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Editorial

In this issue, we have 5 articles, including both original studies and reviews. Climate change and global warming are among the major threats to global health. The pediatric population is a vulnerable group highly susceptible to the detrimental effects of climate change. The review by Dr. Almohammadi[1] clearly outlined the factors associated with climate change and discussed how these factors might affect the developing respiratory system. Since we cannot reverse the trend of climate change in the short term, we need to understand what we can do to mitigate the long-term adverse effects. With regards to high-risk populations, the preterm infants represent a special group as they were born before the respiratory system was properly developed. Both oxygenation and positive pressure could damage the developing respiratory tract and lung parenchyma. Cheung and colleagues[2] reported in this issue a long-term assessment of lung function in 239 infants. Among them, 70 (40%) were term babies. Subgroups of these infants had infant lung function testing at a mean age of 14.3 months, and subsequent IOS assessment at 3 years of age. Infants born between 24-28 weeks of gestation showed persistent obstructive deficits. Early assessment using raised-volume rapid thoracoabdominal compression (RVRTC) could reliably predict subsequent small airway disease. The challenge will be to identify effective interventions that can modify the natural history of these lung function deficits in preterm infants. Despite medical advancements, respiratory failure remains one of the major challenges in the pediatric ICU. Pediatric respiratory failure is the result of a group of heterogeneous conditions with variable prognosis, and they require different therapeutic interventions at different stages of their disease. The lack of reliable biomarkers to predict prognosis and guide therapeutic interventions makes the management of this group of conditions very difficult. Dr. Takaba and colleagues[3] summarized the current state of the art and the potential of metabolomics to address the unmet need. There are many new platforms for metabolomic studies, such as nuclear magnetic resonance and liquid chromatography-mass spectrometry, for the determination of various metabolites, which in turn could provide important information about the course of the disease in a particular patient. Due to the vast amount of data generated, prospective assessments, along with advanced data processing, would be needed to determine the utility of these metabolomic measurements. Bronchoscopy has been well established for both diagnostic and therapeutic purposes in the adult population. Successive generations of bronchoscopes have significantly improved their diagnostic and therapeutic capabilities. Pediatric bronchoscopy has become a standard procedure in the developed world. Data on pediatric bronchoscopy from developing countries are limited. Dr. Harder and colleagues[4] reported a retrospective study of 230 flexible bronchoscopies from India. Their study clearly indicated the utility of such procedures in the developing world. Their results demonstrated that important information regarding diagnosis and treatment options could be reliably obtained by the procedure. Furthermore, in experienced hands, such procedures are relatively safe. This highlights the importance of establishing bronchoscopy suites staffed by trained personnel in developing countries, despite financial constraints. Although the COVID-19 pandemic is over, the timely review by Dr. Hon and colleagues[5] reminded us that COVID-19 still contributes significantly to the morbidity, especially among at-risk populations. Vaccinations remain one of the most important strategies in minimizing the morbidity associated with COVID-19. The articles in the current issue not only provide up-to-date information on the daily care of pediatric patients with respiratory disorders, but also novel research data on the use of flexible bronchoscopy and infant lung function studies.

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Review Article

Climate Change and Pediatric Respiratory Health: An Emerging Paradigm in Prevention and Critical Care

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Abstract

Climate change represents one of the most significant public health challenges of the twenty-first century, with profound implications for pediatric respiratory health. Children are disproportionately vulnerable to climate-related respiratory hazards due to their developing physiology, higher respiratory rates, and greater time spent outdoors. This narrative review examines the intersection of climate change and pediatric respiratory disease, focusing on preventive strategies and critical care implications. We explore the mechanisms by which rising temperatures, altered air quality, increased wildfire activity, and changing allergen patterns affect pediatric respiratory health. The review addresses climate-sensitive respiratory conditions, including asthma exacerbations, bronchiolitis, pneumonia, and emerging threats such as valley fever and fungal infections. We discuss the concept of climate-sensitive critical illness and examine how extreme weather events strain pediatric intensive care resources. Preventive medicine approaches, including air quality monitoring, climate-resilient healthcare infrastructure, community preparedness, and policy interventions, are evaluated. The roles of healthcare professionals in climate advocacy and in integrating climate considerations into pediatric respiratory care protocols are highlighted. Understanding these relationships is essential for developing adaptive healthcare strategies that protect vulnerable pediatric populations.

Keywords: Air pollution, climate change, critical care, pediatric respiratory disease, preventive medicine

INTRODUCTION

Climate change has emerged as a defining health crisis of our generation, with children bearing a disproportionate burden of its health consequences.[1] The Intergovernmental Panel on Climate Change has documented that global average temperatures have risen by approximately 1.1°C since pre-industrial times, with projections indicating further increases that will fundamentally alter environmental conditions worldwide.[2] These changes have direct and indirect effects on pediatric respiratory health through multiple pathways, including air quality deterioration, altered patterns of infectious disease transmission, increased allergen exposure, and extreme weather events.[3]

Children represent a uniquely vulnerable population for several physiological and behavioral reasons. Their respiratory systems are in active development until late adolescence, making them more susceptible to environmental insults.[4] Furthermore, children spend more time outdoors engaged in physical activity, increasing their exposure to environmental hazards.[5] These factors converge to create a population at heightened risk for climate-related respiratory disease.

This narrative review synthesizes current evidence on the relationship between climate change and pediatric respiratory health, with emphasis on preventive strategies and critical care implications relevant to respiratory and critical care practitioners. The review was conducted through comprehensive literature searches of PubMed, Web of Science, and Google Scholar databases

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covering publications from 2000 to 2025. Search terms included combinations of climate change, global warming, pediatric respiratory health, air pollution, extreme weather, and related terms. Priority was given to recent systematic reviews, meta-analyses, and large epidemiological studies. References from relevant articles were also reviewed to identify additional sources. While most cited studies are from 2021 and earlier due to publication lag times and the established evidence base in climate health research, key recent publications through 2022 were incorporated where available to ensure current perspectives.

The field of preventive medicine must evolve to address climate change as a fundamental determinant of respiratory health. Traditional prevention frameworks focused on individual-level interventions must expand to incorporate environmental and policy-level strategies that address the root causes of climate-related health threats.

CLIMATE CHANGE AND AIR QUALITY: IMPLICATIONS FOR PEDIATRIC RESPIRATORY HEALTH

Particulate matter (PM) and ozone exposure

Air pollution represents one of the most significant mechanisms by which climate change affects pediatric respiratory health. Rising temperatures increase ground-level ozone formation through photochemical reactions, with each 1°C increase in temperature associated with a 1%–3% increase in ozone concentrations.[6] Ozone is a potent respiratory irritant that causes airway inflammation, decreased lung function, and increased airway hyperreactivity in children.[7] Studies have demonstrated that short-term ozone exposure is associated with increased pediatric emergency department visits for asthma, with effect sizes larger in children compared to adults.[8] PM, particularly PM2.5 and PM10, has been extensively linked to adverse respiratory outcomes in children. Climate change influences PM concentrations through multiple mechanisms, including increased wildfire activity, dust storms in drought-affected regions, and enhanced formation of secondary organic aerosols.[9] Exposure to elevated PM2.5 levels during childhood is associated with numerous respiratory outcomes [Table 1].

Wildfire smoke and pediatric respiratory disease

Wildfire activity has increased dramatically in frequency, intensity, and duration across multiple continents due to climate change.[14] In the western United States, the area burned by wildfires has increased by approximately 1000% since the 1980s, with anthropogenic climate change contributing to over half of this increase.[14] Wildfire smoke contains a complex mixture of PM, carbon monoxide, volatile organic compounds, and other toxic substances that pose significant respiratory hazards.[15] Children exposed to wildfire smoke demonstrate increased rates of respiratory symptoms, emergency department visits, and hospitalizations.[16] A population-based study in California found that wildfire smoke exposure was associated with a 10% increase in pediatric respiratory emergency department visits during smoke episodes, with effects persisting for up to 5 days following exposure.[17] The composition of wildfire smoke differs from urban air pollution, with higher concentrations of ultrafine particles and organic compounds that may have unique toxicological properties.[18] Prolonged exposure during major wildfire events has been associated with persistent respiratory symptoms lasting weeks to months after the exposure period.[19]

CLIMATE-SENSITIVE RESPIRATORY INFECTIONS IN CHILDREN

Altered patterns of respiratory viral infections

Climate change influences the seasonality, geographic distribution, and severity of respiratory viral infections through multiple mechanisms. Temperature and humidity affect viral survival in the environment, with implications for transmission dynamics.[20] The traditional understanding of respiratory syncytial virus and influenza seasonality has been challenged by climate change, with some regions experiencing shifts in typical epidemic periods of up to 2–4 weeks.[21] Extreme weather events, particularly flooding and hurricanes, create conditions conducive to respiratory infection transmission through population displacement, overcrowding in shelters, and disruption of healthcare infrastructure.[22] Studies following major hurricanes have documented 20%–30% increases in rates of pneumonia and bronchiolitis in pediatric populations, with effects persisting for several weeks post-event.[23] Various climate factors influence the incidence and severity of pediatric respiratory infections [Table 2].

Emerging fungal respiratory infections

Climate change has facilitated the geographic expansion of fungal pathogens that cause respiratory disease.

Table 1: Health effects of PM2.5 exposure in pediatric populations

Health outcome	Effect size	References
Decreased lung function (FEV1)	3.4% reduction per 10 μg/m^3 increase	[10]
Asthma emergency department visits	OR 1.04 per 10 μg/m^3 increase	[11]
Lower respiratory infections	RR 1.12 per 10 μg/m^3 increase	[12]
Incident asthma	HR 1.20 per 4 μg/m^3 increase	[13]

FEV1 = forced expiratory volume in 1 s, OR = odds ratio, RR = relative risk, HR = hazard ratio

Coccidioides species, the causative agent of valley fever (coccidioidomycosis), has expanded its endemic range northward in the United States by approximately 500 km over the past two decades due to warming temperatures and altered precipitation patterns.[25] Pediatric cases of valley fever have increased by 800% in previously non-endemic areas between 2000 and 2020, presenting diagnostic challenges for clinicians unfamiliar with the disease.[26] Valley fever can manifest as a spectrum of disease from asymptomatic infection to severe pneumonia requiring intensive care, with children and immunocompromised individuals at higher risk for disseminated disease. Climate models predict further expansion of suitable habitat for Coccidioides, potentially exposing an additional 50 million children to this pathogen by 2050.[27] Other fungal pathogens, including Aspergillus and emerging thermotolerant species, may become more prevalent as global temperatures rise.[28]

ALLERGEN EXPOSURE AND ALLERGIC RESPIRATORY DISEASE

Pollen season lengthening and intensification

Climate change has resulted in earlier onset, longer duration, and increased intensity of pollen seasons across much of the Northern Hemisphere.[29] Between 1990 and 2020, the pollen season in North America lengthened by an average of 20 days, with pollen concentrations increasing by 21%.[30] Elevated atmospheric carbon dioxide concentrations enhance plant growth and pollen production, with some studies demonstrating 50%–90% increases in pollen production by ragweed under elevated CO_2 conditions.[31] Temperature increases advance the timing of spring pollen release by 10–20 days in many regions.[30] These changes have significant implications for children with allergic rhinitis and asthma, who experience symptom exacerbations during peak pollen periods.[32] Thunderstorm asthma, a phenomenon where severe asthma outbreaks occur during certain weather conditions, has been linked to climate patterns and represents an extreme manifestation of climate-related allergic respiratory disease.[33] During a 2016 thunderstorm asthma epidemic in Melbourne, Australia, over 3500 pediatric emergency presentations occurred within 30 h, resulting in 10 deaths.[34] The interaction between air pollution and aeroallergens may amplify allergic responses by 2–4 fold, with pollutants acting as adjuvants that enhance sensitization.[32]

Table 2: Climate factors and pediatric respiratory infections

Climate factor	Associated infection	Mechanism	References
Temperature extremes	RSV bronchiolitis	Altered viral survival and transmission	[21]
Humidity fluctuations	Influenza	Enhanced aerosol transmission	[24]
Flooding events	Bacterial pneumonia	Population displacement, overcrowding	[22,23]

RSV = respiratory syncytial virus

Indoor allergens and extreme weather events

Climate change influences indoor allergen exposure through increased humidity and temperature extremes that favor mold growth and dust mite proliferation.[35] Flooding events, which are becoming more frequent and severe due to climate change, with a 20%–40% increase in flood frequency in many regions,[36] result in water-damaged buildings that support mold colonization. Children living in flood-damaged housing demonstrate 2–3 fold increased rates of respiratory symptoms and asthma exacerbations compared to unexposed children.[37] Various indoor and outdoor allergen exposures are modified by climate change, with downstream effects on pediatric respiratory health [Table 3]. Heat waves may paradoxically increase time spent indoors with air conditioning, potentially increasing exposure to indoor allergens while reducing outdoor pollen exposure.[38]

HEAT-RELATED RESPIRATORY STRESS IN CHILDREN

Physiological vulnerability to heat exposure

Extreme heat events have increased in frequency, intensity, and duration due to climate change, with the number of heat wave days increasing by 3–5 days per decade globally.[39] Children have reduced capacity for thermoregulation compared to adults, with higher surface area-to-mass ratios and less efficient sweating mechanisms. Heat stress can directly affect respiratory function through increased respiratory rate (10%–20% increase per 1°C rise in core temperature), altered ventilation-perfusion matching, and in severe cases, heat

Table 3: Climate change effects on allergen exposure and pediatric respiratory outcomes

Allergen type	Climate effect	Respiratory outcome	References
Tree/grass pollen	Extended season, increased production	Allergic rhinitis, asthma exacerbations	[29,31]
Ragweed pollen	Enhanced production under elevated CO_2	Seasonal asthma exacerbations	[31]
Indoor molds	Flooding, increased humidity	Persistent asthma symptoms	[36,37]
Dust mites	Temperature and humidity increase	Year-round allergic symptoms	[35]
Thunderstorm-associated	Pollen fragment dispersion	Epidemic asthma	[34]

CO_2 = carbon dioxide

stroke with associated respiratory failure.[40] Children with preexisting respiratory conditions, including asthma and cystic fibrosis, may experience exacerbations during heat waves, with studies showing a 7%–15% increase in asthma emergency visits during heat wave periods.[41,42] Exercise-induced bronchospasm may be triggered or worsened by breathing hot, dry air during physical activity in extreme heat. Studies have documented 12%–18% increases in pediatric emergency department visits for asthma during heat waves, independent of air pollution.[42]

Heat and medication interactions

Many medications used in pediatric respiratory disease can impair thermoregulation or increase heat-related health risks. Beta-agonist bronchodilators may increase metabolic heat production by 5%–10%, while systemic corticosteroids can affect temperature regulation.[43] Children using these medications require special consideration and monitoring during extreme heat events. Healthcare providers should educate families about heat safety precautions specific to children with chronic respiratory conditions.

CLIMATE CHANGE AND PEDIATRIC INTENSIVE CARE

Surge capacity challenges during climate events

Extreme weather events strain pediatric intensive care unit (PICU) resources through multiple mechanisms. Direct effects include increased admissions for respiratory failure related to air quality emergencies, flooding-related pneumonias, and heat-related illness.[44] Indirect effects include infrastructure damage, power outages affecting life-support equipment, supply chain disruptions, and staff displacement.[45] Hurricane events have been associated with 40%–60% increases in PICU admissions in the weeks following landfall, with respiratory infections representing a major contributor to this surge.[46] Wildfires can cause sustained increases of 20%–35% in PICU occupancy during prolonged smoke episodes, stressing capacity in affected regions.[47] Various climate events pose specific challenges to pediatric critical care delivery [Table 4].

Table 4: Climate events and pediatric critical care challenges

Climate event	Direct health impact	PICU challenge	References
Wildfires	Smoke inhalation, asthma exacerbations	Respiratory failure admissions surge	[47]
Hurricanes/flooding	Pneumonia, displacement-related illness	Infrastructure damage, supply disruption	[45,46]
Heat waves	Heat stroke, dehydration	Multiorgan failure, resource strain	[44]
Air quality emergencies	Asthma status asthmaticus	Mechanical ventilation demand	[48]

PICU = pediatric intensive care unit

Resource allocation and triage considerations

Climate-related disasters may necessitate crisis standards of care when demand exceeds pediatric critical care capacity.[49] High-risk pediatric patients include those with preexisting chronic respiratory conditions (severe asthma, cystic fibrosis, bronchopulmonary dysplasia), immunocompromised children, infants under 12 months, children with neuromuscular disorders affecting respiratory function, and those from socioeconomically disadvantaged backgrounds with limited access to healthcare resources. These populations require prioritized access to preventive interventions and enhanced monitoring during climate events. Triage protocols must be adapted to account for climate-specific presentations and the unique vulnerabilities of pediatric patients.[50] Mechanical ventilation resources may be particularly strained during air quality emergencies affecting large populations simultaneously.[51] Telemedicine and inter-facility transfer networks become critical during climate events, enabling resource sharing and expertise distribution.[52] However, transportation challenges during extreme weather may limit transfer capabilities, requiring local facilities to manage more complex patients than usual.[53] Pediatric hospitals in climate-vulnerable regions should develop specific disaster plans addressing respiratory surge scenarios.[54]

PREVENTIVE STRATEGIES AND PUBLIC HEALTH INTERVENTIONS

Air quality monitoring and alert systems

Real-time air quality monitoring coupled with health alert systems represents a key preventive strategy for climate-related respiratory health protection.[55] Air quality index (AQI) forecasting enables families to modify outdoor activities during poor air quality days, reducing exposure. Schools and childcare facilities should implement activity modification protocols based on AQI readings, particularly for children with asthma.[56] Smartphone applications and text-based alert systems can deliver personalized air quality warnings based on location and health status.[57] Studies have demonstrated that air quality alerts are associated with 8%–12% reductions in pediatric asthma emergency department visits on high-pollution days, suggesting that these systems effectively modify behavior.[58] However, socioeconomic disparities exist in access to information and the ability to modify activities, with low-income families often having fewer options for avoiding exposure.[59] Addressing these disparities requires multi-level strategies including enhanced community education programs delivered through trusted local organizations, provision of portable air purifiers to vulnerable households, establishment of clean air shelters in underserved neighborhoods, subsidized access to air conditioning during concurrent heat and air quality events, and mobile health clinics providing respiratory care during climate emergencies. International organizations, particularly the World Health Organization (WHO), play a crucial role in developing global climate health guidelines, providing technical assistance to resource-limited countries, coordinating international research efforts, facilitating knowledge transfer and capacity building, and mobilizing financial resources for climate health adaptation in low- and middle-income countries. WHO's climate and health initiatives specifically target vulnerable populations, including children, providing evidence-based frameworks for national adaptation planning.

