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Volume 9 ¦ Issue 1 ¦ January-March 2025

Contents

Paediatric Respiratory Health in Focus: Key Updates from this Issue

Respiratory diseases in children and adolescents remain a significant global health burden. These conditions, whether infectious or non-infectious, chronic or acute life-threatening, require accurate diagnosis and timely intervention to optimize management and improve outcomes. Prevention, early recognition, and prompt treatment are essential in reducing disease burden and mortality. In addition, understanding risk factor and epidemiology is critical for developing effective public health strategies. Four articles in this edition of the journal address different but important aspects of respiratory diseases in children and adolescent.

Acute respiratory distress syndrome (ARDS) is a complex condition associated with high mortality rates and long-term complication.[1,2] Historically, paediatric ARDS (PARDS) was diagnosed using adult-based criteria until the Paediatric Acute Lung Injury Consensus Conference (PALICC) established a specific definition in 2015.[3] In this issue, Su *et al.* presents a comprehensive review of the updated recommendations from PALICC-2, published in 2023.[4] Key updates include refined diagnostic criteria and novel oxygenation indices such as PaO2/FiO2 ratio, SpO2/FiO2 ratio, and the oxygen index. These tools enhance the accuracy or PARDS assessment with various respiratory interventions, including invasive and non-invasive ventilation. The introduction of "possible PARDS" and "at risk for PARDS" facilitates early recognition and timely intervention, which will improve patient outcomes. This comprehensive review deepens our understanding of PARDS and provides valuable insight into diagnostic algorithms, management strategies, and emerging treatment options.

Chronic respiratory conditions in children, such as asthma, bronchiectasis, and cystic fibrosis (CF), pose significant challenges due to recurrent exacerbations that contribute to decline lung function and structural airway changes. Azithromycin, a macrolide antibiotic with anti-inflammation and immunomodulator properties, has gained attention for its potential role in reducing exacerbations and improving clinical outcomes. Most of the evidence supporting the prophylactic use of azithromycin in children is derived from studies on CF and bronchiectasis. While clinical trials on the use of azithromycin in asthmatic children are limited, some studies have shown promise in reducing asthma exacerbation rates, particularly in those with neutrophilic airway inflammation.[5,6] In this journal, Tung provides a comprehensive review on this topic; highlighting both the benefit of azithromycin in reducing pulmonary exacerbations and its limited impact on lung function. The review also underscores potential risks, including antimicrobial resistance and adverse effects.[7] These findings encourage clinicians to carefully balance the benefit against the risk, ensuring that therapy is tailored to appropriate patent populations. Ongoing research and antimicrobial stewardship will be key to maximizing its therapeutical potential while mitigating risks.

Airway hyper-responsiveness (AHR) is a key physiological feature of asthma, serving as an indicator of disease severity. Childhood Asthma Control Test (C-ACT) and the Asthma Control Test (ACT) are self-reported questionnaire, that has been used widely to assess asthma control. Yeung *et al.* investigated the relationship between C-ACT and ACT with AHR, finding that these subjective tools did not correlate well with AHR as measured by methacholine challenge test. The retrospective design with its inherent limitation of the study should be taken into account, but a recent cross sectional study in Hong Kong reported similar finding, showing that more than 50% of children who self-evaluated with good asthma control exhibited mild and moderate AHR.[8] These findings suggest that while C-ACT and ACT are useful for symptom monitoring, they may not be sensitive for detecting AHR in children and adolescent. Therefore, additional objective assessment is advised for a comprehensive evaluation of asthma severity.

The COVID-19 pandemic has reshaped our understanding of respiratory infections in children, with increasing attention to viral induced airway inflammation. The risk of croup among children with COVID-19 is higher, particularly during the Omicron wave, as shown in a retrospective study by Hu *et al*. presented in this journal.[9] This study provides valuable insights to guide pediatric healthcare strategies. Future research should aim to elucidate the long-term impact of SARS-CoV-2 on pediatric airway diseases and explore potential intervention to mitigate its burden on young children.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Advances in the Diagnosis and Management of Pediatric Acute Respiratory Distress Syndrome: An Overview of PALICC-2 Guidelines

Chih-Ting Su[1,2], Chia-Sui Chou[1,2], Wei-Yu Chen[1,2,3], Pei-Chen Tsao[1,2], Mei-Jy Jeng[1,2,3], Yu-Sheng Lee[1,2]

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Abstract

This review article presents a comprehensive overview of the advancements in diagnosis and management of pediatric acute respiratory distress syndrome (PARDS) as delineated in the Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) guidelines published in 2023. The manuscript revisits the initial definition of acute respiratory distress syndrome (ARDS) and the nuanced distinctions between ARDS and PARDS to provide a foundational understanding. An approach algorithm for PARDS has been developed to improve the precision of disease detection. Central to the PALICC-2 updates are the new diagnostic criteria, which incorporate the use of oxygenation indices such as the PaO_2/FiO_2 ratio, SpO_2/FiO_2 ratio, the oxygen index (OI), and the oxygen saturation index (OSI) for stratifying the severity of PARDS in patients on invasive and noninvasive ventilation. Notably, the guidelines introduce "possible PARDS" and "at risk for PARDS" to assist in early recognition and intervention. For managing PARDS, PALICC-2 emphasizes on using a lung-protective ventilation bundle and fine-tuning positive end-expiratory pressure (PEEP) according to the ARDS Network's lower PEEP/higher FiO_2 table. Ancillary management strategies, including the judicious use of extracorporeal membrane oxygenation (ECMO) and neuromuscular blockade, are also discussed. Due to insufficient evidence for supporting their efficacy, the guidelines advise against the routine use of therapies such as recruitment maneuvers, inhalation of nitric oxide, and corticosteroids. Specific follow-up programs are recommended in children with PARDS. In conclusion, the PALICC-2 guidelines offer an essential update to improve outcomes for pediatric patients with ARDS by promoting a strategic approach to diagnosis and evidence-based management practices. This review highlights the critical aspects of these guidelines, thereby aiding clinicians in effectively caring for patients afflicted with PARDS.

Keywords: Acute lung injury, acute respiratory distress syndrome, pediatric acute respiratory distress syndrome

Introduction

The initial documentation of acute respiratory distress syndrome (ARDS) dates back to 1967 in a case series authored by Ashbaugh *et al.*[1] The case series described 12 patients exhibiting symptoms such as rapid breathing, refractory hypoxemia, and widespread opacities observed on chest X-rays. Additionally, notable hyaline membranes were observed lining the alveolar spaces.[1]

The American-European Consensus Conference (AECC), 1994 introduced the definition of ARDS. They defined acute lung injury as the rapid deterioration of oxygenation, with a PaO_2/FiO_2 ratio <300 and bilateral interstitial or alveolar infiltrates observed on chest X-ray. The term "acute lung injury" is used when the PaO_2/FiO_2 ratio <300. ARDS is identified explicitly in patients with a PaO_2/FiO_2 ratio of less than 200.[2]

The Berlin criteria, introduced in 2011, updated the definition of ARDS. According to these criteria, ARDS should manifest as an acute onset (within one week) of

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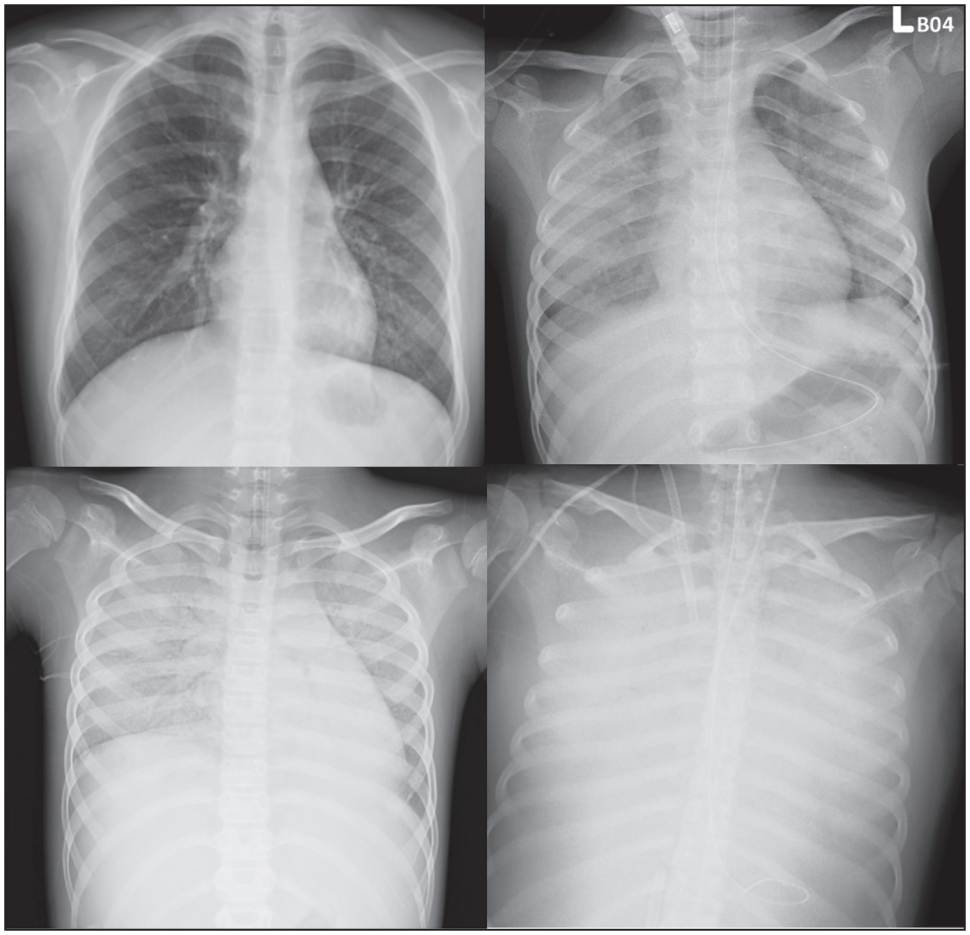

Figure 1: Representative chest X-ray (CXR) images of children with varying severities of pediatric acute respiratory distress syndrome (PARDS). (a) CXR of a healthy 14-year-old male. (b) CXR of a 4-year-old girl with mild to moderate PARDS caused by Staphylococcus aureus infection. (c) CXR of a 13-year-old male patient with severe PARDS caused by Klebsiella pneumonia sepsis. (d) CXR of a 17-year-old female patient with acute leukemia and severe PARDS caused by cytokine release syndrome after donor lymphocyte infusion, who is receiving extracorporeal membrane oxygenation (ECMO) support

bilateral opacities on chest X-ray, excluding pleural effusions, lung collapse, or nodules. The presence of pulmonary edema should not be attributable to cardiac failure or fluid overload. The severity of ARDS is determined by the PaO_2/FiO_2 ratio, with ratios of 200–300, 100–200, and <100 indicating mild, moderate, and severe ARDS, respectively.[3]

Pediatric ARDS (PARDS), while sharing a similar pathophysiology with adult ARDS, was first defined in 2015 by the Pediatric Acute Lung Injury Consensus Conference (PALICC) due to anatomical and physiological differences between pediatric and adult patients.[4] The focused definition aims to facilitate earlier diagnosis and intervention for those with significant lung injury. The PALICC criteria for PARDS include patients receiving noninvasive ventilation, as well as those with chronic lung disease (CLD), congenital heart disease (CHD), and left ventricular dysfunction.[5] We consider PARDS in patients with new-onset unilateral infiltrates on chest X-rays, in contrast to the bilateral pulmonary opacities required for an ARDS diagnosis in adults. The severity stratification for PARDS patients undergoing invasive mechanical ventilation (IMV) is based on the oxygen index (OI) or oxygen saturation index (OSI).[4] Examples of chest X-rays showing varying severities of PARDS are displayed in Figure 1.

Diagnosis of PARD

Diagnosing PARDS remains challenging for pediatricians due to the variability in initial presentations and the lack of specific laboratory tests or biomarkers. PARDS has a complex pathophysiology and diverse causes. Relevant clinical histories may include conditions such as pneumonia, sepsis, aspiration or inhalation injury, trauma, blood transfusion, pancreatitis, drug overdose, disseminated intravascular coagulation, cardiopulmonary bypass surgery, and burns.[6,7] Common signs and symptoms include tachypnea, shortness of breath, and a dry or productive cough. Laboratory results for a child with PARDS exhibit a decreased PaO_2/FiO_2 ratio. A chest X-ray typically reveals new opacities in one or both lungs. An algorithm for evaluating suspected PARDS in children is summarized in Figure 2.

PALICC-2, a refinement of the diagnosis and management of PARDS, was published in 2023. The diagnosis criteria proposed by PALICC-2 are summarized in Table 1.[8]

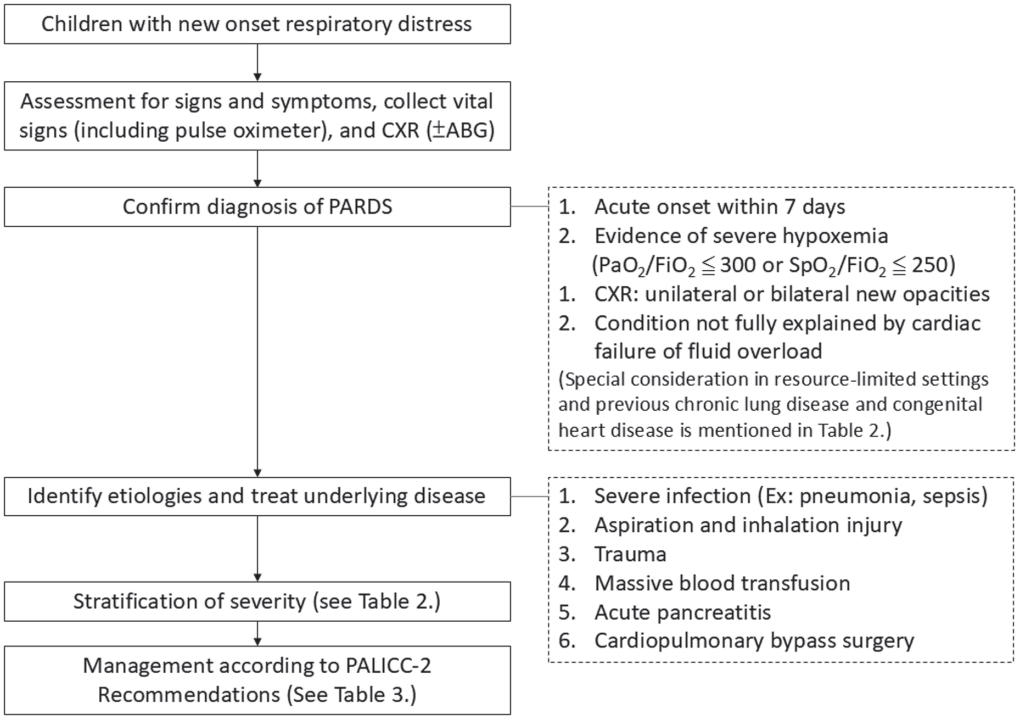

Figure 2: An algorithm for evaluating suspected pediatric acute respiratory distress syndrome in children

Table 1: Diagnosis summary of pediatric acute respiratory distress syndrome (PARDS), possible PARDS, and at risk for PARDS according to PALICC-2 Guidelines[6]*

	PARDS				Possible PARDS	At risk for PARDS
Age	<18 years old (perinatal lung disease excluded)					
Onset time	Within 7 days (known clinical insult)					
Origin of edema	Not fully explained by cardiac failure or fluid overload					
Chest imaging	New opacities (not due to atelectasis or pleural effusion)†					
Oxygenation‡	**IMV-PARDS**		**NIV-PARDS§**		**CPAP/BiPAP or HFNC (≥1.5 L/kg/min or ≥ 30 L/min): $PaO_2/FiO_2 \leq 300$ or $SpO_2/FiO_2 \leq 250$**	**Any oxygen supplementation‖ to maintain $SpO_2 \geq 88\%$**
PARDS severity	Mild/moderate	Severe	Mild/moderate	Severe		
	4≤OI<16 or 5≤OSI<12	OI≥16 or OSI≥12	300≥PaO_2/FiO_2 > 100 or 250≥SpO_2/FiO_2 > 150	$PaO_2/FiO_2 \leq 100$ or $SpO_2/FiO_2 \leq 150$		
CHD/CLD¶	Acute deterioration in oxygenation not explained by cardiac disease or baseline CLD.					

