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

Out-of-hospital cardiac arrest and in-hospital mortality among COVID-19 patients: A population-based retrospective cohort study

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KEYWORDS
SARS-CoV-2;
COVID-19;
Out-of-hospital cardiac arrest;
Mortality;
Hypoxemia

Abstract *Background/purpose:* Predictors for out-of-hospital cardiac arrest (OHCA) in COVID-19 patients remain unclear. We identified the predictors for OHCA and in-hospital mortality among such patients in community isolation centers.
Methods: From May 15 to June 20, 2021, this cohort study recruited 2555 laboratory-confirmed COVID-19 patients admitted to isolation centers in Taiwan. All patients were followed up until death, discharge from the isolation center or hospital, or July 16, 2021. OHCA was defined as cardiac arrest confirmed by the absence of circulation signs and occurring outside the hospital. Multinomial logistic regressions were used to determine factors associated with OHCA and in-hospital mortality.
Results: Of the 37 deceased patients, 7 (18.9%) had OHCA and 30 (81.1%) showed in-hospital mortality. The mean (SD) time to OHCA was 6.6 (3.3) days from the symptom onset. After adjusting for demographics and comorbidities, independent predictors for OHCA included age ≥65 years (adjusted odds ratio [AOR]: 13.24, 95% confidence interval [CI]: 1.85—94.82), fever on admission to the isolation center (AOR: 12.53, 95% CI: 1.68—93.34), and hypoxemia (an oxygen saturation level below 95% on room air) (AOR: 26.54, 95% CI: 3.18—221.73). Predictors for in-hospital mortality included age ≥65 years (AOR: 10.28, 95% CI: 2.95—35.90), fever on admission to the isolation centers (AOR: 7.27, 95% CI: 1.90—27.83), and hypoxemia (AOR: 29.87, 95% CI: 10.17—87.76).
Conclusions: Time to OHCA occurrence is rapid in COVID-19 patients. Close monitoring of patients' vital signs and disease severity during isolation is important, particularly for those with older age, fever, and hypoxemia.

Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global pandemic since January 2020. As of April 30, 2022, 510.3 million individuals have been infected with SARS-CoV-2, with the number of deaths reaching 6.2 million.[1]

Taiwan had the first COVID-19 community outbreak in May 15, 2021, with 187 laboratory-confirmed COVID-19 cases reported to Taiwan CDC in a single day.[2] Since then, 12,530 COVID-19 cases with the predominance of the alpha-variant were reported to Taiwan CDC from May 15 to June 20, 2021.[2,3] As of May 16, 2021, 0.8% of the Taiwanese population received the first dose of the COVID-19 vaccine.[4] During the COVID-19 outbreak in Taiwan, infectious patients with moderate or severe symptoms were admitted to hospitals, and received antiviral treatment.[5] However, asymptomatic COVID-19 patients and those with mild disease were referred to designated isolation centers to avoid hospital ward overloading.[5]

The COVID-19 pandemic has overloaded hospital wards and challenged the intensive care unit bed capacity in many countries.[6] According to the Centers for Disease Control (CDC) guidelines, COVID-19 patients with mild or asymptomatic disease are recommended to be self-isolated at home or in community isolation centers.[7] However, some patients with mild clinical presentation may progress to severe disease during the COVID-19 isolation.[8] Therefore, during patient isolation, it is important to closely monitor patients' symptoms to avoid severe outcomes, such as out-of-hospital cardiac arrest (OHCA).

Reports have documented an increasing incidence of OHCA during the COVID-19 pandemic.[9—11] A study from Paris showed a transient two-fold increase in OHCA incidence during the COVID-19 pandemic.[9] Another study from Italy showed a 58% increase in OHCA early in the COVID-19 outbreak.[11] Coleman et al. found that an increasing burden of regional COVID-19 infection was positively associated with an increasing incidence of OHCA.[10] However, these previous reports were only able to show an increasing incidence of OHCA during the COVID-19 pandemic but did not address the issue to clarify the risk factors associated with OHCA in SARS-COV-2-infected individuals.[9—11] To the best of our knowledge, no study has determined the predictors for OHCA in COVID-19 patients. Therefore, we conducted this cohort study to identify the predictors for OHCA and death after admission to the hospitals among COVID-19 patients in community isolation centers.

