

Article

Not peer-reviewed version

Risk Factors and Clinical Manifestations of Post-Acute Sequelae of SARS-CoV-2 Infection in Children Previously Hospitalized for COVID-19 in Taiwan

Huan-Cheng Lai [†], [Yu-Lung Hsu](#) [†], Pei-Chi Chen, [Yi-Fen Tsai](#), [Chi-Hung Wei](#), Kai-Sheng Hsieh, [Lawrence Shi-Hsin Wu](#), [Chien-Heng Lin](#), Hsiao-Chuan Lin, Kao-Pin Hwang, [Hui-Ju Tsai](#) ^{*}, [Jiu-Yao Wang](#) ^{*}

Posted Date: 5 February 2026

doi: 10.20944/preprints202602.0349.v1

Keywords: clinical features; children; COVID-19; hospitalization; post-acute sequelae of SARS-CoV-2 infection; risk factors



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a [Creative Commons CC BY 4.0 license](#), which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Article

Risk Factors and Clinical Manifestations of Post-Acute Sequelae of SARS-CoV-2 Infection in Children Previously Hospitalized for COVID-19 in Taiwan

Huan-Cheng Lai ^{1,2,†}, Yu-Lung Hsu ^{1,2,†}, Pei-Chi Chen ³, Yi-Fen Tsai ⁴, Chi-Hung Wei ⁵, Kai-Sheng Hsieh ⁵, Lawrence Shi-Hsin Wu ², Chien-Heng Lin ⁶, Hsiao-Chuan Lin ¹, Kao-Pin Hwang ¹, Hui-Ju Tsai ^{4,7,*} and Jiu-Yao Wang ^{8,9,*}

¹ Department of Pediatric Infectious Diseases, China Medical University Children's Hospital, China Medical University, Taichung, Taiwan

² Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan

³ Department of Microbiology and Immunology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

⁴ Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan

⁵ Department of Medical Research, China Medical University Children's Hospital, China Medical University, Taichung, Taiwan

⁶ Department of Pediatric Pulmonology and Intensive Care, China Medical University Children's Hospital, China Medical University, Taichung, Taiwan

⁷ Department of Medical Science, National Tsing-Hua University, Hsinchu, Taiwan

⁸ Research Center of Allergy, Immunology and Microbiome (A.I.M), China Medical University Hospital and Children's Hospital, Taichung, Taiwan

⁹ Department of Allergy and Immunology, China Medical University Children's Hospital, China Medical University, Taichung 404327, Taiwan

* Correspondence: tsaihj@nhri.edu.tw; wangji@mail.cmu.edu.tw, +886-4-22052121-4698

† These authors contributed equally to this work.

Abstract

Background: The clinical features and risk factors of post-acute sequelae of SARS-CoV-2 infection (PASC) in children remain incomplete. This study aims to clarify the manifestations and identify predictors of PASC in pediatric patients previously hospitalized for COVID-19. **Methods:** We conducted this retrospective cohort study at the China Medical University Children's Hospital in Taiwan, including 143 children aged 3-18 hospitalized for the acute COVID-19 during the Omicron pandemic from April 2022 to July 2023. PASC was assessed through phone calls, online survey, and in-person follow-ups. Data encompassing demographics, clinical presentations, laboratory results, and acute-phase treatment were collected and compared between children with and without PASC. Each child was assigned total clinical scores based on the acute-phase symptoms and treatment. We evaluated the association of the total clinical scores with PASC among study children. The receiver operating characteristic (ROC) analysis was used to determine the optimal cutoff for total clinical scores, which best differentiated occurrence of PASC. **Results:** Among the 143 discharged children, 35.7% (n = 51) developed PASC. Children with PASC tended to be older (mean age: 7.6 vs. 6.3 years, $p = 0.05$) and greater body weight (29.1 vs. 23.7 kg, $p = 0.05$). PASC children exhibited higher reverse transcriptase-polymerase chain reaction (RT-PCR) cycle threshold (Ct) values (17.1 vs. 14.2, $p = 0.04$) during the acute phase than those without PASC. There were no significant disparities in other laboratory results, length of intensive care unit (ICU) stays, bacterial coinfections, oxygen supplementation, and medication usage between two groups. Notably, compared to the control group, the total clinical scores were significantly higher in the PASC group (37.9 vs. 31.5, $p = 0.02$), with an optimal cutoff value of 37.7 yielding an area under the curve (AUC) of 0.70. **Conclusions:** This study identified a significant proportion of children developing PASC following hospitalization

for acute COVID-19. Older age, greater body weight, and larger RT-PCR Ct values during the acute phase emerged as potential risk factors for developing PASC. Moreover, the clinical scoring system constructed in this study may help to predict the risk of developing PASC after discharge.

Keywords: clinical features; children; COVID-19; hospitalization; post-acute sequelae of SARS-CoV-2 infection; risk factors

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which emerged in late 2019, has rapidly become a global pandemic affecting individuals of all age groups [1]. Initially, pediatric patients appeared to experience milder forms of coronavirus disease 2019 (COVID-19). However, increasing evidence demonstrates that pediatric patients with persistent symptoms after recovering from the acute infection phase, known as post-acute sequelae of SARS-CoV-2 infection (PASC) or long COVID [2,3]. PASC refers to patients with persist clinical symptoms occurring beyond four weeks following initial acute infection which affects multiple organ systems and significantly impair quality of life [4–6].

A meta-analysis of adult studies has demonstrated that the risk of developing PASC is closely related to the severity of the initial COVID-19 infection. The study has identified that age, hospitalization due to initial COVID-19 infection, and various comorbidities, such as diabetes, obesity, and cardiovascular disease, may serve as potential predictors [7]. While extensively documented in adults, limited studies have assessed the incidence, risk factors, and clinical manifestations of PASC in pediatric populations, and heterogeneous in methodology and ethnicities, making conclusive evidence challenging [8,9]. Several studies have identified potential risk factors, including age, obesity, and pre-existing comorbid conditions, affect the development of PASC among children [5,10]. Furthermore, hospitalization during the acute phase has been recognized as a pivotal risk factor, suggesting a link between the severity of initial COVID-19 and PASC in children [11,12]. Nonetheless, data addressing post-acute sequelae among hospitalized pediatric populations remain sparse [11,12].

