BMC Infectious Diseases

RESEARCH

Open Access

Comparison of characteristics of children hospitalized for respiratory syncytial virus infection during the pre- and post-COVID-19 eras: a multicenter retrospective study

Hai-Feng Liu[1], Ya-Yu Wang[2], Xue-Zu Zhang[3], He-Yun Li[4], Mei Xiang[5], Rui Lu[6], Cong-Yun Liu[7], Wang Li[8], Quan-Li Feng[1], Yun-Jie Guo[1], Rong-Wei Huang[1] and Hong-Min Fu[1*]

Abstract

Background Respiratory syncytial virus (RSV), a leading cause of lower respiratory tract infection (LRTI) among children, has resurged in the form of endemic or even pandemic in many countries and areas after the easing of COVID-19 containment measures. This study aimed to investigate the differences in epidemiological and clinical characteristics of children hospitalized for RSV infection during pre- and post-COVID-19 eras in Yunnan, China.

Methods A total of 2553 pediatric RSV inpatients from eight hospitals in Yunnan were retrospectively enrolled in this study, including 1451 patients admitted in 2018–2019 (pre-COVID-19 group) and 1102 patients admitted in 2023 (post-COVID-19 group). According to the presence or absence of severe LRTI (SLRTI), patients in the pre- and post-COVID-19 groups were further divided into the respective severe or non-severe subgroups, thus analyzing the risk factors for RSV-associated SLRTI in the two eras. Demographic, epidemiological, clinical, and laboratory data of the patients were collected for the final analysis.

Results A shift in the seasonal pattern of RSV activity was observed between the pre-and post-COVID-19 groups. The peak period of RSV hospitalizations in the pre-COVID-19 group was during January–April and October–December in both 2018 and 2019, whereas that in the post-COVID-19 group was from April to September in 2023. Older age, more frequent clinical manifestations (fever, acute otitis media, seizures), and elevated laboratory indicators [neutrophil-to-lymphocyte ratio (NLR), c-reactive protein (CRP), interleukin 6 (IL-6), co-infection rate] were identified in the post-COVID-19 group than those in the pre-COVID-19 group (all $P < 0.05$). Furthermore, compared to the pre-COVID-19 group, the post-COVID-19 group displayed higher rates of SLRTI and mechanical ventilation, with a longer length of hospital stay (all $P < 0.05$). Age, low birthweight, preterm birth, personal history of atopy, underlying condition, NLR, IL-6 were the shared independent risk factors for RSV-related SLRTI in both pre- and post-COVID-19 groups, whereas seizures and co-infection were independently associated with SLRTI only in the post-COVID-19 group.

*Correspondence:
Hong-Min Fu
fuhongmin@kmmu.edu.cn

Full list of author information is available at the end of the article

Conclusions An off-season RSV endemic was observed in Yunnan during the post-COVID-19 era, with changed clinical features and increased severity. Age, low birthweight, preterm birth, personal history of atopy, underlying condition, NLR, IL-6, seizures, and co-infection were the risk factors for RSV-related SLRTI in the post-COVID-19 era.

Keywords Respiratory syncytial virus, Children, Post-COVID-19 era, Severe lower respiratory tract infection, Risk factors

Introduction

Respiratory syncytial virus (RSV) represents a leading cause of lower respiratory tract infection (LRTI) in young children across the globe [1]. It was estimated that there were approximately 33.1 million episodes of RSV-related LRTI per year, resulting in 3.2 million hospital admissions and 59,600 in-hospital deaths among children aged below 5 years [2]. Of which, severe LRTI (SLRTI) has long been identified as the most dominant factor responsible for pediatric RSV-associated deaths, especially in developing countries [3, 4]. In the past, RSV activity was highly predictable due to marked seasonality in transmission, with peak seasons from October to the following April in the Northern Hemisphere and from April to September in the Southern Hemisphere [5]. However, this stable seasonal pattern of RSV spread was broken by the COVID-19 pandemic, which had posed catastrophic consequences to public health worldwide [6].

