Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

Relationship between SARS-CoV-2 antibody titer and the severity of COVID-19

Joung Ha Park [a,1], Min Jae Cha [b,1], Hyewon Choi [b], Min-Chul Kim [a], Jin-Won Chung [c], Kyu-Sun Lee [d], Dae Gwin Jeong [d], Moon Seong Baek [e], Won-Young Kim [e], Yaeji Lim [f], Sun Woo Yoon [d,], Seong-Ho Choi [c,*]**

[a] *Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, South Korea*
[b] *Department of Radiology, Chung-Ang University Hospital, Seoul, South Korea*
[c] *Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, South Korea*
[d] *Bionanotechnology Research Center, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea*
[e] *Department of Internal Medicine, Chung-Ang University Hospital, Seoul, South Korea*
[f] *Department of Applied Statistics, Chung-Ang University, Seoul, South Korea*

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Abstract *Background:* It remains unclear whether high titers of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies aggravate clinical manifestations in patients or whether severe clinical manifestations result in high antibody titers. Thus, we investigated the cause—effect relationship between SARS-CoV-2 antibody titers and disease severity.
Methods: We prospectively enrolled patients admitted with the diagnosis of coronavirus disease-19 (COVID-19) from February 2020 to August 2020. We measured SARS-CoV-2 antibody titers, namely anti-receptor-binding domain (RBD) antibody and neutralizing antibody (NAb), from blood samples and calculated the chest radiograph (CXR) scores of the patients to evaluate the severity of COVID-19.
Results: Overall, 40 patients with COVID-19 were enrolled. Pneumonia was observed in more than half of the patients (25/40, 60%). SARS-CoV-2 antibody titers were higher in patients who were aged >60 years (anti-RBD antibodies, P = 0.003 and NAb, *P* = 0.009), presented with pneumonia (*P* = 0.006 and 0.007, respectively), and required oxygen therapy (*P* = 0.003 and 0.004, respectively) than in those who were not. CXR scores peaked (at 15

* Corresponding author. Fax: +82 2 6299 2064.
** Corresponding author. Bionanotechnology Research Center, Korea Research Institute of Bioscience and Biotechnology, Daejeon, South Korea.
E-mail addresses: syoon@kribb.re.kr (S.W. Yoon), tobeservant@cau.ac.kr (S.-H. Choi).
[1] These authors equally contributed to this work.

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−21 days after the onset of symptoms) statistically significantly earlier than SARS-CoV-2 antibody titers (at 22−30 days for NAb and at 31−70 days for anti-RBD antibody). There was a close correlation between the maximum CXR score and the maximum SAR-CoV-2 antibody titer.
Conclusions: Based on the comparison of the peak time of SARS-CoV-2 antibody titers with the CXR score after symptom onset, we suggest that severe clinical manifestations result in high titers of SARS-CoV-2 antibodies.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China at the end of 2019, and the resulting coronavirus disease (COVID-19) pandemic has been threatening the healthcare system worldwide.[1] COVID-19 exhibits various clinical manifestations, from asymptomatic infection to critical illness.[2] The main pathophysiology of COVID-19 is an effect of SARS-CoV-2 itself, such as active viral replication in the early stage of COVID-19. In contrast, the host immune responses to SARS-CoV-2 have a critical role in the late stage of the disease.[3−7] Thus, while treatment strategies for COVID-19 targeted the virus with antiviral agents in the early stage of the disease,[8] the suppression of exuberant host immune responses using immunomodulatory agents and dexamethasone occurred in the late stage.[9−11]

With the emergence of the importance of host immune responses, several studies have assessed the effect of host immune responses against SARS-CoV-2 on the clinical course of COVID-19. Although host immune responses usually control viral replication and protect against viral invasion, inappropriate and overwhelming immune responses such as cytokine release syndrome could worsen the course of COVID-19.[4] Additionally, the role of antibody-mediated immune responses in COVID-19 is not well established. Previous studies reported that severe clinical manifestations in patients with COVID-19, such as the need for mechanical ventilation or death, correlated with high titers of SARS-CoV-2 antibodies.[12,13] However, it remains unclear whether high titers of SARS-CoV-2 antibodies aggravate clinical manifestations in patients or severe clinical manifestations result in high antibody titers.[12] Therefore, in this study, we aimed to investigate the cause−effect relationship between SARS-CoV-2 antibody titers and disease severity. Titers of anti-receptor-binding domain (RBD) antibodies and neutralizing antibodies (NAbs) were used for SARS-CoV-2 antibody titers, and the chest radiograph (CXR) scores for disease severity.