Although age, underlying chronic conditions, and the overall severity of the initial illness have been proposed as potential predictors, these associations with PASC remain inconclusive [10,13]. As such, establishing clear risk profiles and understanding the spectrum of symptomatology among pediatric patients with PASC is crucial for enabling clinicians to identify vulnerable children and implement targeted post-discharge monitoring.

This study aims to evaluate clinical manifestations and identify risk factors associated with PASC in a pediatric cohort previously hospitalized due to acute COVID-19; and develop a composite clinical scoring system via integrating acute-phase clinical features to better predict subsequent risk of PASC among children with severe initial illness in acute COVID-19.

Methods

Data Sources and Study Cohort

This retrospective cohort study was conducted at the China Medical University Children's Hospital (CMUCH), a tertiary medical center located in central Taiwan. In this study, we enrolled children aged 3 to 18 years who were hospitalized with acute COVID-19 from April 2022 to July 2023 during the Omicron wave. Diagnosis of acute COVID-19 was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) or rapid antigen testing (ART). RT-PCR and ART were performed at the time of acute illness onset, when patients first presented with COVID-19-related symptoms. No serial PCR tests were performed after symptom resolution or discharge, as repeated sampling was not part of the institutional protocol for pediatric patients. The ART used in our hospital was the Abbott Panbio™ COVID-19 Antigen Rapid Test (Abbott Diagnostics, USA),

which detects SARS-CoV-2 nucleocapsid protein antigen from nasopharyngeal swabs and has been authorized by the Taiwan Food and Drug Administration (TFDA) for clinical use. Hospitalization was indicated for children with acute illness requiring inpatient management, such as dehydration needing intravenous fluids, respiratory distress or hypoxemia, febrile seizures or other neurological symptoms, suspected bacterial co-infection, or significant comorbid or immunocompromised conditions. Following hospital discharge, participants were monitored for PASC through phone calls, online survey, and in-person visits. PASC was defined as the persistence of symptoms beyond four weeks after recovery from acute COVID-19, consistent with major pediatric studies and intended to capture early post-acute manifestations in children [6,12,14,15]. The PASC evaluation protocol was established in December 2022. Patients hospitalized from April to November 2022 were assessed retrospectively via phone calls and online surveys post-discharge, whereas those hospitalized from December 2022 onward were evaluated prospectively during routine follow-up visits or via phone or online if they did not return.

PASC was evaluated using an institutional questionnaire, the “Post-COVID-19 Physical and Psychological Evaluation Questionnaire”, which was administered uniformly via telephone, online, or in-person at least 4 weeks after discharge. The questionnaire was used to record post-COVID-19 symptoms across multiple domains and to compare them with the child’s pre-COVID-19 status, which helped distinguish PASC-related symptoms from long-standing, unchanged conditions. Assessments were conducted by trained research nurses (via phone or online) or attending pediatricians (in person), and the final determination of PASC was confirmed by pediatric infectious disease specialists. Only new or significantly intensified symptoms persisting for more than four weeks were classified as PASC. Children with persistent or evolving symptoms underwent additional evaluations at eight and/or twelve weeks; no routine follow-up was conducted beyond twelve weeks. The flowchart illustrating the enrollment process in this study is provided in Figure E1. The study was approved by the Institutional Review Board of CMUH (CMUH113-REC1-126), and all study procedures adhered to the applicable guidelines and regulations.

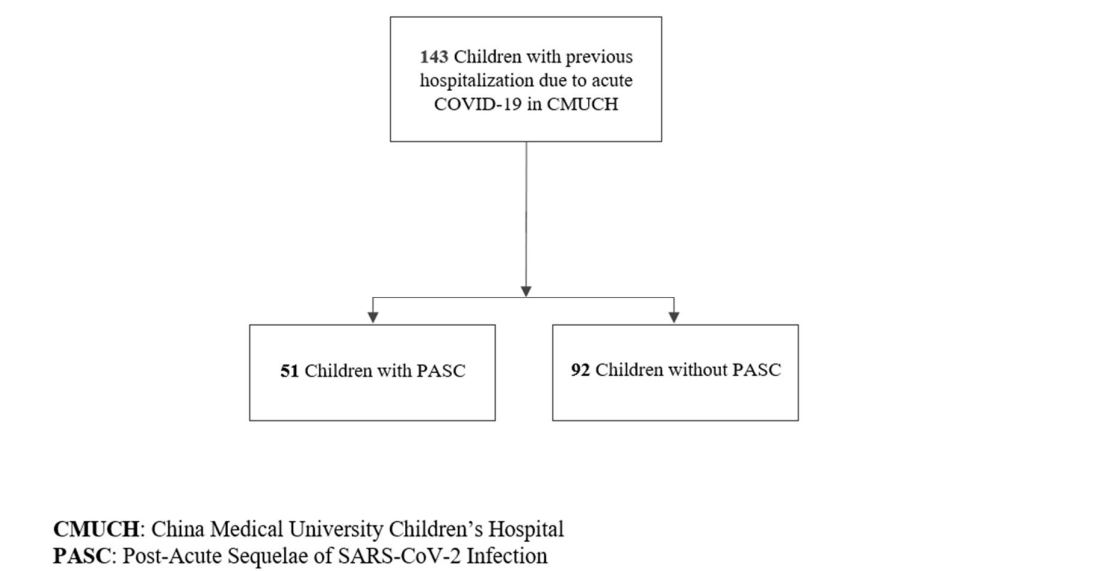


Figure E1. Flow chart of subject identification.

Study Outcome

After being discharged following acute COVID-19 infection, children were stratified into two groups based on the results of the follow-up investigation: those with PASC and those without. Detailed clinical data during hospitalization were collected from electronic medical records (EMR),

including basic demographics, COVID-19 vaccination status, underlying comorbidities, symptoms at admission, disease severity, laboratory test results, supportive therapies, administered medications, and any complications. Diagnosis of PASC was based on a comprehensive follow-up process that included telephone interviews, online surveys, and in-person evaluations. Any child reported one or more persistent symptoms more than four weeks beyond the acute COVID period was classified as having PASC.