Methods

Study subjects

This cohort study recruited COVID-19 patients who were admitted to the designated isolated centers from May 15 to June 20, 2021, in Taipei, Taiwan. The diagnosis of COVID-19 was confirmed by positive real-time reverse transcriptase—polymerase chain reaction (RT-PCR) tests.

When COVID-19 patients were admitted to the designated isolated centers, their demographic data, clinical symptoms, and comorbidities were recorded. All COVID-19 patients were followed up until death, their discharge from the isolated centers or hospitals, or July 16, 2021. This study was approved by the Institutional Review Board of Taipei City Hospital (TCH) (no. TCHIRB-10904014-E).

Clinical management of coronavirus disease 2019 (COVID-19) patients

During the period of COVID-19 isolation, patients' clinical symptoms and body temperature were recorded thrice daily by their primary care nurses. Pulse oximetry was used to assess and monitor patients' oxygenation status. Supplemental oxygen was provided for those with hypoxemia, which was defined as a saturation drop below 95%. If patients developed fever or became ill, a multidisciplinary team (MDT) consisting of physicians, nurses, and pharmacists used telehealth to assess the patients' condition. The MDT members collaboratively discussed the patient's condition during the telehealth service and provided appropriate management for the patient. If a patient at the designated isolation center presented with difficulty breathing or persistent hypoxemia after supplemental oxygen therapy, the patient was transferred to the hospital for further treatment.

Deisolation of COVID-19 patients at the designated isolation centers was contingent on the following conditions: (1) afebrile for more than 24 h and (2) negative PCR assay result or cycle threshold value $\geq$ 30 on the 10th day of isolation.[12]

Outcome variables

The outcome variables in COVID-19 patients included OHCA, in-hospital mortality, and survival. OHCA was defined as a cardiac arrest that occurred outside of a hospital setting and was confirmed by the absence of signs of circulation.[13] Survivals included COVID-19 patients who were discharged from isolation centers or hospitals.

Statistical analyses

First, the demographic data of the study subjects were analyzed. Continuous data are presented as the mean (standard deviation [SD]), and one-way analysis of variance (ANOVA) was used for intergroup comparisons. Categorical data were analyzed using the Pearson χ^2 test, as appropriate.

A timeline infographic was used to display the progression of clinical symptoms in patients with OHCA. Multivariate logistic regression was used to identify the factors associated with mortality in COVID-19 patients. Moreover, this study used multinomial logistic regression to determine the factors associated with OHCA and in-hospital mortality after adjusting for potential confounders. Variables with $p < 0.05$ were considered significant factors associated with OHCA and in-hospital mortality in the multivariate analysis. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were reported to indicate the strength and direction of the association. All data management and analyses were performed using the Statistical Analysis System (SAS) version 9.4 statistical software package (SAS Institute, Cary, NC, USA).

Results

Patient selection

From May 15 to June 20, 2021, 2690 Taiwanese citizens infected with SARS-CoV-2 were admitted to the designated COVID-19 isolation centers in Taipei, Taiwan. After excluding patients aged <18 years (n = 125), those with missing data (n = 8), and those who were still hospitalized (n = 2), the remaining 2555 COVID-19 patients were included in the analysis. The overall mean (SD) age was 50.8 (15.4) years, 50.2% of the subjects were male, and 1.5% of patients received COVID-19 vaccination. During the study follow-up period, 37 patients died in the isolated centers or hospitals, including 7 (18.9%) OHCA and 30 (81.1%) in-hospital mortality. None of the vaccinated individuals died.

Characteristics and clinical features of COVID-19 patients by treatment outcomes

Table 1 shows the characteristics and clinical features of COVID-19 patients in the community isolation centers. Compared to COVID-19 patients with survival, those with OHCA or in-hospital mortality were older and usually male. In terms of clinical symptoms, patients with OHCA or in-hospital mortality were more likely to exhibit fever upon admission to isolation centers and manifest hypoxemia during the COVID-19 isolation period. With respect to comorbidities, patients with OHCA or in-hospital mortality had a higher proportion of diabetes, hypertension, and cardiovascular diseases. During the COVID-19 isolation period, 1046 patients received telehealth services, including 5 (71.43%) in patients with OHCA, 13 (43.33%) in patients with in-hospital mortality, and 1028 (40.83%) in patients with survival.