BiPAP = bilevel positive airway pressure; CHD = cyanotic heart disease; CLD = chronic lung disease; CPAP = continuous airway positive pressure; HFNC = high-flow nasal cannula; IMV = invasive mechanical ventilation; MAP = mean airway pressure; NIV = noninvasive ventilation; OI = oxygenation index; OSI = oxygenation saturation index; PARDS = pediatric acute respiratory distress syndrome; PEEP = positive end-expiratory pressure; SpO_2 = pulse oximeter oxygen saturation.

*This table is summarized from the publication of Emeriaud *et al.*[6]

†If imaging options are unavailable in some resource-limiting area, those who otherwise meet PARDS criteria are considered to have possible PARDS.

‡When SpO_2 is used, ensure that SpO_2 is ≤ 97%. OI = MAP (cm H2O) × FiO_2/PaO_2 (mm Hg). OSI = MAP (cm H_2O) × FiO_2/SpO_2.

Stratification of PARDS severity: Apply ≥ 4 h after initial diagnosis of PARDS.

§Diagnosis of PARDS on NIV (NIV-PARDS) requires a facemask interface with CPAP/PEEP ≥ 5 cm H_2O.

‖Oxygen supplementation is defined as FiO_2 > 21% when using IMV or NIV; or "oxygen flow" from a mask or cannula that exceeds these age-specific thresholds: ≥ 2 L/min (age <1 years), ≥ 4 L/min (age 1–5 years), ≥ 6 L/min (age 6–10 years), or ≥ 8 L/min (age >10 years). For children on a mask or cannula, oxygen flow is calculated as FiO_2 × flow rate (L/min).

¶Stratification of PARDS severity does not apply to these populations

Table 2: ARDS network lower PEEP/higher FiO2 table[14]*

FiO2 (%)	30	40	50	60	70	80	90	100
PEEP (cm H_2O)	5	6-8	8–10	10	10–14	14	14–18	18–24

*This table is modified from Brower *et al*[14]

When assessing the severity of oxygenation impairment, oxygen levels should be adjusted to achieve a SpO_2 of 88%–97% before calculating indices such as OI, O.S.I., PaO_2/FiO_2, or SpO_2/FiO_2. The SpO_2/FiO_2 threshold for PARDS was revised downward from 264 to 250. Severity stratification should be implemented at least 4 h after the initial diagnosis. OI or OSI should be the primary metric for assessing lung disease severity to define PARDS in all patients receiving IMV, with PaO_2 used as the preferred measure when available. Including mean airway pressure in the hypoxemia metrics (i.e., OI and OSI) has consistently, though modestly, enhanced risk stratification in PARDS compared to using PaO_2/FiO_2 or SpO_2/FiO_2 alone. SpO_2/FiO_2 and OSI play a greater role in diagnosing PARDS in resource-limited settings. Unlike the original PALICC criteria 2015, PALICC-2 introduced two severity classifications (mild to moderate and severe) instead of three. The severity stratification for PARDS patients using noninvasive ventilation (NIV-PARDS) was also outlined.[8]

Additionally, PALICC-2 introduced two new terms: "possible PARDS" and "at risk for PARDS." Possible PARDS refers to patients meeting PARDS criteria but lacking imaging due to resource constraints, while at risk for PARDS is used to describe patients needing respiratory support to maintain adequate oxygen levels, but not meeting PARDS criteria [Table 1]. Specific age-based thresholds were established for oxygen flow rates when diagnosing patients at risk for PARDS. However, possible PARDS and at risk for PARDS should not be diagnosed in children solely with respiratory failure caused by airway obstruction.[8]

Main management of PARDS by PALICC-2

Patients at risk for PARDS or possible PARDS, who were on oxygen therapy or high-flow nasal cannula with worsening respiratory failure, may be considered for NIV use. If respiratory status worsens despite a trial of NIV in less than 6 h, endotracheal intubation should be contemplated.[8]

Ventilation bundle for patients with PARDS

For patients with PARDS requiring IMV, it is recommended to follow a lung-protective ventilation bundle.[9]

Ventilation mode

No single ventilator mode is recommended to improve outcomes in patients with PARDS. High-frequency oscillatory ventilation (HFOV) does not reduce mortality or decrease the duration of ventilator use compared to conventional ventilation.[10]

Airway plateau pressure and driving pressure

Due to the lack of RCTs or observational studies, there is low certainty in recommending specific thresholds for airway plateau and driving pressures in PARDS.[11] Current guidance suggests maintaining an airway plateau pressure of ≤28 cm H_2O or ≤32 cm H_2O if chest wall compliance is reduced and a driving pressure of ≤15 cm H_2O.[8]

Tidal volume

Tidal volume should be set at ≤6–8 or ≤ 4–6 mL/kg if necessary to be maintained below the recommended plateau and driving pressure. Supraphysiologic tidal volume (>8 mL/kg) and non-adherence to PALICC-2 tidal volume recommendation would increase the mortality and length of invasive ventilation.[12,13]

Positive end-expiratory pressure (PEEP)

It is strongly advised to optimize PEEP at or above the level indicated in the ARDS Network's lower PEEP/higher FiO_2 table [Table 2].[14] When adjusting PEEP levels to meet the target oxygen range for PARDS, we must ensure that plateau and driving pressure limits are not exceeded.[9]

Target of the ventilator bundle for PARDS

Central venous oxygenation monitoring is required if SpO_2 < 92%. The target oxygen saturation should be 92%–97% for mild-to-moderate PARDS and may accept <92% in severe PARDS with optimized PEEP. Prolonged hyperoxia (>97%) or hypoxemia (<88%) should be avoided. In pediatric ARDS patients, enhanced oxygenation does not consistently lead to better clinical outcomes. Additionally, implementation of lung-protective strategies is generally associated with lower Pao_2 levels and reduced mortality in both adult and pediatric populations.[12] Maintaining a pH ≥ 7.2 is essential to stay within the recommended ranges of plateau pressure, driving pressure, and tidal volume during permissive hypercapnia. The routine use of bicarbonate supplementation is not recommended.[8]

Ancillary management of PARDS by PALICC-2

The prone position and recruitment maneuver cannot be recommended or discouraged for ancillary treatments. Routine use of inhaled nitric oxide (NO), surfactants, and corticosteroids is not advised. Electronic algorithms should be utilized to aid in identifying PARDS. In addition to oxygenation-based risk stratification, the dead space-to-tidal volume ratio or end-tidal alveolar dead-space fraction may also be used for risk assessment.[8]

Table 3: Management strategies and follow-up suggestion for pediatric acute respiratory distress syndrome (PARDS) from PALICC-2 recommendations[8]*

	Invasive ventilation		Noninvasive support	Follow-up
	Ventilation related	Other therapy		
Good practice statement	1. Adjust PEEP according to oxygen target range.† 2. Avoid prolonged hypoxemic (<88%) or hyperoxia (>97%). 3. Monitor central venous saturation if SpO_2 < 92%.	1. Be aware of iatrogenic withdrawal syndrome if weaning from ≥5 days of sedation. 2. Assess possibility of delirium daily. 3. Early enteral nutrition (<72 h).	1. Use heated humidification. 2. Sedation can be used to improve NIV tolerance.	1. Evaluate ECMO survivors for neurological or physical function impairment. 2. Screen for post-ICU morbidities within 3 months of discharge using a stepwise approach 3. Screen for pulmonary function (by spirometry if feasible) within three months after discharge 4. Health-related quality of life, physical, neurocognitive, emotional, family, and social function should be evaluated within 3 months after discharge. (additional one evaluation for infants and toddler prior to entering school)
Moderate certainty of evidence	1. PEEP level at or above the lower PEEP/higher FiO_2 table from the ARDS Network protocol.			
Low certainty of evidence	1. Lung-protective ventilation bundle 2. Target fluid management. ‡ 3. Inhaled NO 4. Keep SpO_2 92%–97% in mild-to-moderate PARDS			
Very low certainty of evidence	1. Vt 6–8 mL/kg or Vt 4–6 cm/kg if needed to stay below target plateau and driving pressure limits. 2. Plateau pressure ≤28 cm H_2O, and driving pressure ≤15 cm H_2O. 3. Minimal neuromuscular blockade to achieve ventilation strategy.	ECMO: 1. Be considered according to cause of PARDS and clinical condition. § 2. Maintain normal PaO_2 rather than hyperoxia	1. CPAP or BiPAP 2. Intubated if failed the trial of NIV within 6 h 3. At risk for PARDS: CPAP or HFNC over standard oxygenation 4. Possible PARDS: CPAP over HFNC.	
Cannot recommend for or against	Routine use of 1. Recruitment maneuvers 2. H.F.O.V. 3. Close suction system 4. Isotonic saline prior to endotracheal suctioning	Routine use of 1. Prone position 2. Bicarbonate 3. Surfactant therapy 4. Corticosteroids 5. Transfusion in those Hb >7 g/dL		
Ungraded definition statement		1. OI/OSI, in preference to PaO_2/FiO_2 or SpO_2/FiO_2 in determining severity of intubated PARDS children		

CPAP = continuous positive airway pressure; ECMO = extracorporeal membrane oxygenation; Hb = hemoglobin; HFNC = high-flow nasal cannula; H.F.O.V. = high-frequency oscillatory ventilation; OI = oxygen index; OSI = oxygen saturation index; NIV = noninvasive ventilation; NO = nitric oxide; PEEP = positive end-expiratory pressure; pRBC = packed red blood cell; RLS = resource-limited settings; Vt = tidal volume.

* This table is modified from the publication of Emeriaud *et al.*[8]

†Avoid exceeding plateau pressure (≤28 cm H_2O) and/or driving pressure limits (≤15 cm H_2O).

‡Maintain optimal oxygenation and end organ perfusion, while avoiding fluid overload.

§ECMO is considered in patients with a reversible cause of severe PARDS and lung-protective strategies result in inadequate gas exchange

Table 4: New biomarkers associated with pediatric acute respiratory distress syndrome (PARDS) patient outcome[17-27]

Biomarkers category	Outcome	Increased mortality	Prolonged mechanical ventilation	Non-pulmonary organ failure
Vascular endothelial		Ang-2 ↑, vWF↑, sTM↑	vWF↑	sTM↑
Alveolar epithelial		sICAM-1↑, sRAGE↑*, KL-6↑	sICAM-1↑, KL-6↑	sRAGE↑
Dysregulated coagulation and fibrosis		AT-III↓, protein C↓, PAI-1↑	protein C↓	Protein C↓
Inflammatory		IFNγ: IL-10 ratio↑, IL-8↑	IL-8↑	

Ang-2 = angiopoietin=2; AT-III = antithrombin-III; IFNγ = interferon gamma; IL = interleukin; KL-6 = Krebs von den Lungen-6; sICAM = soluble intercellular adhesion molecule; PAI-1 = plasminogen activation inhibitor-1; sRAGE = soluble receptor for advanced glycation end products; sTM = soluble thrombomodulin; vWF = von Willebrand factor.

*sRAGE only have association with mortality in immunocompetent and direct lung injury patients

Extracorporeal membrane oxygenation (ECMO) may be considered for cases of PARDS with a reversible cause and failure of lung-protective strategies. Neuromuscular blockade administration should be considered if protective ventilation goals are not achieved. It is crucial to avoid fluid overload. Early initiation of enteral nutrition support (within 72 h) with a protein intake of ≥ 1.5 g/kg/day is recommended. Transfusion of packed red blood cells is unnecessary if hemoglobin levels are ≥ 7 g/dL and the patient is hemodynamically stable. Essential therapies, management strategies, and follow-up programs for PARDS suggested by PALICC-2 are summarized in Table 3.[8]

Outcome of PARDS patients

The overall mortality rate for PARDS is approximately 24%, showing a general decline over the past three decades.[15] This decrease may be attributed to advancements in ventilator strategies and improved care in pediatric intensive care units.[16] However, multiorgan failure and the degree of hypoxia remain key risk factors for mortality. Higher mortality rates are associated with PARDS cases arising from sepsis (particularly non-pulmonary), leptospirosis infection, and influenza (especially H1N1).[16] Additional risk factors for poor outcomes include patient characteristics such as immunocompromised status, hematologic malignancies, and underlying pulmonary diseases.[16] In contrast, PARDS resulting from RSV infection, trauma, drowning, and burns tend to have lower mortality rates.[16]

In addition to the parameters mentioned above, new biomarkers related to inflammation, vascular endothelium, alveolar epithelium, dysregulated coagulation, and fibrosis have been studied for assessing patients with PARDS.[17] Although direct lung fluid samples may provide more accurate assessments, most PARDS patients are too unstable to undergo standardized bronchoalveolar lavage. Biomarkers obtained from direct tracheal aspirates and exhaled breath condensates are still evaluated. The blood-based biomarkers and their associations with PARDS outcomes are summarized in Table 4.[17-27]

Conclusion

In conclusion, the PALICC-2 criteria for PARDS improve the diagnosis. Different severity classifications are applied to patients undergoing NIV or IMV using metrics such as the PaO_2/FiO_2 ratio, SpO_2/FiO_2 ratio, OI, or OSI assessed 4 h after the initial diagnosis. Healthcare providers should exercise caution when managing patients with possible or at risk for PARDS conditions. A lung-protective ventilation bundle is recommended for respiratory support in PARDS patients. Optimizing PEEP according to the lower PEEP/higher FiO_2 table is strongly advised. A specific follow-up program is recommended for children with PARDS, including screening for morbidity, pulmonary function testing, and comprehensive evaluations of neurological and physical functions.

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Conflicts of interests

There are no conflicts of interests.

Author contributions

Yu-Sheng Lee designed the study. Chih-Ting Su performed literature search and data extraction. Chih-Ting Su wrote the manuscript. Yu-Sheng Lee, Mei-Jy Jeng, Chia-Suo Chou, Wei-Yu Chen, and Pei-Chen Tsao edited and reviewed the manuscript. All authors approved the final version of the manuscript.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Review Article

Long-term Azithromycin Prophylaxis in Pediatric Respiratory Disorders: A Narrative Review and Applications in Hong Kong

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Abstract

Respiratory disorders are a major cause of mortality and morbidity in Hong Kong children, the impact of which is amplified in those with chronic respiratory conditions. Childhood chronic respiratory conditions often involve heightened and sustained airway inflammation, presenting with recurrent symptoms ultimately resulting in lung function decline and structural disease. Thus, there is a growing interest in prophylactic interventions that may improve quality of life and reduce long-term sequelae. Macrolide antibiotics, especially azithromycin, have been utilized in select pediatric respiratory patients for their antimicrobial and immunomodulatory effects, although many uncertainties remain regarding their efficacy, indications, proper usage, and potential long-term effects. This review synthesizes the available evidence on long-term azithromycin use as a means of prophylaxis for children with chronic respiratory disorders, including respiratory infections, airway disorders, and lung parenchymal disorders. Overall, long-term azithromycin use has been shown to reduce pulmonary exacerbation frequency, yet assessments of its effects on quality of life and lung function were less significant. Patients who have suboptimal disease control despite recommended treatments may benefit, but careful and continuous evaluation of individual risk–benefit ratios of azithromycin use is of utmost importance. Furthermore, research studies are needed to enable informed decisions on prescribing long-term azithromycin and to delineate clinical and pathological markers associated with azithromycin response, including randomized trials to investigate its use in diseases pertinent to the Hong Kong context.

Keywords: Asthma, azithromycin, bronchiectasis, chronic lung disease, cystic fibrosis, interstitial lung disease, primary ciliary dyskinesia, prophylaxis

Key Messages

- Long-term azithromycin is a promising method of chemo-prophylaxis in children with chronic respiratory disorders experiencing poor control and frequent exacerbations.
- Potential benefits of prophylaxis must be weighed against individual and population risks, including developing antimicrobial resistance. Future research study is needed to identify select patients who may derive greater benefits.

Introduction

Respiratory disorders are key contributors to childhood disease burden. Globally, lower respiratory tract infections were the second leading cause of death in children in 2021.[1] In addition, asthma is the most common pediatric chronic disease,[2] reinforcing the importance of communicable and noncommunicable respiratory conditions. In Hong Kong, the top causes of respiratory mortality and hospitalization in children were pneumonia, asthma, and influenza respectively.[3] Collectively, childhood respiratory disorders lead to lower quality of life,[4] lower lung function persisting into adulthood,[5] and increased risk of premature death.[6] There are also substantial socioeconomic

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impacts linked to healthcare utilization,[7,8] especially in chronic conditions. Therefore, there is a need for effective strategies that optimize respiratory health via prevention, treatment, and rehabilitation.