Clinical Score Assignment

To comprehensively evaluate the diverse clinical manifestations during the acute COVID-19 phase, we constructed a composite clinical scoring system using EMR data extracted from the study children. In this scoring system, all symptoms were categorized into five distinct domains with total score of 100 points, assigning up to 20 points of each domain (Table E1). The five domains are defined as follows: 1.) the respiratory system domain includes symptoms such as cough, rhinorrhea, sore throat, sputum, and dyspnea; 2.) the gastrointestinal system domain incorporates symptoms as vomiting, diarrhea, and abdominal pain; 3.) the neurologic system domain covers a range of neurological symptoms, including seizures, with the presence of any neurological symptom recorded as positive; 4.) the general appearance domain is characterized by features such as anorexia, fatigue, myalgia, and fever; and 5.) the medication use domain specifically addresses the use of antibiotics during the acute phase.

This scoring system allowed for simultaneous consideration of multifaceted clinical conditions during the acute phase and facilitated the analysis of their relationship with the risk of developing PASC.

Table E1. Scoring assignment of clinical categories during COVID-19 acute phase.

Clinical category	Score
Respiratory system	20
Cough	4
Rhinorrhea	4
Sore throat	4
Sputum	4
Dyspnea	4
Gastrointestinal system	20
Vomiting	6.67
Diarrhea	6.67
Abdominal pain	6.67
Neurologic system	20
Neurological symptoms	20
General appearance	20
Anorexia	5
Fatigue	5
Myalgia	5
Fever	5
Medication	20
Antibiotic use	20
Total score	100

Statistical Analysis

For baseline demographic and clinical characteristics, continuous variables were reported as means and standard deviations (SD) which were tested by Student’s *t* test, while discrete variables were reported as counts and percentages which were tested by the chi-squared test.

Student’s *t* test was used to compare total clinical scores and the scores from each clinical domain between PASC cases and controls. We subsequently conducted logistic regression with adjustment of age and body weight to estimate the association of total clinical scores with PASC among study children. The receiver operating characteristic (ROC) analysis was used to determine the optimal cutoff (the value with optimal sensitivity and specificity) for total clinical scores, representing the best differentiated occurrence of PASC. The discriminatory ability was captured by the area under the curve (AUC). Generally, AUC equal to or greater than 0.7 is considered satisfactory for predictive models [16].

Statistical significance was defined as a *p*-value less than 0.05 or 95% confidence intervals (CIs) that did not include the null value of one. All analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA).

Results

A total of 143 hospitalized children with confirmed SARS-CoV-2 infection (mean age, 6.8 ± 3.8 years; 85 boys, 59.4%) were included. COVID-19 infection was confirmed by either real-time RT-PCR (n = 66) or antigen rapid test (ART, n = 77). Among the 66 children with RT-PCR confirmation, all samples were collected at acute presentation (64 in the emergency department, 2 in outpatient clinics prior to admission). Table 1 presents the demographic and clinical characteristics of the study children (51 PASC cases and 92 controls). Fever characteristics during acute illness were similar between PASC cases and controls (peak temperature 39.5 ± 0.8 °C in both, *p* = 0.96; duration 3.2 ± 1.9 vs. 2.6 ± 1.9 days, *p* = 0.07; Table 1). Significant differences were observed in age (7.6 ± 4.3 vs. 6.3 ± 3.4 years, *p* = 0.05), weight (29.1 ± 16.4 vs. 23.7 ± 12.8 kg, *p* = 0.05) and reverse transcriptase-polymerase chain reaction (RT-PCR) cycle threshold (Ct) value (17.1 ± 6.1 vs. 14.2 ± 3.8, *p* = 0.04) between PASC cases and controls (Table 1).

Table 1. Baseline characteristics among 143 children with PASC in children with hospitalized COVID-19 infection.

	Total (N=143)	Cases (N=51)	Controls (N=92)	<i>P</i> *
Demographic data				
Age, mean ± SD, year	6.8 ± 3.8	7.6 ± 4.3	6.3 ± 3.4	0.05
Age, <i>n</i> (%), year				0.10
3–6	87 (60.8)	27 (52.9)	60 (65.2)	
7–12	41 (28.7)	15 (29.4)	26 (28.3)	
13–18	15 (10.5)	9 (17.7)	6 (6.5)	
Sex, <i>n</i> (%)				0.91
Male	85 (59.4)	30 (58.8)	55 (59.8)	
Female	58 (40.6)	21 (41.2)	37 (40.2)	
Height, mean ± SD, cm	120.0 ± 20.7	124.3 ± 23.0	117.6 ± 19.1	0.06
Weight, mean ± SD, kg	25.6 ± 14.4	29.1 ± 16.4	23.7 ± 12.8	0.05
BMI, mean ± SD	16.5 ± 3.5	17.3 ± 3.7	16.1 ± 3.4	0.06
Clinical data				
Vaccine, <i>n</i> (%)				0.24
No	56 (39.7)	17 (33.3)	39 (43.3)	
Yes	85 (60.3)	34 (66.7)	51 (56.7)	
Comorbidity, <i>n</i> (%)				0.20