Climate-resilient healthcare infrastructure

Healthcare facilities must be designed and retrofitted to maintain functionality during climate extremes.[60] This includes backup power systems for mechanical ventilation and oxygen delivery, robust heating, ventilation, and air conditioning systems with high-efficiency filtration, protection against flooding and extreme heat, and secure medication storage.[61] The concept of green healthcare integrates environmental sustainability with climate resilience, reducing the healthcare sector's carbon footprint while protecting against climate impacts.[62] Pediatric respiratory clinics in climate-vulnerable regions should maintain surge capacity plans, including stockpiles of respiratory medications, nebulizer supplies, and pulse oximeters.[63] Telehealth capabilities enable continued care delivery when in-person visits are unsafe due to air quality or extreme weather.[64] Climate vulnerability assessments should be integrated into healthcare facility planning and risk management.[65]

Community-based prevention programs

Community health workers and school-based programs play vital roles in climate-related respiratory disease prevention.[66] Asthma action plans should incorporate climate-specific triggers, including air quality thresholds, heat advisories, and wildfire smoke exposure.[67] Community education on indoor air quality improvement, including proper use of portable air cleaners and creation of clean air rooms, can reduce exposure during air quality emergencies by 40%–70%.[68] Cooling centers with filtered air provide refuge during concurrent heat waves and air quality events, though uptake varies by community and awareness.[69] Culturally appropriate education materials addressing climate-related respiratory risks should be developed for diverse populations.[70] Community resilience building includes social networks that check on vulnerable children during climate events, ensuring access to medications and healthcare.[71]

Policy interventions and health system adaptations

Climate change mitigation through the reduction of greenhouse gas emissions represents the most fundamental preventive strategy for climate-related health impacts.[72] Healthcare organizations can advocate for clean air policies, renewable energy transitions, and climate-informed urban planning that protects children's respiratory health.[73] Pediatric respiratory specialists have unique credibility to communicate the health impacts of climate change to policymakers and the public.[74] Health system adaptation strategies include integrating climate considerations into clinical guidelines, quality improvement initiatives focused on climate-vulnerable populations, and research to better understand climate-health relationships.[75] Medical education must incorporate climate health competencies, preparing future practitioners to address these challenges.[76] Surveillance systems should track climate-sensitive respiratory outcomes to inform public health responses and measure intervention effectiveness.[77]

THE ROLE OF PREVENTIVE MEDICINE IN THE CLIMATE ERA

Preventive medicine practitioners are uniquely positioned to address climate change as a respiratory health determinant through surveillance, policy advocacy, and program development.[78] Climate-health vulnerability assessments can identify high-risk pediatric populations that require targeted interventions.[79] Integration of environmental health principles into preventive medicine practice enables comprehensive approaches addressing multiple exposure pathways.[80] Collaboration between preventive medicine specialists, pediatric pulmonologists, and critical care physicians is essential for developing climate-adaptive care models.[81] This includes anticipatory guidance addressing climate-related risks during health maintenance visits, climate-informed asthma management protocols, and preparation for climate-related pediatric respiratory emergencies.[82] Preventive medicine frameworks, such as the health impact pyramid, can guide the prioritization of interventions, with policy and environmental changes having population-level effects greater than individual clinical interventions.[83]

FUTURE DIRECTIONS AND RESEARCH NEEDS

Significant knowledge gaps remain regarding the full spectrum of climate change impacts on pediatric respiratory health. Long-term cohort studies are needed to assess how chronic exposure to climate-altered environments affects lung development and respiratory health across the lifespan.[84] The interaction between multiple climate stressors (heat, pollution, allergens) requires investigation to understand cumulative effects.[85] Development and evaluation of novel interventions, including advanced air filtration technologies, climate-informed clinical decision support tools, and community-level adaptation strategies, represent priority research areas. Health equity considerations must be central to this research, as climate change disproportionately affects socioeconomically disadvantaged and marginalized pediatric populations.[83,85] Climate change projection models should be integrated with health outcome modeling to anticipate future disease burdens and inform resource allocation.

CONCLUSION

Climate change represents an urgent and escalating threat to pediatric respiratory health, operating through multiple pathways including air pollution, altered infection patterns, increased allergen exposure, and extreme weather events. Children's physiological vulnerabilities magnify these risks, making them a priority population for climate health interventions. Pediatric respiratory specialists and critical care physicians must recognize climate change as a fundamental determinant of the conditions they treat and adapt clinical practice accordingly.

Preventive strategies spanning individual, community, healthcare system, and policy levels offer pathways to protect children from climate-related respiratory harms. Air quality monitoring and alert systems, climate-resilient healthcare infrastructure, community preparedness programs, and advocacy for climate mitigation policies represent essential components of a comprehensive response. The field of preventive medicine must evolve to incorporate climate considerations into all aspects of practice, from surveillance to intervention design to policy advocacy.

The pediatric healthcare community has both a professional obligation and a unique opportunity to address this challenge. By integrating climate awareness into respiratory care, building resilient healthcare systems, advocating for protective policies, and conducting research to fill knowledge gaps, we can work to ensure that current and future generations of children can breathe freely despite a changing climate.

Author contributions

The author confirms sole responsibility for all aspects of the manuscript, including the concept, design, execution, literature search, drafting of the manuscript, editing, and final approval of the submission.

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Review Article

Metabolomics in Pediatric Thoracic Critical Illness: NMR and LC-MS Insights for Precision Medicine

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Abstract

Pediatric thoracic critical illnesses like severe pneumonia, sepsis, and pediatric acute respiratory distress syndrome challenge intensive care units worldwide, with high prevalence and mortality. Although many clinical biomarkers are available to monitor the disease course, delayed recognition and heterogeneous phenotypes demand better biomarkers. Metabolomics, via nuclear magnetic resonance (NMR, reproducible, nondestructive, and detects 30–100 metabolites) and liquid chromatography-mass spectrometry (LC-MS, high-sensitivity, detects more than 1000 metabolites), profiles dynamic changes in various body fluids including plasma, bronchoalveolar lavage fluid, and breath condensate. NMR excels at quantifying high-concentration metabolites like lactate and amino acids via simple preparation and tools such as NMRProcFlow and Chenomx, while LC-MS targets trace-level compounds including lipids and acylcarnitines using electrospray ionization, MS/MS fragmentation, and MS-Dial processing. Unified workflows with MetaboAnalyst, Kyoto Encyclopedia of Genes and Genomes, and human metabolome database then enable principal component analysis/partial least squares-discriminant analysis modeling, as well as pathway enrichment analysis, to generate robust metabolomics insights. In pediatric critical care, metabolomics biomarkers may surpass C-reactive protein and procalcitonin in prognostic accuracy for predicting ventilation needs and multi-organ failure risk. Integrating NMR and LC-MS enables noninvasive monitoring via breath condensate, urine, or plasma, while elucidating key mechanisms like mitochondrial dysfunction in pediatric thoracic critical illnesses. These biomarkers outperform traditional markers in prognostic modeling. However, future multicenter trials should validate multi-omics panels and develop artificial intelligence-hybrid platforms for point-of-care assays, enabling precision ventilation and adjunct therapies to transform pediatric thoracic critical care.

Keywords: Metabolomics biomarkers, NMR and LC-MS, pediatric critical care, prognostic modeling

INTRODUCTION

Pediatric thoracic critical illnesses, including severe pneumonia, sepsis, and pediatric acute respiratory distress syndrome (PARDS), pose a profound challenge in intensive care units (ICUs), both globally and locally.[1] These conditions demand rapid intervention because of their aggressive clinical progression and high resource utilization in pediatric settings.[2] Worldwide, the prevalence of severe pneumonia requiring ICU care in children ranges from 5% to 15% among hospitalized pneumonia cases, with rates up to 10%–37% in broader pediatric cohorts depending on the region and severity definitions.[3] For pediatric sepsis requiring ICU admission, approximately 20%–30% of hospitalized children with sepsis necessitate intensive care, often linked to underlying infections like pneumonia.[4] Nevertheless, the PARDS incidence ranges from 2 to 12.8 cases per 100,000 children, with mortality historically 10%–40% but now 15%–25% based on the Pediatric Acute Lung Injury Consensus Conference 2

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criteria (3%–5% in ventilated children), driven by sepsis and trauma.[5]

In Asia, similar epidemiological pressures persist, compounded by a high burden of viral respiratory infections and pediatric comorbidities. The specific prevalence for severe pediatric pneumonia requiring ICU admission in Taiwan remains limited in available data, though general pneumonia contributes significantly to pediatric ICU (PICU) cases, often overlapping with sepsis.[6] However, PARDS affects about 28.2% of PICU admissions, with independent risk factors including mechanical ventilation, sepsis, pneumonia, and shock.[7] Nevertheless, significant challenges remain, including delayed disease recognition, marked patient heterogeneity, and the lack of reliable biomarkers for early risk stratification and therapeutic guidance.[8]

Metabolomics offers a promising approach to address these limitations by capturing dynamic metabolic alterations in biofluids such as plasma, bronchoalveolar lavage fluid (BALF), and exhaled breath condensate. Nuclear magnetic resonance (NMR) spectroscopy enables nondestructive, quantitative profiling of abundant metabolites, including lactate, amino acids, and glucose, whereas liquid chromatography-mass spectrometry (LC-MS) provides superior sensitivity for detecting low-abundance metabolites such as lipids, acylcarnitines, and volatile organic compounds. This comprehensive review synthesizes current metabolomics research in pediatric thoracic critical care, highlighting NMR- and LC-MS-derived biomarkers with potential applications in diagnosis, subphenotyping, prognostic modeling, and treatment monitoring. By integrating metabolomics with pediatric medicine, thoracic pathology, and critical care, this review aims to delineate future directions for translational research and clinical implementation.[2]

PLATFORMS OF METABOLOMICS RESEARCH

In metabolomics, NMR and LC-MS are key analytical platforms for comprehensive metabolite profiling. NMR spectroscopy detects molecular structures by measuring the energy differences of nuclei in a magnetic field, making it a powerful tool for metabolomics due to its reproducibility, nondestructive nature, and accurate quantification. LC-MS integrates chromatographic separation with high-resolution mass spectrometry to comprehensively characterize metabolites within complex biological matrices.[9] Owing to its superior sensitivity, selectivity, and broad dynamic range, LC-MS has become an indispensable platform in metabolomics for both qualitative and quantitative analyses.

Nuclear magnetic resonance spectroscopy

NMR spectroscopy relies on nuclei with non-zero spin, such as ^{1}H and ^{13}C, aligning in a strong magnetic field (B_0); an radiofrequency pulse perturbs this alignment, causing precession at the Larmor frequency, with the free induction decay signal detected and Fourier-transformed into a frequency spectrum.[10,11] It requires minimal sample preparation and separates metabolites based on the differences in magnetic frequency,[12] typically detecting 30–100 metabolites or features.[13] Key advantages include providing detailed structural information through multidimensional experiments, nondestructive analysis, rapid preparation, and high reproducibility. However, limitations encompass a high limit of detection (LOD $\approx 10^{-9}$ mol), long acquisition times for dilute or multidimensional samples, and restriction to high-concentration metabolites.[12]

Liquid chromatography-mass spectrometry

LC-MS separates metabolites by polarity on a column, with the eluent ionized via electrospray ionization or atmospheric pressure chemical ionization, followed by separation of gas-phase ions by mass-to-charge ratio (m/z) in quadrupole, Orbitrap, or time-of-flight (TOF) analyzers, yielding intensity versus m/z spectra.[10,11] It demands extraction for sample preparation and detects over 1000 metabolites or features based on the polarity and mass differences.[13] Strengths feature very low LOD (LOD $\approx 10^{-13}$ mol), high specificity via tandem mass spectrometry (MS/MS), and structural identification with authentic standards.[12] Drawbacks include matrix effects, difficulty distinguishing isomers, and the need for reference standards for confident identification. The comparisons and differences between these two platforms are summarized in Table 1.

METABOLITE IDENTIFICATION AND DATA ANALYSIS

Metabolite identification and data analysis represent critical steps in metabolomics workflows, bridging raw spectral data to biological insights. NMR data are typically preprocessed using tools like NMRProcFlow for calibration, baseline correction, and bucketing, while LC-MS workflows involve compound separation, detection, and data processing steps such as ionization mode selection, peak alignment, and normalization.[14] This section delineates platform-specific processing pipelines followed by integrated statistical analyses.

Metabolite identification

^{1}H-NMR data undergo NMRProcFlow for spectral calibration (ppm referencing), baseline correction, and bucketing, followed by Chenomx NMR Suite for targeted metabolite quantification (<5% coefficient of variation).[15] LC-MS workflows utilize MS-Dial for peak detection, retention time alignment, deconvolution, and annotation via MoNA/LipidBlast libraries, supporting MRM/PRM quantification.[16] These processes leverage the human metabolome database (HMDB) for metabolite structures and spectral references, alongside Kyoto Encyclopedia of

Table 1: Comparison of NMR and LC-MS platforms for metabolomics research

Parameter	NMR	LC-MS	References
Instrument operation principle	Nuclei with non-zero spin (e.g., ^{1}H, ^{13}C) align in a strong magnetic field (B_0). RF pulse perturbs alignment, nuclei process at Larmor frequency, FID signal detected, and Fourier-transformed to the frequency spectrum	Liquid chromatography separates by polarity on column. Eluent ionized (ESI/APCI), gas-phase ions separated by *m*/*z* in mass analyzer (quadrupole/Orbitrap/TOF), detected as intensity versus *m*/*z*	[10,11]
Sample preparation	Minimal preparation required	Extraction required	[12]
Separation principle	Differences in the magnetic frequency	Differences in polarity and mass	[11]
Number of detectable metabolites/features	30–100	1000+	[13]
Advantages	• Provides detailed structural information (multidimensional experiments) • nondestructive • Rapid sample preparation and high reproducibility	• Very low limits of detection (LOD ≈ 10^{-13} mol) • High specificity (MS/MS capability) • Enables structural identification with authentic standards	[12]
Limitations	• High LOD (~10^{-9} mol) • Long acquisition times for dilute or multidimensional samples • Limited to high-concentration metabolites	• Affected by matrix effects • Difficulty distinguishing isomers • Requires reference standards for confident identification	[12]

NMR = nuclear magnetic resonance, LC-MS = liquid chromatography-mass spectrometry, ESI = electrospray ionization, APCI = atmospheric pressure chemical ionization, LOD = limit of detection, MS/MS = tandem mass spectrometry, RF = radiofrequency

Genes and Genomes (KEGG) pathway maps for biological context.[17,18]

Data preprocessing and pathway analysis

NMR data analysis typically begins with preprocessing steps such as ppm calibration, baseline correction, and bucketing. NMRProcFlow offers a user-friendly visual interface for spectral calibration, correction, and integration.[19] LC-MS data processing typically involves peak picking, retention-time alignment, deconvolution, and normalization to ensure analytical robustness and inter-sample comparability. MS-dial is a data-processing pipeline for untargeted metabolomics applicable to either data-independent or precursor-dependent MS/MS fragmentation methods. Collectively, LC-MS-based workflows enable high-confidence metabolite identification, biomarker discovery, and mechanistic insights into systems biology and translational research.

MetaboAnalyst integrates preprocessed datasets for principal component analysis (PCA)/partial least squares-discriminant analysis (PLS-DA) multivariate statistics, metabolite set enrichment analysis, and joint pathway mapping using KEGG and HMDB.[20,21] Subsequent statistical analyses, including multivariate approaches (PCA and PLS-DA) and pathway enrichment, are often performed on platforms like MetaboAnalyst to enable accurate metabolite identification and interpretation.[14] In this context, KEGG provides curated pathway maps linking metabolites, reactions, and enzymes,[22] whereas HMDB offers human-specific metabolite structures, physicochemical properties, and reference spectra. Together, they support both pathway-level visualization and compound-level annotation in NMR- and LC-MS-based studies.[23] Together, these tools enhance data quality, enable the identification of differential metabolites, and generate high-quality outputs for scientific interpretation and publication. In addition, these analytical strategies facilitate robust metabolite annotation and pathway interpretation fundamental to pediatric critical care applications.