Clinical symptoms in COVID-19 patients with out-of-hospital cardiac arrest

Table 2 shows the clinical symptoms of COVID-19 patients with OHCA. Of the seven patients with OHCA, the age ranged from 49 to 72 years, and 2 (28.6%) exhibited fever on admission to the COVID-19 isolation centers.

The progression of clinical symptoms in COVID-19 patients with OHCA is shown in Fig. 1. The overall mean (SD) time to OHCA was 6.6 (3.3) days from the symptom onset. Two patients with OHCA manifested hypoxemia and received supplemental oxygen treatment at the isolation centers. One patient developed sudden cardiac arrest on the same day of hypoxemia onset. Another patient

Table 1 Baseline characteristics of COVID-19 patients based on outcomes.

Characteristics	No. (%) of subjects[a]				P value
	Total, N = 2555	Out-of-hospital cardiac arrest, n = 7	In-hospital mortality, n = 30	Survivor, n = 2518	
Demographics					
Age (years)					
Mean ± SD	50.78 ± 15.37	62.29 ± 9.38	70.90 ± 12.48	50.50 ± 15.25	<0.001
18–64	2025 (79.26)	2 (28.57)	4 (13.33)	2019 (80.18)	<0.001
≥65	530 (20.74)	5 (71.43)	26 (86.67)	449 (19.82)	
Sex					
Female	1272 (49.78)	3 (42.86)	5 (16.67)	1264 (50.20)	0.001
Male	1283 (50.22)	4 (57.14)	25 (83.33)	1254 (49.80)	
Symptoms					
Fever on admission to the isolation center	148 (5.79)	2 (28.57)	7 (23.33)	139 (5.52)	<0.001
Cough	1421 (55.62)	6 (85.71)	16 (53.33)	1399 (55.56)	0.268
Dyspnea	361 (14.13)	1 (14.29)	17 (56.67)	158 (6.27)	<0.001
Rhinorrhea	312 (12.21)	2 (28.57)	2 (6.67)	308 (12.23)	0.271
Headache	400 (15.66)	1 (14.29)	3 (10.00)	396 (15.73)	0.689
Diarrhea	449 (17.57)	3 (42.86)	6 (20.00)	440 (17.47)	0.199
Hypoxemia	77 (3.01)	2 (28.57)	21 (70.00)	54 (2.14)	<0.001
Comorbidity					
Diabetes	145 (5.68)	2 (28.57)	5 (16.67)	138 (5.48)	0.001
Hypertension	234 (9.16)	3 (42.86)	6 (20.00)	225 (8.94)	<0.001
Cardiovascular diseases	73 (2.86)	2 (28.57)	4 (13.33)	67 (2.66)	<0.001
Telehealth service	1046 (40.96)	5 (71.43)	13 (43.33)	1028 (40.83)	0.250
Hospitalization	448 (17.53)	0	30 (100.00)	418 (16.60)	<0.001

[a] Unless stated otherwise.
SD, standard deviation.

experienced loss of consciousness and cardiac arrest 4 days after receiving supplemental oxygen treatment at the isolation centers and was transferred to the emergency department during cardiopulmonary resuscitation, where chest radiography revealed patchy opacities in the bilateral lung fields.

Predictors for hospitalization among COVID-19 patients

Of the 2555 study participants, 448 (17.5%) were hospitalized during the 14-day quarantine period. Predictors for

Table 2 Clinical symptoms in COVID-19 patients with out-of-hospital cardiac arrest.