No	94 (65.7)	30 (58.8)	64 (69.6)	
Yes	49 (34.3)	21 (41.2)	28 (30.4)	
Duration of hospitalization, mean ± SD, day	3.5 ± 3.0	3.9 ± 3.0	3.3 ± 3.1	0.34
Duration of hospitalization, n (%), day				0.25
1–3	101 (70.6)	33 (64.7)	68 (73.9)	
≥ 4	42 (29.4)	18 (35.3)	24 (26.1)	
Fever temperature, mean ± SD, °C	39.5 ± 0.8	39.5 ± 0.8	39.5 ± 0.8	0.96
Fever temperature, n (%), °C				0.86
37.8 – 38.9	29 (24.0)	12 (26.7)	17 (22.4)	
39.0 – 39.9	51 (42.1)	18 (40.0)	33 (43.4)	
≥ 40.0	41 (33.9)	15 (33.3)	26 (34.2)	
Duration of fever day, mean ± SD	2.9 ± 1.9	3.2 ± 1.9	2.6 ± 1.9	0.07
Duration of fever day, n (%)				0.29
0	6 (4.4)	2 (4.0)	4 (4.6)	
1–3	97 (70.8)	31 (62.0)	66 (75.9)	
4–6	27 (19.7)	13 (26.0)	14 (16.1)	
≥ 7	7 (5.1)	4 (8.0)	3 (3.4)	
RT-PCR Ct value, mean ± SD	15.4 ± 5.1	17.1 ± 6.1	14.2 ± 3.8	0.04
Antigen rapid test (ART) positive, n (%)	77 (53.8)	23 (45.1)	54 (58.7)	0.12

Abbreviation: PASC: post-acute sequelae of SARS-CoV-2 infection; BMI: body mass index; SD: standard deviation; RT-PCR: reverse transcriptase-polymerase chain reaction; Ct: cycle threshold. * $P \leq 0.05$ is in bold. **Vaccine** Vaccinated children were defined as those who had received at least one dose of any COVID-19 vaccine (Moderna or Pfizer-BioNTech) before hospitalization, consistent with Taiwan’s national pediatric vaccination policy during the Omicron wave (April 2022 – July 2023). **Comorbidities included:** Congenital heart diseases (e.g., ASD, PFO, double outlet right ventricle, pulmonary hypertension), neurologic disorders (e.g., epilepsy, cerebral palsy, hypoxic encephalopathy), chromosomal or genetic abnormalities (e.g., 17q12 deletion, SCN1A and NAXE mutations), chronic lung diseases (e.g., bronchopulmonary dysplasia, asthma, ventilator dependence), autoimmune or hematologic disorders (e.g., SLE, autoimmune polymyositis, acute lymphoblastic leukemia, hereditary spherocytosis), endocrine/metabolic disorders (e.g., type I diabetes mellitus, rickets of prematurity), and other chronic conditions (e.g., ileal atresia post-operation, pituitary neoplasm, atopic dermatitis).

The distributions of clinical features during the acute phase between PASC cases and controls were shown in Figure 1 and Table E2. We examined the associations of clinical features and biomedical data during the acute phase, separately, with PASC in the study children. Table 2 and Table E3 summarize the in-hospital management characteristics between children with and without PASC. Most treatment and care-related parameters during hospitalization were comparable between the two groups. Among the study population, 13 children (9.1%) received remdesivir and 3 (2.1%) received paxlovid during hospitalization. Remdesivir and paxlovid were used more often in children with PASC than in controls (15.7% vs. 5.4%, $p = 0.08$; 3.9% vs. 1.1%, $p = 0.60$), but these differences did not reach statistical significance. When remdesivir and paxlovid were considered together as any antiviral therapy, use was significantly more frequent in PASC cases than in controls (19.6% vs. 6.5%, $p = 0.02$). Table 3 shows that total clinical scores from five composite clinical domains during the acute phase were positively associated between PASC cases and controls (adjusted odds ratios (AOR) = 1.03; 95% CI: 1.00-1.05).

Table 2. Association between clinical features during the acute phase with PASC in 143 children with hospitalized COVID-19 infection.

Total	Cases	Control (N=92)	P
-------	-------	----------------	---

	(N=143)	(N=51)		
ICU, n (%), day				0.52
0	128 (89.5)	44 (86.3)	84 (91.3)	
1–7	12 (8.4)	5 (9.8)	7 (7.6)	
8–14	1 (0.7)	1 (2.0)	0 (0.0)	
≥ 15	2 (1.4)	1 (2.0)	1 (1.1)	
HFNC oxygen, n (%)				0.10
No	136 (95.1)	46 (90.2)	90 (97.8)	
Yes	7 (4.9)	5 (9.8)	2 (2.2)	
Oxygen use, n (%)				0.33
No	133 (93.0)	46 (90.2)	87 (94.6)	
Yes	10 (7.0)	5 (9.8)	5 (5.4)	
Antibiotic use, n (%)				0.15
No	95 (66.4)	30 (58.8)	65 (70.7)	
Yes	48 (33.6)	21 (41.2)	27 (29.3)	
Bacteria co-infection, n (%)				0.42
No	136 (95.1)	50 (98.0)	86 (93.5)	
Yes	7 (4.9)	1 (2.0)	6 (6.5)	
Dexamethasone, n (%)				1.00
No	136 (95.1)	49 (96.1)	87 (94.6)	
Yes	7 (4.9)	2 (3.9)	5 (5.4)	
IVIG, n (%)				0.13
No	139 (97.2)	48 (94.1)	91 (98.9)	
Yes	4 (2.8)	3 (5.9)	1 (1.1)	
Antiviral agents, n (%)				
Remdesivir	13 (9.1%)	8 (15.7%)	5 (5.4%)	0.08
Paxlovid	3 (2.1%)	2 (3.9%)	1 (1.1%)	0.60
Remdesivir or Paxlovid	16 (11.2%)	10 (19.6%)	6 (6.5%)	0.02

Abbreviation: PASC: post-acute sequelae of SARS-CoV-2 infection; ICU: intensive care unit; HFNC: high-flow nasal cannula; IVIG: intravenous immunoglobulin. **Bacterial co-infection (n = 7):** *Campylobacter jejuni* enteritis (n = 2) and *Salmonella* spp. enteritis (n = 2) by gastrointestinal multiplex PCR; *Escherichia coli* UTI (n = 2) by urine culture; *Mycoplasma pneumoniae* bronchitis (n = 1) by IgM serology. Blood cultures were performed in all 143 patients; all were negative.”.