In response to the COVID-19 pandemic, most countries around the world implemented a series of rigorous non-pharmaceutical interventions (NPIs). Substantial evidence suggested that while the strict NPIs were effective in controlling COVID-19 pandemic, they also limited the seasonal circulation of RSV, with a significant decline in detection rates reaching up to 98% during the pandemic [7, 8]. However, as widely known, because of the lack of licensed RSV vaccines and the gradual decrease of maternal RSV neutralizing antibodies with increasing age, seasonal exposure to RSV has served as the primary way for children to acquire immune protection against RSV infection [9, 10]. Logically, the reduced seasonal exposure to RSV during the COVID-19 pandemic would enhance susceptibility to RSV in children, thereby increasing the severity of RSV infection. Indeed, with the gradual lifting of NPIs in the post-COVID-19 era, numerous countries, such as Australia, New Zealand, Italy, Japan, and China, have reported out-of-season RSV outbreaks, with increased proportions of RSV hospitalizations and intensive care unit (ICU) admissions [7, 11–14]. Given that COVID-19 pandemic and its related NPIs have affected the seasonal pattern, natural course, and severity of RSV infection in children, studies regarding RSV infection in post-COVID-19 era are urgently needed to further elucidate its epidemiological and clinical characteristics.

In the present study, we retrospectively collected the data on pediatric RSV inpatients at multiple hospitals in Yunnan, China, in 2018–2019 and 2023. A detailed analysis of epidemiology and clinical characteristics of these patients during the pre- and post-COVID-19 eras was performed to evaluate the seasonal and clinical evolution of RSV. In addition, we also compared the risk factors of RSV-associated SLRTI between the two eras, aiming to facilitate the early recognition of severe cases and reducing mortality in such patients during the post-COVID-19 era.

Methods

Study design and population

This multicenter retrospective study was conducted at eight public tertiary hospitals in Yunnan, China, enrolling children (≤14 years) hospitalized for RSV infection in 2019 and 2023. Patients admitted during January 2018–December 2019 and January–December 2023 were divided into the pre- and post-COVID-19 groups, retrospectively. Besides, to compare risk factors for RSV-associated SLRTI between the two eras, patients in pre- and post-COVID-19 groups were further classified into the respective severe and non-severe subgroups according to the presence or absence of SLRTI (Fig. 1).

SLRTI was defined as pneumonia or bronchiolitis accompanied by at least one of following conditions [15–17]: (1) a reduction in feeding amount to less than half of the normal, dehydration or refusal to feed; (2) disturbed consciousness; (3) manifestations of hypoxemia, including cyanosis, age-specific tachypnea (≥60 breaths/min for children under 2 months; ≥50 breaths/min for children aged 2 months to 1 year; ≥40 breaths/min for children aged > 1 to 5 years; ≥30 breaths/min for children older than 5 years), three concave signs, nasal flaring, grunting, intermittent apnea, or oxygen saturation < 88%; (4) persistent high fever for more than 5 days; (5) pulmonary imaging suggesting ≥ 2/3 unilateral lung infiltration, multilobar pulmonary infiltration, pleural effusion, pneumothorax, atelectasis, pulmonary necrosis, or pulmonary abscess; (6) extrapulmonary complications.

Ethical approval for this study was granted by the Ethics Committees of Kunming Children's Hospital Affiliated to Kunming Medical University (approval number: 2023-05-012-K01), who also waived the written informed consent due to the retrospective design of the study.