Symptoms	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age/sex	49/F	71/F	66/M	53/M	71/M	72/M	68/F
Fever on admission to the isolation center	+	−	−	−	++	−	−
Body temperature on admission (°C)	37.8	36.9	36.6	36.4	37.7	36.7	36.2
Fever during the period of isolation	+	+	+	−	+	+	−
Cough	+	−	+	+	+	+	+
Dyspnea	−	−	−	+	−	−	−
Rhinorrhea	−	−	−	+	−	−	+
Headache	−	+	−	−	−	−	−
Diarrhea	−	−	+	+	−	+	−
Hypoxemia	−	+	−	+	−	−	−
Chest X-ray findings	N/A	N/A	N/A	Patchy opacities in bilateral lung fields	N/A	N/A	N/A
Comorbidity							
Diabetes	−	−	−	+	−	−	+
Hypertension	−	−	−	+	+	−	+
Cardiovascular diseases	−	−	−	+	−	−	+
Telehealth service	+	+	+	+	−	+	−

COVID-19, coronavirus disease 2019.

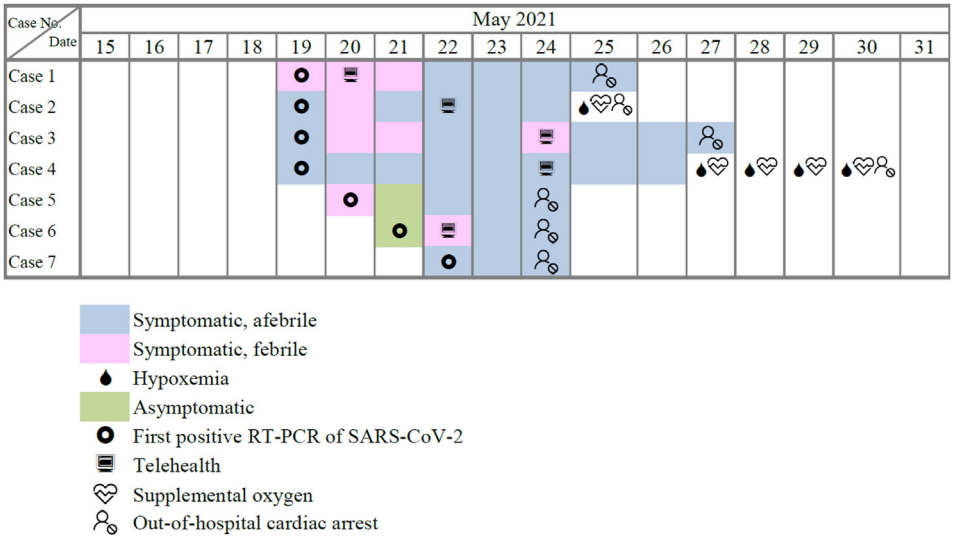

Figure 1. Progression of clinical symptoms in COVID-19 patients with out-of-hospital cardiac arrest. Abbreviations: COVID-19, coronavirus disease 2019.

hospitalization in COVID-19 patients in the community isolation centers included age ≥65 years, diarrhea, dyspnea, cough, and hypoxemia (Supplementary Table 1).

Factors associated with mortality among COVID-19 patients

Table 3 shows the univariate and multivariate analyses of the factors associated with mortality among COVID-19 patients. After adjusting for demographic factors, clinical symptoms, and comorbidities, independent predictors for mortality included age ≥65 years (AOR: 10.68, 95% CI: 3.82—29.89), fever on admission to the isolation centers (AOR: 10.24, 95% CI: 3.40—30.89), hypoxemia (AOR: 29.52, 95% CI: 11.86—73.48), and hospitalization (AOR: 4.26, 95% CI: 1.55—11.72).

Factors associated with in-hospital mortality and out-of-hospital cardiac arrest among COVID-19 patients

Multinomial logistic regression showed that compared with patients aged 18—64 years, those aged ≥65 years had a higher risk of OHCA (AOR: 13.24, 95% CI: 1.85—94.82) and in-hospital mortality (AOR: 10.28, 95% CI: 2.95—35.90) (Table 4). Moreover, patients with fever on admission to isolation centers had a higher likelihood of developing OHCA (AOR: 12.53, 95% CI: 1.68—93.34) and in-hospital mortality (AOR: 7.27, 95% CI: 1.90—27.83). Additionally, hypoxemia during the isolation period was an independent predictor for OHCA (AOR: 26.54, 95% CI: 3.18—221.73) and in-hospital mortality (AOR: 29.87, 95% CI: 10.17—87.76) in COVID-19 patients.