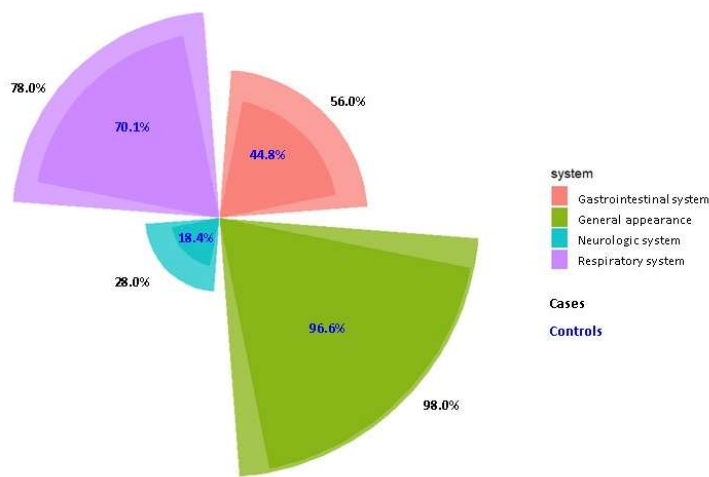


Figure 1. Distribution of clinical symptoms during the acute phase with regards to the status of PASC in 143 children with hospitalized COVID-19 infection. Note: PASC: post-acute sequelae of SARS-CoV-2 infection.

Table E2. Association between clinical symptoms during the acute phase with PASC in 143 children with hospitalized COVID-19 infection.

Symptoms	Total (N=143)	Cases (N=51)	Controls (N=92)	P
Cough, <i>n</i> (%)	93 (65.0)	35 (68.6)	58 (63.0)	0.50
Rhinorrhea, <i>n</i> (%)	60 (42.0)	21 (41.2)	39 (42.4)	0.89
Sore throat, <i>n</i> (%)	39 (27.3)	15 (29.4)	24 (26.1)	0.67
Sputum, <i>n</i> (%)	39 (27.3)	16 (31.4)	23 (25.0)	0.41
Dyspnea, <i>n</i> (%)	16 (11.2)	9 (17.6)	7 (7.6)	0.07
Vomiting, <i>n</i> (%)	45 (31.5)	17 (33.3)	28 (30.4)	0.72
Diarrhea, <i>n</i> (%)	18 (12.6)	7 (13.7)	11 (12.0)	0.76
Abdominal pain, <i>n</i> (%)	31 (21.7)	14 (27.5)	17 (18.5)	0.21
Anorexia, <i>n</i> (%)	74 (51.8)	27 (52.9)	47 (51.1)	0.83
Fatigue, <i>n</i> (%)	66 (46.2)	26 (51.0)	40 (43.5)	0.39
Neurological symptoms, <i>n</i> (%)	40 (28.0)	15 (29.4)	25 (27.2)	0.78
Seizure, <i>n</i> (%)	23 (16.1)	7 (13.7)	16 (17.4)	0.57
Myalgia, <i>n</i> (%)	27 (18.9)	10 (19.6)	17 (18.5)	0.87

Abbreviation: PASC: post-acute sequelae of SARS-CoV-2 infection.

Table E3. Association between biomedical tests during the acute phase with PASC in 143 children with hospitalized COVID-19 infection.

	Total (N=143)	Cases (N=51)	Controls (N=92)	P
Mean ± SD				
WBC, per µL	7150.9 ± 4285.7	7326.1 ± 3353.7	7052.7 ± 4743.4	0.69
Neutrophil	66.3 ± 19.9	69.2 ± 18.9	64.7 ± 20.4	0.21
Lymphocyte	21.7 ± 18.0	19.4 ± 16.5	23.0 ± 18.7	0.26
Monocyte	9.9 ± 4.5	9.7 ± 4.1	10.0 ± 4.7	0.69
Eosinophil	1.1 ± 2.2	1.1 ± 2.8	1.1 ± 1.9	0.94
Basophil	0.4 ± 0.3	0.3 ± 0.2	0.4 ± 0.4	0.43
Band neutrophil	0.5 ± 2.0	0.3 ± 1.8	0.6 ± 2.2	0.45
MDW	24.8 ± 4.8	24.0 ± 5.2	25.2 ± 4.6	0.20
Platelet, per µL	211635.9 ± 87300.2	224396.1 ± 83649.0	204484.6 ± 88931.4	0.19
MPV	7.7 ± 0.9	7.6 ± 0.9	7.7 ± 0.9	0.51
Hb, g/dL	12.9 ± 1.6	12.9 ± 1.2	12.9 ± 1.8	0.95
RBC, x10 ⁶ per µL	4.6 ± 0.5	4.6 ± 0.4	4.6 ± 0.5	0.56
Hct	37.2 ± 3.6	37.5 (3.6)	37.1 (3.6)	0.49
hsCRP, mg/dL	1.8 ± 3.7	1.7 ± 3.4	1.9 ± 3.9	0.76
ALT, U/L	23.9 ± 61.4	19.2 ± 40.0	26.6 ± 71.0	0.44
Cr, mg/dL	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.1	0.13
GFR, mL/min/1.73m ²	123.9 ± 22.2	121.8 ± 23.1	125.1 ± 21.7	0.42
Glucose, mg/dL	103.1 ± 26.5	108.1 ± 33.9	100.3 ± 20.9	0.15
Na, mmol/L	137.8 ± 2.6	138.0 ± 2.7	137.8 ± 2.6	0.67
K, mmol/L	3.9 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	0.95

Abbreviation: PASC: post-acute sequelae of SARS-CoV-2 infection; WBC: white blood count; MDW: monocyte distribution width; MPV: mean platelet volume; Hb: hemoglobin; RBC: red blood count; Hct: hematocrit; hsCRP: high-sensitivity *C-reactive protein*; ALT: alanine aminotransferase ; Cr: *Creatinine*; GFR: *glomerular filtration rate*; Na: Sodium; K: potassium.

Table 3. Association between total scores and scores of clinical categories during the acute phase with PASC in 143 children with hospitalized COVID-19 infection.

Clinical categories	Cases	Controls	P*
	mean ± SD		
Respiratory system	6.85±5.52	7.68±5.98	0.41
Gastrointestinal system	4.22±5.49	5.07±5.31	0.38
Neurologic system	3.68±7.79	5.60±9.07	0.19
General appearance	10.98±5.33	11.10±5.92	0.90
Medication	5.75±9.10	8.40±9.97	0.12
Total score	31.47±15.34	37.85±15.50	0.02

Abbreviation: PASC: post-acute sequelae of SARS-CoV-2 infection. **P*_{trend} ≤0.05 is in bold.