Chemo-prophylaxis refers to using medications to prevent disease development. In respiratory disorders, chemo-prophylaxis aims to improve clinical and laboratory parameters, such as symptom severity, quality of life, exacerbation frequency, antibiotic use, lung function, and inflammatory markers.[9] In chronic conditions, it may be used to prevent disease progression or functional decline. An emerging candidate for chemo-prophylaxis in pediatric respirology is macrolide antibiotics, which have demonstrated antibiotic and immunomodulatory effects.[10] Its use has been extensively studied in diffuse panbronchiolitis and cystic fibrosis (CF),[11,12] where macrolide treatment reduced morbidity and mortality. In adults, azithromycin prophylaxis in chronic obstructive pulmonary disease (COPD) decreased acute exacerbation frequency and improved quality of life.[13] These effects suggest that macrolides may be useful in pediatric respiratory conditions involving heightened inflammation as a pathogenic mechanism.

However, there is a lack of consensus on the appropriate prophylactic use of macrolides in children with respiratory conditions and which groups may derive clinical benefit justifying the risks of additional antibiotics. This review aims to evaluate the current evidence regarding azithromycin prophylaxis and its impacts on disease outcomes in children with chronic respiratory disorders.

Azithromycin: Mechanism of Action and Guidelines

Azithromycin is a macrolide antibiotic, which exhibits a bacteriostatic effect by inhibiting bacterial 50S ribosomes.[14] Regarding its immunomodulatory effects, reduced neutrophilic inflammation is most consistently reported, with subsequent reduction in pro-inflammatory cytokines.[10] Notable examples include neutrophil elastase, interleukin-8, tumor necrosis factor-alpha, and matrix metalloproteinase,[10] which are implicated in many inflammatory conditions. Reduction in eosinophil function and Th2 cytokines has also been demonstrated.[10] Within the respiratory system, macrolides have been associated with increased mucociliary clearance, decreased bronchial hyperresponsiveness, and protection against epithelial damage.[14]

In Hong Kong, no specific guidelines mention long-term macrolide use in managing respiratory disease. Internationally, current guidelines reference long-term macrolide use target adults. According to British Thoracic Society guidelines,[15] azithromycin therapy is indicated in symptomatic patients with asthma, COPD, and bronchiectasis who experience frequent severe exacerbations despite optimizing other treatment modalities and adherence. The Global Initiative for Asthma states that add-on azithromycin may be considered in adults with moderate-to-severe asthma.[16] Long-term azithromycin is recommended for adults with CF experiencing repeated exacerbations and declining lung function.[17]

Although there are no specific guidelines for children, long-term macrolide therapy for at least six months is recommended in children with non-CF-related bronchiectasis or chronic suppurative lung disease and recurrent exacerbations (defined as more than one hospitalized or three or more nonhospitalized exacerbations in the previous 12 months).[18,19] The above recommendations are made based on the adequate risk–benefit assessment by the prescriber.

Methods

The literature search was conducted using the MEDLINE, Embase, and Cochrane databases, including articles published in English from January 2000 up to June 2024. Medical Subject Headings terms and keywords related to azithromycin ("azithromycin OR macrolide") and chronic pediatric respiratory conditions ("asthma" OR "cystic fibrosis" OR "bronchiectasis" OR "ciliary motility disorders" OR "primary ciliary dyskinesia" OR "bronchiolitis obliterans" OR "interstitial lung disease" OR "recurrent respiratory tract infections") were utilized. Inclusion criteria were the study population including children aged under 18 years, and evaluation of the use of long-term maintenance azithromycin (defined as at least 1 month in duration) with the aim of prophylaxis. Articles were excluded if azithromycin was primarily used for acute treatment. Study design was not designated as part of the inclusion criteria owing to the rarity of several conditions described and thus the difficulty of conducting randomized controlled trials (RCTs). The search was not limited by study outcome measures because of the heterogenous clinical presentation of the conditions described and various clinical and laboratory outcomes used for assessment. Relevant endpoints examined were related to symptom burden, quality of life, lung function, and laboratory investigations.

Current Landscape of Long-Term Azithromycin Use

Airway diseases

Asthma

Although azithromycin is recommended for adult asthma,[16] this guideline does not apply to children, despite reports that up to 20% of children hospitalized with critical asthma were prescribed azithromycin.[20] Usually, asthma is mild and adequately controlled with inhaled

corticosteroid-containing treatments.[21] Yet in a select group of children with "difficult-to-treat" or "severe" asthma, their condition remains uncontrolled despite optimized inhaled corticosteroids, a second controller therapy, and inhaler technique.[21] These patients are at higher risk of poor outcomes, especially those with non-type 2 or non-eosinophilic asthma for which treatment options are scarce.[22] Two double-blind RCTs presented mixed results on azithromycin prophylaxis in adults. Gibson *et al*.[23] found reduced exacerbation rate per year and improved quality of life when oral azithromycin was used for 48 weeks in adults with uncontrolled asthma. Brusselle *et al*.[24] reported improved quality of life in azithromycin users with severe asthma. On the other hand, there were no reductions in exacerbation rate or incidence of lower respiratory tract infections overall, but significant improvements were recorded in subjects with noneosinophilic severe asthma.[24]

Studies in adults have prompted interest in the potential utility of azithromycin in pediatric difficult-to-treat asthma. An open-label RCT in children with poorly controlled asthma compared azithromycin plus standard treatment with standard treatment alone.[25] After 3 months, Asthma Control Test scores differed significantly between the two groups even after adjusting for baseline score, favoring azithromycin treatment. Number of severe exacerbations was lower in the azithromycin group regardless of eosinophilic or noneosinophilic endotype. No between-group differences were seen in spirometry and microbiological outcomes. Lung function assessment in pediatric asthma may not be a reliable outcome, as high baseline values make detection of treatment effects challenging.[25] The open-label design and lack of placebo control were limitations of this trial.

Two other placebo-controlled trials have been performed. Azithromycin for 8 weeks, administered for three consecutive days every week, resulted in reductions in bronchial hyperresponsiveness and sputum neutrophil count not observed in the placebo group.[26] No significant change in lung function was found. This trial was limited by its small sample size but provides insight into azithromycin's anti-inflammatory mechanisms. Based on this, authors postulated that azithromycin may be useful in asthma patients experiencing predominantly neutrophil inflammation, which has been linked to impaired inhaled corticosteroid response.[26,27] In the other trial, Strunk *et al*.[28] explored the role of azithromycin as a steroid-sparing agent, finding no differences in time to inadequate control between azithromycin and placebo. The authors acknowledged that alternative primary outcomes with a longer follow-up period may be more appropriate in children with moderate-severe asthma. However, many of the children screened for the trial could not be randomized due to improved asthma control after close medical supervision or poor adherence. This brings out an important message that optimizing medications and maximizing adherence are important pillars of asthma treatment before considering adjunctive therapies such as azithromycin. Altogether, azithromycin use in asthmatic children is a promising option, especially in the subgroup with difficult-to-treat asthma.[29] Although optimal regimens are not known, azithromycin could be beneficial in children with non-type 2 asthma or type 2 asthma as an alternative to biologics. Further prospective studies are needed.

Bronchiectasis

Bronchiectasis is a chronic lung disease with airway dilatation often following recurrent bacterial infections. This section focuses on bronchiectasis unrelated to CF. A meta-analysis of four RCTs for long-term macrolides in non-CF bronchiectasis in children showed significant decreases in exacerbation frequency and sputum purulence score but with increased incidence of azithromycin-resistant bacteria (particularly *Streptococcus pneumoniae* and *Staphylococcus aureus*).[30] No effect was found on pulmonary function, sputum inflammatory markers, or adverse events.[30] Only one out of these four trials studied azithromycin, demonstrating similar reductions in exacerbation frequency but not severity (examined by length of hospital stay and need for supplemental oxygen).[31] In this trial, azithromycin was used for 12–24 months. Alarmingly, the odds of nasopharyngeal carriage of azithromycin-resistant bacteria were seven times higher in the azithromycin group than in the placebo group. Despite this, azithromycin reduced the number of nonpulmonary bacterial infections, which may present as co-morbidities in pediatrics. A secondary analysis of this trial found that the most effective reduction in exacerbations was observed between weeks 17 and 62 of treatment, and higher reduction was found in children with nasopharyngeal carriage of bacterial pathogens and higher weight-for-height *z* scores, with lower response in children born preterm.[32] This analysis enables a better understanding of the suitable duration of azithromycin and patients who may exhibit a greater response to prophylaxis. This trial was performed on Indigenous Australian children, therefore its generalizability to Hong Kong children is limited. Given the potential impact of frequent exacerbations on disease progression and quality of life, azithromycin may be recommended as an option for exacerbation prevention. However, the accompanying risks of azithromycin-resistant pathogens should be examined and prophylaxis prescribed after individualized consideration.

Cystic fibrosis

CF is a rare autosomal recessive condition, with an estimated prevalence of 1 in 300,000 live births in Hong Kong.[33] In the lungs, impaired mucociliary clearance leads to repeated infection, inflammation, and progressive

lung destruction. Research in CF is mostly conducted in Caucasian populations in North America, Europe, and Australia. Three-times weekly azithromycin is the most commonly investigated regimen, with duration ranging from 6 to 18 months.[34-38] The most consistent benefit reported is a decreased number of pulmonary exacerbations.[34,36,38-42] These effects have been observed in children with and without chronic *Pseudomonas aeruginosa* infection, suggesting that azithromycin affects CF disease activity via anti-inflammatory mechanisms beyond its antibiotic properties.[36,38,39] This is further supported by the sustained drop in systemic inflammatory markers such as absolute neutrophil count, neutrophil elastase, serum amyloid A, and calprotectin,[35] which have also been found to predict azithromycin response.[43] Evidence for the effects of prolonged treatment was questioned by Samson *et al*.,[40] who found retrospectively that reductions in pulmonary exacerbations and antibiotic courses were not maintained beyond 12 months of therapy. Therefore, although azithromycin is beneficial in reducing adverse outcomes, this highlights the need for regular review of its indications, especially in light of the high preexisting treatment burden in CF.

Studies reporting a change in pulmonary function have yielded mixed results. A meta-analysis of azithromycin use in children and adults with CF concluded that there were small but consistent improvements in lung function represented by forced expiratory volume in one second (FEV_1) percent predicted compared to placebo (mean difference = 3.97, 95% confidence interval 1.74–6.19).[44] Yet, in several randomized trials involving only children, no difference in forced expiratory volume (FEV_1) between azithromycin and placebo groups was found.[34,36,39,40] (FEV_1) improvements were observed in patients chronically infected with *P. aeruginosa*,[38] as well as in another study in which most patients had *Pseudomonas* infection.[41] This may suggest greater lung function benefits in those chronically infected with *Pseudomonas*. The lack of lung function effects in other trials may also be due to relatively normal baseline (FEV_1) in children.

A recent trial investigating structural lung disease measured by ultra-low-dose computed tomography found no differences in bronchiectasis prevalence or airway disease severity in infants who started azithromycin after CF diagnosis up until the age of 36 months compared to placebo, despite finding decreased hospital stay for exacerbations and less additional antibiotic use.[42] Ultimately, prophylaxis aims to improve quality of life—in CF children with *P. aeruginosa* infection, azithromycin led to improved physical function, but not in psychosocial or body image domains of quality of life.[38]

Another outcome of interest in CF is the risk of emergent pathogens, possibly linked to airway bacterial modulation. Two studies found no difference in airway colonization by common CF pathogens after azithromycin.[34,36,40] Indeed, chronic azithromycin users had a lower risk of new methicillin-resistant *S. aureus*, nontuberculous mycobacteria (NTM), and *Burkholderia cepacia* complex compared with nonusers.[45] However, microbiological outcomes are difficult to assess in children due to the relatively low number of isolates and sampling difficulty. Despite the low risk of pathogen acquisition, long-term azithromycin use may result in macrolide resistance among airway colonizers. Resistance patterns have been studied, revealing increases in macrolide-resistant *Staphylococcus aureus* and *Hemophilus influenzae* with azithromycin use compared with placebo.[36] A retrospective study found that resistance emerges as early as six months after treatment initiation, and persists in the airway thereafter.[40] These changes may not be clinically meaningful as macrolides are not first-line agents for the treatment of these organisms,[36] but are nevertheless important epidemiologically and their clinical implications are not fully understood.

With the advent of highly effective CF transmembrane conductance regulator therapies, the role of azithromycin therapy is uncertain in the road ahead. However, it does provide clinical benefit—reducing pulmonary exacerbations, and increasing lung function in select groups, with minimal impact on new respiratory infections. Its use should be evaluated on a case-by-case basis with regular monitoring and careful consideration of the appropriate treatment duration.

Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a rare condition caused by heterogenous mutations. Impaired ciliary structure and motility lead to respiratory manifestations similar to CF, characterized by exacerbations and progressive functional decline. In addition, a hallmark feature of PCD is chronic rhinitis and recurrent otitis media.[46] While its prevalence in Hong Kong is unknown, previous studies have indicated the issues of underdiagnosis and underrecognition of this disease.[47] Treatment of PCD is largely symptomatic and aims to slow progression. In the only randomized clinical trial of azithromycin in PCD,[48] three times weekly azithromycin for 6 months halved the rate of respiratory exacerbations (involving both upper and/or lower airways) and demonstrated a reduction in the number of pathogenic airway bacterial species. However, no differences were observed in pulmonary function and quality of life between azithromycin and placebo groups, for which the authors stated that longer treatment duration may be required to observe these changes. Azithromycin was generally well-tolerated, except for increased reports of mild diarrhea. It is worth noting that this study included children over the age of 7 years and adults due to the rarity of PCD and did not meet initial sample size calculations, but it provides valuable preliminary evidence for the maintenance of azithromycin in PCD, especially for patients with frequent exacerbations.[48]

Bronchiolitis obliterans

Bronchiolitis obliterans (BO) is characterized by inflammation and fibrosis of small airways, in severe forms leading to complete obstruction.[49] In children, the most common entity is post-infectious BO involving adenovirus, influenza, respiratory syncytial virus, and *Mycoplasma pneumoniae*.[49-51] While BO also occurs after lung and bone marrow transplantations,[52] these are less pertinent in pediatrics. Two retrospective and prospective studies have investigated the use of azithromycin combined with prednisolone in postinfectious BO, describing improvements in clinical condition and high-resolution computed tomography features after 6 months of treatment.[50,51] One studied a regimen containing azithromycin, budesonide, montelukast, and acetylcysteine,[53] demonstrating some improvements in respiratory symptoms, lung function, and imaging morphology after 3 months. However, these were not RCTs, had small cohort sizes, and their outcomes were not clearly defined. It was also difficult to assess the effect of azithromycin as it was used with other agents. In an RCT of once weekly azithromycin for 48 weeks in children with perinatal human immunodeficiency virus (HIV) infection and HIV-associated chronic lung disease radiologically consistent with BO, azithromycin was associated with fewer respiratory exacerbations than placebo but did not impact lung function.[54] This may not be applicable in Hong Kong since perinatally-acquired HIV is exceedingly uncommon but provides a reference point for diseases with similar pathology. Overall, evidence on long-term azithromycin use in BO is lacking and warrants further study.

Respiratory infections

Studies appraising azithromycin use in respiratory infections largely involve short medication courses. Azithromycin, administered during early acute illness, has displayed benefits toward clinical outcomes in children with respiratory syncytial virus bronchiolitis and recurrent respiratory infections, including progression to severe disease and recurrence of respiratory symptoms.[55-57] Since this review focuses on long-term azithromycin prophylaxis, these studies will not be discussed. A randomized placebo-controlled trial has been conducted to investigate the effect of azithromycin for 3–6 months in reducing morbidity associated with viral respiratory illnesses in children with chronic lung disease.[58,59] Formal results have not been published.

Pneumonia

Pneumonia is treated acutely with supportive treatment and appropriate antimicrobials; prophylaxis is not indicated in otherwise healthy children. However, in children experiencing recurrent pneumonia, there is value in contemplating prophylactic therapies given the risks of long-term sequelae.[60] In a 10-year retrospective study determining underlying factors for recurrent pneumonia, oropharyngeal incoordination was the top cause,[61] explained by aspiration of colonized airway secretions. Aspiration in children is often diagnosed clinically since access to the gold standard videofluoroscopic swallowing study is limited. One caveat of this is silent aspiration, which cannot be detected clinically. Silent aspiration occurred in 34% of children presenting with feeding difficulties and was significantly associated with higher odds of aspiration lung disease.[62] Therefore, this is a notable cause of pneumonia that may be under-detected and thus under-managed. No randomized trials have evaluated azithromycin prophylaxis for aspiration pneumonia, but its use has been indicated in the British Thoracic Society clinical statement for children with recurrent aspiration pneumonia for its potential pro-motility and anti-inflammatory benefits.[63] Azithromycin also has broad antimicrobial activity covering anaerobic organisms commonly the culprit in aspiration pneumonia.[64] Early identification of aspiration in children may allow effective multidisciplinary management, and azithromycin may be an advantageous preventive measure for certain individuals until safe swallowing is established. However, the lack of systematic evidence remains a barrier to its regular clinical use.