METABOLOMICS APPLICATIONS IN PEDIATRIC THORACIC CRITICAL CARE

Building on the analytical advances of NMR and LC-MS, metabolomics has been increasingly applied to investigate metabolic disturbances in critical illnesses. In pediatric and thoracic intensive care, conditions such as pneumonia, sepsis, and acute respiratory distress syndrome (ARDS) involve complex metabolic and inflammatory responses. Metabolomic profiling provides valuable insights into these pathophysiological changes and offers potential biomarkers for early diagnosis and prognosis. Relevant literature was identified through targeted searches in PubMed/MEDLINE, Embase, Scopus, and Web of Science databases, spanning January 1, 2000, to December 31, 2025. This timeframe encompasses the maturation of NMR and LC-MS metabolomics in clinical research. Search terms combined metabolomics techniques ("metabolomics," "NMR," "LC-MS," and "mass spectrometry") with pediatric critical care contexts ("pediatric," "children," "ICU," "pneumonia," "sepsis," "ARDS," "thoracic," OR "respiratory").

Pneumonia

Pneumonia is an inflammatory infection of the lungs caused by bacteria, viruses, or fungi. It leads to impaired gas exchange and remains a major cause of morbidity and mortality among children worldwide, particularly in community-acquired pneumonia (CAP). In low- and middle-income countries, the burden is further amplified by delayed care access, under-immunization, and malnutrition, which contribute to higher rates of severe and treatment-refractory disease in young children.

Nuclear magnetic resonance for pneumonia

Metabolomic analyses using ultra-performance liquid chromatography-TOF mass spectrometry and ^{1}H-NMR have revealed distinct metabolic signatures in pediatric pneumonia, including altered levels of uric acid, hypoxanthine, glutamic acid, and L-tryptophan associated with oxidative stress and energy metabolism.[24] In a larger cohort, urine metabolomic profiling accurately differentiated CAP cases from healthy controls with high diagnostic performance (area under the curve [AUC] = 0.97–0.99), identifying metabolites such as hypoxanthine, fumarate, and citrate as key markers.[25] Moreover, NMR profiling distinguished complicated parapneumonic effusions by showing lower glucose but higher levels of bacterial fermentation metabolites, including lactic and 3-hydroxybutyric acids, which serve as predictors for pleural drainage needs.[26] Building on these findings, ^{1}H-NMR with PLS-DA ($Q^2/R^2 = 0.84$) further elucidated fibrin formation mechanisms in fibrinous infectious pleural effusions, identifying anaerobic fermentation (lactic acid and 3-hydroxybutyric acid via glucose consumption) and ATP hydrolysis (hypoxanthine) as key drivers, significantly correlating with IL-1β inflammation and plasminogen activator inhibitor-1 fibrinolytic impairment.[27]

Liquid chromatography-mass spectrometry for pneumonia

Untargeted urine metabolomic profiling using LC-MS distinguished viral from pneumococcal CAP in children. Among 59 hospitalized cases, multivariate modeling identified 93 discriminatory metabolites, including 20 potential biomarkers. Notably, six metabolites were linked to adrenal steroid synthesis and degradation pathways, which were highly disrupted in pneumococcal pneumonia.[28] These results highlight the potential of metabolomics to reveal etiology-specific metabolic patterns and guide personalized diagnosis and treatment for pediatric CAP and suggest that integrating such signatures with clinical and radiologic data could improve early etiologic classification and antimicrobial stewardship in routine practice.

Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It remains a major cause of morbidity and mortality in pediatric populations. Early recognition and appropriate treatment are critical for improving survival outcomes; however, clinical differentiation between sepsis, infection, and postoperative inflammation remains challenging.

Nuclear magnetic resonance for sepsis

^{1}H-NMR metabolomics was applied to serum samples from 60 pediatric septic shock patients, 40 PICU patients with noninfectious systemic inflammation, and 40 healthy children to identify metabolic differences. Multivariate analysis revealed distinct metabolite patterns that separated patient groups, suggesting a composite metabolic response associated with septic shock and its outcomes.[29] These findings indicate that NMR-based metabolite profiling could serve as a promising tool for the diagnosis and prognosis of pediatric septic shock and may ultimately support risk-adapted therapeutic strategies by identifying children at highest risk for progression to multiple organ dysfunction or death.

Liquid chromatography-mass spectrometry for sepsis

LC-MS-based serum metabolomics identified six key metabolites, including prolylhydroxyproline, phosphatidylethanolamine, and cytidine diphosphate–choline, with prolylhydroxyproline showing strong diagnostic performance (AUC = 0.832) and the combined model reaching AUC = 0.859.[30] Additionally, combining LC-MS metabolomics with machine learning distinguished septic infants with and without comorbidities, identifying key metabolites such as hexylamine, psychosine sulfate, and lysophosphatidylcholine (LysoPC), with the combined model achieving AUC = 1.[31] These findings indicate that metabolomic profiling provides robust biomarkers for early diagnosis, prognosis, and assessment of sepsis severity in pediatric populations and also underscores the value of integrating data-driven models with biologically interpretable metabolites to support precision risk stratification in the PICU setting.

Pediatric acute respiratory distress syndrome

PARDS is a severe lung condition in children characterized by acute hypoxemia and often requires mechanical ventilation. It is associated with significant morbidity, prolonged intensive care stays, and high healthcare burden. Emerging data also indicate that PARDS survivors may experience long-term sequelae, including impaired lung function, reduced exercise capacity, and neurodevelopmental challenges that extend beyond ICU discharge.

Liquid chromatography-mass spectrometry for pediatric acute respiratory distress syndrome

LC-MS/MS-based metabolomic analysis of tracheal aspirates was conducted in 74 immunocompetent

Table 2: Metabolomics studies of NMR and LC-MS applications in pediatric thoracic critical care

Clinical applications	Year	Author	Platform	Age	Sample	Target metabolites	Metabolic pathways	References
Pneumonia								
	2010	Laiakis *et al.*	UPLC-TOFMS + ^{1}H-NMR	Children	Serum/ urine	Uric acid, hypoxanthine, glutamic acid, and L-tryptophan	Oxidative stress and energy metabolism	[24]
	2016	Chiu *et al.*	^{1}H-NMR	Children	Pleural effusion	Glucose↓, lactic acid↑, and 3-hydroxybutyric acid↑	Glycolysis and bacterial fermentation	[26]
	2019	Chiu *et al.*	^{1}H-NMR + PLS-DA	Pediatric	Pleural fluid	Glucose↓, lactic acid↑, 3-hydroxybutyric acid↑, and hypoxanthine↑	Anaerobic fermentation and ATP hydrolysis	[27]
	2020	Del Borrello *et al.*	LC-MS	1–17 years	Urine	93 discriminatory metabolites and adrenal steroids	Adrenal steroid synthesis/degradation	[28]
	2025	Ambroggio *et al.*	^{1}H-NMR	Children	Urine	Hypoxanthine, fumarate, and citrate	Purine metabolism and TCA cycle	[25]
Sepsis								
	2013	Mickiewicz *et al.*	^{1}H-NMR	1–17 years	Serum	Mixed (amino acids, energy, and lipids)	Energy and amino acid metabolism	[29]
	2023	Wang *et al.*	LC-MS	Infants	Serum	Hexylamine, psychosine sulfate, and LysoPC (18:1)	Lysosomal and phospholipid pathways	[31]
	2024	Bian *et al.*	LC-MS	Neonates	Serum	Prolylhydroxyproline, PE, and CDP-CHO	Collagen degradation and phospholipid metabolism	[30]
PARDS	2021	Grunwell *et al.*	LC-MS/ MS	Children	Tracheal aspirate	Cysteine/methionine, selenocompounds, and BCAA	Cysteine/methionine, selenocompound, and BCAA biosynthesis	[32]

NMR = nuclear magnetic resonance, LC-MS = liquid chromatography–mass spectrometry, UPLC-TOFMS = ultra-performance liquid chromatography–time-of-flight mass spectrometry, ATP = adenosine triphosphate, TCA = tricarboxylic acid, PE = phosphatidylethanolamine, CDP-CHO = cytidine diphosphate–choline, BCAA = branched-chain amino acids

children with acute hypoxemic respiratory failure, 41 had PARDS, and tracheal aspirate metabolites were analyzed using LC-MS/MS. Hierarchal clustering identified three metabolite clusters differing in hypoxemia severity and ventilator-free days.[32] Key metabolic pathways involved cysteine and methionine metabolism, selenocompound metabolism, and branched-chain amino acid biosynthesis, suggesting airway metabolite patterns may reflect disease severity and recovery. This review paper does not mention NMR as an analytical platform for PARDS studies because NMR applications remain scarce in this specific domain compared to the prevalence of LC-MS, with limited published research utilizing NMR for PARDS tracheal aspirate analysis.

These representative studies demonstrate good methodological validity as they were conducted in well-defined pediatric cohorts, applied standardized NMR or LC-MS analytical pipelines, and used appropriate multivariate statistics with independent validation or cross-validation (e.g., AUC and Q^2/R^2). The consistent identification of biologically plausible metabolic pathways, such as energy metabolism, oxidative stress, amino acid turnover, and lipid signaling, across independent cohorts supports the robustness and translational relevance of these platforms. The current applications of NMR and LC-MS platforms for pediatric thoracic critical illnesses, including pneumonia, sepsis, and PARDS, are shown in Table 2.

CONCLUSIONS AND FUTURE PROSPECTS

NMR-based metabolomics has identified key perturbations in pediatric thoracic critical care, such as elevated lactate, altered amino acid profiles (e.g., glutamine and branched-chain amino acids), and disrupted energy metabolism in plasma and BALF from pneumonia patients, enabling early severity stratification. LC-MS platforms complementarily detect low-abundance lipid mediators (e.g., sphingolipids and eicosanoids) and acylcarnitines, revealing inflammatory and oxidative stress signatures that correlate with ventilation duration and outcomes, achieving higher sensitivity for subphenotyping heterogeneous cohorts.

Despite these advances, metabolomics faces significant limitations in pediatric thoracic critical care. Technical challenges include NMR's limited sensitivity for low-abundance metabolites and LC-MS's variability from sample preparation, matrix effects, and instrument reproducibility, complicating cross-study comparisons. Interpretation hurdles arise from metabolic heterogeneity across age, etiology, and comorbidities, risking overinterpretation of correlations as causation without longitudinal validation. Small pediatric cohorts hinder statistical power, while confounding by nutrition, medications, and circadian rhythms demands rigorous normalization. Standardization gaps (e.g., inconsistent biofluid protocols) and high costs further impede clinical translation, necessitating robust quality control and multicenter harmonization.

In pediatric critical care, these biomarkers outperform traditional markers such as C-reactive protein and procalcitonin for prognostic modeling, particularly in distinguishing the need for invasive mechanical ventilation and the risk of multiorgan failure. NMR/LC-MS integration may facilitate noninvasive monitoring via exhaled breath condensate, reducing procedural burdens in vulnerable children. These metabolic patterns also provide mechanistic insights into mitochondrial dysfunction, endothelial injury, and dysregulated immune responses underlying pediatric lung failure. Additionally, pathway-level readouts derived from these datasets can highlight druggable nodes, supporting hypothesis generation for adjunctive therapies such as antioxidant or immunometabolic modulation.

Future research must address current gaps as metabolomics thrives in general pediatrics (e.g., neonatal sepsis and congenital heart disease), while its thoracic critical care applications lag owing to small cohorts and standardization issues. Prospective multicenter trials are needed to validate multiomics panels across etiologies beyond ARDS (e.g., bronchopulmonary dysplasia, and status asthmaticus). NMR offers reproducibility but limited sensitivity; LC-MS provides depth yet faces reproducibility challenges-hybrid platforms with artificial intelligence–driven feature selection could optimize biomarker discovery. Ultimately, translating these into point-of-care assays will enable personalized ventilation and adjunct therapies, transforming pediatric thoracic ICU management.

Author contributions

RT conceptualized the review, performed literature search and data analysis, and wrote the original draft; CNK and MHC contributed to metabolomics methodology sections and figure preparation; HJL and YYY provided clinical data insights on pediatric thoracic cases; EYLS supervised critical care aspects and edited the manuscript; CYC supervised the project, acquired funding, and revised the final version.

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Conflicts of interest

There are no conflicts of interest.

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Is Immunization Still Necessary in the COVID-19 Post-pandemic Era: An Asian City's Perspective for Asia

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Abstract

Hong Kong continues to face endemic waves of coronavirus disease 2019 (COVID-19) with substantial consequences for unvaccinated or under-vaccinated older adults and those with chronic medical and immunocompromised conditions. Low booster uptake among high-risk individuals remains a critical vulnerability. Periodic surges of COVID-19 activity occur approximately every 6–9 months in Hong Kong, primarily driven by newly emerging severe acute respiratory syndrome Coronavirus-2 variants and changes in herd immunity. Hospitalization rates, incidence rates of severe cases, and mortality rates remain significantly higher among residents of residential care homes for the elderly (RCHE) and the elderly aged ≥65 years. Local surveillance data show that the NB.1.8.1 variant (a descendant lineage of JN.1) is currently the dominant strain in Hong Kong, but NB.1.8.1 does not cause more severe disease. Members of the public are recommended to receive age-appropriate initial doses of COVID-19 vaccine from the respective vaccine manufacturers. The Joint Scientific Committee recommends COVID-19 booster vaccination in 2026 for RCHE residents; community dwelling elderly aged ≥65 years; persons aged 50–64 years with underlying comorbidities including individuals having chronic cardiovascular, lung, metabolic or kidney disease, obesity (body mass index [BMI] ≥30 kg/m^2), and those with chronic neurological conditions that can compromise respiratory function; persons with immunocompromising conditions aged ≥6 months and pregnant women. Healthcare workers may receive the COVID-19 vaccine for personal protection. Either the monovalent JN.1 vaccine or LP.8.1 vaccine is recommended as the vaccine choice in 2026. Hong Kong perspective on COVID-19 immunizations may serve as advocacy advice, especially for Southeast Asian countries.

Keywords: COVID-19, immunizations, SARS-CoV-2, vaccines, NB.1.8.1

INTRODUCTION

Hong Kong, like other parts of the region, is currently experiencing an upsurge in coronavirus disease 2019 (COVID-19) cases. This serves as a reminder that while the pandemic phase has officially ended, COVID-19 remains a significant public health concern and continues to cause hospitalizations, severe illness, and even deaths, particularly among high-risk groups. Since the transition to the endemic phase on 29 January 2023, Hong Kong has seen recurring COVID-19 upsurges every 4–6 months, without any consistent seasonal pattern. Notably, despite a 6-month period of very low disease activity in the winter months of the 2024–25 season, another significant upsurge occurred in April 2025.[1]

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VARIANT SURVEILLANCE AND DOMINANCE

Recent genomic surveillance using sewage sampling identified NB.1.8.1, a descendant of the XDV lineage, as the most dominant severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) variant as of June 19, 2025, accounting for 90.3% of cases. In addition

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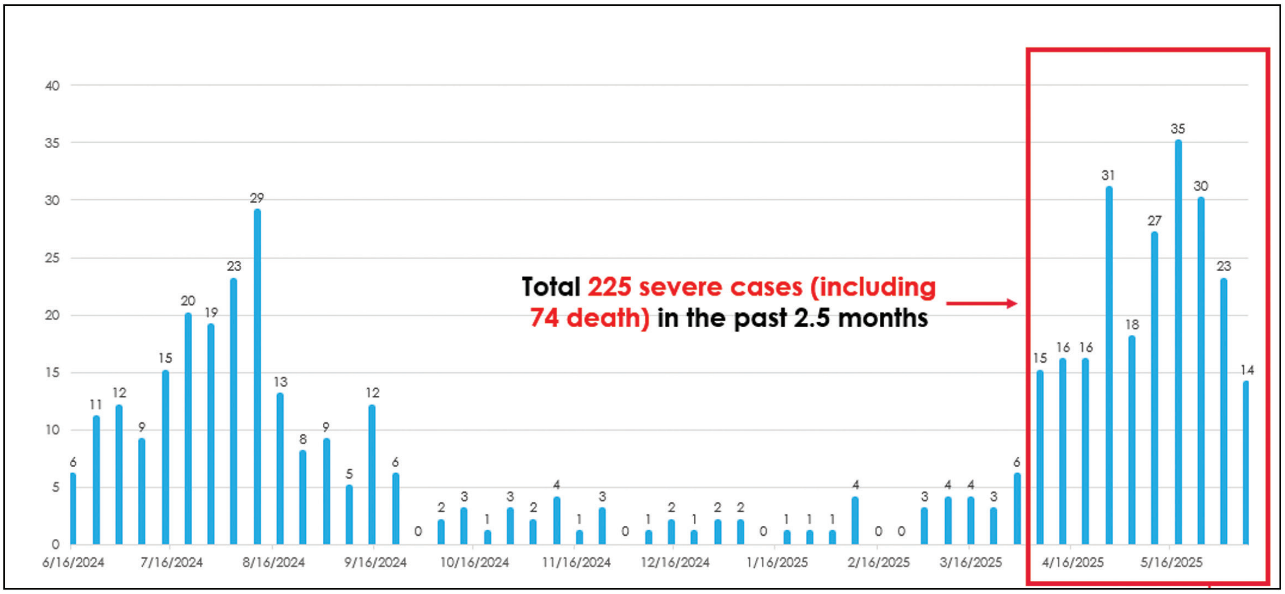