The association between various clinical parameters during the acute phase and the development of PASC is presented in Table E4. A model incorporating total clinical scores, age, body mass index (BMI), and fever duration yielded a c-statistic of 0.70 (95% CI, 0.61–0.79). The discriminative ability of total clinical scores during the acute phase was evaluated using ROC analysis (Figure 2). The analysis identified an optimal cutoff value of 37.7 for the total clinical scores, with a corresponding area under the curve (AUC) of 0.70.

Table E4. Association between scores of composite clinical conditions during the acute phase with PASC in 143 children with hospitalized COVID-19 infection.

Effect	Odds ratio (95% CI)	P
Total clinical scores	1.02 (1.00- 1.05)	0.06
Age	1.08 (0.96- 1.23)	0.20
BMI	1.07 (0.94- 1.22)	0.30
Fever duration	1.17 (0.95- 1.43)	0.14
c-statistic (95% CI)	0.7 (0.61- 0.79)	

Abbreviation: PASC: post-acute sequelae of SARS-CoV-2 infection.

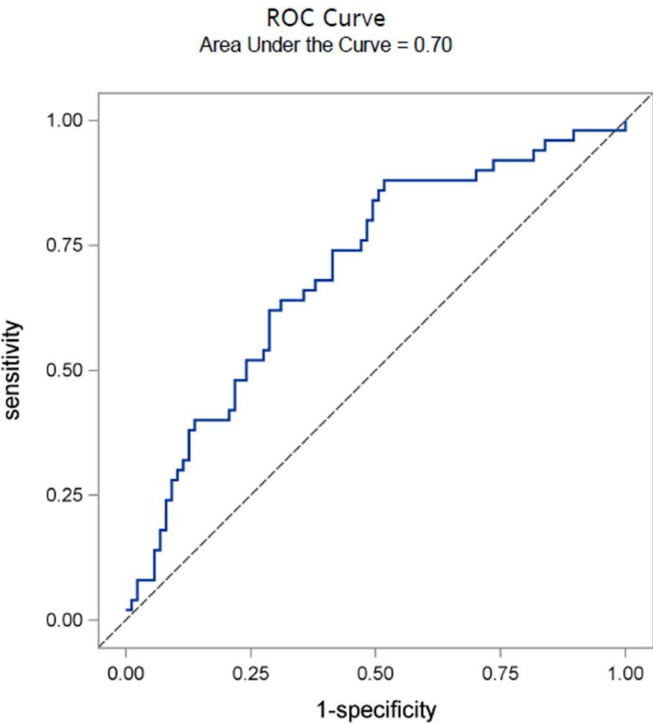


Figure 2. Receiver operating characteristic curves for total clinical scores from composite clinical conditions during the acute phase in PASC children by using a cutoff value of 37.7.

Among the 51 children identified with PASC, the most frequent persistent symptom domains at 4 weeks were respiratory (44.8%), constitutional/psychological (30.2%), neurologic/cognitive (17.7%), and gastrointestinal (10.4%).

Discussion

In this retrospective cohort study of 143 children discharged after the acute COVID-19 hospitalization, we observed a notable prevalence (35.7%) of PASC. Our findings indicate that older age, greater body weight, and larger RT-PCR cycle threshold (Ct) values during the acute phase are associated with an increased risk of developing PASC. Furthermore, we developed a novel composite clinical scoring system which integrates respiratory, gastrointestinal, neurologic, and constitutional symptoms, as well as antibiotic use. This system demonstrated moderate discriminative ability (AUC = 0.70) under the optimal cutoff value 37.7 for total clinical scores during the acute phase for predicting PASC after discharge. This scoring system represents a promising tool for capturing pediatric COVID-19 survivors at risk.

The composite clinical score offers a simple, bedside tool using routinely documented symptoms and treatments to identify children at higher risk of PASC during hospitalization. A total score ≥ 37.7 (AUC = 0.70) flags patients who may benefit from earlier and more structured post-discharge intervention, including earlier follow-up for higher-risk children, multidisciplinary assessment (pediatric infectious disease, pulmonology, neurology, or rehabilitation), targeted symptom management (e.g., fatigue recovery, respiratory therapy, cognitive support), and strengthened caregiver education on red-flag symptoms and expected recovery.

Several adult models have been proposed to predict long COVID using acute-phase data, including: the LC risk score [17], the Gutenberg COVID-19 Study (GCS) Post-COVID Risk and Diagnostic Scores [18], a community-based model from the United States [19], and a hospitalized cohort model from Ukraine [20]. Similar pediatric tools are scarce. Our study represents an early attempt to adapt such acute-phase clinical risk stratification to children, emphasizing its potential utility in early identification and intervention. Unlike adult models heavily weighted by age or obesity, ours prioritizes clinical severity to remain actionable across developmental stages. Future harmonization with adult tools could enable lifespan risk prediction.

The prevalence of PASC symptoms remains uncertain, especially among children hospitalized in the acute phase. Recent studies have reported a wide range in the prevalence of pediatric PASC, with estimates ranging from 10% to 27% in children after hospitalized discharge 2 to 5 months [5,10]. The estimated prevalence of 35.7% derived from our study is higher than that in previous reports, which may be attributable to differences in patient populations, follow-up duration, and PASC definitions across studies.

In adult cohorts, severe initial COVID-19, older age, and multiple comorbidities have been linked to an increased risk of long-term sequelae [7]. Although children typically experience milder acute COVID-19 disease courses, emerging evidence indicates that pediatric PASC is not uncommon, which may be related to various risk factors, such as age, a history of allergic diseases [5], pre-existing comorbidities [21], and obesity [11]. In this study, we also observed that age and body weight were associated with an increased risk of developing PASC. Additionally, we observed that an elevated RT-PCR cycle threshold (Ct) value during the acute phase, which may reflect delayed viral clearance or an altered host immune response, was associated with an increased risk of PASC. Ct values were interpreted with the understanding that lower Ct values correspond to higher viral loads; however, single time-point measurements and the lack of standardized serial testing limit the precision of virologic inferences.