A subgroup of patients susceptible to aspiration-related pneumonia is children with neurological disorders. Neurological dysfunction contributes to key mechanisms in pneumonia development, including oropharyngeal incoordination, gastroesophageal reflux, impaired gastrointestinal motility, weak cough, and iatrogenic factors such as endotracheal intubation and nasogastric tubes.[64] Since neurological impairments tend to be known before recurrent pneumonia and lung damage occur,[61] prophylaxis may be important for reducing disease risk and burden. Studies in this population are difficult to perform; results of an ongoing RCT of prophylactic azithromycin in children with neurological impairment at risk of lower respiratory tract infections are anticipated.[65] Whilst concrete evidence is limited, the low risk–benefit ratio points toward a role for azithromycin in this group.[66]

Children with immunodeficiencies

Another group of children vulnerable to recurrent pneumonia is those with immune disorders.[61] In adults with primary antibody deficiencies and chronic infection-related lung disease, a double-blind placebo-controlled RCT demonstrated a lower risk of exacerbations, hospitalizations, and additional antibiotic use with increased quality of life following two years of low-dose azithromycin.[67] Although lung function did not improve, this trial was the first to demonstrate the utility and safety of azithromycin in immunodeficiency-related lung disease. No comparable study has been conducted in pediatrics,

but 12-month azithromycin treatment was efficacious in preventing recurrent nonallergic acute rhinosinusitis compared with placebo in a cohort of children of whom 85% had underlying antibody deficiencies.[68] Results showed reductions in rhinosinusitis episodes, medication requirements, and subjective symptom scores.[68] However, this study was limited by a small sample size. Different regimens of azithromycin prophylaxis have been used for children with common variable immunodeficiency and ataxia–telangiectasia, in the absence of evidence demonstrating clear benefits.[69] For children with recurrent infections resulting in bronchiectasis, there is a stronger basis for azithromycin prophylaxis (refer to the "Bronchiectasis" section above). Although some benefits of azithromycin prophylaxis have been shown and are mechanistically plausible, the lack of evidence hinders its application. Further trials are awaited, which must also address the challenge of antimicrobial resistance that is, crucial in this group as resistant organisms may limit treatment options for severe, atypical infections.

Other Conditions

Interstitial lung disease in children (ChILD) is a rare group of disorders involving diffuse parenchymal changes, with causes ranging from genetic or developmental disorders in infants to systemic disorders in older children.[70] Treatment is largely empirical and supportive, and no RCTs have been performed. A Delphi consensus was conducted to establish a best-practice protocol for the treatment of ChILD, finding that corticosteroids, hydroxychloroquine, and azithromycin were the most commonly used medications.[71] A previous case report showed promising results with dramatic improvement in respiratory symptoms, lung function, oxygen requirement, number of exacerbations, quality of life, and growth after long-term azithromycin in a child with ChILD due to genetic surfactant protein deficiency.[72] Azithromycin was also steroid-sparing in this case, with no treatment-related complications or side effects. Even so, since azithromycin is usually combined with steroids and immunosuppressants,[73] its effects as monotherapy are not known and remain to be studied.

Optimal Strategies

Azithromycin was chosen for discussion as it is the most studied macrolide for long-term use. Compared with other macrolides, azithromycin is preferred for long-term oral therapy due to its high level of tissue penetration and accumulation targeted to inflammatory sites, and its lack of effect on cytochrome P450 enzymes.[74] While ideal dosing regimens and treatment durations are not known, there have been suggestions that sub-antimicrobial doses may be sufficient to achieve anti-inflammatory effects.[34] The most common regimen adopted is three times weekly azithromycin (on Monday, Wednesday, and Friday). The technicalities of azithromycin prescription in pediatrics require further study.

In addition, potential side effects are important considerations. Gastrointestinal side effects are common but rarely severe.[15] Serious side effects raising concern are cardiac risks and hearing impairment.[15] In children receiving long-term azithromycin for chronic lung disease, QTc prolongation and hearing loss were not observed.[75,76] Nonetheless, patients and caretakers must be adequately informed of the risks and appropriate baseline assessments should be performed. There could also be potential shifts in gut microbiota diversity, especially in young children.[77] The above factors reinforce the importance of analyzing the benefits and risks associated with azithromycin before initiating prophylaxis. Once therapy has been initiated, regular reviews of patients' conditions are necessary to adjust azithromycin administration and to examine the continual need for prophylaxis.

Challenges and Limitations

A major factor limiting the widespread use of long-term azithromycin is the risk of increasing macrolide-resistant organisms.[31,36,48] The most common macrolide-resistant organisms detected were *S. pneumoniae*, *S. aureus*, and *H. influenzae*.[31,36,48] Regrettably, the clinical consequences of this are inadequately understood, but the emergence of particular resistant organisms such as *Mycoplasma* may pose serious threats to child health. To counteract antimicrobial resistance, patients suitable for azithromycin should be carefully selected and educated on proper antibiotic use. Doctors should stress the importance of adherence, which has been shown to decrease macrolide-resistant pathogens and overall pathogen carriage.[78] Although rarely reported in children, sputum testing for NTM should be considered as long-term azithromycin is contraindicated in NTM disease.[15] Macrolide susceptibility testing should be performed regularly for monitoring.[48] On a community level, azithromycin may also induce resistance—therefore, the use of azithromycin should be thoroughly examined and restricted to select patients.[79]

Other challenges against azithromycin prophylaxis include regulatory and cost issues since the uses described in this review would mostly be considered off-label, raising questions about its accessibility. There are research and ethical concerns regarding the testing of long-term medications in children. It is also difficult to determine what constitutes a meaningful benefit, especially in long-term studies where illnesses may impact individuals to varying extents.

Future Directions

Currently, long-term azithromycin prophylaxis is most well-studied in CF. Studies of azithromycin in other

respiratory conditions may reference the multi-center double-blind RCT design that has been adopted in CF studies. Trials with longer follow-up periods may also aid the understanding of the scale of prophylactic effect and establish appropriate treatment durations. Future research can focus on azithromycin mechanisms in respiratory disease, its effects on quality of life, and the identification of patient groups mostly likely to benefit. The latter may be achieved by studying relevant inflammatory, proteomic, or genetic markers associated with azithromycin response. At present, there is little published evidence on the landscape of pediatric respiratory disease in Hong Kong. Furthermore, audit initiatives are needed to fully understand the disease burden, before trials of azithromycin prophylaxis should be carried out.

Conclusion

Long-term azithromycin prophylaxis has demonstrated clinical benefit principally via preventing exacerbations in chronic respiratory disease, but its effects on lung function and quality of life are less clear. Commencing antibiotic prophylaxis in children may prevent early pulmonary damage and lifelong respiratory comorbidity. Most high-quality evidence for prophylactic azithromycin in children is derived from studies in CF, bronchiectasis, and other severe manifestations of respiratory disease. Collectively, these conditions may not be commonly encountered in routine practice in Hong Kong, but provide evidence for the potential immunomodulatory benefits of azithromycin. RCTs performed locally are needed to delineate the role of azithromycin prophylaxis and its applications in Hong Kong children. An individualized approach to azithromycin prophylaxis must be taken and its use scrutinized to achieve maximal benefit in the target group whilst balancing the risks of resistance to the wider population.

Author contribution

Nicole Wing Hei Tung: concepts, design, definition of intellectual content, literature search, data acquisition and analysis, manuscript preparation, editing and review, guarantor.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Association of Childhood Asthma Control Test and Asthma Control Test with Airway Hyper-responsiveness in Children and Adolescents

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Abstract

Introduction: We aimed to investigate the association of childhood asthma control test (CACT) and asthma control test (ACT) with airway hyper-responsiveness (AHR) defined by the methacholine challenge test in asthmatic children and adolescents. **Materials and Methods:** This study was a retrospective analysis of a hospital-based cohort. Each subject has completed the CACT or ACT, spirometry, and methacholine challenge test. A CACT or ACT score of 20 or above was defined as symptoms controlled. AHR was defined by a positive methacholine challenge test. **Results:** A total of 101 asthmatic children and adolescents were included. There was no statistically significant difference in the proportion of subjects with controlled or uncontrolled symptoms defined by CACT or ACT when compared to AHR defined by the methacholine challenge test. If a negative methacholine challenge test was regarded as a gold standard to define controlled "AHR," CACT and ACT had a sensitivity of 0%, specificity of 94.4%, positive predictive value of 0%, and negative predictive value of 68.1% to detect controlled subjects in our sample. **Conclusion:** In this study, CACT or ACT did not correlate well with AHR defined by the methacholine challenge test. CACT or ACT alone may not be comprehensive enough to detect subclinical hyperactive airways in children and adolescents.

Keywords: Airway hyper-responsiveness, asthma control test, childhood asthma control test, children

Introduction

Asthma is a significant cause of morbidity in childhood, resulting in activity limitation and school absence.[1] The prevalence of asthma in Hong Kong children has remained significant over the past two decades: 6.6%–7.9% in 6- to 7-year-old children and 10.2%–11.2% in 13- to 14-year-old adolescents.[2-6] In 2008, there were around 1,000 hospitalizations due to asthmatic attacks per 100,000 population in Hong Kong children.[7]

Asthma is defined as a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation, and is usually associated with airway hyper-responsiveness (AHR) and airway inflammation.[8,9] Assessment of asthma control is mainly based on clinical assessment and lung function tests to look for AHR and inflammation.[10] In primary care, lung function tests are rarely performed apart from clinical assessment.

Bronchial challenge tests are used to assess AHR, which is defined as an increased sensitivity and exaggerated response to non-allergenic stimuli that cause airway narrowing.[11] They are done to assess the presence and degree of airway responsiveness to a stimulus, measured by an index of bronchoconstriction, as a result of smooth muscle contraction along with edema and airway closure.[11] The degree of AHR may increase during exacerbations

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and decrease during treatment with anti-inflammatory medications.[11] In the absence of a "gold standard" test to confirm or refute the diagnosis of asthma, bronchial challenge testing could potentially be a more objective method to complement the clinical diagnosis of asthma when the diagnosis is more equivocal.[12] Management of asthma, with the consideration of reducing AHR, has been demonstrated to lead to more effective asthma control.[13,14]

Direct bronchial challenge tests include methacholine and histamine. They have high sensitivity since they directly stimulate airway smooth muscle cells.[15] Methacholine mimics the neurotransmitter acetylcholine to directly interact with muscarinic receptors on airway smooth muscle, resulting in contraction and airway narrowing.[11,16] Histamine causes a similar effect but is less commonly used due to its side effects of cough, headache, throat irritation, hoarse voice, and flushing.[17] Thus, methacholine is preferable due to its limited systemic side effects.[18]

Asthma control test (ACT) and childhood asthma control test (CACT) are commonly utilized to assess patients' asthma control during clinic visits.[19] ACT is a patient-reported 5-question questionnaire completed by adults and adolescents 12 years of age or older and is commonly used as a screening tool in outpatient settings. It is validated with a specialist's rating of asthma control; however, it has a fair correlation with spirometry results.[20] CACT is a 7-question questionnaire for children aged 4–11 years, filled by both the child and their caregivers, and includes seven questions regarding asthmatic symptoms; it is also validated with a specialist's rating of asthma control.[21] For both questionnaires, a score of ≥20 is considered controlled asthma, whereas a score of <20 is considered uncontrolled asthma.[20,21]

Multiple foreign studies have investigated the correlation of CACT and ACT to lung function tests. To the best of our knowledge, this is the first Hong Kong study to investigate the association of CACT and ACT with AHR defined by the methacholine challenge test in asthmatic children and adolescents.

As a secondary outcome, we would also like to investigate the association of CACT and ACT with obstructive spirometry patterns and bronchodilator response.

Materials and Methods

Participants

We retrospectively reviewed all children aged 5 years or above followed up for asthma in a respiratory clinic in the Department of Paediatrics and Adolescent Medicine in Kwong Wah Hospital between January 1, 2014, and December 31, 2021, with CACT or ACT, spirometry, and methacholine challenge test performed were included.

Children with underlying neuromuscular diseases, cardiovascular diseases, syndromal diseases, underlying rib cage deformity, and those who failed to complete all tests were excluded.

The following data were collected: (1) demographics: patient's age, gender, weight, and height on the date of tests; (2) spirometry readings: forced vital capacity (FVC), forced expiratory volume in one second (FEV1), ratio of forced expiratory volume in 1 s to FVC (FEV1/FVC), and post-bronchodilator FEV1 changes; and (3) methacholine challenge test result: provocation dose or concentration of methacholine. Other factors, including patients' serum immunoglobulin E (IgE) level, skin prick test results, smoking status, and recent inhaled corticosteroid use (in the past 4 weeks), were reviewed. Ethical approval was obtained from the Research Ethics Committee of the Kowloon Central/Kowloon East Clusters of the Hospital Authority in Hong Kong.

ACT/CACT

ACT was used for adolescents aged ≥12 years,[20] and CACT was used for children aged 4–11 years.[21] A score of ≤19 in either questionnaire denotes uncontrolled symptoms.

Spirometry

Spirometry was performed using MedGraphics Platinum Elite DX Real-Time Diffusion Body Plethysmography Pulmonary Function System (Serial No. 239000159) with the presence of designated staff for supervision. Forced expiratory maneuvres were performed according to American Thoracic Society and European Respiratory Society (ATS/ERS) standards.[22] Race-specific reference values are used.[23] Bronchodilator response was defined as equal or more than a 12% increase in FEV1 after administration of inhaled short-acting beta-agonist (400 μg of salbutamol). The results were interpreted by paediatric respiratory medicine specialists.

Methacholine challenge test

Methacholine challenge test was performed with standard guidelines.[11] We used the five-breath dosimeter method and the cut-off values of 16, 4, 1, and 0.25 mg/mL for the provocative concentration of methacholine (PC20) as the cut-off for normal, borderline, mild, moderate, and marked AHR. We have switched to the 1-min tidal breath method (using Aeroeclipse Breath Actuated Nebulizer, which allows comparable results from different nebulizers or dosimeters) since 2019 following the latest ERS technical standard,[11] and the cut-off values of 400, 100, 25, and 6 mg for provocative dose of methacholine (PD20) was used as cut off for normal, borderline, mild, moderate and marked AHR. The endpoint of the methacholine challenge test is the methacholine dose or concentration that causes a drop of 20% in FEV1.

Data analysis

We assumed the prevalence of AHR in asthmatic children and adolescents under ambulatory care was around 40%. With an expected sensitivity of 80% and the maximum marginal error of estimate not exceeding 10%, with a 95% confidence level, the total required sample size calculated by Buderer's formula was 103 subjects. The normality of data was assessed by the Shapiro–Wilk test. Continuous variables were presented as median (interquartile range [IQR]). Categorical variables were summarized as frequencies and percentages. Parametric and non-parametric data were compared using the Student's *t* test or Mann–Whitney *U* test, respectively. The chi-square tests or Fisher's exact tests were used to compare the difference in proportions between groups. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed by using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp. Armonk, NY, USA).

Results

Participants

A total of 101 eligible children and adolescents were included. Their demographic characteristics are shown in Table 1.

Of those 101 subjects, 77 were males (76%); the median (IQR) age was 10.7 (8.3–13.6) years old, and the body mass index (BMI) *z*-score was 0.3 (−0.4 to 1.1). About 96 (95%) were Chinese; others were South Asian. Serum IgE level was measured in 38 children and positive in 26 of them (68.4%). Skin prick test was measured in 70 children and positive in 58 of them (82.9%).

Baseline spirometry, methacholine challenge test, and ACT data

Spirometry

The median FEV1 *z*-score was −0.16 (IQR = −1.1 to 0.64) and the median FEV1/FVC *z*-score was −0.95 (IQR = −1.78 to −0.28). Using the definition of FEV1 *z*-score or FEV1/FVC *z*-score <−1.96 as obstructive lung pattern, 26 children (26%) had obstructive airway disease. Ten patients (10%) had bronchodilator response with an increase of FEV1 equal and more than 12% after post-bronchodilator. Those with obstructive lung patterns were older (median = 12.6, IQR = 10.1–16.7) than those who did not (median = 10, IQR = 7.8–12.7; $P = 0.001$), whereas there was no statistically significant difference in other characteristics. Those with bronchodilator response did not have a statistically significant difference in patient characteristics compared with those without bronchodilator response.