Total 225 severe cases (including 74 death) in the past 2.5 months

Figure 1: Number of severe and death cases by COVID-19 in the past 52 weeks (June 16, 2024 to June 14, 2025)[1]

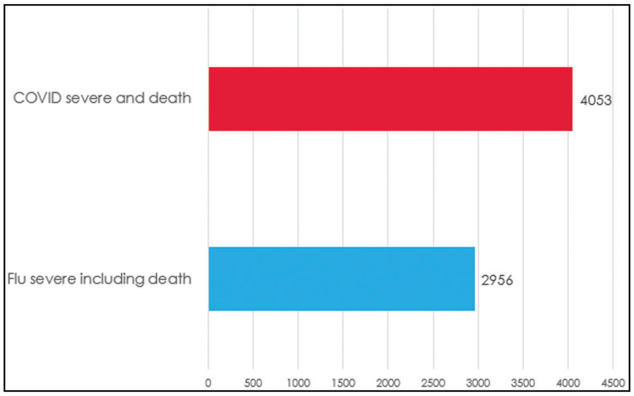

Figure 2: COVID-19 and flu severe cases from post-pandemic to 2025 in Hong Kong (January 29, 2023 to June 14, 2025).[1] #For COVID-19, fatal cases include cases with cause of death preliminarily assessed to be related to COVID-19. *For influenza, the reported severe cases by age include fatal cases

to NB.1.8.1, the dominant strains include multiple descendants of JN.1, such as KP.3, KP.3.1.1, LB.1, LP.8.1, and XEC.[1]

SEVERE AND FATAL CASES

As of June 14, 2025, the cumulative number of fatal COVID-19 cases reported by the Centre for Health Protection (CHP) stands at 1481. During the recent upsurge of COVID-19 (April to June 2025), 225 severe cases were reported, including 74 deaths, which included the highest number of severe cases per week in the past 52 weeks [Figure 1].[1]

From the end of the pandemic (January 29, 2023) to mid-June 2025, there were a total of 4053 severe and fatal cases documented in Hong Kong. These numbers mirror the burden of influenza in the same period [Figure 2], highlighting that COVID-19's impact remains serious, particularly in vulnerable populations.[1]

AGE AND VACCINATION STATUS OF SEVERE COVID CASES

During the pandemic, the older adult population in Hong Kong was disproportionately affected and had the highest rates of morbidity and mortality. Government statistics released on the mortality of COVID-19 during the pandemic found that over 95% of fatal cases were in older adults aged 60 years or above, and about 90% of fatal cases had known chronic conditions.[2] Post pandemic, from January 2023 to July 2024, the elderly population (60+ years) continues to be the most affected population, with 87.1% of severe cases and 96.8% of deaths occurring in this age group.[3]

A recent Asia Pacific literature review also found that risk factors for severe COVID-19 disease include older age, obesity, diabetes, heart failure, renal disease, and dementia, as well as less commonly, hypertension, chronic obstructive pulmonary disease, cardio- and cerebrovascular disease, immunocompromise, autoimmune disorders, and mental illness were reported.[4]

In terms of vaccination status, around 85% of all severe and death cases involved individuals who were either unvaccinated or had not received a booster dose in the past 6 months.[3]

VACCINATION UPTAKE: A CAUSE FOR CONCERN

Booster vaccine uptake among high-risk individuals in Hong Kong has been significantly lower than that of its global counterparts. For the 2024–25 season, estimated booster uptake with updated vaccine (KP.2 in the U.S. and Canada, and JN.1 in the rest of the world) in those aged 65 and above was 59% for the UK,[5] 44% for the US,[6] and around 19% for Taiwan.[7] By comparison, Hong Kong's uptake is lagging, with the latest JN.1 vaccine uptake rate in the oldest populations below 5%.[8]

VACCINE SAFETY AND TOLERABILITY

Across multiple COVID-19 vaccine seasons, including different variants (ancestral, BA.1, BA.4/5, XBB.1.5, and JN.1), adverse events were mostly mild to moderate and short-lived, and lower with each successive booster dose (i.e., reactogenicity decreased with additional doses).[9] Generally, the rate of reported adverse events per 1000 doses has declined over time, especially in Korea.[10,11]

A global safety assessment of pre-specified adverse events of special interest (AESIs) following administration of COVID-19 vaccines using post-marketing surveillance data and comparing observed rates of AESIs to background rates in the general population found that for most AESIs, the observed-to-expected ratios were below 1.0, indicating no increased risk attributable to vaccination.

Notably, a rare but statistically significant increase in myocarditis and pericarditis was observed post-vaccination, particularly in teenagers and young man 7 days after the second dose. However, rates remained low, and lower than those seen following natural infection.[12,13]

Regardless of vaccine safety and tolerability, Hong Kong health professionals must be aware of the problems of vaccine phobia and vaccine hesitancy and be proficient in tackling these deterring factors.[14]

CLINICAL IMMUNOGENICITY OF JN.1 COVID-19 VACCINE

In a phase 3b/4 study, an authorized JN.1 vaccine demonstrated strong immunogenicity, generating robust neutralizing antibody responses by day 29 post-vaccination. However, the study also observed reduced cross-neutralization efficacy against tested JN.1 subvariants, including KP.2, KP.3.1.1, XEC, and LP.8.1, indicating a potential limitation in coverage as the virus continues to evolve.[15]

Reflecting the ongoing adaptation of public health strategy to viral evolution, several major regulatory bodies, including the World Health Organization (WHO), the European Medicines Agency (EMA), and the U.S. Food and Drug Administration (FDA), have recommended incorporating the JN.1 lineage in the 2025/26 COVID-19 vaccine formulation.[16-18] Notably, both the EMA and FDA have specifically advised to include the LP.8.1 variant to enhance alignment with currently circulating and emerging strains.[17,18]

REAL-WORLD EVIDENCE ON COVID-19 VACCINE EFFECTIVENESS (VE)

Real-world data from large U.S. healthcare databases covering the 2022 to 2025 respiratory virus seasons indicate that updated booster vaccines have consistently maintained their effectiveness. These boosters have shown sustained protection against COVID-19-related hospitalizations and medically attended illnesses, with no significant waning in VE observed over time.[19-23]

VACCINE AVAILABILITY AND PUBLIC HEALTH GUIDANCE

Under the Government COVID-19 vaccination program, the five high-risk priority groups in Hong Kong: (1) 50 years and above; (2) 18–49 years old with underlying comorbidities; (3) 6 months and above with immunocompromised conditions; (4) pregnant women; and (5) healthcare workers (HCWs) can receive the JN.1 monovalent booster free of charge.[24] The CHP continues to recommend that individuals, especially those over 50 or with comorbidities, get vaccinated if their previous dose of vaccine or last infection was more than 6 months ago, especially given the resurgence in cases since April 2025.[24]

IMMUNIZATION RECOMMENDATIONS: HONG KONG, JAPAN, AND SINGAPORE

Hong Kong

To recap, as of Oct 2025, Hong Kong's COVID-19 immunization recommendations and vaccine availability are as follows (https://www.chp.gov.hk/tc/features/106934.html; https://covid19.med.hku.hk/en/cvc/booking).

Immunization recommendations

The Hong Kong CHP advises high-risk individuals, especially the elderly and those with chronic illnesses, to receive a free additional booster dose of the JN.1 COVID-19 vaccine if it has been 6 months since their last dose or infection (whichever is later). Individuals who have never received a primary COVID-19 vaccination, including infants and children, are also urged to get vaccinated with the JN.1 vaccine. The JN.1 vaccine is specifically targeted at the JN.1 variant and its subvariants, which remain the dominant strains in Hong Kong.

Vaccine availability

The JN.1 vaccine is available free of charge at designated community vaccination centers. A pediatric formulation of the JN.1 vaccine became available starting February

2025. Appointments are required and can be made through the government's 24-h online booking system.

Japan

As of October 2025, Japan's COVID-19 immunization policy and vaccine availability are guided by the Ministry of Health (MOH), Labor and Welfare. (https://japan.kantei.go.jp/ongoingtopics/vaccine.html; https://joyn.tokyo/about-japan/useful-resources/covid-vaccine-in-japan; https://en.wikipedia.org/wiki/COVID-19_vaccination_in_Japan).

Immunization recommendations

Japan continues to offer booster vaccinations for COVID-19, particularly targeting high-risk groups such as the elderly, individuals with underlying health conditions, and HCWs. The government encourages seasonal booster doses, especially in autumn, to coincide with increased respiratory virus activity. Vaccination is voluntary but strongly recommended for those who have not yet received a booster in the past 6 months.

Vaccine availability

COVID-19 vaccines are available free of charge to eligible residents at designated medical institutions and municipal health centers. Japan has deployed updated vaccines targeting Omicron subvariants, including formulations adapted for newer strains like JN.1. Appointments can be made through local government portals, and foreign residents are also eligible with residence documentation.

Singapore

As of October 2025, Singapore's COVID-19 immunization recommendations and vaccine availability are based on updated guidance from the MOH and the Expert Committee on Immunization (https://www.moh.gov.sg/newsroom/update-to-covid-19-vaccination-recommendations-and-rollout-of-updated-jn-1-vaccines/; https://vaccine.gov.sg/covid).

Immunization recommendations

Individuals aged 6 months and above are eligible for COVID-19 vaccination. The 2024/2025 vaccination schedule recommends an additional dose for those at increased risk of severe illness, including Seniors, medically vulnerable individuals, HCWs, and people living or working with vulnerable individuals. The recommended interval for the additional dose is around 1 year, with a minimum of 5 months since the last dose.

Vaccine availability

Singapore rolled out updated JN.1 variant-targeted vaccines (Pfizer-BioNTech/Comirnaty and Moderna/Spikevax) starting October 28, 2024. Vaccines are available at Healthier SG GP clinics and polyclinics. Vaccination is free of charge for eligible individuals.

THE HONG KONG PERSPECTIVES

While the acute threat of COVID-19 has subsided with the end of the pandemic, Hong Kong continues to face endemic waves with substantial consequences for unvaccinated or under-vaccinated older adults and those with chronic medical and immunocompromised conditions. Despite a relatively well-established vaccination infrastructure, low booster uptake among high-risk individuals remains a critical vulnerability. The current wave, dominated by the NB.1.8.1 variant, underscores the need for enhanced vaccination efforts and public health messaging. The Hong Kong perspective on COVID-19 immunizations may serve as advocacy advice, especially for Southeast Asian countries.

In early June 2025, the U.S. Trump administration contemplated new clinical trials for COVID boosters and moved to restrict COVID vaccines for children and others (https://www.theguardian.com/us-news/2025/jun/02/vaccine-rule-change-child-trial-volunteers). Meanwhile, Marty Makary, the head of the U.S. FDA, and Vinay Prasad, the FDA's vaccines chief, outlined in a recent editorial a plan to restrict COVID boosters for anyone under the age of 65 without certain health conditions. The Canadian administration is likely to echo its U.S. counterpart in restricting COVID vaccine administration to the public. Nations in Southeast Asia must formulate their immunization recommendations in the years ahead in the war against COVID. From our U.S. and European perspectives, it might be unnecessary to mandate annual COVID immunizations, except perhaps in high-risk groups. Our Hong Kong experience may serve as a reference for other Asian cities.

In October 2025, the Hong Kong CHP of the Department of Health updated the recommendations on booster COVID-19 vaccination and composition of COVID-19 vaccines for 2026 (Scientific Committee on Emerging and Zoonotic Diseases and Scientific Committee on Vaccine Preventable Diseases). COVID-19 has become endemic, with periodic surges in activity approximately every 6–9 months in Hong Kong, primarily driven by newly emerging SARS-CoV-2 variants and changes in herd immunity. The hospitalization rates, incidence rates of severe cases, and mortality rates remain significantly higher among residents of residential care homes for the elderly (RCHE) and the elderly aged ≥65 years. Local surveillance data show that the NB.1.8.1 variant (a descendant lineage of JN.1) is currently the dominant strain in Hong Kong, and there is no evidence that NB.1.8.1 causes more severe disease. The Joint Scientific Committee (JSC) continues to recommend COVID-19 booster vaccination in 2026 for RCHE residents; community dwelling elderly aged ≥65 years; persons aged 50–64 years with underlying comorbidities including individuals having chronic cardiovascular, lung, metabolic or kidney disease, obesity (BMI ≥30 kg/m^2), and those with chronic neurological condition that can compromise respiratory function; persons with immunocompromising conditions aged ≥6 months and pregnant women. HCWs are encouraged to receive the COVID-19 vaccine for personal protection. The timing for receiving a booster dose is at least 6 months since the last dose or infection. The JSC recommends either the monovalent JN.1 vaccine or the LP.8.1 vaccine as preferred vaccine in 2026.

SUMMARY

Regarding the US administration's 2025 shift to restrict boosters for those under 65, Southeast Asian nations should prioritize local demographic risks over Western policy trends. It is reasonable to recommend initial doses for the general public and to restrict booster doses for high-risk groups and for individuals over 65 years of age.

In Asia, pediatric patients with chronic pulmonary (e.g., asthma, chronic lung disease), neurological (e.g., cerebral palsy, epilepsy), and immunocompromising conditions remain a critical focus for 2025–2026 COVID-19 vaccination policies.[25]

These groups have a significantly heightened risk for severe disease, hospitalization, and intensive care admission, and therefore should be prioritized for COVID-19 vaccination. Asian clinical data indicate that while most children experience mild illness, those with comorbidities may represent a disproportionate share of pediatric intensive care unit cases and complications, such as multisystem inflammatory syndrome in children and secondary bacterial infections.[26] Regional health authorities, such as those in Hong Kong and South Korea, provide free initial and booster doses (e.g., LP.8.1-adapted vaccines) specifically for these high-risk children.[27] Furthermore, the American Academy of Pediatrics emphasizes that vaccination offers essential protection against Long COVID and post-acute sequelae, which can further complicate existing chronic health issues.[28] Maintaining up-to-date immunization is the most effective strategy to mitigate life-threatening outcomes in these vulnerable pediatric groups, given the continued emergence of variants like JN.1 sublineages.

The evolution from the JN.1 lineage to the newer LP.8.1 variant necessitates a shift in clinical prioritization and policy to maintain real-world protection for high-risk groups. While JN.1-adapted vaccines demonstrated robust effectiveness (roughly: 70%–85%) against hospitalization and death during early 2025, the emergence of LP.8.1 has introduced significant immune resistance. The WHO Technical Advisory Group and the EMA have formally recommended monovalent LP.8.1 as the preferred antigen for the 2025/2026 vaccination cycle.[29] In Hong Kong, authorities plan to introduce LP.8.1-targeted vaccines by early 2026 to counter the dominance of descendant lineages like NB.1.8.1, which now accounts for nearly 100% of characterized severe cases.[30] Clinical guidance for high-risk pediatric and adult populations emphasizes that the updated LP.8.1 formulation offers superior breadth and durability. Consequently, vaccination policy should prioritize early access for these vulnerable cohorts to minimize the gap in protection caused by the 2-to-4-fold reduction in neutralization against older vaccine strains. Maintaining high uptake of the most current antigen remains the effective strategy to mitigate the resurgent disease burden in these medically complex groups.

Beyond the historical impacts of SARS-CoV, MERS-CoV, and the ongoing challenges posed by SARS-CoV-2, the emergence of a new SARS-CoV-3 variant may just be a matter of time, driven by continuous viral evolution and zoonotic spillover risks. However, the landscape of pandemic preparedness has fundamentally changed. The current vaccine technology, particularly with rapid mRNA platforms, has revolutionized the prevention of these emerging coronaviruses, allowing for swift updates to combat new variants. Furthermore, with the increased availability of highly efficacious anti-drugs against SARS-CoV-2, such as nirmatrelvir (Paxlovid) and other evolving therapeutics, our capability to manage infections has grown significantly. Although future coronaviruses will inevitably emerge, this combination of advanced vaccine platforms and effective antiviral treatments provides a robust defense mechanism. Consequently, it is hoped that future emerging coronaviruses will no longer pose catastrophic threats to humanity, but rather be managed as endemic respiratory diseases. Ongoing vigilance and the development of broad-spectrum countermeasures remain critical to ensuring that future threats are neutralized effectively.[31]

Author contributions

All authors contribute to the concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review.

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Original Article

Lung Function Trajectory from Infants to Primary School Children in the Chinese Population

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Abstract

Background: Preterm birth impairs early lung development and may lead to long-term respiratory morbidity. This study describes lung function trajectories from infancy to early childhood in a contemporary Chinese cohort. **Methods:** A single-center retrospective observational study (2013–2025) of 239 infants who underwent infant lung function (ILF) testing. A subgroup had follow-up impulse oscillometry and spirometry. **Results:** A total of 172 infants were enrolled after inclusion and exclusion criteria. Preterm infants showed a significantly higher respiratory rate, lower Tpef/Tex, lower forced expiratory volume at 0.5 s (FEV0.5)/forced vital capacity (FVC), and the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled (FEF25-75) on raised volume rapid thoracoabdominal compression (RVRTC) compared with term infants. Gestational age and birth weight positively correlated with Tpef/Tex, FEV0.5/FVC, and FEF25-75 ($r = 0.2$ to 0.3). Infant Tpef/Tex, FEV0.5, and FEF25-75 negatively correlated with preschool Impulse Oscillometry System (IOS) small-airway marker zR5–R20 ($r = -0.3$ to –0.4). Bronchodilator responsiveness in infancy predicted responsiveness on later IOS in 67% of cases. The original National Institute of Child Health and Human Development 2001 BPD definition was more discriminative of ILF impairment than the Jensen 2019 definition. **Conclusions:** In Chinese children, extreme prematurity leads to persistent obstructive deficits from infancy into early childhood. RVRTC parameters (especially FEV0.5/FVC and FEF25–75) and Tpef/Tex are useful early predictors of subsequent small-airway dysfunction.