Methods

Study population and study design

The study was performed prospectively from February 2020 to August 2020 at Chung-Ang University Hospital in Seoul, South Korea. We prospectively enrolled 40 patients with COVID-19 who were admitted to specially designed isolation rooms with negative pressure and provided consent for the use of their blood samples for detecting SARS-CoV-2 antibody titers and respiratory samples for detecting the *RdRp* gene of the virus. Demographic and clinical characteristics of the patients were reviewed using electronic medical records. Informed consents were obtained from all participants, and the study protocol was approved by the institutional review board of the hospital (IRB No. 2060-001-418).

Definitions

The severity of COVID-19 was defined based on the COVID-19 treatment guidelines suggested by the National Institutes of Health.[2] Among the patients who test positive for SARS-CoV-2 using a virologic test, we defined asymptomatic cases as those with no symptoms, mild illness as those with any of the various signs and symptoms of COVID-19 but without shortness of breath, dyspnea, or abnormal chest imaging, moderate illness as those with evidence of lower respiratory disease and an oxygen saturation (SpO2) $\geq$94% on room air at sea level, severe illness as those with SpO2 $<$94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) $<$300 mm Hg, respiratory frequency $>$30 breaths/min, or lung infiltrates $>$50%, and critical illness as those with respiratory failure, septic shock, and/or multiple organ dysfunction. Fever was defined as a body temperature of $>$37.5 °C. Severe pneumonia was defined based on air-space opacity of more than half of the whole lung. Oxygen (O2) requirement was defined as patients who were applied with oxygen therapy because they had evidence of lower respiratory disease and SpO2 $<$94% on room air at sea level. The viral load of SARS-CoV-2 was evaluated using the cycle threshold (Ct) value of the *RdRp* gene of the virus obtained from nasopharyngeal swab and sputum samples.

SARS-CoV-2 antibody tests for patients with COVID-19

We obtained blood samples of patients to evaluate the changes in total antibody titers to SARS-CoV-2 from the date of admission and throughout their hospitalization periods. We planned to collect samples at 2-day intervals of weekdays, although this was not always possible. We

detected anti-RBD antibodies against the RBD of the SARS-CoV-2 S protein using an enzyme-linked immunosorbent assay. The assay provided semiquantitative results regrading anti-RBD antibodies by calculating the ratio of the optical density (OD, 450 nm) of the serum sample over the OD (450 nm) of the calibrator. Additionally, to detect NAbs against SARS-CoV-2, the SARS-CoV-2 strain (BetaCoV/South Korea/KUMC01/2020), which was isolated from a Korean patient with COVID-19, was purchased from the National Culture Collection for Pathogens (Osong, South Korea). The virus was titrated in serial dilutions (1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, and 1:1280) and mixed with 1×10^2 50% tissue culture infective dose (TCID50) on 96-well culture plates of Vero E6 cells for 1 h. We then observed the plates after 72 h for the presence of cytopathogenic effect using an inverted optical microscope (DMiL Inverted Microscope, Leica).[14] All SARS-CoV-2 experiments conducted at KRIBB (Daejeon, South Korea) under the approval and in accordance with the guidelines of the Institutional Biosafety Committee (IBC, approval number KRIBB-IBC-20200208) of KRIBB. Experimental work with SARS-CoV-2 conducted in a biosafety level-3 (BL-3) facility at KRIBB.