Methacholine challenge test

Methacholine challenge test was negative in 51 children (50.5%), borderline in 20 children (19.8%), mild in 21 children (20.8%), moderate in 6 children (5.9%), and marked in 3 children (3.0%). There was no statistically significant difference in baseline characteristics between them.

Table 1: Baseline characteristics of recruited children

Variables	Overall (*n* = 101)	CACT (*n* = 62)	ACT (*n* = 39)
Male, *n* (%)	77 (76.2%)	47 (75.8%)	30 (76.9%)
Age (years), median [IQR]	10.7 [8.3 to 13.6]	8.8 [7.6 to 10.5]	14.6 [12.9 to 16.9]
BMI *z*-score, median [IQR]	0.3 [−0.4 to 1.1]	0.1 [−0.7 to 0.9]	0.6 [−0.3 to 1.4]
Chinese, *n* (%)	96 (95.0%)	58 (93.5%)	38 (97.4%)
Smoker, *n* (%)	1 (1.0%)	0 (0.0%)	1 (2.6%)
Recent inhaled steroid, *n* (%)	52 (51.5%)	34 (54.8%)	18 (46.2%)
Serum IgE positivity (≥100 IU/mL), *n* (%)	26/38 (68.4%)	16/22 (72.7%)	10/16 (62.5%)
Skin prick test positivity, *n* (%)	58/70 (82.9%)	41/51 (80.4%)	17/19 (89.5%)
Spirometry			
FEV1 *z*-score, median [IQR]	−0.16 [−1.10 to 0.64]	0.01 [−0.72 to 0.95]	−0.77 [−1.85 to 0.18]
FEV1/FVC *z*-score, median [IQR]	−0.95 [−1.78 to −0.28]	−0.92 [−1.54 to −0.14]	−1.34 [−2.36 to −0.32]
Methacholine challenge test			
Negative, *n* (%)	51 (50.5%)	27 (43.5%)	24 (61.5%)
Borderline, *n* (%)	20 (19.8%)	15 (24.2%)	5 (12.8%)
Mild, *n* (%)	21 (20.8%)	13 (21.0%)	8 (20.5%)
Moderate, *n* (%)	6 (5.9%)	4 (6.5%)	2 (5.1%)
Marked, *n* (%)	3 (3.0%)	3 (4.8%)	0 (0.0%)
CACT/ACT			
Controlled symptoms (CACT/ACT score ≥20), *n* (%)	94 (93%)	60 (96.8%)	34 (87.2%)
Uncontrolled symptoms (CACT/ACT score <20), *n* (%)	7 (7%)	2 (3.2%)	5 (12.8%)

CACT = childhood asthma control test, ACT = asthma control test

ACT and CACT

ACT was used in 39 adolescents and CACT was used in 62 children. Seven (7%) of them reported uncontrolled symptoms and 94 (93%) reported symptoms controlled. The age was higher in the group with uncontrolled symptoms than the control group (median = 13.3 [IQR = 10.9–17.6] vs. 10.5 [IQR 8.1–13.4], $P = 0.025$). When only CACT was considered, there was no statistical difference in age between those with uncontrolled symptoms and controlled symptoms (median = 8.7 [IQR = 7.5–10.4] vs. 10.6 [10.3–10.9], $P = 0.150$). There was also no statistical difference in age when only ACT was considered (median = 14.3 [IQR = 12.7–16.7] vs. 15.3 [IQR = 13.1–17.7], $P = 0.501$).

Relationship between CACT and ACT with a methacholine challenge test

In Figure 1, the box plots showed that the median CACT/ACT scores had no statistically significant difference between methacholine positive and negative groups. For CACT, the median score is 25 (IQR = 23–27) in those with a negative methacholine challenge test and the median score is also 25 (IQR = 23.3–26) in those with a positive methacholine challenge test, $P = 0.650$. For ACT, the median score is 24 (IQR = 22–25) in those with a negative methacholine challenge test and the median score is 25 (IQR = 23–25) in those with positive methacholine challenge test ($P = 0.377$). Subjects with uncontrolled symptoms by CACT/ACT scores did not have a significant difference in the proportion of methacholine challenge test positivity compared to subjects who reported controlled symptoms (0/30 vs. 7/71, $P = 0.100$). The results are illustrated in Table 2.

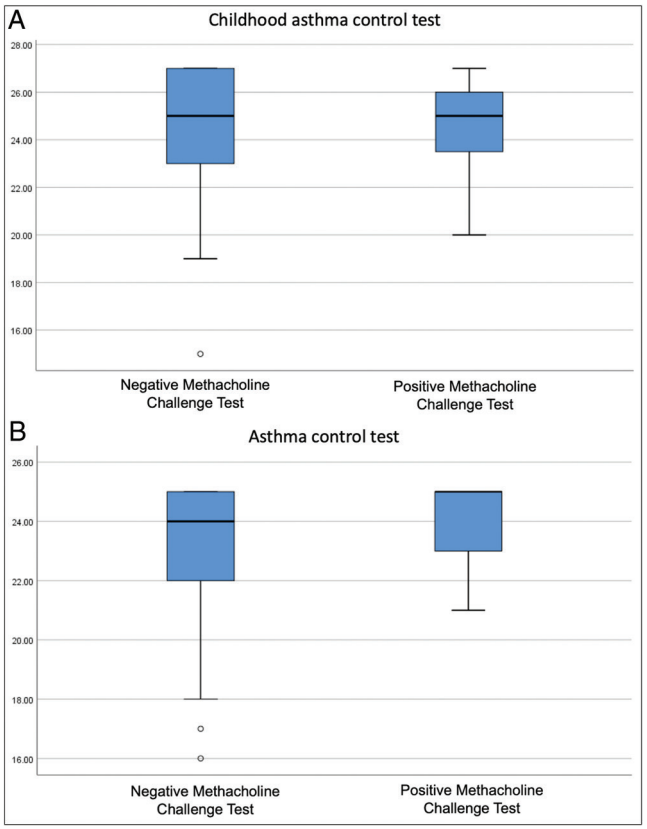

Figure 1: Box plots of CACT score and ACT score by methacholine challenge test positivity. (a and b) Boxes denote the median and 25th–75th percentiles with whiskers extending to the minimum and maximum within 1.5 times the box height. Outliers are plotted as a small circle

If the methacholine challenge test was assumed as the gold standard, CACT/ACT had a sensitivity of 0%, specificity of 94.4%, positive predictive value of 0%, and negative predictive value of 68.1% to detect AHR.

Relationship between CACT and ACT with spirometry

In Figure 2, the box plots showed that the median CACT/ACT scores had no statistically significant difference between the spirometry obstructive and spirometry non-obstructive groups. For CACT, the median score is 25 (IQR = 23.3–27) in those with non-obstructive spirometry and the median score is 24.5 (IQR= 23–26.3) in those with obstructive spirometry ($P = 0.532$). For ACT, the median score is 24 (IQR = 20–25) in those with non-obstructive spirometry and the median score is 25 (IQR = 23.3–25) in those with obstructive spirometry ($P = 0.117$). Moreover, there was no statistically significant difference between CACT/ACT-defined symptoms uncontrolled and spirometry-defined obstructive lung pattern (1/26 vs. 6/75, $P = 0.674$). This is summarized in Table 2. If spirometry was assumed as the gold standard, CACT/ACT had a sensitivity of 3.8%, specificity of 92%, positive predictive value of 14.3%, and negative predictive value of 73.4% to detect an obstructive lung pattern.

In Figure 3, the box plots showed that the median CACT/ACT scores had no statistically significant difference between positive and negative bronchodilator response. For CACT, the median score is 23.5 (IQR = 22.3–25.0) in those with bronchodilator response and the median score is 25 (IQR = 23.8–27) in those without bronchodilator response ($P = 0.083$). For ACT, the median score is 22 (IQR = 21–23) in those with bronchodilator response and the median score is 25 (IQR = 22–25) in those without bronchodilator response ($P = 0.230$). Moreover, there was no statistically significant difference between CACT/ACT-defined uncontrolled symptoms and spirometry-defined bronchodilator response (0/10 vs. 7/91, $P = 1.000$). This is summarized in Table 2. If spirometry was assumed as the gold standard, CACT/ACT had a sensitivity of 0%, specificity of 92.3%, positive predictive value of 0%, and negative predictive value of 89.4% to detect a bronchodilator response.

Table 2: Percentage of children with positive and negative methacholine challenge test, obstructive spirometry, and bronchodilator response among children with controlled and uncontrolled symptoms according to CACT/ACT

Variables	Positive	Negative	Overall	*P* value
Methacholine challenge test				
Overall (*n* = 101)				
Uncontrolled symptoms (ACT or CACT score <20), *n* (%)	0 (0.0%)	7 (6.9%)	7 (6.9%)	0.100
Controlled symptoms (ACT or CACT score ≥20), *n* (%)	30 (29.7%)	64 (63.4%)	94 (93.1%)	
CACT (*n* = 2)				
Uncontrolled symptoms (CACT score <20), *n* (%)	0 (0.0%)	2 (3.2%)	2 (3.2%)	1.000
Controlled symptoms (CACT score ≥20), *n* (%)	20 (32.3%)	40 (64.5%)	60 (96.8%)	
ACT (*n* = 39)				
Uncontrolled symptoms (ACT score <20), *n* (%)	0 (0.0%)	5 (12.8%)	5 (12.8%)	0.302
Controlled symptoms (ACT score ≥20), *n* (%)	10 (25.6%)	24 (61.5%)	34 (87.2%)	
Obstructive spirometry (FEV1 or FEV1/FVC *z*-score <1.96)				
Uncontrolled symptoms (ACT or CACT score <20), *n* (%)	1 (1.0%)	6 (5.9%)	7 (6.9%)	0.674
Controlled symptoms (ACT or CACT score ≥20), *n* (%)	25 (24.8%)	69 (68.3%)	94 (93.1%)	
Bronchodilator response (change in FEV1 ≥12%)				
Uncontrolled symptoms (ACT or CACT score <20), *n* (%)	0 (0.0%)	7 (6.9%)	7 (6.9%)	1.000
Controlled symptoms (ACT or CACT score ≥20), *n* (%)	10 (9.9%)	84 (83.2%)	94 (93.1%)	

CACT = childhood asthma control test, ACT = asthma control test

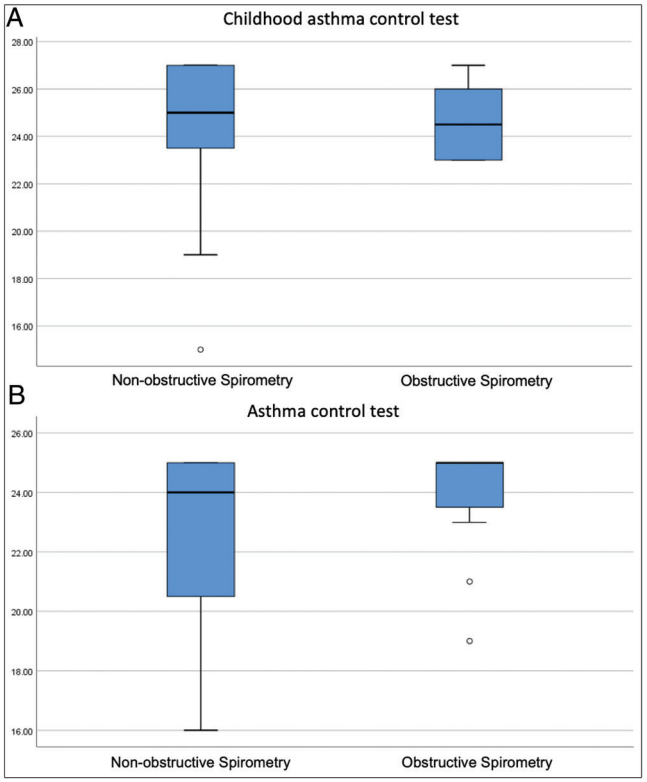

Figure 2: Box plots of CACT score and ACT score by spirometry defined obstructive lung pattern. (a and b) Boxes denote the median and 25th–75th percentiles with whiskers extending to the minimum and maximum within 1.5 times the box height. Outliers are plotted as a small circle

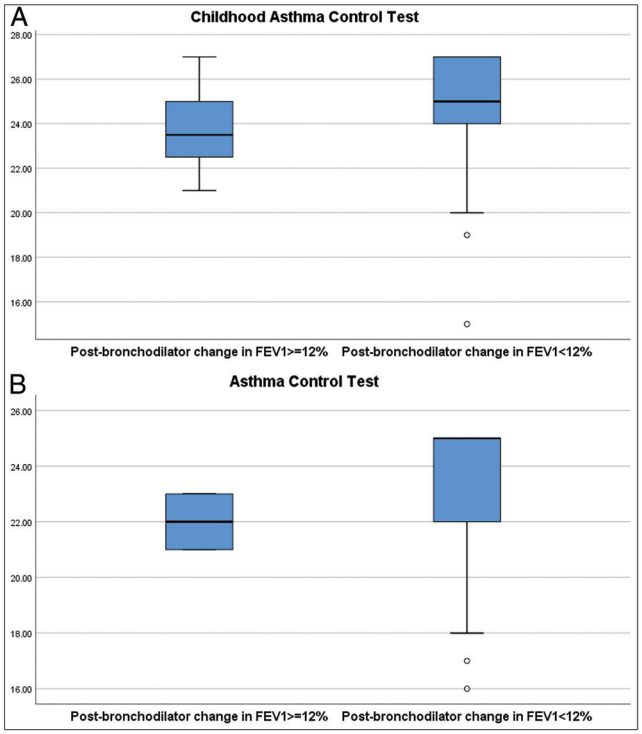

Figure 3: Box plots of CACT score and ACT score by spirometry defined bronchodilator response. (a and b) Boxes denote the median and 25th–75th percentiles with whiskers extending to the minimum and maximum within 1.5 times the box height. Outliers are plotted as a small circle

To conclude, we found no statistically significant relationship between CACT/ACT scores and either spirometry or methacholine challenge test results.

Discussion

The observation from this study showed that CACT/ACT did not predict AHR nor obstructive lung pattern as defined by spirometry or methacholine challenge test.

A positive methacholine challenge test was identified in 30% of our subjects, which was similar to the proportion of asthmatic children reported by a tertiary center located in the United States.[24] Abnormal spirometry was identified in one-quarter of our subjects, which was also similar to the proportion reported in the United Kingdom and North American studies involving children and adolescents with asthma.[25-27] Given the high proportion of abnormal lung function tests in asymptomatic children and adolescents with asthma, reliance on symptoms reporting alone may underestimate the actual disease activity.

The incongruent findings between CACT/ACT and spirometry or methacholine challenge test may be due to a difference in patients' or carers' perception of symptoms,[28,29] inaccurate recall,[30] and the similarity of symptoms in co-morbid diseases in patients.

On the contrary, some subjects in the study with marked responses to the methacholine challenges test had frequent symptoms and/or frequent attacks that required controllers. However, their CACT/ACT scores did not reflect the situation. This could be due to disease acceptance or tolerance which has been reported in a previous study.[31] We postulate that children may have severe symptoms but they accepted them thus high CACT scores were provided. Parents, as surrogate responders, may also over- or under-estimate children's asthma control.[28,29]

In this study, the methacholine challenge test was chosen over other challenge tests for its better safety profile and richer local experience. Indirect challenge tests (e.g., exercise challenge) may reflect more directly the ongoing airway inflammation and are more specific, but less sensitive, to asthma.[15,32] Methacholine challenge test is highly sensitive and is used serially to guide asthma therapies.[33] In our study, the methacholine challenge test is performed using standardized protocols. This can be the strength of this study. No side effects were experienced in all the methacholine challenge tests performed.