Keywords: Bronchodilator responsiveness, bronchopulmonary dysplasia, Chinese, infant lung function, RVRTC, trajectory

INTRODUCTION

There is evidence that perinatal and early infancy lung development predicts childhood and even adult lung function.[1] Infants with decreased expiratory flow seem to continue to have more obstructive lung diseases and have a higher risk of preschool wheeze beyond school age.[2,3] Survivors of prematurity, especially those with bronchopulmonary dysplasia (BPD), are at a risk of increased respiratory morbidity throughout life.[4,5] The more widespread use of antenatal steroids, surfactants, and lung-protective ventilation had greatly increased the survival of extremely preterm infants. Hence, longitudinal follow-up among preterm survivors and those with early respiratory disease is becoming increasingly important to understand the long-term outcomes and healthcare needs in this population.

The most commonly performed tests in infants are noninvasive tidal breathing assessments. Meanwhile, forced expiratory maneuver, by using external pressure compression to the chest and abdomen to assess lung and airway dynamics, has also been increasingly utilized. Measurements of maximal flow at functional residual capacity (V’maxFRC) is a widely accepted parameter to characterize the airway function and delineate pulmonary abnormalities during infancy.[6,7] In the recent decade, the raised-volume rapid thoracoabdominal compression (RVRTC) technique has been

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gaining increasing recognition. By inflating infant lungs over an extended volume range before compression, the results generate flow-volume curves that more closely resemble full flow-volume curves in older children and adults. The American Thoracic Society/European Respiratory Society workforce has jointly published recommendations and guidelines for best practice on RVRTC in 2006,[8] making this practice more widely achievable at different centers. Even so, RVRTC remains a more invasive procedure that requires the infant to be sedated and is mostly carried out at specialized pediatric respiratory centers, hence limiting the number of published data.

We aimed to characterize lung function trajectories in a contemporary cohort of Chinese infants followed in our respiratory clinic of an acute hospital setting. Our objectives were to (1) describe tidal and rapid thoracoabdominal compression (RTC) infant lung function (ILF) results of the group and identify risk factors for poor lung growth and development, (2) measure changes in lung function values over time with serial pulmonary measurements with Impulse Oscillometry System (IOS) and spirometry, and (3) identify the most-at-risk group associated with persistent bronchodilator responsiveness (BDR) that may predict preschool wheeze and asthma. We hypothesized that survivors of prematurity would perform worse than their counterparts during infancy and potentially into early childhood. We hope to elucidate ILF parameters that will better foretell future performances.

MATERIALS AND METHODS

Study design

This was a single-center retrospective observational cohort study conducted at Kwong Wah Hospital, a local public hospital with a specialized Pediatric Respirology Research Center in Hong Kong.

Subjects

This study was initiated in 2013, and data collection was conducted from 2013 to 2025. Patients who underwent an infant lung study between June 14, 2013 and February 25, 2025 were recruited. Subjects were invited as clinically indicated, targeting to detect, classify, and quantify early lung disease such as BPD and to determine the response to interventions. Informed consent was obtained for each participant. Patients with respiratory tract infection within a 3-week period and ongoing respiratory insufficiency requiring continuous oxygen therapy and mechanical ventilation support were excluded. Those with known severe genetic disorder, cyanotic heart condition, or congenital malformation that render patients unstable for testing were also excluded. If patients had repeated ILF tests, only the first results were considered. Patients with baseline characteristics incompatible with available reference values including non-Chinese ethnicity and body weight below 3 kg or above 13 kg were excluded as well.

Baseline measurements

Demographics and baseline characteristics including gestational age, gender, race, weight, and height were documented. Data on antenatal, neonatal, and perinatal history, including maternal information such as maternal age, maternal smoking, use of antenatal steroid, diagnosis and grading of respiratory distress syndrome and BPD, and significant comorbid diseases, were collected from the hospital Clinical Management System. BPD severity grading was based on the original National Institute of Child Health and Human Development (NICHD) definition in 2001 and newer modified Jensen 2019 definitions [Supplementary Table 1].[9,10] Personal atopy was defined as having other atopic diseases such as allergic rhinitis and eczema or a positive skin prick test. Family atopy was defined as any first- or second-degree relative with any atopic disease.

Lung function measurements

All ILF data were recorded in and extracted from the CareFusion MasterScreen Babybody Plethysmograph in the laboratory. Infants were first sedated with oral chloral hydrate at a dose of 100 mg/kg. Heart rate and oxygen saturation were monitored continuously. Infants first performed tidal breath test to measure the respiratory rate (RR), tidal volume (VT), flow volume loop, and time to peak tidal expiratory flow as a ratio of total expiratory time (Tpef/Tex). Compliance (Crs) and airway resistance (Rrs) were obtained using single- and double-occlusion techniques. Specific effective airway resistance (sRaw) and plethysmographic functional residual capacity (FRCpleth) were measured in body plethysmography.

The next step would be RTC technique measurements. Infants were wrapped with a jacket and an inflatable bladder over the chest and abdomen. The jacket was inflated at the end of total inspiration to force expiration. The partial expiratory flow volume curve could produce maximal forced expiratory flow rate at the point of functional residual capacity (V’maxFRC). Optimal jacket pressure was assessed till no further increase in V’maxFRC was observed. Then, raised volume RTC (RVRTC) was performed by delivering standardized positive inspiratory pressure of 30cmH2O via facemask. Three to five augmented breaths were applied to induce respiratory muscle relaxation before rapid inflation of the jacket at the optimal jacket pressure. This mimicked forced expiration from total lung capacity to residual volume. Forced vital capacity (FVC), forced expiratory volume at 0.5 second (FEV 0.5), forced expiratory volume at 1 second (FEV1), and the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled (FEF25-75) were assessed. Lung function parameters z scores were calculated according to Chinese population reference.[11-14] Three maneuvers with FVC, FEV0.5, and FEF25-75 within 10% variation of each other were considered acceptable. Finally, the ILF test was concluded with a bronchodilator (BD) test. Two puffs of salbutamol (Ventolin) were administered, with the post-bronchodilator RVRTC maneuvers repeated. A greater or equal to 13% increase in FEV0.5 was considered bronchodilator-responsive.

When clinically indicated, some of the patients were invited back to undergo an IOS test when they are at preschool age. The Jaeger IOS machine was used. Steady tidal breathing into a mouthpiece was required. Clinically useful parameters measured via IOS include resistance at 5 Hz (R5) reflecting total airway resistance, resistance at 20 Hz (R20) reflecting large airway resistance, resistance difference between 5 Hz and 20 Hz (R5-R20) reflecting small airways resistance, and reactance at 5 Hz (X5) indicating the elastic recoil of the peripheral airways. Ventolin 2 puffs would then be given, and post-bronchodilator measurements were repeated. A 29% decrease in R5 or a 44% decrease in R5-R20 was considered bronchodilator-responsive. For a small number of patients, follow-up spirometry with bronchodilator testing was done at later childhood. FEV1, FVC, FEF25-75, FEV1/FVC, and forced expiratory flow at 50% and 75% of FVC (FEF50 and FEF75) were recorded. A 12% increase in FEV1 or 35% increase in FEF25-75 after administration of Ventolin was considered bronchodilator-responsive.

Statistical analysis

Data normality was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation, whereas non-normally distributed variables were reported as median (interquartile range). Categorical variables were summarized as frequencies and percentages. Comparisons of continuous variables between two groups were performed using Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the chi-squared test or Fisher's exact test. For comparisons across multiple groups, one-way analysis of variance

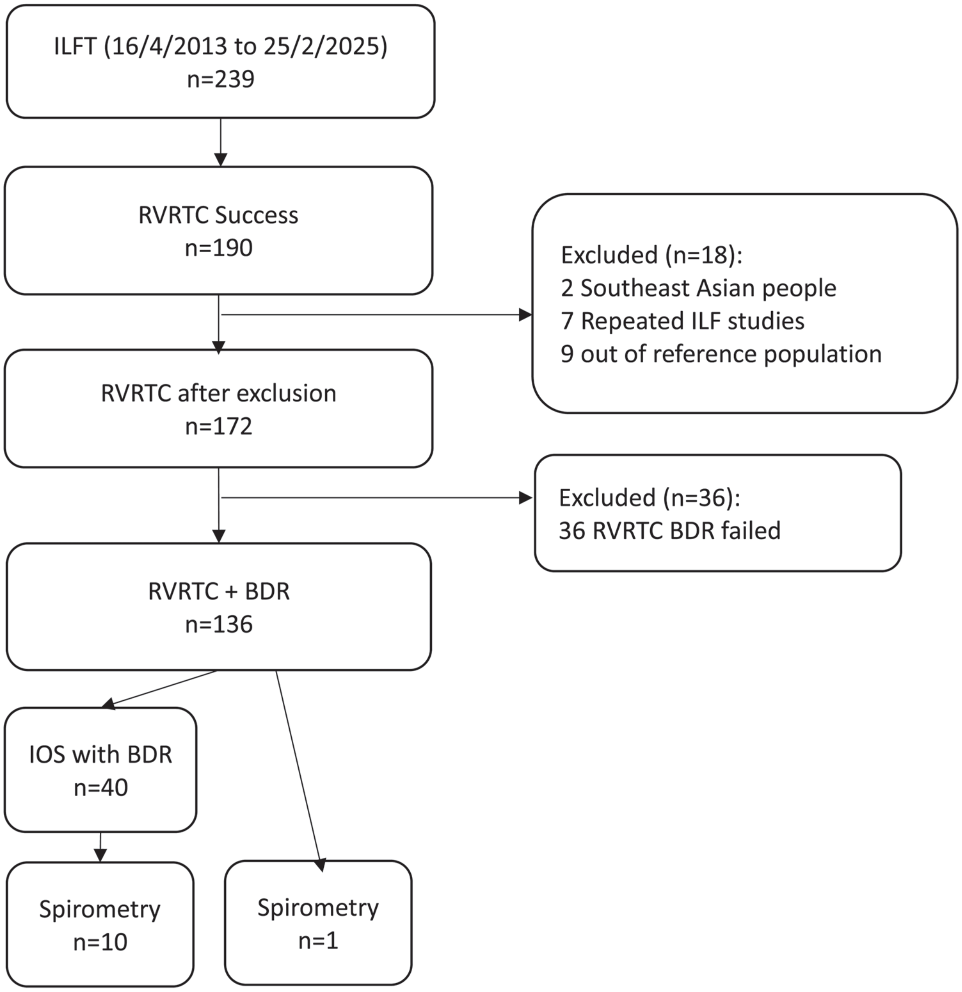

Figure 1: Study flowchart. Abbreviations: ILFT = Infant lung function test, RVRTC = raised volume rapid thoracoabdominal compression, IOS = impulse oscillometry, BDR = bronchodilator responsiveness test

was used for normally distributed data; otherwise, the Kruskal–Wallis H test was applied. Relationships between RVRTC parameter z-scores, IOS parameter z-scores, and spirometry parameter z-scores were evaluated using Pearson or Spearman correlation coefficients depending on the data normality. A *P* value <0.05 was considered statistically significant. All analyses were performed using IBM Statistical Package for the Social Sciences Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Ethics

The study was approved by the Hospital Authority Central Institutional Review Board on 8 December 2025 (approval number: PAED-2025-128).

RESULTS

A total of 239 infants who underwent ILF testing met the inclusion criteria. Of these, 190 had successful RVRTC data. A total of 172 remained after applying the exclusion criteria, of which 136 had successful bronchodilator testing. Subsequently, 40 of them were followed-up with IOS at around 3 years. Ten subsequently underwent spirometry, and one additional patient underwent spirometry without IOS [Figure 1].

Baseline demographics

The mean age at the ILF test was 14.3 months, mean body weight 9.3 kg, and mean body length 74.8cm. Seventy (40%) of them were term babies, 21 (18%) were preterm infants born at 33–36 weeks, 26 (15%) were very-preterm babies born between 29 and 32 weeks, and 55 (32%) were extremely preterm babies born between 24 and 28 weeks. There was no significant difference in their ages and corrected ages at test, but they had significant differences in body weight (*P* = 0.005) and body height (*P* = 0.040). Meanwhile, the groups have no difference in personal atopy, family atopy, or passive smoking. All the term infants had no BPD using either the NICHD 2001 or the Jensen 2019 BPD definition. Most of the extremely preterm infants (54.5%) had severe BPDs (the highest grade) under the NICHD definition, but most (69.1%) were classified as Grade 2 (second highest grade) according to Jensen. Only one patient had Jensen Grade 3 BPD [Table 1].

Infant lung function study data

Gestational age and birth weight

During quiet tidal breathing, preterm infants had significantly higher RR (*P* = 0.011) and lower Tpef/Tex (*P* = 0.044), suggestive of faster breathing and earlier termination of expiration at rest [Table 2]. No significant difference was found in V'maxFRC by using the RTC technique. Using the RVRTC technique, preterm infants demonstrated significantly lower FEV0.5/FVC (*P* = 0.024) and FEF25-75 (*P* = 0.042). There was a positive correlation between gestational age and three infant lung

Table 1: Baseline demographics of 172 infants undergoing lung function testing categorized by different gestational age groups

	Extremely preterm (24–28 weeks) (*n* = 55) Mean (SD)	Very preterm (29–32 weeks) (*n* = 26) Mean (SD)	Preterm (33–36 weeks) (*n* = 21) Mean (SD)	Term (≥37 weeks) (*n* = 70) Mean (SD)	Total (*n* = 172) Mean (SD)	*P* value
Age at ILFT, months	16.0 (5.8)	13.3 (5.2)	13.0 (6.8)	13.7 (5.9)	14.3 (6.0)	0.055
Corrected age at ILFT, months	13.4 (5.8)	11.7 (5.2)	12.3 (6.8)	14.0 (6.1)	13.2 (6.0)	0.362
Body weight at ILFT, kg	8.9 (1.6)	8.9 (1.6)	8.7 (2.2)	9.9 (1.7)	9.3 (1.8)	0.005
Body height at ILFT, cm	74.1 (7.6)	73.1 (6.4)	72.5 (8.2)	76.7 (7.2)	74.8 (7.5)	0.040
Personal atopy, *n* (%)	3 (5.5 %)	4 (15.4 %)	2 (9.5%)	15 (21.4 %)	24 (14.0 %)	0.073
Family atopy, *n* (%)	21 (38.2%)	11 (42.3 %)	11 (52.9%)	37 (52.9 %)	80 (46.5 %)	0.370
History of wheeze, *n* (%)	20 (36.4%)	8 (30.8 %)	9 (42.9%)	42 (60.0%)	79 (45.9%)	0.018
Passive smoking, *n* (%)	16 (29.1%)	8 (30.8%)	7 (33.3%)	29 (41.4%)	60 (34.9%)	0.503
BPD, NICHD definition						
- No BPD, *n* (%)	3 (5.5%)	11 (42.3%)	18 (85.7%)	70 (100%)	102 (59.3%)	<0.001
- Mild, *n* (%)	3 (5.5%)	0 (0%)	1 (4.8%)	0 (0 %)	4 (2.3 %)	
- Moderate, *n* (%)	18 (32.7%)	5 (19.2%)	2 (9.5 %)	0 (0%)	25 (14.5 %)	
- Severe, *n* (%)	30 (54.5%)	10 (38.5%)	0 (0 %)	0(0%)	40 (23.3%)	
BPD, Jensen definition						
- No BPD, *n* (%)	5 (9.1%)	11 (42.3%)	18 (85.7 %)	70 (100%)	104 (60.5%)	<0.001
- Grade 1, *n* (%)	8 (14.5%)	4 (15.4 %)	1 (4.8%)	0 (0%)	13 (7.6%)	
- Grade 2, *n* (%)	38 (69.1%)	11 (42.3%)	2 (9.5%)	0 (0%)	51 (29.7%)	
- Grade 3, *n* (%)	1 (1.8%)	0 (0 %)	0 (0 %)	0 (0%)	1 (0.6%)	

Abbreviations: ILFT = Infant lung function test, BPD = bronchopulmonary dysplasia, NICHD = Eunice Kennedy Shriver National Institute of Child Health and Human Development, a part of the National Institutes of Health (NIH) of the United States

Table 2: Infant lung function test results of 136 infants (with successful RVRTC and bronchodilator testing) categorized by different gestational age groups