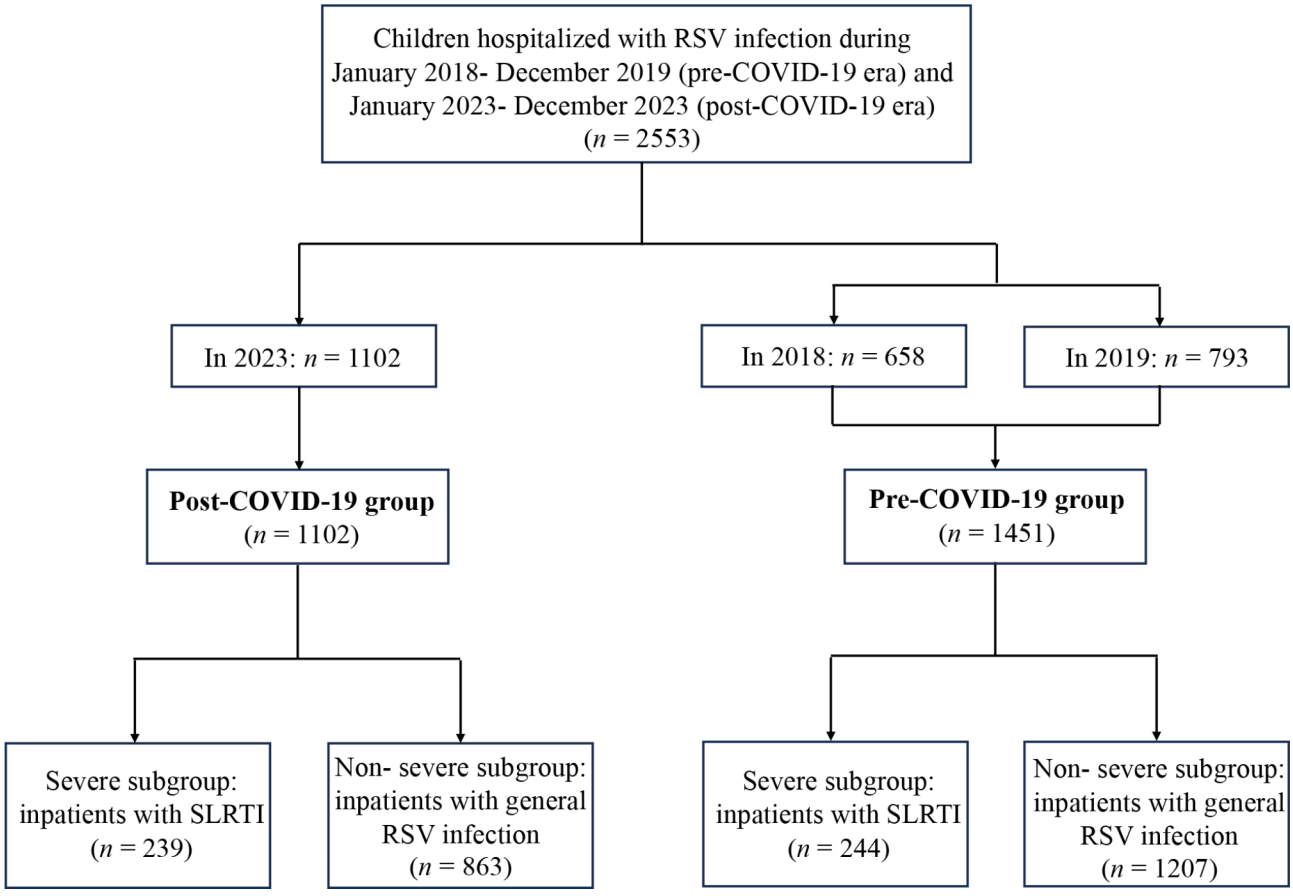

Fig. 1 Flowchart of the overall study design. RSV, respiratory syncytial virus; SLRTI, severe lower respiratory tract infection

Data extraction and definition

Data obtained from electronic medical records included demographic information (age, gender), clinical characteristics [low birthweight, preterm birth, personal and family histories of atopy, non-exclusively breastfeeding (non-EBF), underlying condition, duration of symptoms prior to admission, fever, fever peak, cough, rhinorrhea, nasal congestion, wheezing, acute otitis media, seizures, poor appetite, diarrhea, vomiting], laboratory indicators [oxygen saturation, leucocyte count, neutrophil-to-lymphocyte ratio (NLR), $CD4^+/CD8^+$ T cell ratio, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), procalcitonin (PCT), interleukin 6 (IL-6), alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), creatinine (Cr), urea, creatine kinase myocardial band (CK-MB), co-infection], and outcome measures [SLRTI, mechanical ventilation, ICU admission, length of hospital stay (LOS)].

In the above-mentioned data, low birthweight was defined as a birth weight of less than 2500 g; preterm birth was defined as gestational age < 37 weeks; underlying diseases included congenital heart diseases, bronchopulmonary dysplasia, pectus excavatum, malignant tumors, immunodeficiency, or severe malnutrition; non-EBF was defined as that the feeding practice within 6 months after birth was formula feeding or mixed feeding. In addition, all patients in this study had received the molecular detection of multiple respiratory pathogens, including RSV, influenza A virus (IAV), influenza B virus (IBV), human parainfluenza virus (HPIV), human adenovirus (HAdV), human rhinovirus (HRV), human metapneumovirus (HMPV), SARS-COV-2 (only in the post-COVID-19 era), *mycoplasma pneumoniae* (*M. pneumoniae*), *chlamydophila pneumoniae*, and *legionella pneumophila*. Co-infection referred to detection of another pathogen concurrent to RSV diagnosis. All data were cross-checked by two trained Ph.D. students to ensure accuracy.