The Association of ACT with lung function has been previously studied with conflicting results. Three studies performed in Taiwan comparing the CACT score and spirometry parameters showed poor correlation;[34-36] whereas one study performed in Japan showed a significant correlation between CACT score and spirometry parameters.[37] For ACT, a study performed in the United States including children >12 years old and adults only showed a weak correlation ($r = 0.29$).[38]

Studies comparing ACT and AHR were also conflicting. Two studies performed in Italy comparing CACT and ACT with an exercise challenge test showed no statistically significant association,[29,39] while a study performed in Switzerland comparing CACT and exercise challenge test showed a statistically significant association of CACT score 19–25 to spirometry but not scores below 19.[40] A study performed in Italy comparing ACT to the exercise challenge test showed significant correlations,[41] whereas a study also performed in Italy compared ACT with the mannitol challenge test also showed a correlation.[42]

There were several limitations in this study. Firstly, it was performed in a single center. The small sample size, including the low percentage of children with uncontrolled symptoms by CACT/ACT, limited the ability the demonstrate a possible correlation. The low percentage of children with uncontrolled ACT may be due to the limited perception of children and their carers regarding asthmatic symptoms, with the patients being young and their carers being surrogate responders.[28,29]

There are also significant differences regarding patient's baseline characteristics. Those with obstructive lung patterns were older than those who did not.[43] This finding could be due to the time-dependent process of airway remodeling secondary to chronic asthma causing airway obstruction.[44] The age was higher in the group with uncontrolled symptoms than in the control group within the whole study population. However, when CACT and ACT were considered separately, there were no significant differences. Keeping in mind that CACT was used at 4–11 years old and ACT was used at 12 years or above, this could explain the difference as only two children had uncontrolled asthma in the CACT group and five children had uncontrolled asthma in the ACT group.

As the initial diagnosis of asthma in our subjects was not standardized (i.e., some by clinical symptoms or lung function test alone, whereas others by both), these groups of patients may represent a heterogeneous sample. Moreover, there may be differences in AHR in children with atopic compared to those with non-atopic asthma.[45]

As challenge tests are usually ordered under circumstances when the diagnosis of asthma is doubtful, this would create selection bias. Potential recall bias can occur with CACT and ACT being retrospective questionnaires.[46]

Another way to improve the accuracy of this study would be verifying the CACT and ACT scores by the clinician during consultation. It is not uncommon for subjects to misinterpret the questionnaire and reply differently during face-to-face conversation.[47]

Conclusion

In conclusion, this study observed that CACT and ACT may not be associated with AHR defined by methacholine challenge. The risk of uncontrolled underlying AHR may still be present even if the patient is reported asymptomatic. Lung function tests may be useful to early identify and treat the underlying disease burden and

improve long-term respiratory outcomes in asthmatic children and adolescents.

It is well known that uncontrolled asthma leads to airway remodeling and chronic fixed obstructive lung disease.[44] Lately, AHR has also been shown to correlate with the long-term prognosis of lung function development and the risk of persistence of disease into adulthood.[48,49] Thus controlling AHR has been increasingly recognized in the management of asthmatic control. More significant AHR also predicts a slower response to treatment with inhaled corticosteroids aiming to abolish AHR.[50]

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Conflict of interest

There are no conflicts of interest.

Author contributions

TT Yeung designed the study, supervised all aspects of the research, supervised analyses, interpreted the results, wrote sections of the initial draft, and reviewed and approved the final version. K. Kwok, E.Y. Chan, A.C. Hou, and S. Leung conducted and interpreted analyses, wrote sections of the initial draft, and reviewed and approved the final version. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Ethical policy and Institutional Review Board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Hong Kong Hospital Authority Kowloon Central Cluster Ethics Committee.

Data availability statement

Data are available upon reasonable request made to the corresponding author.

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Original Article

The Latest COVID-19-associated Croup Rate in Children: A Retrospective Cohort Study from the TriNetX US Collaborative Networks

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Abstract

Background: Croup (laryngotracheobronchitis) is the most common pediatric disease often associated with viral infection. The incidence of croup was also high during the coronavirus disease 2019 (COVID-19) pandemic. **Materials and Methods:** This retrospective cohort study is based on the TriNetX US Collaborative Network. Cases were patients with croup and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by positive ribonucleic acid findings or other related diagnoses, whereas controls were participants with croup but no evidence of COVID-19. The hazard ratio (HR) of incident croup was calculated for the case and control groups, and the 95% confidence interval (95% CI) was considered evidence of statistical significance. **Results:** Among the COVID-19 group, 854 patients developed croup within 7 days after the diagnosis of COVID-19 (HR = 2.77, 95% CI = [2.44, 3.15]). The incidence of croup was higher in the first 3 days after the diagnosis of COVID-19. Compared with the non-COVID group, the highest risk ratio was between 5 and 7 years of age (HR = 4.37, 95% CI = [2.87, 6.64]). The highest incidence was during the Omicron wave, followed by the Alpha and Delta waves. The risk of croup was highest from January 2023 to June 2023 (HR = 5.40, 95% CI = [3.52, 8.28]). **Conclusion:** Our results showed that the incidence of croup caused by the SARS-CoV-2 virus did not decrease due to the weakening of the virus. It is also because the subsequent COVID-19 virus is of the Omicron subtype. Therefore, in children with croup, and especially those over 5 years of age, SARS-CoV-2 virus infection should still be taken into consideration.

Keywords: COVID-19, croup, incidence of croup, risk of croup, SARS-CoV-2

Introduction

Croup (laryngotracheobronchitis) is a common pediatric disease characterized by barking cough, stridor, and hoarseness. It is often associated with viral infections such as parainfluenza virus, influenza, and respiratory syncytial virus.[1] However, the incidence was also high during the coronavirus disease 2019 (COVID-19) pandemic, which was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The Omicron variant of SARS-CoV-2 has increasingly been recognized as a potential etiology of croup,[2] and COVID-19-related croup has been reported to be more severe than non-COVID-related croup.[3] This study aimed to examine whether the COVID-19 pandemic had an impact on the incidence of croup and whether this impact persists.

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Materials and Methods

Patients

This retrospective cohort study was conducted using the TriNetX analytics platform, a global federated health research network, and a web-based database housing de-identified electronic health records from over 100 million patients across multiple countries. The

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data, primarily sourced from large academic medical institutions providing both inpatient and outpatient services across all 50 US states, includes a comprehensive range of information such as demographics, diagnoses, procedures, medications, laboratory values, and genomic data from major healthcare organizations (HCOs). This study includes 66 HCOs, with data extraction and analysis completed in August 2024.[4] Due to personal information, the exact geographical distribution cannot be known. The US network geographic distribution includes the United States Census Bureau defines four statistical regions, with nine divisions [Supplementary Table 1]. TriNetX officially claims that the data has been de-identified, so no Institutional Review Board (IRB) is needed. This study received ethical approval from the IRB of Chung Shan Medical University Hospital (IRB number: CS2-24101).

Data on patients who were diagnosed with croup between 1 January 2020 and 31 December 2023 were collected. The inclusion criteria were age under 18 years and data on at least two healthcare visits. We classified the patients into two groups: those with croup and SARS-CoV-2 infection confirmed by positive ribonucleic acid (RNA) findings or other related diagnoses (based on International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-10-CM codes; the COVID-19 group) [Supplementary Table 2], and those with croup but without evidence of COVID-19 (the non-COVID-19 group). The incidence of croup was compared between the two groups. Subgroup analyses were performed to investigate whether the risk of croup in the COVID-19 group differed by sex, age, race, and SARS-CoV-2 variant.[5]

Statistical analysis

To reduce the effect of confounding factors, we employed TriNetX's built-in function to create groups with matched baseline characteristics through 1:1 propensity score matching.[6] We matched the two groups at a 1:1 ratio by age at index, sex, race, medical utilization, and comorbidities, and then evaluated the balance of baseline characteristics using the standardized mean difference (SMD). SMD values below 0.10 serve as an indicator of balance within the studied population.

Kaplan–Meier analysis was used to estimate the probability of croup incidence at daily time intervals. Cox proportional hazard models were used to compare the two matched cohorts, with the proportional hazard assumption tested

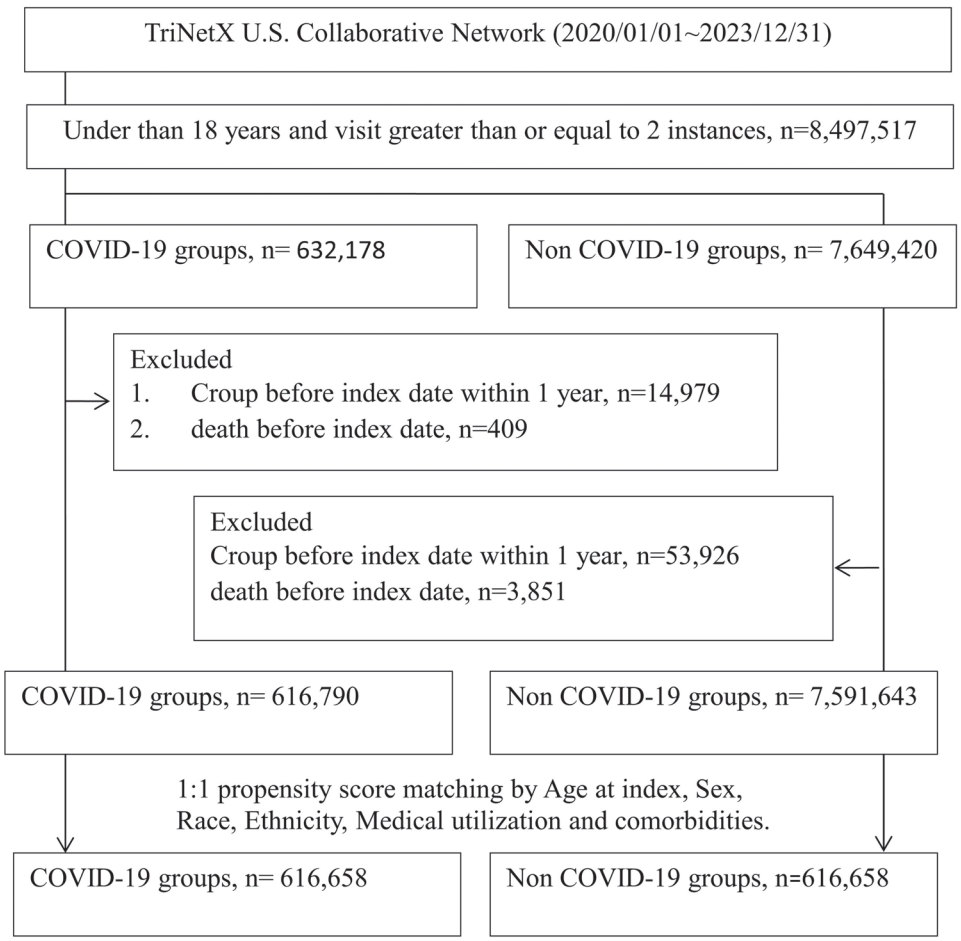

Figure 1: Flow chart of cohort construction from TriNetX. Abbreviation: *n*: total number

using the generalized Schoenfeld approach. HRs and their corresponding confidence intervals were calculated using R's Survival package v3.2-3 within the TriNetX platform. All statistical analyses were performed using the TriNetX Analytics Platform, with statistical significance set at $P < 0.05$ (two-sided).

Cohort

A flowchart of cohort selection is provided in Figure 1. A total of 8,497,517 patients under 18 years of age who visited an HCO at least twice between 1 January 2020 and 31 December 2023 were included in the study. Those with recurrent croup (two or more episodes/year) who were diagnosed within 1 year before the index day and those who died before the index date were excluded from the study.[7] The remaining patients were divided into COVID-19 ($n = 616,790$) and non-COVID-19 ($n = 7591,643$) groups. After propensity score matching, 616,658 patients in the COVID-19 group and 616,658 in the non-COVID-19 control group were enrolled in this study. The patients were longitudinally followed from 1 day after the index date to 7 days to estimate the risk of incident croup.

Results

Characteristics of the study patients

The demographic characteristics, comorbidities, and laboratory measurements of the COVID-19 and non-COVID-19 groups before and after propensity score matching are presented in Table 1. The mean age of the COVID-19 group at the index was 8.6 years after matching, and 49.4% were girls. Most of the patients were White (56.4%). After matching, the differences in age at index, sex, race, medical utilization, and comorbidities between the two groups were small and well-matched (SMD <0.1).

Incidence of croup in the COVID-19 and non-COVID-19 groups

Among the COVID-19 group, 854 patients (0.14%) developed croup within 7 days after the diagnosis of COVID-19 (hazard ratio [HR] = 2.77, 95% CI = [2.44, 3.15]) [Table 2; Figure 2a]. The incidence of croup in the COVID-19 is more than non-COVID-19 groups. The cumulative probabilities were 0.05% for day 1, 0.09% for day 2, and 0.11% for day 3. The probability then increased by about 0.01% per day until day 7. The HR of croup incidence was highest in the first 3 days (HR = 3.38, 95% CI = [2.91, 3.92]) after the diagnosis of COVID-19 [Table 3].

Subgroup analyses

In subgroup analyses of the COVID-19 group, we analyzed differences in sex, age, race, and the year during which a particular SARS-CoV-2 variant was predominant [Figure 3].[8]

Regarding sex, the incidence of croup was 0.16% in boys (HR = 2.71, 95% CI = [2.31, 3.18]) compared with 0.10% in girls (HR [95% CI] = 2.62 [2.14, 3.20]). The HR was similar between the boys and girls.

In the subgroup analysis of age, we divided the patients into five groups: <1, 1–<3, 3–<5, 5–<7, and >7 years [Figure 2b]. Among the five groups, the highest incidence of croup was in the 1–<3 years group (0.63%), followed by the < 1-year group (0.35%) and 3–<5 years group (0.22%). However, compared with the non-COVID group, the highest risk ratio was in the 5–<7 years group (HR = 4.37, 95% CI = [2.87, 6.64]), followed by the 1–<3 years group (HR = 4.34, 95% CI = [3.53, 5.33]) and 3–<5 years group (HR = 3.54, 95% CI = [2.45, 5.11]).

In the analysis of race, the highest incidence rate was among Asian patients (0.18%), followed by White patients (0.14%). The risk ratio was also highest among Asian patients (HR = 3.48, 95% CI = [2.02, 5.99]), followed by Black patients (HR = 2.80, 95% CI = [1.97, 3.98]).

We collected data from 2020 to 2023. Comparing the incidence of croup during the SARS-CoV-2 Alpha, Delta, and Omicron variant waves between 2021 and 2022, the highest incidence was during the Omicron wave (0.24%), followed by the Alpha (0.09%) and Delta (0.10%) waves [Figure 2c]. However, the incidence was highest during the Omicron subvariants wave after 2022 (>0.32%). The risk of croup was highest from January 2023 to June 2023 (HR = 5.40, 95% CI = [3.52, 8.28]), followed by from January 2022 to April 2022 (HR = 4.74, 95% CI = [3.69, 6.08]) and from July 2023 to December 2023 (HR = 4.49, 95% CI = [3.18, 6.35]).

Discussion

COVID-19 infection causes lower airway diseases in adults such as pneumonia and acute respiratory distress syndrome. However, in children, it can also cause croup, which is an upper airway disease. In our study, the children aged 5–<7 years old had the highest risk ratio. We also found that the risk of croup was highest in Asian patients and that the incidence was highest from January 2023 to June 2023, when the Omicron subvariants were predominant.