Discussion

In this cohort study, the mortality rate was 1.5% among COVID-19 patients in community isolation centers. To the best of our knowledge, this is the first cohort study to identify the predictors for OHCA and in-hospital mortality in COVID-19 patients. Our results showed that 18.9% of all deceased COVID-19 patients had OHCA. The mean time to OHCA occurrence was 6.6 days from the onset of symptom. After controlling for demographics, clinical symptoms, and comorbidities, the independent predictors for OHCA in COVID-19 patients were older age, hypoxemia, and fever on admission to the isolation centers. Furthermore, predictors for in-hospital mortality were older age, hypoxemia, fever on admission to the isolation centers, and dyspnea.

This study found that COVID-19 patients with hypoxemia had a higher likelihood of developing OHCA in the community isolation centers. Silent hypoxemia may explain the higher risk of OHCA in COVID-19 patients. During COVID-19 pandemic, silent hypoxemia has been reported in SARS-COV-2 infected individuals, which is characterized by a low oxygen saturation level but lacks difficulty breathing.[14] Although COVID-19 patients with silent hypoxemia may not experience respiratory distress, the chest X-ray (CXR) in these patients could show severe abnormality,[15] which results in the rapid deterioration of patients' clinical conditions. Our cohort study found that two patients with OHCA manifested hypoxemia in the isolation center but lacked difficulty breathing. Although supplemental oxygen treatment was provided for these two patients, cardiac arrest occurred in these two patients 1 and 4 days after supplemental oxygen treatment, respectively. The CXR in one of these two patients revealed increased infiltration and patchy opacities in the bilateral lung fields during cardiopulmonary resuscitation. Since silent hypoxemia in COVID-19 patients is associated with poor prognosis,[16] the findings of our study suggest that patients with hypoxemia should be under intensive care, including close monitoring of vital signs and progression of disease severity.

This study found that fever at the initial presentation of SARS-COV-2 infection was associated with a higher risk of OHCA in COVID-19 patients. Fever-related arrhythmia and systemic inflammation may account for the higher risk of

Table 3 Univariate and multivariate analyses of risk factors for mortality in COVID-19 patients.

Factors	Number of subjects	Mortality	Univariate analysis	Multivariate analysis
		n (%)	OR (95% CI)	AOR (95% CI)
Demographics				
Age (years)				
18–64	2025	6 (0.30)	1	1
≥65	530	31 (5.85)	20.90 (8.67–50.38)***	10.68 (3.82–29.89)***
Sex				
Female	1272	8 (0.63)	1	1
Male	1283	29 (2.26)	3.65 (1.66–8.02)***	1.50 (0.60–3.77)
Symptoms				
Fever on admission to the isolation center				
No	2407	28 (1.16)	1	1
Yes	148	9 (6.08)	5.50 (2.55–11.88)***	10.24 (3.40–30.89)***
Cough				
No	1134	15 (1.32)	1	1
Yes	1421	22 (1.55)	1.17 (0.61–2.27)	0.57 (0.23–1.43)
Dyspnea				
No	2194	19 (0.87)	1	1
Yes	361	18 (4.99)	6.01 (3.12–11.56)***	1.12 (0.45–2.81)
Rhinorrhea				
No	2243	33 (1.47)	1	1
Yes	312	4 (1.28)	0.87 (0.31–2.47)	1.59 (0.41–6.19)
Headache				
No	2155	33 (1.53)	1	1
Yes	400	4 (1.00)	0.65 (0.23–1.84)	0.67 (0.18–2.49)
Diarrhea				
No	2106	28 (1.33)	1	1
Yes	449	9 (2.00)	1.52 (0.71–3.24)	1.82 (0.69–4.80)
Hypoxemia				
No	2478	14 (0.56)	1	1
Yes	77	23 (29.87)	74.96 (36.60–153.55)***	29.52 (11.86–73.48)***
Comorbidity				
Diabetes				
No	2410	30 (1.24)	1	1
Yes	145	7 (4.83)	4.02 (1.74–9.33)***	1.64 (0.55–4.90)
Hypertension				
No	2321	28 (1.21)	1	1
Yes	234	9 (3.85)	3.28 (1.53–7.03)**	0.76 (0.27–2.17)
Cardiovascular diseases				
No	2482	31 (1.25)	1	1
Yes	73	6 (8.22)	7.08 (2.86–17.54)***	2.80 (0.84–9.31)
Telehealth service				
No	1509	19 (1.26)	1	1
Yes	1046	18 (1.72)	1.37 (0.72–2.63)	1.74 (0.74–4.08)
Hospitalization				
No	2107	7 (0.33)	1	1
Yes	448	30 (6.70)	21.53 (9.39–49.35)***	4.26 (1.55–11.72)**