Statistical analysis

Categorical variables were expressed as frequencies (n) and percentages (%) and compared using Pearson's chi-square or Fisher's exact test, while continuous variables with non-normal distributions tested by the Shapiro-Wilk test were summarized as medians with interquartile range (IQR) and then compared using Mann-Whitney U test. Multivariate logistic regression analysis was performed to identify the independent risk factors for SLRTI

Table 1 General characteristics of patients in the pre- and post-COVID-19 groups

Characteristics	Total (*n* = 2553)	Post-COVID-19 group (*n* = 1102)	Pre-COVID-19 group (*n* = 1451)	*P* value
Age, months, median (IQR)	7.4 (3.3, 13.1)	15.1 (10.5, 21.6)	5.5 (2.1, 11.2)	< 0.001
Male, n (%)	1492 (58.4)	628 (57.0)	864 (59.5)	0.194
Low birthweight, n (%)	330 (12.9)	155 (14.1)	175 (12.1)	0.135
Preterm birth, n (%)	336 (13.2)	136 (12.3)	200 (13.8)	0.286
Personal history of atopy, n (%)	554 (21.7)	249 (22.6)	305 (21.0)	0.339
Family history of atopy, n (%)	362 (14.2)	168 (15.2)	194 (13.4)	0.179
Non-EBF, n (%)	1157 (45.3)	505 (45.8)	652 (44.9)	0.654
Underlying condition, n (%)	361 (14.1)	163 (14.8)	198 (13.6)	0.411
Duration of symptoms prior to admission, days, median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	0.219

IQR, interquartile ranges; Non-EBF, non-exclusively breastfeeding

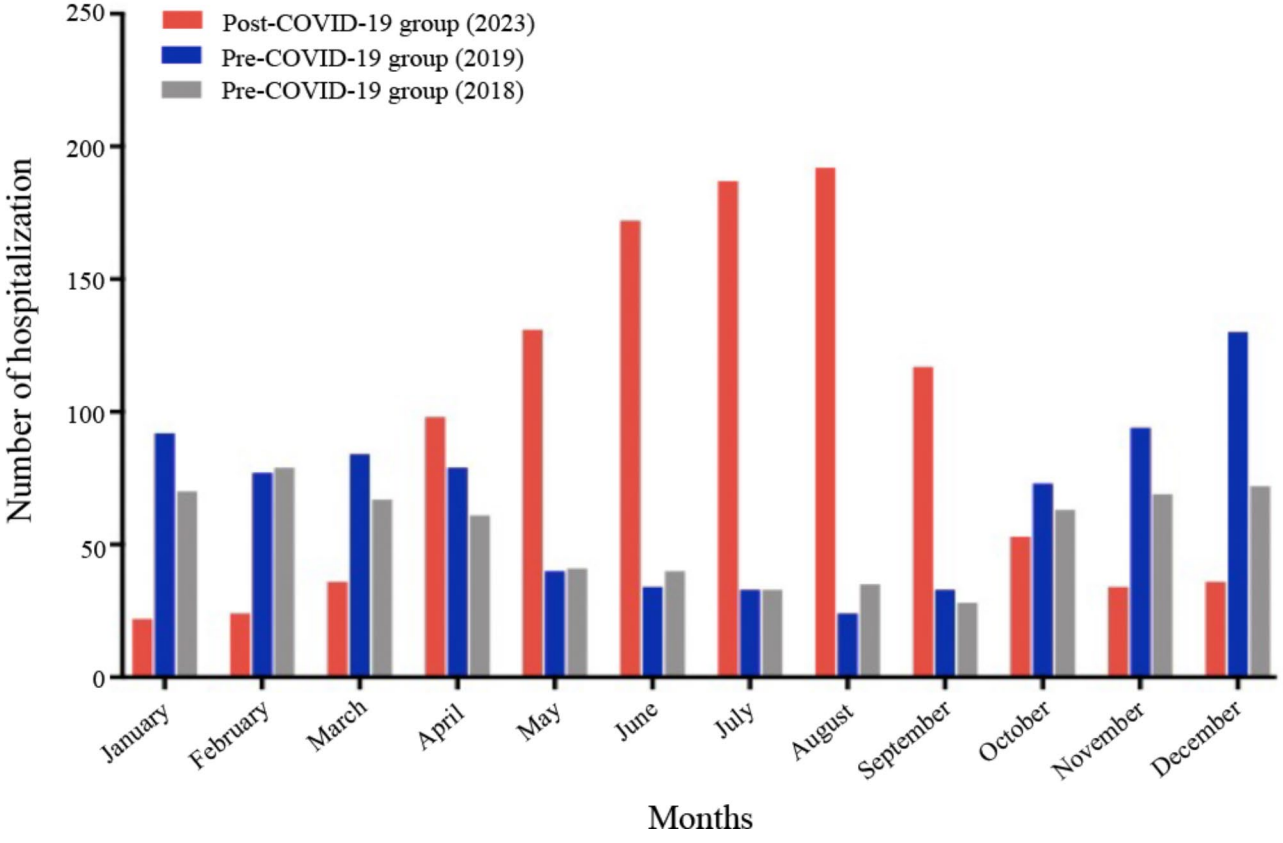

Fig. 2 The temporal distribution of admissions in the pre- and post-COVID-19 groups

among pediatric RSV inpatients. All statistical analyses were carried out using R 3.5.1 (R Foundation, Vienna, Austria) with a significance level set at a two- tailed *P* value < 0.05.