CXR acquisition

All CXRs were obtained using a digital radiography system (DRX-Revolution, Carestream Health, Rochester, NY, USA). Patients underwent initial CXRs on their hospital day 1 and serial CXRs (interval, 1–7 days) according to their clinical status during hospitalization. All CXRs comprised a single frontal view, either an anteroposterior or a posteroanterior projection.

CXR scoring system for evaluating the severity of pneumonia caused by COVID-19

A chest radiologist (MJC, with 11 years of clinical experience in thoracic imaging), blinded to patients' information except for the knowledge that these were SARS-CoV-2 pneumonia cases, evaluated CXRs. On each radiograph, the lung was divided into six lung zones: upper lung zones (above carina), middle lung zones (upper half of the craniocaudal distance of the remaining lung), and lower lung zones (lower half of the craniocaudal distance of the remaining lung). The parenchymal abnormality on CXRs was graded on a 3-point scale (1, normal; 2, ground-glass attenuation; and 3, consolidation), and the extent was graded on a 5-point scale according to the affected lung area (0, not affected; 1, <25%; 2, 25%–50%; 3, 50%–75%; and 4, >75%). In each zone, the parenchymal abnormality grade and extent grade were multiplied, and final severity scores were obtained by adding scores from each lung zones (ranging from 0 to 72).[15]

Statistical analyses

SARS-CoV-2 antibody titers were compared according to clinical variables using the Student's *t*-test or Mann–Whitney *U* test, as appropriate. To investigate the cause–effect relationship between antibody titers and severity of COVID-19, we computed the differences between the peak time of CXR score and the peak time of NAb (or anti-RBD antibody). Then we performed one-sample Wilcoxon signed rank test with continuity correction to test the median of the peak time differences is less than zero, which implies the peak time of CXR score occurs before the peak time of NAb (or anti-RBD antibody). We further conducted the linear regression model between the maximum CXR score and the maximum NAb (or anti-RBD antibody). A P value < 0.05 indicated statistical significance. All statistical analyses were performed using the R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Overall, 40 patients with COVID-19 were enrolled in this study. The clinical characteristics of these patients are presented in Table 1. Most patients had mild (14/40, 35%), moderate (12/40, 30%), and severe manifestations (11/40, 27%) of COVID-19. Pneumonia was observed in more than half of the patients (25/40, 60%) and severe pneumonia in approximately one-third of the patients (12/40, 30%). Most

Table 1 Clinical characteristics of the study population.

Variables	Patients (n = 40)
Age, years, median (IQR)	61 (37–69)
Male sex (%)	27 (68)
Underlying diseases	23 (58)
Hypertension	15 (38)
Diabetes mellitus	7 (18)
Underlying lung diseases	2 (5)
Malignancy	2 (5)
Others	2 (5)
Disease severity	
Asymptomatic	1 (3)
Mild	14 (35)
Moderate	12 (30)
Severe	11 (27)
Critical	2 (5)
Clinical manifestations	
Fever for >7 days	8/39[a] (21)
Pneumonia	25 (63)
Severe (≥50% air-space opacity in the whole lung)	12 (30)
O_2 requirement	13/39[a] (33)
High-flow or mechanical ventilation	5/39[a] (13)
Treatment	
Remdesivir	2 (5)
Dexamethasone	4 (10)

[a] One patient was transferred from another hospital after more than 1 month because she was diagnosed with deep neck infection during hospitalization. After transfer, her respiratory samples showed continuously negative results for severe acute respiratory syndrome coronavirus 2.
Data are presented as number (%) unless otherwise indicated.
Abbreviations: IQR, interquartile range.

patients received conservative care for COVID-19. The viral loads of SARS-CoV-2 based on the Ct value of the *RdRp* gene were the highest in the early phase of the disease and had a tendency to decrease according to the days after the onset of symptoms (Supplementary figure 1). We compared SARS-CoV-2 antibody titers, both anti-RBD antibody and NAb titers, according to patients' clinical variables (Table 2). Patients who were aged >60 years had higher titers of both anti-RBD antibody (1.22 vs. 0.46, $P = 0.003$) and NAb (320.0 vs. 40.0, $P = 0.009$). Moreover, both antibody titers were higher in patients with pneumonia (anti-RBD antibody, $P = 0.006$ and NAb, $P = 0.007$) or those who required oxygen (anti-RBD antibody, $P = 0.003$ and NAb, $P = 0.004$) than in those without pneumonia or oxygen requirement. There was no significant difference in SARS-CoV-2 antibody titers between the groups stratified by sex, underlying diseases, fever, and high-flow oxygen requirement or the need for mechanical ventilation.

