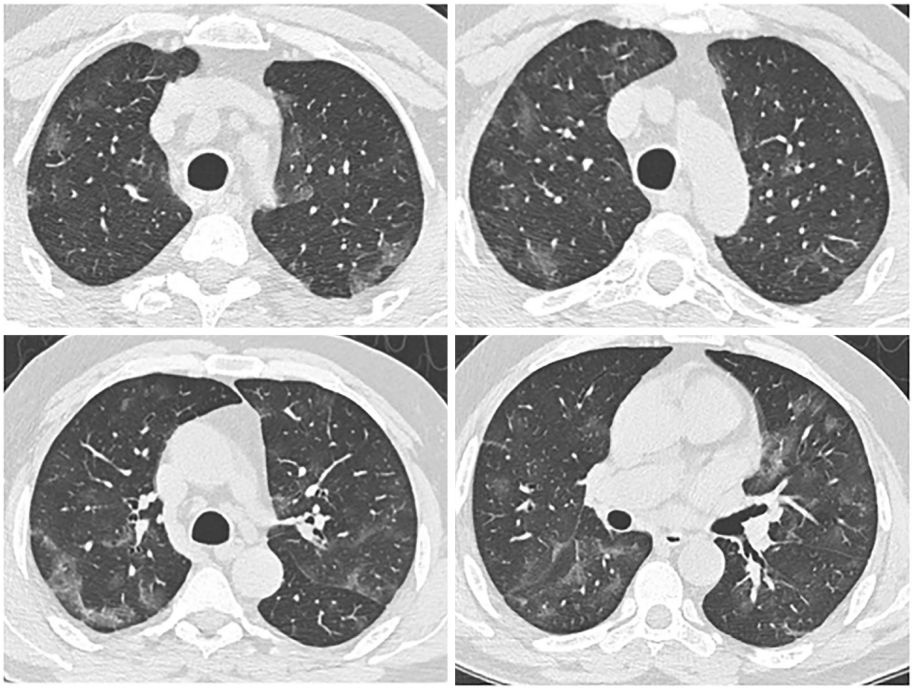

Figure 4 High resolution computed tomography images showing the bilateral patchy ground-glass opacities in a coronavirus disease 2019 patient.

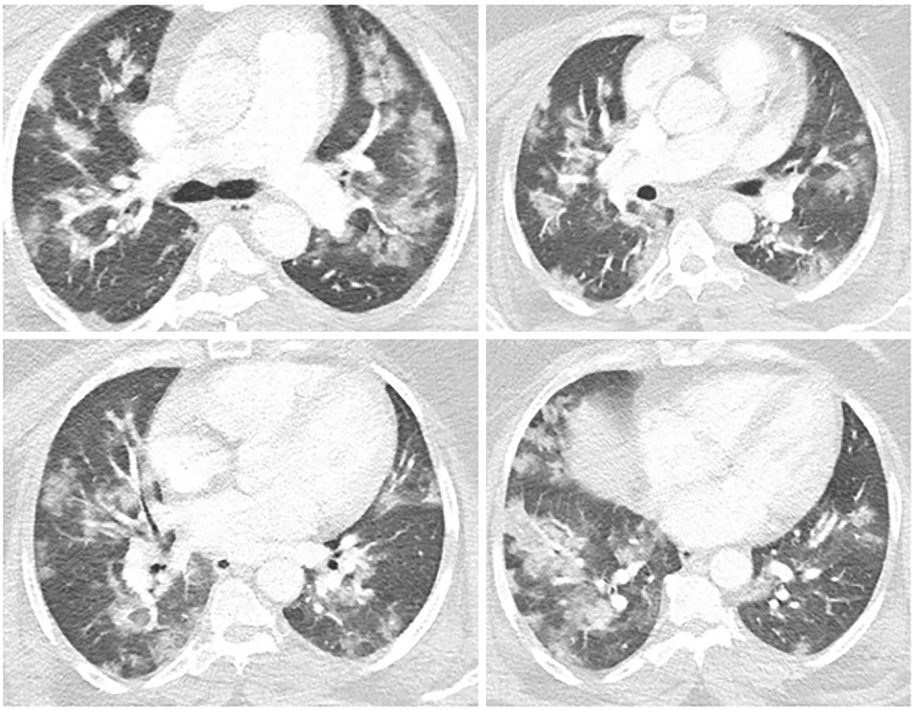

Figure 5 High resolution computed tomography images in a severe coronavirus disease 2019 patient showing the bilateral patchy ground-glass opacities with consolidations.

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-

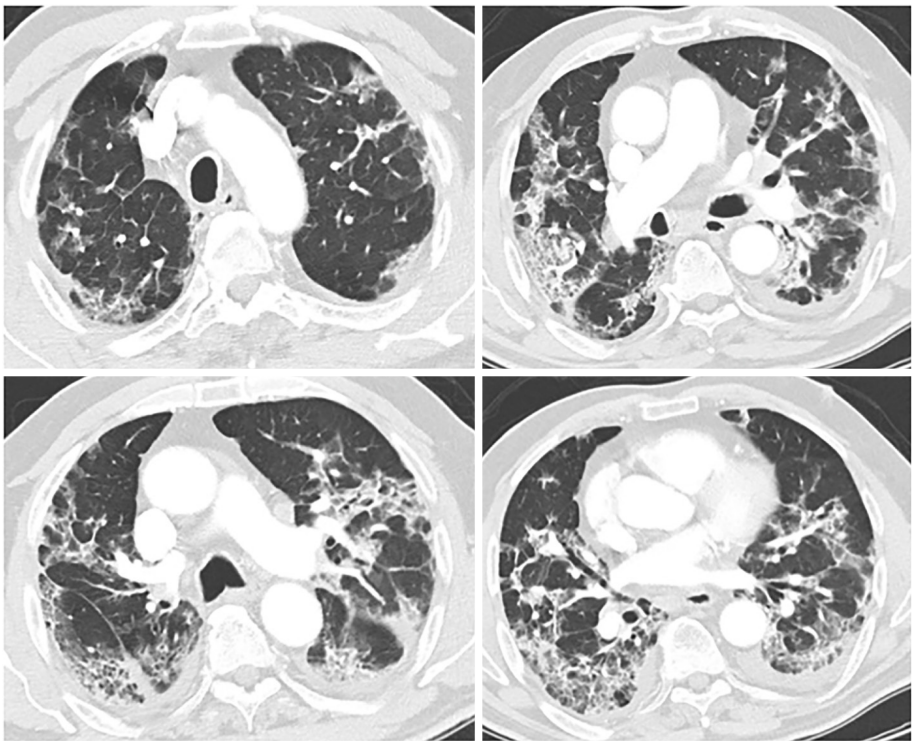

Figure 6 High resolution computed tomography images of a severe coronavirus disease 2019 patient showing the bilateral fibroreticular infiltrates with crazy-paving pattern.

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 establish 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.

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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