COVID-19, coronavirus disease 2019; AOR, adjusted odds ratio; CI, confident interval.

cardiac arrest in febrile COVID-19 patients. A previous report showed that fever in COVID-19 patients could induce arrhythmia and result in cardiac arrest.[17] Moreover, in patients with underlying heart disease, fever can unmask the electrocardiogram manifestation with ST-segment elevation, which can cause syncope and sudden cardiac death.[18]

Fever-related systemic inflammation may also explain the higher risk of sudden cardiac arrest in febrile COVID-19 patients. A previous report showed that patients with prolonged fever had high level of induced protein–10 (IP-10).[19] IP-10 is an interferon gamma-inducible biomarker and has been associated with the severity and death of COVID-19.[20] Since the clinical manifestation in SARS-COV-2-infected

Table 4 Multinomial regression analyses of risk factors for in-hospital mortality and out-of-hospital cardiac arrest in COVID-19 patients.[a]

Factors	In-hospital mortality		Out-of-hospital cardiac arrest	
	AOR (95% CI)	P value	AOR (95% CI)	P value
Age (years)				
18-64	1		1	
≥65	10.28 (2.95—35.90)	<0.001	13.24 (1.85—94.82)	0.010
Fever on admission to the isolation center	7.27 (1.90—27.83)	0.004	12.53 (1.68—93.34)	0.014
Hypoxemia	29.87 (10.17—87.76)	<0.001	26.54 (3.18—221.73)	0.003

[a] Reference is COVID-19 patients with survival.
COVID-19, coronavirus disease 2019; AOR, adjusted odds ratio; CI, confident interval.

patients could deteriorate promptly,[21] the findings of our study suggest that COVID-19 patients with fever should be closely monitored for the progression of clinical conditions.

Consistent with the findings of previous reports,[22,23] older age was associated with a higher risk of in-hospital mortality in COVID-19 patients.

This cohort study is the first to determine the predictors for OHCA and in-hospital mortality in COVID-19 patients in community isolation centers. Although isolation is an effective way to curb the spread of SARS-COV-2,[24] our results showed that the time to OHCA occurrence is rapid in unvaccinated patients. Since old age and hypoxemia were independent predictors for OHCA, our study findings suggest that elderly patients or those with hypoxemia should be isolated in the hospital settings for close monitoring of vital signs and progression of disease severity.

Nevertheless, the present study has some limitations. First, there may be important factors (e.g., obesity and chronic obstructive pulmonary disease) associated with patients' mortality, which were not collected in this study. Second, the information regarding the antiviral or anti-inflammation treatment administered to the patients with COVID-19 was not available, which precludes this study from determining the impact of the antiviral or anti-inflammation treatment on the patient outcomes. Finally, the external validity of our findings may be a concern because all our patients were Taiwanese. The generalizability of our results to other non-Asian ethnic groups requires further verification. However, our findings suggest new avenues for future studies.

In conclusion, this cohort study found that the mortality rate was 1.5% among COVID-19 patients in the community isolation centers. Of all deceased COVID-19 patients, 18.9% had OHCA. The mean time to OHCA was 6.6 days from the symptom onset. Predictors for OHCA in COVID-19 patients were age ≥65 years, hypoxemia, and fever on admission to the isolation centers. Since the time to OHCA occurrence is rapid in COVID-19 patients, it is important to closely monitor patients' vital sign and disease severity during isolation, particularly for those with older age, fever, and hypoxemia.

Declaration of competing interest

No conflict of interest exists for the author.

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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.2022.07.009.