SARS-CoV-2 antibody titers and CXR score

We described the change in antibody titers and CXR scores according to the days after the onset of symptoms to investigate the cause–effect relationship between the antibody titers and severity of COVID-19 in Fig. 1. The NAb titer peaked at 22–30 days after the onset of symptoms, whereas the CXR score peaked earlier at 15–21 days. Similarly, the peak time of the CXR score was earlier than that of the anti-RBD antibody titer (15–21 days vs. 31–70 days). To determine the temporal relationships are statistically significant, we performed one-sample Wilcoxon signed rank test with continuity correction. The median of peak time differences between the CXR score and the NAb titer was less than zero ($V = 20$, $P < 0.0001$), and that of peak time differences between the CXR score and the anti-RBD antibody titer was also less than zero ($V = 3$, $P < 0.0001$). Thus, the change in the CXR score appears earlier than that in the NAb titer or anti-RBD antibody titer. The linear regression model between the maximum CXR score and the maximum NAb titer ($Y = 130 + 19X$, $R^2 = 0.41$, $P < 0.0001$) and that between the maximum CXR score and the maximum anti-RBD antibody titer ($Y = 0.74 + 0.023X$, $R^2 = 0.32$, $P = 0.000127$) were shown in Fig. 2.

Discussion

In our study, SARS-CoV-2 antibody titers were higher in patients with COVID-19 who were elderly, presented with pneumonia, and required oxygen supply. When we compared the peak time of SARS-CoV-2 antibody titers and CXR scores, CXR scores peaked statistically significantly earlier than SARS-CoV-2 antibody titers (NAb and anti-RBD antibody titers). There was a close correlation between the maximum CXR score and the maximum SAR-CoV-2 antibody

Table 2 SARS-CoV-2 antibody titer according to clinical variables in the study population.

Variables	RBD ELISA, median (IQR)	*P*-value	NAb, median (IQR)	*P*-value
Sex		0.113		0.303
Male (n = 27)	0.80 (0.36–1.27)		80.0 (20.0–320.0)	
Female (n = 13)	1.20 (0.68–1.58)		320.0 (45.0–640.0)	
Age, years		0.003		0.009
≥60 (n = 21)	1.22 (0.85–1.66)		320.0 (80.0–640.0)	
<60 (n = 19)	0.46 (0.36–1.04)		40.0 (10.0–160.0)	
Underlying disease		0.165		0.066
Yes (n = 23)	0.91 (0.52–1.33)		160.0 (40.0–640.0)	
No (n = 17)	0.53 (0.30–1.36)		40.0 (10.0–320.0)	
Fever		0.279		0.132
≥7 days (n = 8)	1.12 (0.49–1.84)		480.0 (50.0–640.0)	
<7 days (n = 31)	0.83 (0.36–1.27)		80.0 (20.0–320.0)	
Pneumonia		0.006		0.007
Yes (n = 25)	1.22 (0.49–1.59)		320.0 (60.0–640.0)	
No (n = 15)	0.53 (0.30–0.89)		40.0 (10.0–160.0)	
Severe pneumonia (≥50% airspace opacity in the whole lung)		0.052		0.014
Yes (n = 12)	1.47 (1.00–1.88)		640.0 (320.0–1120.0)	
No (n = 13)	0.87 (0.42–1.25)		80.0 (30.0–240.0)	
O_2 requirement		0.003		0.004
Yes (n = 13)	1.43 (0.94–1.81)		320.0 (80.0–960.0)	
No (n = 26)	0.61 (0.35–0.99)		60.0 (10.0–160.0)	
High-flow O_2 or MV		0.639		0.610
Yes (n = 5)	1.33 (0.33–1.74)		320.0 (25.0–640.0)	
No (n = 34)	0.88 (0.38–1.28)		80.0 (20.0–320.0)	