	Extremely preterm (24–28 weeks) (*n* = 42) Median (IQR)	Very preterm (29–32 weeks) (*n* = 21) Median (IQR)	Preterm (33–36 weeks) (*n* = 16) Median (IQR)	Term (≥37 weeks) (*n* = 57) Median (IQR)	*P* value
Tidal breath					
zRR	0.7 (0.02 to 1.8)	0.8 (−0.2 to 2.0)	1.6 (0.6 to 2.1)	0.1 (−0.5 to 1.0)	0.011
zVT	−0.1 (−1.0 to 0.7)	−0.3 (−0.9 to 0.1)	−0.5 (−1.3 to 0.2)	0.2 (−0.6 to 0.9)	0.193
zTpef/Tex	−0.5 (−1.0 to −0.1)	−0.2 (−0.5 to 0.6)	−0.2 (−0.7 to 0.6)	−0.1 (−0.7 to 1.0)	0.044
Single occlusion					
zCrs	−0.5 (−1.1 to 0.2)	−0.3 (−1.2 to −0.1)	−0.7 (−1.0 to −0.1)	−0.5 (−1.1 to 0.4)	0.991
zRrs	0.3 (0.1 to 1.0)	0.1 (−0.3 to 1.3)	0.4 (−1.0 to 1.8)	0.4 (−0.2 to 0.9)	0.984
RTC					
zV’maxFRC	−1.6 (−2.3 to −1.0)	−1.5 (−1.8 to −1.2)	−1.5 (−2.3 to −0.9)	−1.5 (−2.3 to −0.9)	0.946
RVRTC					
zFEV0.5	−1.3 (−2.1 to −0.3)	−1.0 (−1.7 to −0.3)	−1.6 (−2.9 to −0.6)	−1.0 (−1.6 to −0.1)	0.161
zFVC	−1.1 (−1.6 to −0.4)	−1.0 (−1.5 to −0.6)	−1.7 (−2.2 to −1.0)	−1.1 (−1.6 to −0.7)	0.147
zFEV0.5/FVC	−0.4 (−1.0 to 0.4)	0.8 (−0.4 to 1.5)	0.1 (−0.8 to 1.8)	0.7 (−0.4 to 1.7)	0.024
zFEF25-75	−1.2 (−2.3 to −0.1)	−0.4 (−1.2 to 0.8)	−0.8 (−2.4 to 0.1)	−0.4 (−1.2 to 0.6)	0.042

Abbreviations: z = z score calculated by Chinese population reference as detailed in Reference section, RR = respiratory rate, VT = tidal volume, Tpef/Tex = time to peak tidal expiratory flow as a ratio of total expiratory time, Crs = airway compliance, Rrs = airway resistance, RTC = rapid thoracoabdominal compression, V’maxFRC = maximal forced expiratory flow rate at the point of functional residual capacity, RVRTC = raised volume rapid thoracoabdominal compression, FEV0.5 = forced expiratory volume at 0.5 s, FVC = forced vital capacity, FEF25-75 = the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled

parameters: Tpef/Tex (*R* = 0.293, *P* = 0.001), FEV0.5/FVC (*R* = 0.218, *P* = 0.011), and FEF25-75 (*R* = 0.208, *P* = 0.015), suggesting that in infants born closer to term, the better the parameters that reflect small airway performance. The R values for them range from 0.2 to 0.3 [Table 3]. Birth weight correlates to ILF in a very similar pattern to gestational age. A positive correlation is shown in the same three parameters (Tpef/Tex (*R* = 0.242, *P* = 0.007), FEV0.5/FVC (*R* = 0.189, *P* = 0.029), and FEF25-75 (*R* = 0.206, *P* = 0.018)), with R values around 0.2, hinting that birth weight also plays a role in predicting ILF but is slightly less strongly correlated than gestational age [Supplementary Figure 1].

BPD definitions

In our investigation, we examined whether the two definitions of BPD lead to differences in ILF outcomes. Both definitions demonstrated significant differences in the Tpef/Tex parameter between the groups no BPD versus severe BPD (*P* = 0.007) and no BPD versus grade 2 BPD group (*P* = 0.023) [Supplementary Table 2]. No notable differences were observed in the RTC data. According to the RVRTC data, the original NICHD definition of BPD provides more predictive information regarding RVRTC outcomes. The parameters reflecting small airway function, namely, FEV0.5 (*P* = 0.049), FEV0.5/FVC (*P* = 0.020), and FEF25-75 (*P* = 0.015), were demonstrated to be statistically significantly worse in those with severe BPD.

Correlation with longitudinal lung function studies

Impulse oscillometry (IOS)

In our longitudinal study, we compared ILF data with IOS measurements to assess airway resistance. The median age of the 40 infants who underwent follow-up IOS assessments was 3 years. Key IOS parameters, including R5, R20, R5-R20, and X5, were analyzed. Our findings demonstrated a negative correlation between ILF parameters—specifically Tpef/Tex, FEV0.5, and FEF25-75—and IOS R5-R20 (*R* = −0.416, *P* = 0.008; *R* = −0.350,

Table 3: Correlation coefficients between infant lung function parameters and gestation age and between infant lung function parameters and birth weight

Pearson correlation	zTpef/Tex	zCrs	zRrs	zV'maxFRC	zFEV0.5	zFVC	zFEV0.5/FVC	zFEF25-75
Gestational age, weeks	0.293**	0.043	0.046	0.001	0.106	−0.036	0.218*	0.208*
Birth weight, grams	0.242**	0.007	0.015	−0.042	0.134	0.019	0.189*	0.206*

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

Abbreviations: z = z score calculated by Chinese population reference as detailed in Reference section, Tpef/Tex = time to peak tidal expiratory flow as a ratio of total expiratory time, Crs = airway compliance, Rrs = airway resistance, V'maxFRC = maximal forced expiratory flow rate at the point of functional residual capacity, FEV0.5 = forced expiratory volume at 0.5 s, FVC = forced vital capacity, FEF25-75 = the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled

$P = 0.027$; $R = -0.319$, $P = 0.045$, respectively), suggesting that improved airway function in infancy is associated with lower small airway resistance in toddlers. Particularly, the correlation coefficient for zTpef/Tex and zR5-R20 was −0.416, denoting a moderate inverse relationship [Figure 2].

Spirometry

Moving forward, we compared ILF with spirometry results at a median age of 6.8 years for 11 participants. Although the small sample size limits definitive conclusions, we note a positive correlation between infant FEV0.5 and childhood FVC ($R = 0.773$, $P < 0.01$) and between infant FVC and childhood FVC ($R = 0.755$, $P < 0.01$) [Supplementary Table 3]. Another noteworthy negative correlation was observed between infant FVC and childhood FEV1/FVC ($R = -0.664$, $P < 0.05$). This aligns with the findings of previous studies suggesting that the catch-up growth of FVC may exceed that of FEV1, leading to a decline in the FEV1/FVC ratio over time and indicating a more obstructive lung pattern in individuals with higher infant FVC.

Bronchodilator responsiveness

In the final segment of our results, we explored BDR in ILF and IOS. For those infants with IFT done successfully, 14.7% demonstrated BDR. Our findings revealed that a significant proportion of infants who exhibited positive BDR also showed responsiveness in IOS several years later. Specifically, among infants with positive BDR in infancy, 66.7% also demonstrated positive BDR in IOS assessments. Conversely, the majority of those with negative BDR in infancy maintained negative BDR results when evaluated with IOS (61.3%).

Moreover, the infants who showed BDR positivity in IOS had significantly lower FEV0.5 ($p < 0.001$), FEV0.5/FVC ($p = 0.005$) and FEF25-75 ($p = 0.004$) in ILF comparing to those who were BDR negative. This may reflect that small airway insufficiencies in early infancy may be related or translated to airway hyperresponsiveness in toddlerhood. Furthermore, by comparing the infants with persistent BDR positivity in both ILF and subsequent IOS studies (n=6), to those who only had transient BDR during ILF testing (n=3), no significant differences were found between them in background demographics nor ILF parameters. This may be due to small sample number.

DISCUSSION

Summary

Preterm infants demonstrated higher RRs and lower time to peak expiratory flow ratios (Tpef/Tex). Significant correlations were observed between gestational age and key ILF parameters (Tpef/Tex, FEV0.5/FVC, and FEF25-75), as well as between birth weight and these parameters, suggesting that both factors significantly impact airway function at the time of test around 1 year of age. Our data suggested that the original NICHD definition of BPD was found to provide more predictive value for lung function outcomes, particularly in parameters regarding small airway function.

In longitudinal assessments, negative correlations were identified between ILF parameters (Tpef/Tex, FEV0.5, FEV0.5/FVC, and FEF25-75) and IOS resistance (R5–R20) measurements, indicating that better airway performance in infancy may be associated with lower small airway resistance later. Additionally, a positive correlation was noted between infant FVC and childhood FVC, while a negative correlation between infant FVC and childhood FEV1/FVC suggested that catch-up growth of FVC may exceed that of FEV1. Finally, early BDR assessments showed that a majority of infants retained their responsiveness in later IOS evaluations, highlighting the potential for Infant RVRTC to speculate long-term airway responsiveness.

Clinical relevance

To our knowledge, this is the first study of lung function trajectories in young Chinese patients. Our cohort included preterm infants as well as infants followed-up for ongoing respiratory diseases, representative of a population with significant respiratory morbidity.

Our study demonstrated that preterm infants' respiratory performances fail to catch up at early stages of their lives despite modern-day advancements in NICU treatments, such as the use of antenatal steroids, exogenous surfactants, improved ventilation strategies, and vaccinations for

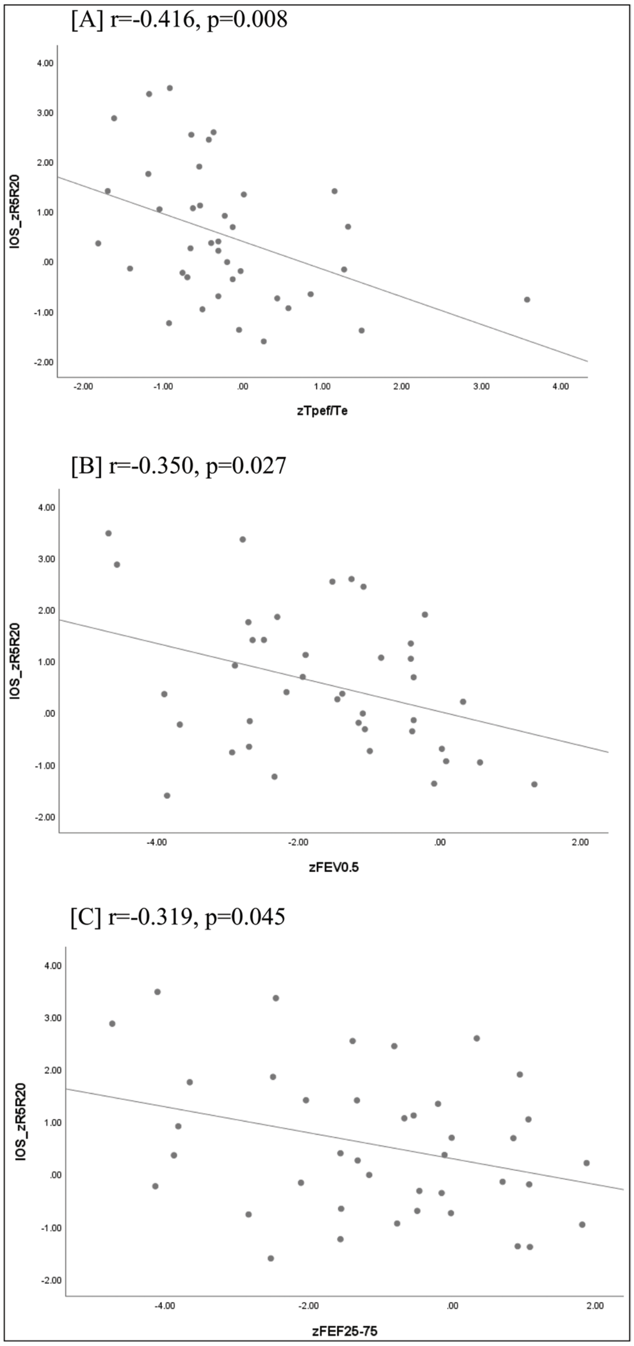

Figure 2: Correlation scatter plots between infant lung function parameters and IOS parameters. (A) Scatter plot showing a negative correlation between zTpef/Tex and IOS zR5-R20. (B) Scatter plot showing a negative correlation between zFEV0.5 (via RVRTC) and IOS zR5-R20. (C) Scatter plot showing a negative correlation between zFEF25-75 (via RVRTC) and IOS zR5-R20. Abbreviations: z = z score calculated by the Chinese population reference, as detailed in Reference section, r = correlation coefficient, IOS_R5R20 = airway resistance difference between 5 Hz and 20 Hz by impulse oscillometry test, Tpef/Te = time to peak tidal expiratory flow as a ratio of total expiratory time, FEV0.5 = forced expiratory volume at 0.5 s, FVC = forced vital capacity, FEF25-75 = the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled, IOS = impulse oscillometry

respiratory syncytial virus prevention. The two identified risk factors in the neonatal period that correlated with worse airway functions were extreme prematurity and low birth weight. We demonstrate that interruptions in intrauterine lung development and significant early-life pulmonary trauma may pose a lasting risk to respiratory health.[15] Early management is desired in this population as impairment may persist and progress to adulthood, with study data linking to early chronic obstructive lung disease.[16-18]

These persistent inadequacies in lung functions in preterm babies are best reflected via the RVRTC technique. FEV0.5/FVC and FEF25-75 were the two most informative RVRTC parameters. Not only do they correlate significantly with gestational age and birth weight, they also correlate significantly to future small airway resistance (R5–R20) in IOS testing. This is important because R5-R20 is known to associate with clinical wheezing and asthma diagnosis in preschool children.[19] Furthermore, BDR via the RVRTC technique during infancy appears to translate into persistent BDR in IOS at toddler age. This may help guide medical treatment during airway exacerbation among this cohort.

In our study, tidal breathing measurement of Tpef/Tex also had a significant correlation with gestational age, birth weight, and also longitudinal IOS measurement of R5–R20 in our study. Tpef/Tex is associated with the initial portion of tidal breathing expiration until the point of peak flow. Morris and Lane[20] were the first to observe that Tpef/Tex is shortened in obstructed patients, speculating that this is due to the reduced inhibitory effect of the inspiratory muscles during the initial phase of expiration. And Tpef/Tex is considered relatively stable after the first 3 months of life.[21] In centers where expertise and resources for RVRTC are unavailable, Tpef/Tex may provide a good alternative for airway assessment.

Interestingly, partial flow RTC measurement (V'maxFRC) did not yield a significant correlation with gestational age nor longitudinal lung function in our study. This may contradict older beliefs that partial flow-volume (RTC technique) and maximal flow-volume (RVRTC technique) can be used interchangeably.[22] The unstable nature of tidal breathing and FRC in infants may have caused inter-test and intra-test variability in V'maxFRC,[23,24] making it a less useful parameter in practice.

Although the number of patients who had undergone follow-up spirometry were too few to draw any meaningful conclusion, it was noted that infant FVC correlates negatively with FEV1/FVC in childhood. This may be agreeable to some studies which suggested that "catch up" growth of FVC outpaces that of FEFV1 due to dysanaptic growth or differential growth of the airways and lung parenchyma,[25] resulting in a decline in FEV1/FVC over time. Clinically, it may indicate to us that small airway performance becomes more unpredictable as children grow older. Further complicating our interpretation of longitudinal data, the variations in post-infancy respiratory morbidity and treatments became difficult to quantify and analyze. Each clinical case was treated as per the clinical presentation and taking into account a combination of auxiliary references including but not limited to the following: skin prick test result, eosinophil level, response to medication, compliance issues, coexisting atopies, family and environmental factors, etc. The use of types and duration of inhaled corticosteroids, bronchodilators, number of wheezing episodes or BPD exacerbations and number of rehospitalizations were potential confounders that may mitigate outcomes IOS and spirometry data. Respiratory clinicians in our center try their best to unify and adhere to our department protocol in treatments of preschool wheeze and early asthma taking reference from the latest Global Initiative for Asthma and local guidelines [Appendix A]. As our study spanned over the course of 10 years, guidelines and practices certainly also varied with time. Hence, it is difficult to quantify and summarize the effect of post-infancy and childhood respiratory treatments.

Finally, we noted that the original NICHD BPD definition based on oxygen requirement at the 36-week corrected age was more informative in terms of ILF outcomes comparing to the Jensen 2019 definition, which was based solely on the level of ventilatory support. Higher oxygen usage seems to be linked to worse RVRTC performances. This is compatible with findings of previous studies showing that more prolonged or higher cumulative oxygen usage during in the first weeks of life can predict BPD outcomes or even death.[26] Hence, it may be wise to consider oxygen level-based BPD definitions over others when making clinical judgments and risk stratification among preterm babies.