In classic croup, boys are more commonly affected than girls.[9] However, in the present study, we found that the risk of croup in the COVID-19 group was about the same for boys and girls. Classic croup is most common in children under 6 years of age,[9] with a peak in children under 3 years of age.[10] This is consistent with our results, which showed that the highest incidence rate was in the 1–<3 years group (0.63%). The incidence of croup in our study declined with age. However, compared with the non-COVID-19 control group, the COVID-19 group had a significantly higher risk of croup before 7 years of age. We also found another peak

Table 1: Baseline characteristics of study subjects (before and after PSM[1])

Code from TriNetX		Before PSM			After PSM		
		COVID-19	Non-COVID-19	SMD	COVID-19	Non-COVID-19	SMD[2]
	Total number	616,790	7591,643		616,658	616,658	
	Age at index (mean ± SD)	8.6 ± 6.1	8.3 ± 6.0	0.035	8.6 ± 6.1	8.6 ± 6.1	<0.001
	Sex						
	Girl	304,655 (49.4%)	3,732,889 (49.2%)	0.005	304,579 (49.4%)	304,875 (49.4%)	0.001
	Boy	311,613 (50.5%)	3,849,747 (50.7%)	0.004	311,558 (50.5%)	311,139 (50.5%)	0.001
	Unknown gender	522 (0.1%)	9007 (0.1%)	0.011	521 (0.1%)	644 (0.1%)	0.007
	Ethnicity						
85,865	Hispanic or Latino	115,692 (18.8%)	1,368,608 (18.0%)	0.019	115,673 (18.8%)	114,805 (18.6%)	0.004
104,582	Not Hispanic or Latino	458,012 (74.3%)	5,623,964 (74.1%)	0.004	457,900 (74.3%)	458,285 (74.3%)	0.001
	Unknown ethnicity	43,086 (7.0%)	599,071 (7.9%)	0.035	43,085 (7.0%)	43,568 (7.1%)	0.003
	Race						
1002-5	American Indian or Alaska Native	2819 (0.5%)	37,666 (0.5%)	0.006	2816 (0.5%)	2895 (0.5%)	0.002
46,997	Asian	26,337 (4.3%)	359,702 (4.7%)	0.023	26,334 (4.3%)	27,120 (4.4%)	0.006
56,370	Black or African American	125,831 (20.4%)	1,412,818 (18.6%)	0.045	125,780 (20.4%)	122,844 (19.9%)	0.012
64,498	Native Hawaiian or Other Pacific Islander	1914 (0.3%)	21,789 (0.3%)	0.004	1914 (0.3%)	1960 (0.3%)	0.001
75,301	White	396,675 (64.3%)	4,947,745 (65.2%)	0.018	396,606 (64.3%)	396,591 (64.3%)	0.001
84,373	Other race	63,214 (10.2%)	811,923 (10.7%)	0.015	63,208 (10.3%)	65,248 (10.6%)	0.011
	Medical utilization						
1,013,626	Office or other outpatient services	268,916 (43.6%)	1,839,958 (24.2%)	0.418	268,785 (43.6%)	267,394 (43.4%)	0.005
1,013,659	Hospital inpatient services	20,566 (3.3%)	84,354 (1.1%)	0.151	20,536 (3.3%)	15,334 (2.5%)	0.050
1,013,711	Emergency department services	156,448 (25.4%)	920,995 (12.1%)	0.344	156,318 (25.3%)	156,838 (25.4%)	0.002
	Comorbidities						
J30-J39	Other diseases of the upper respiratory tract	88,174 (14.3%)	427,611 (5.6%)	0.292	88,044 (14.3%)	87,180 (14.1%)	0.004
J00-J06	Acute upper respiratory infections	188,158 (30.5%)	737,664 (9.7%)	0.537	188,026 (30.5%)	189,339 (30.7%)	0.005
B25-B34	Other viral diseases	87,599 (14.2%)	197,359 (2.6%)	0.428	87,467 (14.2%)	87,002 (14.1%)	0.002
Q31	Congenital malformations of larynx	2225 (0.4%)	11,509 (0.2%)	0.041	2224 (0.4%)	1855 (0.3%)	0.010
Q32	Congenital malformations of the trachea and bronchus	732 (0.1%)	2531 (0.0%)	0.031	732 (0.1%)	606 (0.1%)	0.006

COVID-19 = coronavirus disease 1029, PSM = propensity score matching, SMD: standardized mean difference, SD = standard deviation.

[1]PSM: Matching includes age at index, sex, race, ethnicity, medical utilization, and comorbidities.

[2]SMD: <0.1 serves as an indicator of balance within the studied population

in HR in the patients aged 5–<7 years. We hypothesize that although the incidence of croup caused by COVID-19 infection in children older than 5 years was not higher than that in children younger than 5 years, fewer children older than 5 years developed classic croup, resulting in a higher risk ratio for those aged 5–<7 years.

Table 2: Risk of croup among COVID-19 group compared with non-COVID-19 group subjects (after prosperity score matching)

	Patients with outcome	Cumulative probability (%)							Hazard ratio* (95% CI)
		1 day	2 days	3 days	4 days	5 days	6 days	7 days	
Croup									
COVID-19	854	0.05	0.09	0.11	0.12	0.13	0.13	0.14	2.77 (2.44, 3.15)
Non-COVID-19	325	0.00	0.03	0.03	0.04	0.04	0.05	0.05	reference

COVID-19 = coronavirus disease 2019, 95% CI = 95% confidence interval.

*Follow up 0–7 days

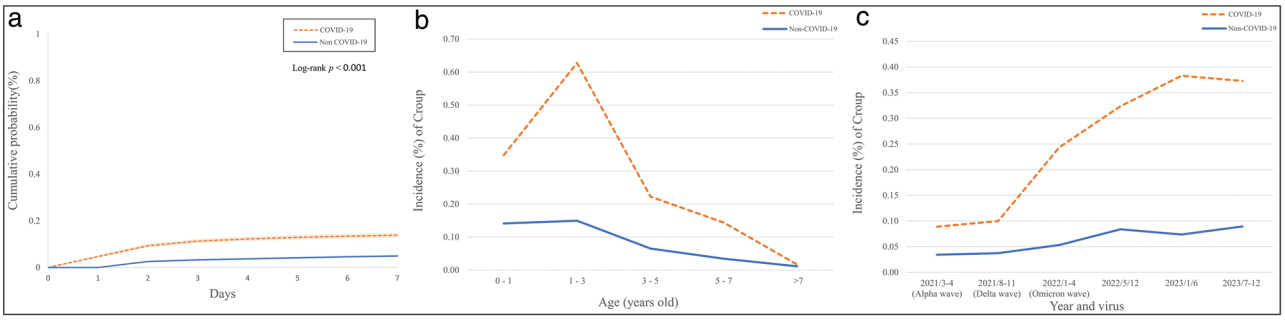

Figure 2: (a) Incidence of croup between the coronavirus disease 2019 (COVID-19) group and control group in the first 7 days. (b) Incidence of croup between the COVID-19 group and control group in the different ages. (c) Incidence of croup between the COVID-19 group and control group in the different years and COVID-19 variant

Table 3: Risk of croup on day 3 and day 6 after COVID infection

Different follow-up duration	Patients in cohort	Patients with outcome	Hazard ratio (95% CI)
Day 3			
COVID-19	616,658	734	3.38 (2.91, 3.92)
Non-COVID-19	616,658	225	Reference
Day 6			
COVID-19	616,658	818	2.85 (2.50, 3.25)
Non-COVID-19	616,658	302	Reference

COVID-19 = coronavirus disease 2019, 95% CI = 95% confidence interval.

The transmission and morbidity rates were different during different waves of the COVID-19 pandemic associated with different SARS-CoV-2 variants. An increase in children with COVID-19 presenting with croup was reported during the Omicron surge.[11] The Omicron variant of COVID-19 has been associated with more severe croup compared with classic croup.[3] COVID-19-associated croup has also been associated with frequent hospitalizations and intensive care unit admissions due to respiratory distress.[12] In our study, the number of COVID-19 patients diagnosed with croup was higher in 2022, which coincided with the Omicron wave. In 2023, the Centers for Disease Control and Prevention (CDC) reported that circulating Omicron subvariants such as BA.1, BA.2, BA.5, and XBB.1 were contagious and dominant globally.[12] The number of COVID-19 patients declined in 2023 in our study, which may be due to widespread immunity from both acquired infections and vaccinations. However, the incidence of croup in 2023 was higher than that during the Omicron wave in 2022. The HR also increased. This may be due to the large number of mutations leading to atypically high infectivity and the ability to evade antibody protection enhanced by viral infections and vaccinations.[12] Otherwise, only certain subtypes, such as PIV1/3, CoV NL63, or the Omicron variant of SARS-CoV-2, are associated with croup.[13] It is also because the subsequent COVID virus is of the Omicron subtype, so the incidence of croup has not decreased. Furthermore, research studies are needed to better understand the underlying mechanisms.

There are several limitations to this study. First, the diagnosis of COVID-19 was not entirely based on SARS-CoV-2 nucleic acid testing, so there may still be some deviations in the results. Second, although TriNetX is a global network more than half of the patients were White, especially Americans, and so the conclusions may not be generalizable to other groups. However, our results still have reference value regarding the risk of croup. Finally, we did not compare differences in severity in the subgroup analyses. According to the CDC, the COVID-19 mortality rate declined in 2023 compared with previous years; however, the incidence and risk of croup were not lower in our study.

Conclusion

Our results showed that the incidence of croup caused by the SARS-CoV-2 virus did not decrease due to the weakening of the virus. Although the number of infected patients fell

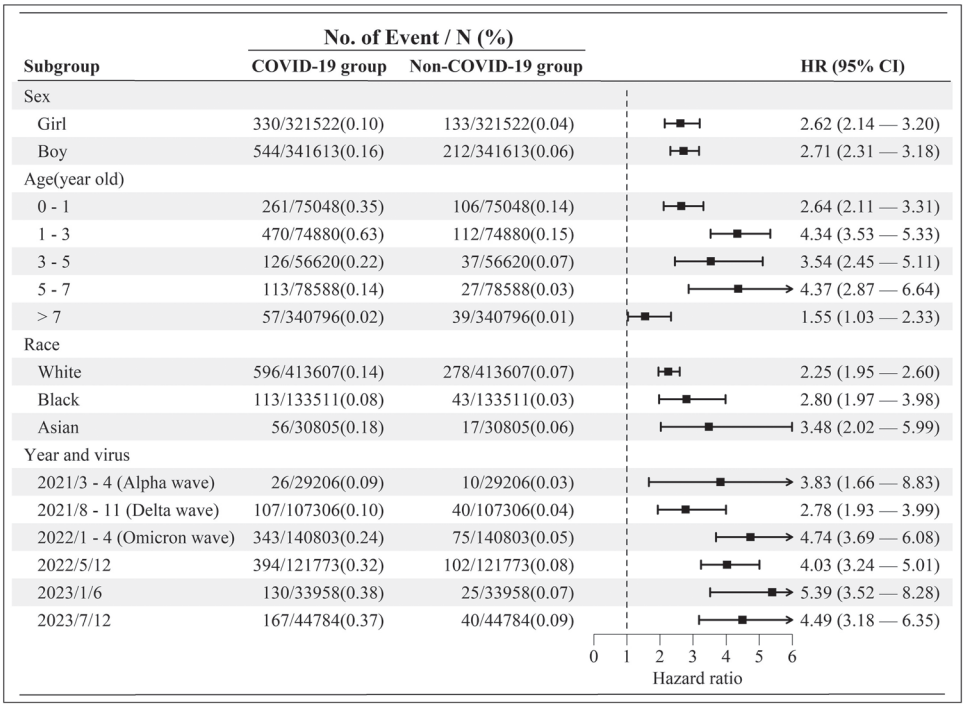

Figure 3: Forest plot of the risk for croup in subgroup analysis

significantly, the incidence of croup remained high. Of note, the severity of croup caused by the SARS-CoV-2 virus is higher than that of classic croup. Therefore, in children with croup, and especially those over 5 years of age, SARS-CoV-2 virus infection should still be taken into consideration.

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Authors contributions

Y.C.H. and P.L.L. collected the data and wrote the first manuscript. K.H.L. participated in data collection. Y.C.H. and P.L.L. made the figures and wrote the figure legends. H.L.S. coordinated and supervised data collection critically revised the manuscript and submitted the final draft.

Data availability statement

The data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: The US network geographic distribution

Region 1: Northeast	Division 1: New England, Division 2: Mid-Atlantic
Region 2: Midwest	Division 3: East North Central, Division 4: West North Central
Region 3: South	Division 5: South Atlantic, Division 6: East South Central, Division 7: West South Central
Region 4: West	Division 8: Mountain, Division 9: Pacific

Supplementary Table 2: SARS-CoV-2 infection related Code in TriNetX and ICD-10-CM codes

Variable	Code(s)
SARS coronavirus 2 and related RNA [Positive Presence]	TNX:9088 94,307-694309-294316-794500-694502-294533-794534-594559-294565-994758-0, 94759-894845-595406-595409-995608-696763-894760-6
COVID-19	U07.1
Coronavirus infection, unspecified	B34.2
Pneumonia due to SARS-associated coronavirus disease 2019	J12.82
Other coronavirus as the cause of diseases classified elsewhere	B97.29

*ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification

Original Article

Trends in Caregiver-Reported Prevalence and Severity of Pediatric Asthma During the COVID-19 Pandemic

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Abstract

Introduction: Asthma is one of the most common chronic conditions in pediatric patients and has been increasing in prevalence over the last several decades. Proper diagnosis and treatment of pediatric asthma is important, especially during the COVID-19 pandemic, which introduced uncertainty and drastic changes in care. The aim of this study was to understand the trends surrounding pediatric asthma prevalence and severity during the pandemic. **Materials and Methods:** We used data on children aged 0–17 years from the 2016–2021 National Survey of Children's Health. Presence and severity of diagnosed asthma were reported by children's caregivers. Asthma prevalence and severity were analyzed using multivariable logistic regression controlling for a linear measure of survey year and a categorical measure of era (2020–2021 vs. 2016–2019). **Results:** Based on a sample of 207,972 children, we estimated that 8% of children had been diagnosed with asthma, of whom 34% had moderate or severe asthma. We found no change in asthma prevalence during the pandemic (pandemic era vs. pre-pandemic era odds ratio [OR]: 0.87; 95% confidence intervals [CI]: 0.75, 1.01) and no statistically significant decrease in asthma severity during the pandemic (OR vs. pre-pandemic era: 0.81; 95% CI: 0.61, 1.08). We did not find significant changes in caregiver-reported pediatric asthma prevalence or severity during the COVID-19 pandemic. **Conclusions:** These data suggest the underlying population-level burden of pediatric asthma has remained constant, despite decreases in asthma-related healthcare use during the pandemic. This implies healthcare systems should prepare for a possible resurgence in pediatric asthma-related healthcare use in the post-pandemic years.

Keywords: Asthma, caregiver-reported asthma, COVID-19, pandemic, pediatric

Introduction

Asthma is one of the most common chronic conditions in pediatric patients. From 1980 to 2010, asthma prevalence in children age <18 years nearly tripled, from 3.6 to 9.3%.[1] At the outset of the COVID-19 pandemic, experts expected an increase in asthma prevalence and severity of pediatric asthma due to a variety of factors, including but not limited to barriers to accessing health care during the pandemic,[2-6] but it is unclear whether those changes have materialized in recent years. Pandemic-related decreases in preventive care use may have led to a greater burden of pediatric asthma due to undertreatment and undermanagement of the condition and symptoms.[2] However, it is also possible that the pandemic may have been associated with decreased severity or underdiagnosis of pediatric asthma. Studies of patients diagnosed with asthma before the pandemic found a potential increase in medication adherence, due to increased patient motivation and concerns about the risk of COVID-19 infection.[2,3,7] Furthermore, lockdowns, school closures, and mask use may have been associated with reduced exposure to allergens.[8]

Current evidence regarding trends in pediatric asthma prevalence and severity during the pandemic is mixed. Two studies found a reduction in well-child and acute

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primary care visits for pediatric asthma in 2020, compared to 2018 and 2019.[4,9] Another study found a 52% decrease in asthma diagnoses during the first year of the pandemic,[10] while emergency department visits for asthma exacerbations decreased during the pandemic by 60%–80%.[11] While these data illuminate trends in asthma-related healthcare utilization, they could have resulted either from improved asthma control and reduced asthma prevalence or, on the other hand, from hesitation to seek care during the pandemic and from asthma underdiagnosis. Furthermore, these data focused on the occurrence of asthma-related healthcare encounters but did not specifically query asthma severity. Therefore, we used repeated cross-sectional data from a nationally representative survey to investigate trends in caregiver-reported prevalence and severity of pediatric asthma during the pandemic. We hypothesized that the pandemic was associated with a decrease in both prevalence and severity of caregiver-reported pediatric asthma.

Materials and Methods

The National Survey of Children's Health (NSCH) is an annual, nationally representative sample of non-institutionalized children aged 0–17 in the United States. Randomly selected households across the United States received mailed instructions to access the survey online, and some addresses also received a paper version of the screening questionnaire. Full surveys were completed by each child's caregiver using a self-administered paper or web questionnaire, and participation was completely voluntary. The survey collected information about the physical and mental health, access to healthcare, and social context of one randomly selected child from each participating household.[12,13] The NSCH has been used by previous studies as a source of population-based data on asthma prevalence and severity.[14,15] For this study, we analyzed data from the 2016 to 2021 surveys, where the 2020 and 2021 surveys were conducted after the onset of the COVID-19 pandemic.[16] For our analysis, we included all cases where caregivers responded to questions about asthma diagnosis and severity and excluded cases missing data on any study variables. Analysis of these deidentified publicly available data was not considered to include human subject research by the local Institutional Review Board.