Abbreviations: RBD, receptor-binding domain; ELISA, enzyme-linked immunosorbent assay; NAb, neutralizing antibody; IQR, interquartile range; MV, mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

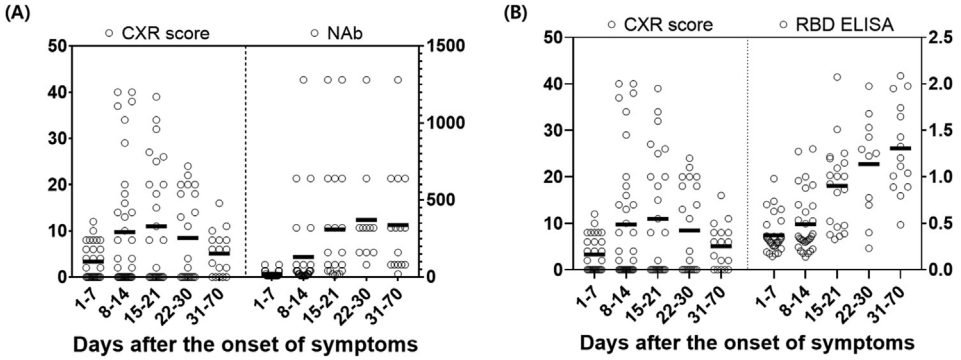

Figure 1. SARS-CoV-2 antibody titer and chest X-ray (CXR) score according to the days after the onset of COVID-19 symptoms. **(A)** Serum virus neutralization assay and CXR score, and **(B)** ELISA-based anti-RBD antibody assay and CXR score. RBD, receptor-binding domain; ELISA, enzyme-linked immunosorbent assay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NAb, neutralizing antibody.

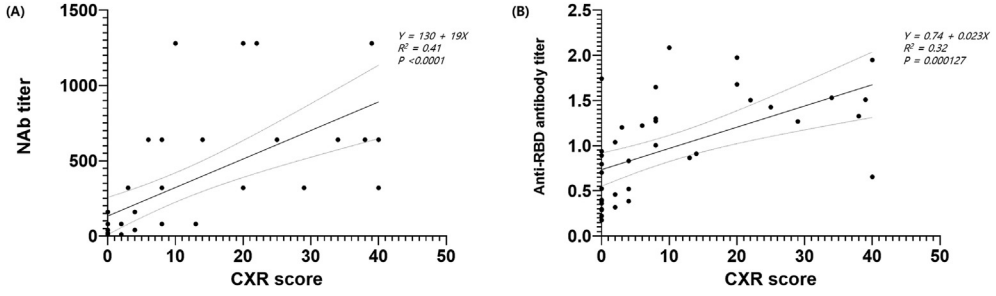

Figure 2. Linear regression models between SARS-CoV-2 antibody titer and the severity of pneumonia based on the chest X-ray (CXR) score. **(A)** Between serum virus neutralization assay and CXR score, and **(B)** between ELISA-based anti-RBD antibody assay and CXR score. RBD, receptor-binding domain; ELISA, enzyme-linked immunosorbent assay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NAb, neutralizing antibody.

titer. Thus, we speculated that high SARS-CoV-2 antibody titers resulted from severe clinical manifestations of COVID-19.