Strengths and limitations

This study benefits from a considerable cohort size, comprising a well-phenotyped population with detailed neonatal histories documented. The recency of the cohort allows for the evaluation of lung function over time, providing valuable insights into longer-term outcomes. Conducting the study at a single center minimizes the risk of heterogeneity, ensuring consistency in data collection and analysis. Additionally, the use of Asian reference values, which are generally smaller compared to Caucasian values, enhances the relevance of the findings and accuracy of the analysis within this specific population.[11-14,27]

Despite these strengths, there are some limitations. Infants who were very ill and not suitable for squeeze or raised volume procedures were excluded. The absence of a control population of healthy term babies for comparison limits the ability to relate against a true standard. Furthermore, the study lacked an ideal standardized follow-up schedule for pulmonary function assessments, which could affect the consistency of longitudinal data. Since the follow up lung function tests were conducted based on clinical indications, there was a considerable number of dropouts. We should keep in mind that sample attrition may create selection bias toward those who have more severe respiratory morbidity and include those who choose to have follow-up at our center. Additionally, more data can be collected and compared regarding the babies' backgrounds including use of antenatal steroids, exogenous surfactants, maternal educational, economic status, and breastfeeding duration. To address these limitations, future studies should aim to include a broader range of subjects, establish a standardized follow-up protocol, and gather comprehensive demographic and clinical data to enhance the robustness of the findings.

Conclusion

In our lung function trajectory analysis, we revealed that Chinese infants, particularly those born extremely preterm below 28 weeks, fail to catch up with their term counterparts even by toddler age. The obstructive lung pattern during infancy carries a higher risk of airway restrictions during early childhood. This is important as this impairment may persist and progress to adulthood. We have identified that some RVRTC parameters are particularly useful in identifying these at-risk populations. Early identification of these infants may allow timely intervention with appropriate therapies such as corticosteroids and bronchodilators, in turn to reduce long-term health implications such as physical inactivity and early development of chronic obstructive pulmonary disease. Future larger comprehensive studies are necessary to translate lung function parameters to the probability of developing diseases such as preschool wheezing and early asthma.

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Author contributions

YSCC: Conceptualization, funding acquisition, methodology, formal analysis, writing – original draft, and writing – review and editing. YTEC: Conceptualization, methodology, formal analysis, writing – review and editing, and supervision. CMSN: Conceptualization, methodology, investigation, and formal analysis. SYL: Conceptualization, methodology, formal analysis, writing – original draft, writing – review and editing, and project administration.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix A:Our Center's protocol in guiding management of preschool wheeze or early asthma adopted since 2019

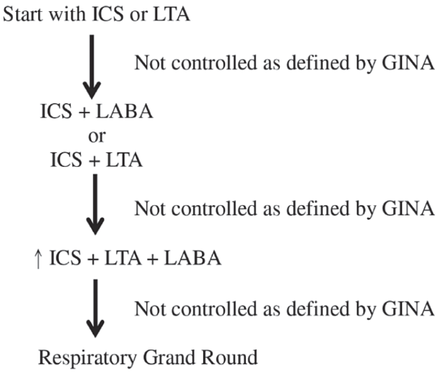
Table A1: Assessment of the severity of asthma and start prophylaxis if ≥ step 2

	Daytime symptoms- Wheeze, coughing bout, and SOB	Nighttime symptoms	Lung function
STEP 5 Severe Persistent (Continuous)	- Continual symptoms - Limited physical activity - Frequent exacerbations	>3 nights per Week	- FEV1 or PEF ≤ 60% predicted - PEF variability > 30%
STEP 4 Moderate Persistent (Daily)	- Daily symptoms - Daily use of inhaled short-acting B2-agonist - Exacerbations affect the activity - Exacerbations ≥ 2 times a week; may last days	> 1 time per week	- FEV1or PEF > 60% to < 80% predicted - PEF variability >30%
STEP 3 Mild Persistent (Frequent weekly)	- Symptoms > 2 times a week but < 1 time a day - Exacerbations may affect activity	> 2 times per month	- FEV1or PEF ≥ 80% predicted - PEF variability 20-30%
STEP 2 Frequent Episode (weekly to monthly)	- Symptoms ≥ 1 time a month but <2 times a week - Asymptomatic and normal PEF between exacerbations - Exacerbations brief (from a few hours to a few days); intensity may vary	1–2 nights per Month	- FEV1or PEF ≥ 80% predicted - PEF variability <20%
STEP 1 Infrequent Episode (< monthly)	- Symptoms < 1 time a month - Asymptomatic and normal PEF between exacerbations - Exacerbations brief (from a few hours to a few days); intensity may vary	< 1 time a month	- FEV1 or PEF ≥ 80% predicted - PEF variability <20%
Asymptomatic	- No troubling cough - No SOB - No wheeze - Normal exercise tolerance	No sleep disturbance	Ditto

Table A2: Assessment of the level of control and treatment direction

Characteristic	Controlled (all of the following)	Partly controlled (any measure present in any week)	Uncontrolled
Daytime symptoms	None (≤ 2/week)	> 2/week	> 3 features of partly controlled asthma present in any week
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue medication	None (≤ 2/week)	> 2/week	
Limitations of activities	None	Any	
Lung function (PEF or FEV1)	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year	One in any week
Treatment direction	Consider step down after 3–6 months	Consider step up after 3–6 months	Step up

Table A3: Treatment steps


Start with ICS or LTA

Not controlled as defined by GINA

ICS + LABA
or
ICS + LTA

Not controlled as defined by GINA

↑ ICS + LTA + LABA

Not controlled as defined by GINA

Respiratory Grand Round

Abbreviations: ICS = inhaled corticosteroids, LTA = leukotriene receptor antagonists, LABA = long-acting beta agonists, GINA = Global Initiative for Asthma guidelines

SUPPLEMENTARY INFORMATION

Supplementary Table 1: BPD definitions

NICHD 2001 definition

Gestational age	<32 weeks	>32 weeks
Time point of assessment	>36 weeks or discharge to home, whichever comes first	28 days but <56 days, postnatal age or discharge to home, whichever comes first
Treatment with oxygen >21% for at least 28 days plus:		
Mild BPD	Breathing room air at 56 days postnatal age or discharge, whichever comes first	Breathing room air by 36 week PMA or discharge, whichever comes first
Moderate BPD	Need for <30% oxygen at 36 week PMA or discharge, whichever comes first	Need for <30% oxygen at 56 days postnatal age or discharge whichever comes first
Severe BPD	Need for≥30% oxygen and/ or positive pressure (PPV or NCPAP) at 36-week PMA or discharge, whichever comes first	Need for≥30% oxygen and/ or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge, whichever comes first

Jensen 2019 definition

Grade	Level of respiratory support needed at 36 weeks postmenstrual age (PMA)
No BPD	On room air, no respiratory support
Grade 1	Nasal canula (NC)≤2L/min
Grade 2	NC >2L/min or noninvasive positive airway pressure (NIPPV, CPAP)
Grade 3	Invasive mechanical ventilation

Supplementary Table 2: Comparison of lung function test results in infants with different severities of BPD based on different BPD definition criteria

BPD, NICHD definition ($n = 136$)

Median (IQR)	No BPD ($n = 81$)	Mild–moderate BPD ($n = 22$)	Severe BPD ($n = 33$)	*P*-value
Tidal breath				
zTpef/Tex	−0.2 (−0.7 to 0.7)	0.1 (−0.5 to 0.3)	−0.5 (−1.2 to −0.1)	0.007
RTC				
zV'maxFRC	−1.6 (−2.2 to −1.0)	−1.3 (−1.8 to −1.0)	−1.5 (−2.3 to −1.2)	0.411
RVRTC				
zFEV0.5	−1.0 (−1.9 to −0.2)	−0.8 (−1.7 to −0.1)	−1.6 (−2.1 to −0.8)	0.049
zFVC	−1.1 (−1.7 to −0.7)	−1.0 (−1.5 to 0.2)	−1.3 (−1.9 to −0.5)	0.325
zFEV0.5/FVC	0.6 (−0.4 to 1.7)	−0.1 (−0.8 to 0.9)	−0.4 (−1.0 to 0.6)	0.020
zFEF25-75	−0.5 (−1.3 to 0.6)	−0.4 (−1.9 to 0.3)	−1.5 (−2.4 to −0.3)	0.015

BPD, Jensen definition ($n = 135$)

Median (IQR)	No BPD ($n = 82$)	Grade 1 BPD ($n = 11$)	Grade 2 BPD ($n = 41$)	Grade 3 BPD ($n = 1$)	p-value
Tidal breath					
zTpef/Tex	−0.2 (−0.7 to 0.6)	−0.1 (−0.3 to 0.4)	−0.5 (−1.1 to 0.1)	NA	0.023
RTC					
zV'maxFRC	−1.5 (−2.2 to −1.0)	−1.2 (−1.6 to −0.8)	−1.5 (−2.3 to −1.2)	−1.2	0.412
RVRTC					
zFEV0.5	−1.0 (−1.9 to −0.2)	−1.0 (−1.5 to −0.3)	−1.5 (−2.1 to −0.5)	−1.0	0.488

Supplementary Table 2: Continued

BPD, Jensen definition (*n* = 135)

Median (IQR)	**No BPD (*n* = 82)**	**Grade 1 BPD (*n* = 11)**	**Grade 2 BPD (*n* = 41)**	**Grade 3 BPD (*n* = 1)**	**p-value**
zFVC	−1.1 (−1.7 to −0.7)	−1.2 (−1.5 to −0.2)	−1.3 (−1.9 to −0.4)	−0.9	0.911
zFEV0.5/FVC	0.6 (−0.4 to 1.7)	0.8 (−1.8 to 1.7)	−0.4 (−0.9 to 0.4)	0.5	0.037
zFEF25-75	−0.5 (−1.3 to 0.6)	−0.2 (−2.0 to 1.0)	−1.1 (−2.1 to −0.1)	−0.9	0.058

Abbreviations: BPD = bronchopulmonary dysplasia, NICHD = Eunice Kennedy Shriver National Institute of Child Health and Human Development, a part of the National Institutes of Health (NIH) of the United States, Tpef/Tex = time to peak tidal expiratory flow as a ratio of total expiratory time, V'maxFRC = maximal forced expiratory flow rate at the point of functional residual capacity, FEV0.5 = forced expiratory volume at 0.5 s, FVC = forced vital capacity, FEF25-75 = the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled

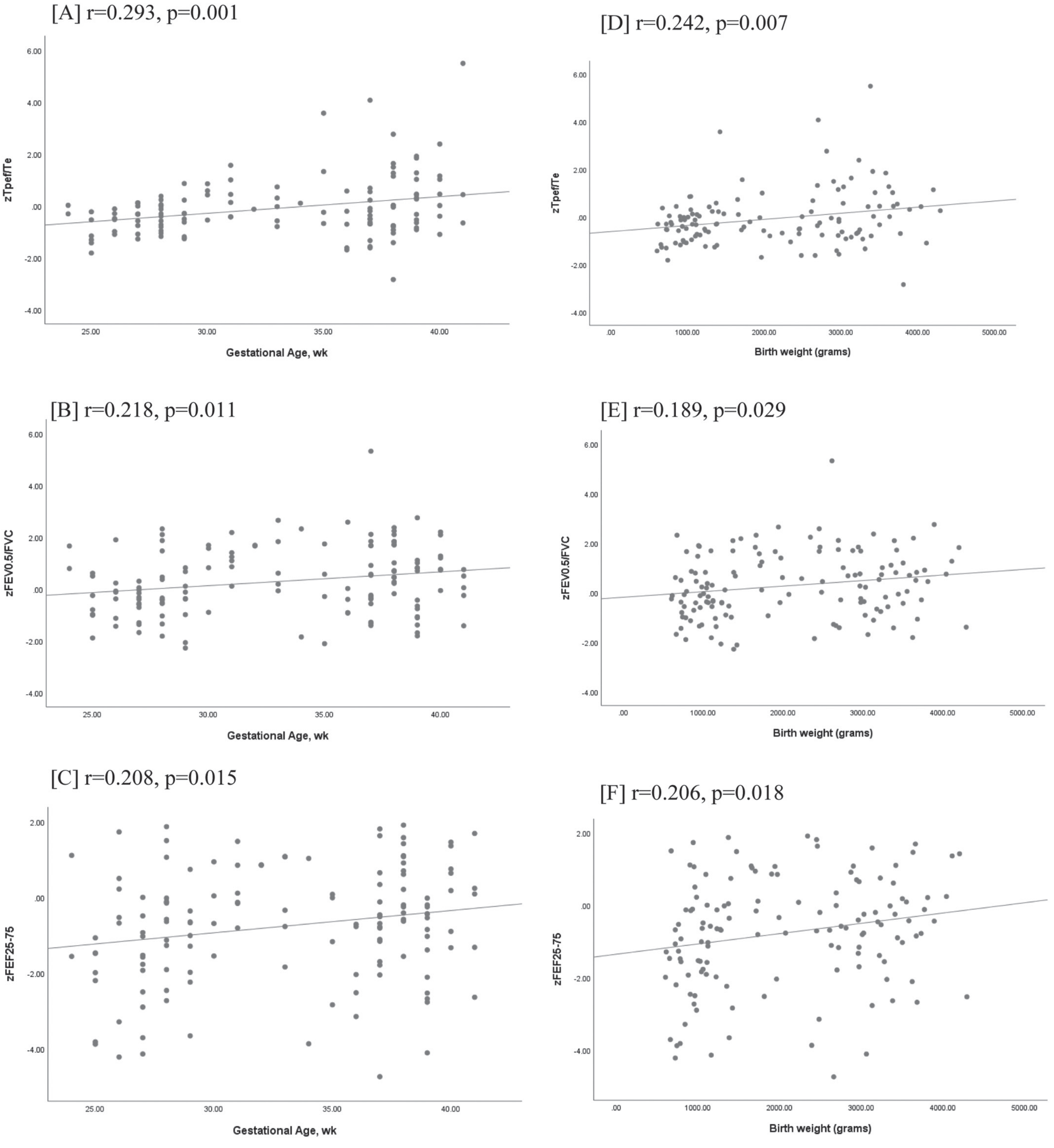
Supplementary Table 3: Correlation coefficients between infant lung function parameters and spirometry parameters

Spearman's rho	**Spir zFEV1**	**Spir zFVC**	**Spir zFEV1/FVC**	**Spir zFEF25-75**	**Spir zFEF50**	**Spir zFEF75**
zTpef/ex	−0.009	0.364	−0.191	0.073	0.018	−0.118
zCrs	0.167	0.024	−0.143	0.000	−0.143	−0.286
zRrs	−0.395	−0.060	−0.287	−0.503	−0.407	−0.060
zV'maxFRC	0.009	0.182	0.036	0.136	0.127	−0.055
zFEV0.5	0.318	0.773[**]	−0.564	−0.073	−0.218	−0.355
zFVC	0.227	0.755[**]	−0.664[*]	−0.182	−0.318	−0.436
zFEV0.5/FVC	0.364	0.036	0.073	0.382	0.245	0.155
zFEF25-75	0.291	0.191	−0.055	0.255	0.109	−0.036

[**] Correlation is significant at the 0.01 level (2-tailed)

[*] Correlation is significant at the 0.05 level (2-tailed)

Spir = spirometry, z = z score calculated by Chinese population reference as detailed in the Reference section, Tpef/Tex = time to peak tidal expiratory flow as a ratio of total expiratory time, Crs = airway compliance, Rrs = airway resistance, V'maxFRC = maximal forced expiratory flow rate at the point of functional residual capacity, FEV0.5 = forced expiratory volume at 0.5 s, FEV1 = forced expiratory volume at 1 s, FVC = forced vital capacity, FEF25-75 = the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled, FEF50 = the flow when 50% of the FVC has been exhaled, FEF75 = the flow when 75% of the FVC has been exhaled



[A] r=0.293, p=0.001

[D] r=0.242, p=0.007

[B] r=0.218, p=0.011

[E] r=0.189, p=0.029

[C] r=0.208, p=0.015

[F] r=0.206, p=0.018

Supplementary Figure 1: Correlation scatter plots between infant lung function parameters and gestational age and also with birth weight. Scatter plot showing a positive correlation between gestational age (weeks) and zTpef/Tex (A), zFEV0.5/FVC (B), and FEF25-75 (C). Scatter plot showing a positive correlation between birth weight (grams) and zTpef/ex (D), zFEV0.5/FVC (E), and FEF25-75 (F). Abbreviations: z = z score calculated by the Chinese population reference, as detailed in the Reference section, r = correlation coefficient, Tpef/Te = time to peak tidal expiratory flow as a ratio of total expiratory time, FEV0.5 = forced expiratory volume at 0.5 s, FVC = forced vital capacity, FEF25-75 = the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled

Original Article

Diagnostic Yield, Management Impact, and Safety of Flexible Bronchoscopy in Pediatric Airway Disorders: A 5-Year Retrospective Study from a Tertiary-Care Center in India

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Abstract

Background: Flexible bronchoscopy (FB) is an essential diagnostic tool in pediatric airway disorders; however, the reported diagnostic yields and safety profiles vary widely across centers, and contemporary data from low- and middle-income settings remain limited. This study evaluated the diagnostic yield, management impact, and safety profile of FB in children at a tertiary-care center in Eastern India. **Methods:** We conducted a retrospective observational study of children aged 0–16 years who underwent FB for airway-related indications between January 2018 and December 2023. Indications, bronchoscopic findings, bronchoalveolar lavage (BAL) results, complications, and post-procedure management changes were analyzed. The diagnostic yield was stratified into (1) definitive structural/pathological diagnoses and (2) management-altering findings. Outcomes are reported with 95% confidence intervals (CIs). **Results:** A total of 230 procedures were performed in 218 children (median age: 18 months [interquartile range: 6–48]; 62% male). The overall diagnostic yield was 74% (95% CI: 68.0–79.3). Definitive structural or pathological diagnoses were established in 56% (95% CI: 49.5–62.4), and management-altering findings were observed in 58% (95% CI: 51.6–64.4). BAL contributed to diagnosis in 41% of procedures. The yield was highest in suspected foreign body aspiration and focal atelectasis. Predominantly minor and transient procedure-related complications occurred in 9.6% (95% CI: 6.3–13.9). Major complications occurred in 1.3% (95% CI: 0.3–3.8), without long-term sequelae. **Conclusions:** FB demonstrated high diagnostic yield and meaningful clinical impact with a low rate of serious complications. These findings support its safe and effective use in experienced tertiary-care pediatric centers and underscore the importance of standardized procedural protocols.