Acute COVID-19 is inherently a multisystem disease; its pathophysiology is complex and multifaceted, involving direct viral injury, immune-mediated damage, cytokine storm, and

coagulation dysregulation [7,22–25]. Proposed mechanisms responsible for the development of PASC include immune dysregulation, disruption of the gut microbiota, autoimmunity, clotting abnormalities, and endothelial dysfunction, as well as dysfunctional neurological signaling [22,26]. Recognizing that acute COVID-19 affects multiple organ systems, we developed a comprehensive clinical scoring system derived from acute-phase conditions to predict the occurrence of PASC. This scoring tool integrates data from the acute phase including respiratory, gastrointestinal, neurologic, and constitutional symptoms, as well as the use of antibiotics. We included antibiotic use as one domain in calculating total clinical scores because antibiotics can have broad effects on the body, including impacts on the gut microbiome, which has been suggested to play a role in the pathophysiology of PACS [27].

Although older age and higher body weight were associated with PASC in univariate analyses, they were not included in the composite scoring system. The tool was designed to quantify acute multisystem clinical involvement using universally documented symptoms and treatments, independent of demographic variables. In an exploratory model that combined the composite score with age, BMI, and fever duration, the c-statistic was 0.70 (95 % CI 0.61–0.79), comparable to the AUC of 0.70 using the score alone, indicating that adding demographic variables provided only limited incremental discrimination. Future iterations may explore hybrid models incorporating age or BMI to improve discriminative performance, particularly in external validation cohorts

Strengths and Limitations

This study has several strengths. First, the study utilized data from a tertiary medical center in central Taiwan during the Omicron wave, providing a contemporary snapshot of clinical features in an Asian pediatric population, a underrepresented group in previous reports predominantly from Western countries [3,12]. Secondly, we comprehensively collected demographic and clinical data as well as laboratory data during both the acute and post-COVID-19 phases. Third, our multimodal follow-up strategy (via phone, electronic communication, or in-person visits) ensured that persistent symptoms were reliably captured, enhancing the quality of outcome ascertainment.

However, several limitations should be noted. First, as a retrospective, single-center cohort study, our findings may be subject to selection bias, and may not be fully generalizable to other pediatric populations. Secondly, although our total clinical scoring system may be a promising tool, it requires external validation in independent cohorts to confirm its predictive utility. More analyses exploring the associations between specific acute symptoms and subsequent PASC will require larger pediatric cohorts with sufficient statistical power and longer follow-up. Third, unmeasured confounding factors, such as genetic, environmental, or behavioral influences, could not be accounted for. Fourth, the study defined PASC as symptoms persisting beyond four weeks, consistent with major pediatric studies. However, duration beyond two months, as specified by the WHO definition (October 2021), was not assessed. This limits duration-based classification but remains informative for pediatric risk stratification and follow-up planning. Fifth, post-COVID-19 assessments relied on a self-developed questionnaire without standardized, validated patient-reported outcome measures. Fatigue, pain, and functional ability were captured qualitatively rather than through validated scoring instruments, limiting reproducibility and cross-cohort comparability. Sixth, the study did not systematically distinguish upper from lower respiratory tract infection or include standardized imaging assessments, thereby limiting evaluation of whether lower respiratory involvement or radiographic abnormalities predict PASC.

Conclusions

Our study demonstrates that PASC is a significant concern among children following COVID-19 hospitalization. Age, body weight, RT-PCR Ct values and during the acute phase are associated with PASC. Our total clinical scoring system may serve as a valuable tool for early identification of children at risk for PASC, enabling timely and targeted interventions. Future prospective,

multi-center studies are needed to validate these findings and further elucidate the underlying mechanisms of pediatric PASC.

Ethics approval and consent to participate: The study was approved by the Institutional Review Board of China Medical University Hospital (CMUH113-REC1-126); informed consent was waived due to the retrospective design of the study.

Clinical Trial: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analyzed during this study are included in this published article and its Supplementary Information files. No additional individual level data are available.

Competing interests: The authors declare no conflicts of interest in relation to this work.:

Funding: This study was supported by following grants: NSTC 113-2314-B-039-057-; NSTC 114-2314-B-039-012- from the National Science and Technology Council, Taiwan; a research grant (1JA8) from the Center for Allergy, Immunology, and Microbiome (A.I.M.), China Medical University Hospital, Taichung, Taiwan; DMR-112-043, DMR-112-047, DMR-112-052, DMR-113-042, C1110831002-6, DMR-114-024, and DMR-114-109 from the China Medical University Hospital, Taichung, Taiwan.

Authors' contributions: H.-C.L. (Huan-Cheng Lai), Y.-L.H., P.-C.C., H.-J.T., and J.-Y.W. in conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. H.-C.L. (Huan-Cheng Lai), Y.-L.H., P.-C.C., Y.-F.T., C.-H.W., and L.S.-H.W. designed the data collection instruments, collected data, performed the initial analyses, and reviewed and revised the manuscript. K.-S.H., C.-H.L., H.-C.L. (Hsiao-Chuan Lin), and K.-P.H. conceptualized and designed the study, designed the data collection instruments, and reviewed the manuscript. H.-J.T. and J.-Y.W. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors have read and agreed to the published version of the manuscript.

Acknowledgments: We are grateful to all the medical staff of China Medical University Children's Hospital (CMUCH) and China Medical University Hospital for providing administrative, technical, and funding support. We thank the staff of the medical research unit of CMUCH.