Generally, when pathogens such as viruses invade the human body, innate and adaptive immune responses protect us from virus invasion and replication. Among adaptive immunity against viruses, cellular immunity has a major role in viral clearance. However, the role of humoral immunity in viral clearance is controversial and usually plays a role in prevention and protection from new viral infections, which is the basis for the development of vaccination against viruses.[16] Since high titers of SARS-CoV-2 antibodies correlated with disease severity and mortality, there has been an argument that the overproduction of antibodies against SARS-CoV-2 induced disease progression of COVID-19 via antibody-dependent enhancement (ADE), which is well documented for the dengue virus.[7,17] The possibility of ADE was supported by a high titer but low NAb potency against SARS-CoV-2, which was more common in severe cases of COVID-19, and proinflammatory cytokines such as interleukin-6 correlated with low NAb potency in these cases.[18] However, previous studies on convalescent plasma therapy for COVID-19 patients reported no significant severe adverse events when compared with standard care for COVID-19 patients.[19–21] Additionally, animals vaccinated SARS-CoV-2 did not show any symptoms and signs of ADE.[22] Thus, these results supported that ADE would not be the major pathogenesis of the disease progression of COVID-19. Rather, other researchers argued that uncontrolled viral replication and hyperinflammatory status aggravates the course of COVID-19, which induces high titers of antibodies against SARS-CoV-2. Therefore, the cause—effect relationship between SARS-CoV-2 antibody titers and disease severity remains controversial.

In our study, SARS-CoV-2 antibody titers were higher in patients with pneumonia or oxygen requirement, which was consistent with the findings of other studies.[12,23] When considering our data about comparing the time of peak level of SARS-CoV-2 antibodies and CXR score, along with several reports to date, we speculated that high titers of SARS-CoV-2 antibodies (NAb and anti-RBD antibodies) would be induced owing to high viral loads, uncontrolled viral replication, and dysregulated immune responses in patients with severe illnesses. Additionally, elderly patients had higher titers of NAb and anti-RBD antibody than young patients in our study. In previous studies, there were more critically ill patients, and the mortality rate was the highest in elderly COVID-19 patients aged 65 years.[6,24] While the mortality rate was $<$5% in younger patients, the rate ranged from 35% to $>$60% in elderly patients aged $>$70 years.[24] Therefore, we believe that these findings may be because of the high risks of presenting with severe manifestations of COVID-19 in elderly patients. Because exhaustion of T cell immunity and cytokine release syndrome could also be

associated with unfavorable prognosis in patients with COVID-19 as described in previous studies,[25, 26] we also tested the changes of proinflammatory cytokines, including interleukin-6 and tumor necrosis factor-α (Supplementary Figure 2 and Supplementary Figure 3). However, because the results of these tests were available only in 15 patients, we could not draw a firm conclusion of the interactions among T- and B-cell immunity, proinflammatory cytokines and the disease severity of COVID-19. Further studies are needed to analyze these relationships between the immune responses against SARS-CoV-2 and the disease severity in a larger study population.

Our study had several limitations. First, because our study was performed at a single hospital with a relatively small sample size, there could be a selection bias. Second, because this study was performed in the early period of COVID-19 pandemic, there were rare cases using remdesivir and dexamethasone, which is the current treatment of choice recommended for COVID-19 patients with oxygen requirements.[8,11] Because the use of corticosteroids could suppress host immune responses,[12] further studies are needed to investigate how these current treatment agents affect SARS-CoV-2 antibody titers in patients with COVID-19. Third, we did not evaluate the neutralization potency of the SARS-CoV-2 antibody; thus, we could not verify whether the high titers of NAb directly correlated with their potent neutralizing role against SARS-CoV-2. Finally, some patients were transferred from other hospitals for further medical care, and antibody tests from patients' blood samples were not performed on the same schedules for all patients.

In conclusion, although high titers of SARS-CoV-2 antibodies correlated with the severity of COVID-19 as reported in other previous studies, it seems that severe clinical manifestations of COVID-19 resulted in high titers of SARS-CoV-2 antibodies. Elucidating how host immune responses, particularly humoral immunity, are related to disease severity and pathogenesis in COVID-19 patients would be useful to develop novel therapeutics and immunization against SARS-CoV-2 in the future. Therefore, further studies are needed to prove our suggestion and analyze NAbs' potency against SARS-CoV-2 in a larger population.

Declaration of competing interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.04.005.