Keywords: Airway disorders, diagnostic yield, pediatric bronchoscopy

INTRODUCTION

Flexible bronchoscopy (FB) is a cornerstone of pediatric respiratory practice, enabling direct visualization of the airways, dynamic assessment of airway collapse, and targeted sampling through bronchoalveolar lavage (BAL) or biopsy. Its minimally invasive nature and ability to provide real-time anatomical, functional, and microbiological information make it indispensable in evaluating persistent or unexplained respiratory symptoms in children.[1-3]

Airway disorders such as recurrent wheeze, chronic cough, stridor, unresolved pneumonia, and suspected foreign body aspiration frequently pose diagnostic challenges. While imaging may suggest structural abnormalities, definitive characterization often requires endoscopic assessment. FB allows identification of congenital anomalies, dynamic tracheobronchomalacia, mucus impaction, inflammatory changes, and endobronchial

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lesions and frequently influences therapeutic decision-making, including targeted antimicrobial therapy or surgical planning.[4,5]

International series report diagnostic yields of 60%–80%, with overall complication rates below 10% and major complications below 3%.[3,6–9] However, definitions of "diagnostic yield" vary considerably. Some studies restrict yield to definitive structural or microbiological diagnoses, whereas others include findings that alter management.[4,7] This heterogeneity complicates comparisons and may overestimate procedural effectiveness if definitions are not clearly stratified.

Data from low- and middle-income countries remain limited. Differences in disease spectrum, tuberculosis burden, referral patterns, microbiological infrastructure, and procedural standardization may influence both diagnostic yield and complication rates. A recent national survey from India demonstrated variability in sedation practices and BAL handling protocols, highlighting the need for center-specific outcome data and bench-marking.[10] Recent consensus recommendations from national societies further emphasize the importance of standardization.[11]

Given the evolving microbiological diagnostics and post-COVID-19 procedural adaptations, contemporary outcome data are needed.[12,13] We, therefore, evaluated the diagnostic yield, management impact, and safety of pediatric FB in a tertiary-care center in Eastern India, stratifying the diagnostic yield to enhance comparability with existing literature.

MATERIALS AND METHODS

Study design and setting

This retrospective observational study was conducted at the Institute of Child Health, Kolkata, a tertiary-care pediatric referral center in Eastern India with dedicated pediatric pulmonology and intensive care services. All FBs performed for airway-related indications between January 2018 and December 2023 were reviewed.

Ethical approval for retrospective data analysis was obtained from the Research Advisory Committee (RAC), Institute of Child Health, Kolkata (Approval No. RAC/032/2025, dated November 22, 2025). The requirement for informed consent was waived due to the non-interventional design.

Participants

Children aged 0–16 years who underwent FB for airway-related diagnostic or therapeutic indications were eligible. Indications were persistent or recurrent wheeze, recurrent stridor or voice change, suspected foreign body aspiration, persistent or recurrent pneumonia, lobar collapse/atelectasis, preoperative airway evaluation, hemoptysis or suspected endobronchial lesion, and tracheostomy-related complications.

Patients with incomplete medical records or those undergoing bronchoscopy exclusively for diffuse parenchymal lung disease without airway involvement were excluded.

Procedures were analyzed per bronchoscopy episode (n = 230), rather than per patient, to allow complication and yield assessment at the procedural level.

Bronchoscopy procedure and airway management

FB was performed in either

A dedicated bronchoscopy suite (elective cases) or
pediatric intensive care unit (PICU) (critically ill or ventilated patients).

A flexible bronchoscope (Ambu® aScope™ 4, outer diameter 3.5 mm; Ambu A/S, Denmark) was used in all cases.

Sedation strategy

Sedation and airway management were individualized based on age, indication, and clinical status:

Spontaneously breathing children: Procedural sedation using intravenous midazolam and ketamine, with supplemental oxygen administered via a nasal cannula or face mask.
General anesthesia: Used selectively in younger infants, uncooperative children, or when airway intervention was anticipated.
Mechanically ventilated patients: Bronchoscopy was performed via an endotracheal tube using the closed-circuit technique to minimize derecruitment and aerosolization.

Continuous monitoring included pulse oximetry, heart rate, respiratory rate, and noninvasive blood pressure. Capnography was used when available.

Sedation protocols evolved modestly during the study period, particularly with enhanced infection-control measures and aerosol precautions introduced during the COVID-19 pandemic (2020 onward), though core monitoring standards remained consistent.

Bronchoalveolar lavage methodology

BAL was performed selectively for suspicion of infection, diffuse inflammation, alveolar hemorrhage, or unexplained radiological infiltrates.

Technique

Initially normal saline was instilled in aliquots of 1 mL/kg (maximum 20 mL per aliquot). Then, 2–3 aliquots were administered at the target segment, and the total instilled volume ranged from 2 to 3 mL/kg (maximum 60 mL). The bronchoscope was wedged into the segment corresponding to the radiologic abnormality when present. Gentle suction was applied after each aliquot.

Sample adequacy criteria

Samples were considered adequate if

≥30% of the instilled volume was recovered, and
cytological analysis demonstrated minimal squamous epithelial contamination.

BAL was performed at operator discretion based on clinical indication and was not routine for all procedures.

Laboratory processing

BAL specimens were sent for the following: Gram stain and bacterial culture, acid-fast bacilli smear and GeneXpert Mycobacterium tuberculosis/Rifampicin resistance assay when tuberculosis was suspected, fungal microscopy and culture (select cases), and cytology (cell differential and hemosiderin-laden macrophages when indicated).

During the early study period, viral polymerase chain reaction panels were limited. Expanded molecular testing became more available from 2021 onward, which may have influenced the microbiological yield.

Data on prior antibiotic exposure within 72 h of bronchoscopy were extracted when available.

Outcome measures

Primary outcomes

Diagnostic yield (stratified)

Diagnostic yield was categorized into the following:

Definitive structural/pathological diagnosis: Direct visualization of foreign body, congenital anomaly, dynamic airway collapse, mass lesion, or microbiologically confirmed infection.
Management-altering finding: Bronchoscopic or BAL findings that directly resulted in modification of therapy (e.g., antibiotic escalation/de-escalation, surgical referral, airway intervention, and ventilatory strategy modification).

Management change was considered attributable to FB when documentation explicitly linked the change to bronchoscopic findings.

Secondary outcomes

The outcomes included the contribution of BAL to diagnosis, changes in antimicrobial therapy, surgical or interventional planning, modification of the ventilatory strategy, and complications.

Complication definitions

Minor complications: transient desaturation (<90%), bronchospasm, and self-limited bleeding.
Major complications: events requiring invasive intervention (re-intubation and chest drainage), hemodynamic instability, or ICU escalation.

Patients were observed for at least 4 h post-procedure (longer if clinically indicated).

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences version 25 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation or median (interquartile range), depending on the distribution. Categorical variables are presented as frequencies and percentages.

Diagnostic yield and complication rates are reported with 95% confidence intervals (CI). Descriptive subgroup analyses were performed by major indication categories. Complication rates were compared descriptively between intensive care unit (ICU) versus non-ICU procedures and mechanically ventilated versus spontaneously breathing children.

Given the retrospective design and limited event numbers, no multivariable modeling was performed.

RESULTS

Study population

Between January 2018 and December 2023, a total of 230 FBs were performed in 218 children. Analyses were conducted per procedure.

The median age at bronchoscopy was 18 months (interquartile range: 6–48). Infants (<12 months) accounted for 32% of procedures. Males comprised 62% of the cohort. At the time of the procedure, 18% were receiving supplemental oxygen and 7% were mechanically ventilated. Twenty-two percent of procedures were performed in the PICU [Table 1].

Indications for flexible bronchoscopy

The most common indication for FB was persistent or recurrent wheeze (28%), followed by recurrent stridor (22%) and suspected foreign body aspiration (18%). Persistent or recurrent pneumonia with segmental atelectasis accounted for 16% of procedures [Table 2].

Table 1: Baseline characteristics and procedural context (*n* = 230 procedures)

Variable	Value
Median age, months (IQR)	18 (6–48)
Male sex	143 (62%)
Infants (<12 months)	74 (32%)
Receiving supplemental oxygen at the procedure	41 (18%)
Mechanically ventilated at the procedure	16 (7%)
Procedure performed in the PICU	50 (22%)

IQR = interquartile range, PICU = pediatric intensive care unit. Percentages are calculated per procedure unless otherwise specified

Bronchoscopic findings

Abnormal findings were identified in 170 procedures (74%). The most frequent structural abnormality was tracheobronchomalacia or dynamic airway collapse (20%). Mucosal inflammation and mucus plugging were also common. A foreign body was directly visualized in 7.8% of procedures [Table 3].

Diagnostic yield

The overall diagnostic yield was 74% (170/230; 95% CI: 68.0–79.3).

When stratified:

- **Definitive structural/pathological diagnosis:** 56% (95% CI: 49.5–62.4).
- **Management-altering finding:** 58% (95% CI: 51.6–64.4).

In 44% of procedures, findings satisfied both criteria.

The diagnostic yield varied by indication, with the highest yield observed in suspected foreign body aspiration (88%) and persistent lobar atelectasis (81%). The yield was comparatively lower in persistent wheeze (63%).

Bronchoalveolar lavage findings

BAL was performed in 148 procedures (64%).

BAL contributed directly to diagnosis in 94 procedures (41% of total; 63% of BAL-performed cases).

No cases of procedure-attributable worsening tuberculosis or new disseminated infection were observed during hospitalization or documented follow-up.

Table 2: Primary indications for flexible bronchoscopy (n = 230)

Indication	Number (%)
Persistent or recurrent wheeze	65 (28%)
Recurrent stridor or voice change	51 (22%)
Suspected airway foreign body	41 (18%)
Persistent/recurrent pneumonia or atelectasis	37 (16%)
Preoperative airway evaluation	18 (8%)
Other (hemoptysis, suspected mass, and tracheostomy-related issues)	18 (8%)

Table 3: Major bronchoscopic findings (n = 230)

Bronchoscopic finding	Number (%)
Tracheobronchomalacia/dynamic airway collapse	46 (20%)
Mucosal inflammation/bronchitis	41 (18%)
Mucus plugging/segmental atelectasis	37 (16%)
Congenital airway anomalies	33 (14%)
Foreign body visualized	18 (7.8%)
Endobronchial mass or lesion	5 (2%)
Normal study	60 (26%)

Antibiotic modification following bronchoalveolar lavage

Among the 148 BAL procedures, antibiotic therapy was modified in 44 cases (30% of BAL cases; 19% overall procedures). Escalation was done in 28 cases, and de-escalation was done in 11 cases. Targeted anti-tubercular therapy was initiated in five cases.

In all instances, documentation linked antibiotic modification directly to BAL findings.

Clinical management impact

Overall, bronchoscopy resulted in a documented change in clinical management in 134 procedures (58%), including targeted antimicrobial therapy in 19%, surgical/interventional airway planning in 10 and planned/performed foreign body extraction in 17%, and modification of the ventilatory strategy in 13% of procedures [see Tables 4 and 5].

Safety and complications

Procedure-related complications occurred in 22 procedures (9.6%; 95% CI: 6.3–13.9).

Minor complications were observed in 8.3% of procedures.

Among those, transient desaturation was observed in 5.2%, bronchospasm was observed in 2.2%, and minor self-limited bleeding in 0.9% of procedures.

Major complications were observed in 1.3% of procedures (95% CI: 0.3–3.8)

Among those, laryngospasm requiring re-intubation was observed in one case and pneumothorax requiring chest drainage observed in two cases.

Table 4: Diagnostic yield by indication

Indication	Diagnostic yield (%)
Suspected foreign body	88
Lobar atelectasis/persistent pneumonia	81
Recurrent stridor	76
Persistent wheeze	63
Preoperative airway evaluation	67

The yield was highest in focal structural airway disease (foreign body and lobar collapse)

Table 5: Microbiological results of bronchoalveolar lavage (n = 148)

Result	n (%)
Bacterial pathogen isolated	38 (26%)
Mycobacterium tuberculosis detected (GeneXpert or AFB)	6 (4%)
Fungal elements detected	4 (3%)
Mixed flora/nonpathogenic growth	22 (15%)
No growth	78 (53%)

AFB – acid-fast bacilli

There were no procedure-related deaths or long-term morbidity.

Subgroup safety analysis

Complication rates were as follows: 12% in ICU procedures, 8% in non-ICU procedures, 12% in mechanically ventilated patients, and 9% in spontaneously breathing children.

Major complication rates did not significantly differ between ventilated and non-ventilated patients; however, numbers were small.

Discussion

This 5-year retrospective study demonstrates that FB provides a high diagnostic yield (74%), meaningful management impact (58%), and a low major complication rate (1.3%) in children with airway-related disorders. By stratifying the diagnostic yield into definitive structural/pathological diagnoses (56%) and management-altering findings (58%), we aimed to improve transparency and comparability with prior studies.

Diagnostic yield in context

Our overall yield aligns with international reports describing yields between 60% and 80%.[1-3] However, interpretation must account for variability in outcome definitions. Some authors limit yield to definitive structural abnormalities or microbiologically confirmed infections, whereas others include management-altering findings.[4] Stratifying outcomes in our analysis demonstrates that a substantial proportion of procedures provided actionable information even when a discrete structural lesion was not identified.

Yield differed by indication, with highest diagnostic performance observed in suspected foreign body aspiration and focal lobar atelectasis—conditions typically associated with localized structural pathology. In contrast, persistent wheeze demonstrated lower yield, reflecting the multifactorial nature of wheezing disorders and the role of adjunct investigations.

Bronchoalveolar lavage and antimicrobial stewardship

BAL contributed to diagnosis in 41% of procedures and in 63% of cases where lavage was performed, consistent with contemporary systematic reviews.[5] Importantly, BAL findings led to antimicrobial modification in nearly one-third of cases, supporting its role in antimicrobial stewardship.

The microbiological spectrum reflected local epidemiology, including tuberculosis detection in 4% of BAL samples. No procedure-related worsening of tuberculosis or new disseminated infection occurred. Expanded molecular testing availability after 2021 may have influenced microbiological yield and should be considered when interpreting results.

Safety and procedural context

The overall complication rate of 9.6% and major complication rate of 1.3% are within internationally reported ranges.[3,6] Most adverse events were transient and managed conservatively. Although complication rates were slightly higher among ICU and mechanically ventilated patients, major events remained uncommon.

Favorable safety outcomes likely reflect experienced operators, individualized sedation strategies, multidisciplinary collaboration, and structured monitoring. Nonetheless, retrospective data collection may underestimate minor transient events.

Selection bias and generalizability

As a tertiary-care referral center, our cohort may represent more complex or refractory cases, introducing potential selection bias. Referral patterns may increase pretest probability of structural disease, thereby influencing the diagnostic yield. Additionally, procedural practices and resource availability vary across institutions in India, limiting direct generalizability.

While our outcomes parallel international data, differences in tuberculosis burden, microbiological infrastructure, and healthcare access preclude direct equivalence with high-income settings.

Strengths and limitations

Strengths include a sizeable pediatric cohort, stratified yield definitions, detailed BAL methodology, and explicit documentation of management impact. Limitations include retrospective design, possible under-reporting of minor complications, absence of multivariable modeling, evolving laboratory capacity, and lack of long-term follow-up.

Clinical implications

FB should be considered early in children with focal airway disease, recurrent lobar collapse, or suspected foreign body aspiration. BAL remains valuable for microbiological clarification and antimicrobial optimization, even in resource-limited settings. Standardized sedation and monitoring protocols are essential for maintaining safety. Establishing a national pediatric bronchoscopy registry would facilitate benchmarking and quality improvement.

Conclusion

FB is a safe and clinically impactful modality for evaluating pediatric airway disorders in tertiary-care settings. In this cohort, it provided definitive structural or pathological diagnoses in over half of the procedures and influenced management in nearly three-fifths, with a low major complication rate.

Stratified diagnostic reporting underscores that procedural value extends beyond structural diagnosis to therapeutic decision-making, particularly through BAL-guided antimicrobial modification. Continued standardization of definitions and reporting metrics will strengthen comparability and advance pediatric bronchoscopy practice, particularly in low- and middle-income settings.

Author contributions

PPH conceived the study and supervised manuscript development. GM and BD were responsible for data collection. PR performed statistical analysis and contributed to drafting and critical revision. All authors approved the final manuscript.

Data availability statement

De-identified patient-level data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional ethics approval.

Ethical policy and Institutional Review board statement

Ethical approval for retrospective data analysis was obtained from the RAC, Institute of Child Health, Kolkata (approval no. RAC/032/2025, dated November 22, 2025). The study involved a retrospective review of procedures conducted between January 2018 and December 2023. The requirement for informed consent was waived due to the non-interventional, retrospective design.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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