Reference

1. Hu B, Guo H, Zhou P, Shi ZL: **Characteristics of SARS-CoV-2 and COVID-19.** *Nat Rev Microbiol* 2021, **19**(3):141–154.
2. Zimmermann P, Pittet LF, Curtis N: **How Common is Long COVID in Children and Adolescents?** *Pediatr Infect Dis J* 2021, **40**(12):e482–e487.
3. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S: **Long-COVID in children and adolescents: a systematic review and meta-analyses.** *Sci Rep* 2022, **12**(1):9950.
4. Stephenson T, Allin B, Nugawela MD, Rojas N, Dalrymple E, Pinto Pereira S, Soni M, Knight M, Cheung EY, Heyman I *et al*: **Long COVID (post-COVID-19 condition) in children: a modified Delphi process.** *Arch Dis Child* 2022, **107**(7):674–680.
5. Osmanov IM, Spiridonova E, Bobkova P, Gamirova A, Shikhaleva A, Andreeva M, Blyuss O, El-Taravi Y, DunnGalvin A, Comberiati P *et al*: **Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study.** *Eur Respir J* 2022, **59**(2).
6. Chaichana U, Man KKC, Chen A, Wong ICK, George J, Wilson P, Wei L: **Definition of Post-COVID-19 Condition Among Published Research Studies.** *JAMA Netw Open* 2023, **6**(4):e235856.

7. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, Clark A, Ntatsaki E, Vassiliou VS: **Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis.** *JAMA Intern Med* 2023, **183**(6):566–580.

8. Buonsenso D, Munblit D, De Rose C, Sinatti D, Ricchiuto A, Carfi A, Valentini P: **Preliminary evidence on long COVID in children.** *Acta Paediatr* 2021, **110**(7):2208–2211.

9. Ludvigsson JF: **Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19.** *Acta Paediatr* 2021, **110**(3):914–921.

10. Funk AL, Kuppermann N, Florin TA, Tancredi DJ, Xie J, Kim K, Finkelstein Y, Neuman MI, Salvadori MI, Yock-Corrales A *et al*: **Post-COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection.** *JAMA Netw Open* 2022, **5**(7):e2223253.

11. Maddux AB, Berbert L, Young CC, Feldstein LR, Zambrano LD, Kucukak S, Newhams MM, Miller K, FitzGerald MM, He J *et al*: **Health Impairments in Children and Adolescents After Hospitalization for Acute COVID-19 or MIS-C.** *Pediatrics* 2022, **150**(3).

12. Rao S, Lee GM, Razzaghi H, Lorman V, Mejias A, Pajor NM, Thacker D, Webb R, Dickinson K, Bailey LC *et al*: **Clinical Features and Burden of Postacute Sequelae of SARS-CoV-2 Infection in Children and Adolescents.** *JAMA Pediatr* 2022, **176**(10):1000–1009.

13. Asadi-Pooya AA, Nemati H, Shahisavandi M, Akbari A, Emami A, Lotfi M, Rostamihosseinkhani M, Barzegar Z, Kabiri M, Zeraatpisheh Z *et al*: **Long COVID in children and adolescents.** *World J Pediatr* 2021, **17**(5):495–499.

14. Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, Murray B, Klaser K, Kerfoot E, Chen L *et al*: **Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2.** *Lancet Child Adolesc Health* 2021, **5**(10):708–718.

15. Toepfner N, Brinkmann F, Augustin S, Stojanov S, Behrends U: **Long COVID in pediatrics-epidemiology, diagnosis, and management.** *Eur J Pediatr* 2024, **183**(4):1543–1553.

16. Akobeng AK: **Understanding diagnostic tests 3: Receiver operating characteristic curves.** *Acta Paediatr* 2007, **96**(5):644–647.

17. Babicki M, Lejawa M, Osadnik T, Kapusta J, Banach M, Jankowski P, Mastalerz-Migas A, Kaluzinska-Kolat Z, Kolat D, Chudzik M: **LC risk score - development and evaluation of a scale for assessing the risk of developing long COVID.** *Arch Med Sci* 2024, **21**(1):121–130.

18. Baumkotter R, Yilmaz S, Chalabi J, Ten Cate V, Mamoor Alam AS, Golriz Khatami S, Zahn D, Hettich-Damm N, Prochaska JH, Schmidtmann I *et al*: **Risk tools for predicting long-term sequelae based on symptom profiles after known and undetected SARS-CoV-2 infections in the population.** *Eur J Epidemiol* 2025, **40**(7):789–801.

19. Sun X, Di Fusco M, Lupton LL, Yehoshua A, Alvarez MB, Allen KE, Puzniak L, Lopez SMC, Cappelleri JC: **Predictors of Long COVID Among Symptomatic US Adults Testing Positive for SARS-CoV-2 at a National Retail Pharmacy.** *Healthcare (Basel)* 2024, **12**(23):2321.

20. Honchar O, Ashcheulova T, Chumachenko T, Chumachenko D: **Early prediction of long COVID-19 syndrome persistence at 12 months after hospitalisation: a prospective observational study from Ukraine.** *BMJ Open* 2025, **15**(1):e084311.

21. Morello R, Mariani F, Mastrantoni L, De Rose C, Zampino G, Munblit D, Sigfrid L, Valentini P, Buonsenso D: **Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study.** *EClinicalMedicine* 2023, **59**:101961.

22. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS *et al*: **Post-acute COVID-19 syndrome.** *Nat Med* 2021, **27**(4):601–615.

23. Trougakos IP, Stamatelopoulos K, Terpos E, Tsitsilonis OE, Aivalioti E, Paraskevis D, Kastritis E, Pavlakis GN, Dimopoulos MA: **Insights to SARS-CoV-2 life cycle, pathophysiology, and rationalized treatments that target COVID-19 clinical complications.** *J Biomed Sci* 2021, **28**(1):9.

24. Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K: **Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression.** *Physiology (Bethesda)* 2020, **35**(5):288–301.

25. Kumar S, Veldhuis A, Malhotra T: **Neuropsychiatric and Cognitive Sequelae of COVID-19.** *Front Psychol* 2021, **12**:577529.

26. Davis HE, McCorkell L, Vogel JM, Topol EJ: **Long COVID: major findings, mechanisms and recommendations.** *Nat Rev Microbiol* 2023, **21**(3):133–146.
27. Wang C, Ramasamy A, Verduzco-Gutierrez M, Brode WM, Melamed E: **Acute and post-acute sequelae of SARS-CoV-2 infection: a review of risk factors and social determinants.** *Virol J* 2023, **20**(1):124.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.