Presence of diagnosed asthma was defined if the caregiver was ever told by a doctor or healthcare provider that their child had asthma and stated (on a follow-up question) that the child currently had asthma. Asthma severity was reported by caregivers as mild, moderate, or severe, with the moderate and severe groups combined for data analysis.[17] The questionnaire did not specifically define the various severity levels of asthma, and these severity levels were based on caregivers' own interpretation of each category. Covariates included the child's age, biological sex, race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or none of the above), smoke exposure in the home, caregiver-rated general health (dichotomized as good, fair, or poor vs. excellent or very good), special healthcare needs (SHCN) status,[18] and whether the child had visited a doctor in the past 12 months for any reason. Socioeconomic covariates included caregiver education (highest of either caregiver and classified as high school or less, some college, or a 4-year college degree), insurance coverage in the past 12 months (continuous private coverage, continuous public coverage, part-year uninsurance, or year-round uninsurance), and whether the child's family had difficulty meeting their basic needs (e.g., food and housing) at any point during the child's life (dichotomized as "somewhat often" or "very often" vs. "never" or "rarely").[1,17-19]

Data were summarized using weighted means and percentages with 95% confidence intervals (CI). We compared data by era (pandemic era vs. pre-pandemic) using Wald tests. We then fit a multivariable logistic regression model of asthma prevalence, including survey year (entered as a linear term to capture any preexisting trend in asthma prevalence), era (dichotomized as pandemic vs. pre-pandemic to capture any pandemic-related change in prevalence), and all covariates listed above. The same model was re-fit for the outcome of asthma severity, while limiting the sample to children who currently had asthma. All analyses accounted for survey weights and adjusted variance estimation for the complex sampling design. In a *post hoc* analysis, we refit each multivariable model while interacting all child and family characteristics with era (pandemic vs. pre-pandemic) to test whether associations between covariates and asthma prevalence or severity changed during the pandemic. Data analysis was conducted using Stata/SE 16.1 (College Station, TX: StataCorp, LP). A significance level of $P < 0.05$ was used.

Results

The 2016–2021 NSCH included 225,443 cases, of which we excluded 2117 cases missing data on asthma diagnosis; 99 cases missing data on asthma severity; and 15,255 cases missing data on study covariates. The remaining 207,972 cases included 86,592 children sampled during the pandemic era, as compared to 121,380 children sampled before the COVID-19 pandemic. Based on the overall sample, we estimated that 8% of children had asthma, and among children with asthma, 34% had moderate or severe asthma. Bivariate comparisons of study outcomes and covariates by era are summarized in Table 1. Caregiver-reported asthma prevalence decreased from 8% to 7% ($P < 0.001$), but among children with asthma, there was no difference in the prevalence of moderate/severe as compared to mild asthma (35% pre-pandemic vs. 32% during the pandemic, $P = 0.095$).

Table 1: Bivariate comparisons of weighted means or proportions (with 95% confidence intervals) by era (*N* = 207,972)

Variable	Pre-pandemic era (*N* = 121,380)	Pandemic era (*N* = 86,592)	*P*
Asthma prevalence	0.08 (0.08, 0.08)	0.07 (0.06, 0.07)	<0.001
Asthma severity[a]			
Mild	0.65 (0.63, 0.67)	0.68 (0.65, 0.71)	0.095
Moderate/severe	0.35 (0.33, 0.37)	0.32 (0.29, 0.35)	0.095
Age (years)	8.6 (8.5, 8.7)	8.6 (8.6, 8.7)	0.249
Sex			
Female	0.49 (0.48, 0.50)	0.51 (0.50, 0.52)	0.807
Male	0.49 (0.48, 0.50)	0.51 (0.50, 0.52)	0.807
Race and ethnicity			
Non-Hispanic White	0.52 (0.51, 0.52)	0.51 (0.50, 0.52)	0.107
Non-Hispanic Black	0.13 (0.12, 0.13)	0.13 (0.12, 0.14)	0.598
Hispanic	0.25 (0.24, 0.25)	0.25 (0.24, 0.26)	0.320
None of the above	0.11 (0.10, 0.11)	0.11 (0.10, 0.11)	0.779
Smoking in the home	0.02 (0.02, 0.02)	0.02 (0.02, 0.02)	0.280
Caregiver-rated general health			
Excellent or very good	0.90 (0.90, 0.91)	0.90 (0.90, 0.91)	0.808
Good, fair, or poor	0.10 (0.09, 0.10)	0.10 (0.09, 0.10)	0.808
SHCN	0.19 (0.18, 0.19)	0.20 (0.19, 0.20)	0.033
Doctor visits in last year			
None	0.16 (0.16, 0.17)	0.19 (0.18, 0.19)	<0.001
One or more	0.84 (0.83. 0.84)	0.81 (0.81, 0.82)	<0.001
Caregiver education			
High school or less	0.22 (0.22, 0.23)	0.23 (0.22, 0.24)	0.419
Some college	0.27 (0.27, 0.28)	0.25 (0.25, 0.26)	<0.001
4-year college degree	0.50 (0.50. 0.51)	0.52 (0.51, 0.53)	0.001
Health insurance in last year			
Continuous private	0.62 (0.61, 0.62)	0.62 (0.61, 0.63)	0.550
Continuous public	0.29 (0.29, 0.30)	0.29 (0.29, 0.30)	0.710
Part-year uninsured	0.04 (0.04, 0.04)	0.03 (0.02, 0.03)	<0.001
Year-round uninsured	0.05 (0.05, 0.05)	0.06 (0.06, 0.06)	<0.001
Family ever had difficulty meeting basic needs	0.20 (0.19, 0.20)	0.12 (0.12, 0.13)	<0.001

[a]Reported for 9663 children in the pre-pandemic era and 5881 children in the pandemic era who currently had asthma.
SHCN, special healthcare needs

The multivariable model of asthma prevalence is shown in Table 2. After multivariable adjustment, the change in asthma prevalence was no longer statistically significant (pandemic era vs. pre-pandemic era odds ratio [OR]: 0.87; 95% CI: 0.75, 1.01; $P = 0.061$), and there was no perceptible underlying trend in asthma prevalence (year-over-year OR: 0.99; 95% CI: 0.95, 1.03; $P = 0.513$). Increasing age, being of male sex, being of any race other than non-Hispanic white, having SHCN, ever having difficulty meeting basic needs, or having a caregiver-rated health of good, fair, or poor all increased the OR of asthma prevalence. Contrastingly, OR decreased in children who had caregivers with 4-year degrees or had no doctor visits. On a *post hoc* analysis of interaction with each child or family characteristic within the pandemic era, we found that older age was more strongly associated with asthma prevalence during the pandemic (OR: 1.07; 95% CI: 1.05, 1.08) than before the pandemic (OR: 1.04; 95% CI: 1.03, 1.05). Similarly, Black vs. White race was more strongly associated with asthma prevalence during the pandemic (OR: 2.44; 95% CI: 2.06, 2.88) than before the pandemic (OR: 1.96; 95% CI: 1.70, 2.25).

Among children with asthma, Table 3 shows the multivariable model of asthma severity. Consistent with the bivariate analysis, there was no decrease in the odds of moderate/severe asthma during the pandemic era (OR vs. pre-pandemic era: 0.81; 95% CI: 0.61, 1.08; $P = 0.154$); and there was no trend in asthma severity over the entire study period (year-over-year OR: 1.03; 95% CI: 0.95, 1.12; $P = 0.429$). Similar to prevalence, being non-Hispanic black or Hispanic, having SHCN, or having a caregiver-rated health of good, fair, or poor all increased the OR of asthma severity, indicating worse. In addition, compared to continuous private insurance, children with continuous public insurance had an increased OR. Contrasting the results in prevalence, older children had a decreased OR along with those who had exposure to smoking at home. On a *post hoc* analysis, we found that exposure to smoke in the home was associated with lower caregiver-reported asthma

Table 2: Multivariable logistic regression model of caregiver-reported asthma prevalence (N = 207,972)

Variable	OR	95% CI	*P*
Year-over-year trend	0.99	0.95, 1.03	0.513
Era			
Pre-pandemic	Ref.		
Pandemic	0.87	0.75, 1.01	0.061
Age (years)	1.05	1.04, 1.06	<0.001
Sex			
Female	Ref.		
Male	1.17	1.08, 1.27	<0.001
Race and ethnicity			
Non-Hispanic White	Ref.		
Non-Hispanic Black	2.10	1.88, 2.34	<0.001
Hispanic	1.22	1.08, 1.37	0.002
None of the above	1.22	1.08, 1.37	0.001
Smoking in the home	1.01	0.80, 1.26	0.963
Caregiver-rated general health			
Excellent or very good	Ref.		
Good, fair, or poor	1.72	1.55, 1.91	<0.001
SHCN	8.11	7.43, 8.86	<0.001
Doctor visits in last year			
None	0.69	0.60, 0.80	<0.001
One or more	Ref.		
Caregiver education			
High school or less	Ref.		
Some college	1.01	0.89, 1.15	0.831
4-year college degree	0.85	0.74, 0.98	0.024
Health insurance in last year			
Continuous private	Ref.		
Continuous public	1.03	0.92, 1.15	0.645
Part-year uninsured	1.05	0.84, 1.31	0.657
Year-round uninsured	1.06	0.85, 1.32	0.619
Family ever had difficulty meeting basic needs	1.16	1.04, 1.29	0.008

CI, confidence interval; OR, odds ratio; Ref., reference; SHCN, special healthcare needs

severity before the pandemic (OR: 0.51; 95% CI: 0.31, 0.82), but was no longer associated with asthma severity during the pandemic (OR: 1.18; 95% CI: 0.65, 2.15).

Discussion

This study investigated caregiver-reported prevalence and severity of pediatric asthma during the COVID-19 pandemic in the United States using a nationally representative population-based survey. We hypothesized that the pandemic would be associated with a decrease in caregiver-reported prevalence and severity of pediatric asthma. While we found that there was a decrease in asthma prevalence on bivariable analysis, we found no significant changes in asthma prevalence or severity and no noticeable trends over the pandemic on our multivariable analysis. Our study also investigated the risk factors for asthma prevalence before and during the pandemic. We found that increasing age, being of male sex, being of any race other than non-Hispanic white, having SHCN, ever having difficulty meeting basic needs, or having a caregiver-rated health of good, fair, or poor all increased the OR of asthma prevalence. Contrastingly, OR decreased in children who had caregivers with 4-year degrees or had no doctor visits. These risk factors remained relatively consistent before and during the pandemic. However, we also found that older age was more strongly associated with asthma prevalence during the pandemic than before the pandemic. Similarly, Black vs. White race was more strongly associated with asthma prevalence during the pandemic than before the pandemic.

These findings could be associated with concurrent decreases in material hardship and doctor visits, which are associated with increased odds of caregiver-reported asthma; or with a concurrent increase in caregiver educational attainment, which is associated with decreased odds of caregiver-reported asthma. These findings suggest that healthcare systems should prepare for increasing demand for services by children whose asthma was potentially underdiagnosed or undertreated in the early years of the pandemic.

Table 3: Multivariable logistic regression model of caregiver-reported asthma severity (moderate/severe vs. mild) among children with asthma (*N* = 15,544)

Variable	OR	95% CI	*P*
Year-over-year trend	1.03	0.95, 1.12	0.429
Era			
Pre-pandemic	Ref.		
Pandemic	0.81	0.61, 1.08	0.154
Age (years)	0.98	0.96, 0.998	0.031
Sex			
Female	Ref.		
Male	0.86	0.73, 1.02	0.082
Race and ethnicity			
Non-Hispanic White	Ref.		
Non-Hispanic Black	1.44	1.18, 1.75	<0.001
Hispanic	1.34	1.06, 1.69	0.014
None of the above	0.86	0.68, 1.09	0.215
Smoking in the home	0.66	0.44, 0.98	0.037
Caregiver-rated general health			
Excellent or very good	Ref.		
Good, fair, or poor	2.77	2.32, 3.30	<0.001
SHCN	2.31	1.88, 2.83	<0.001
Doctor visits in last year			
None	1.03	0.76, 1.38	0.869
One or more	Ref.		
Caregiver education			
High school or less	Ref.		
Some college	0.83	0.65, 1.06	0.144
4-year college degree	0.83	0.64, 1.08	0.160
Health insurance in last year			
Continuous private	Ref.		
Continuous public	1.34	1.09, 1.65	0.005
Part-year uninsured	1.36	0.88, 2.08	0.162
Year-round uninsured	1.07	0.66, 1.74	0.773
Family ever had difficulty meeting basic needs	1.20	0.99, 1.45	0.061

CI, confidence interval; OR, odds ratio; Ref., reference; SHCN, special healthcare needs

During the pandemic, some clinical cases have been reported where infection with COVID-19 exacerbated asthma disease severity.[8,20,21] However, prior studies identified no change in self-reported pediatric asthma severity among adolescents,[7] and no change in asthma control was reported by clinicians treating pediatric asthma patients.[2] One study found that the acute care burden of asthma in children during the pandemic was profoundly reduced.[22] Another study found that emergency department usage for asthma visits for children decreased during the pandemic.[11] Another study reported a decline in new diagnoses of asthma during the first year of the pandemic, but only included children with commercial insurance coverage.[10] Another study identified a decrease in caregiver-reported asthma prevalence, based on data from the National Health Information survey (NHIS), but speculated that this change may have been confounded by a recent methodological redesign of the NHIS.[23] By contrast, our analysis of the NSCH (conducted using a consistent design from 2016 onward) found no change in caregiver-reported asthma prevalence during the pandemic. Taken together, the evidence suggests that the pandemic may have resulted in transient improvement in asthma control, possibly through decreased exposure to allergens or improved medication adherence,[8,24] but the population-level asthma prevalence did not appear to change, despite a decrease in asthma-related healthcare encounters in the pandemic's early years.[11,25]

As the United States transitions to a post-pandemic era, asthma-related healthcare use among children may rebound, compensating for the potential underdiagnosis and undertreatment of asthma during the pandemic. Therefore, it is important to consider how primary care and subspecialty practices can accommodate increased demand for routine or acute asthma-related visits. During the pandemic, there was a decrease in in-person visits and an increase in virtual visits.[25] The use of virtual visits appeared to work well in adult patients with asthma during the pandemic when in-person visits were not

possible,[26] but it is still unknown whether virtual visits are adequate to properly diagnose and manage pediatric asthma in the long run.[27] Moving forward, healthcare systems might consider partnering with schools and local community centers to provide asthma-related care to pediatric patients where it will be easily accessible to address the potential increase in asthma-related healthcare use post-pandemic.[27]

Our study was limited by a few factors. Since the study was based on caregiver-reported data, there is potential for subjectivity, especially recall bias and nonresponse bias, leading to underestimation of children with asthma. In addition, the reliance on caregivers' subjective rating of asthma severity with no further guidance by the survey questionnaire may have led to biased or inaccurate reporting, depending on individual families' experience of their child's asthma. Our data only included survey responses up to 2021, so we cannot measure longer-term trends in pediatric asthma since the pandemic onset. The pandemic may have disproportionately affected asthma management among children from minoritized or disadvantaged groups, although we did not specifically examine differences among groups in pandemic era trends or explore all potential mediating factors, such as access to medications and healthcare visits, caregiver job and housing stability, and access to transportation. Lastly, survey results were anonymized, and participants differed from year to year, precluding longitudinal analysis of the same children.

Our study demonstrated no significant changes in caregiver-reported prevalence or severity trends in pediatric asthma during the COVID-19 pandemic. We expect that there will be an increasing demand for services for children with potentially underdiagnosed or undertreated asthma after the pandemic because there was a decrease in healthcare use for asthma in the early years of the pandemic, despite our finding that the overall disease burden of pediatric asthma during this period (based on caregiver-reported data) did not change. As we enter a post-pandemic period, it is important to continue monitoring trends in pediatric asthma prevalence, severity, new diagnoses, and associated healthcare use. Lastly, we need to better understand how to deliver care to pediatric patients with asthma, especially those who come from disadvantaged backgrounds or who may not have ready access to care.

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This project has no funding to report.

Conflicts of interest

One of our authors (DT) discloses salary support from Kate B. Reynolds Charitable Trust and Lilly and Co. Inc. for unrelated research and quality improvement projects. All other authors have no conflicts of interest to report.

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This project has no acknowledgments to share.

Author contribution

Supriya Sivadanam: study design, literature search, data acquisition, and manuscript preparation/editing/review Sasank Sivadanam: study design, literature search, data acquisition, and manuscript editing/review Dmitry Tumin: study concept, study design, literature search, data analysis, statistical analysis, and manuscript editing/review.

Data availability

The data used in this project are publicly available and can be found at this link: https://www.census.gov/programs-surveys/nsch/data/datasets.html.

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