Results

General characteristics of patients

During the entire study period, a total of 2553 pediatric RSV inpatients were included in this study. Among which, 1451 cases (658 cases in 2018 and 793 cases in 2019) were enrolled in the pre-COVID-19 group with a median age of 5.5 (2.1, 11.2) months and a male proportion of 59.5% (864/1451), while 1102 cases were enrolled in the post-COVID-19 group with a median age of 15.1 (10.5, 21.6) months and a male proportion of 57.0% (628/1102). Patients in the post-COVID-19 group were significantly older than those in the pre-COVID-19 group ($P < 0.001$) (Table 1).

Epidemiological characteristics of patients

In terms of temporal distribution of admissions (Fig. 2), the post-COVID-19 group showed that the number of

RSV hospitalizations began to increase rapidly in April and culminate in August, followed by a sharp decline in October, indicating a peak period of hospitalization in April–September 2023, with the monthly hospitalization counts successively being 98 (8.9%) in April, 131 (11.9%) in May, 172 (15.6%) in June, 187 (17.0%) in July, 192 (17.4%) in August, and 117 (10.6%) in September.

In contrast, the period from May to September was an relative trough for RSV hospitalizations in the pre-COVID-19 group, which showed a peak period during January–April and October–December in both 2018 and 2019.

Clinical and laboratory characteristics of patients

There were significant differences regarding clinical and laboratory characteristics between the pre- and post-COVID-19 groups (Table 2). Specifically, despite a deceased proportion of wheezing, more frequent clinical manifestations (fever, acute otitis media, seizures) and significantly elevated laboratory indicators (leukocyte count, NLR, CRP, IL-6, co-infection rate) were found in the post-COVID-19 group than the pre-COVID-19 group (all $P<0.05$). More notably, the proportion of patients developing SLRTI was 21.7% (239/1102) in the post-COVID-19 group, with a mechanical ventilation rate of 7.8% (86/1102) and a median LOS of 6.0 (4.0, 8.0) days, all of which were greater than those identified in the pre-COVID-19 group [16.8% (244/1451), 4.8% (70/1451), 5.0 (4.0, 7.0) days, respectively; all $P<0.05$] (Table 3).

Co-infection of patients

Co-infection was detected in 439 cases (39.8%) in the post-COVID-19 group and 518 cases (35.7%) in the pre-COVID-19 group. As summarized in Table 4, dual infection was the most common mixed infection [299 (68.1%)] in the post-COVID-19 group, followed by triple infection [98 (22.3%)] and quadruple infection [42 (9.6%)]. The three most common combinations of co-infection were RSV+IAV [60 (13.7%)], RSV+*M. pneumoniae* [47 (10.7%)], and RSV+HRV [38 (8.7%)].

The concurrent infection in the pre-COVID-19 group was also dominated by dual infection, with a higher

Table 2 Clinical and laboratory characteristics of patients in the pre- and post-COVID-19 groups

Characteristics	Total ($n=2553$)	Post-COVID-19 group ($n=1102$)	Pre-COVID-19 group ($n=1451$)	*P* value
Clinical symptoms				
Fever, n (%)	1284 (50.3)	582 (52.8)	702 (48.4)	0.027
Fever peak, °C, median (IQR)	37.7 (37.2, 38.2)	37.8 (37.2, 38.4)	37.7 (37.2, 38.1)	0.118
Cough, n (%)	2276 (89.2)	993 (90.1)	1283 (88.4)	0.175
Rhinorrhea, n (%)	1117 (43.8)	495 (44.9)	622 (42.9)	0.301
Nasal congestion, n (%)	1086 (42.5)	452 (41.0)	634 (43.7)	0.175
Wheezing, n (%)	1099 (43.0)	448 (40.7)	651 (44.9)	0.033
Acute otitis media, n (%)	553 (21.7)	284 (25.8)	269 (18.5)	< 0.001
Seizures, n (%)	202 (7.9)	131 (11.9)	71 (4.9)	< 0.001
Poor appetite, n (%)	838 (32.8)	351 (31.9)	487 (33.6)	0.362
Diarrhea, n (%)	115 (4.5)	56 (5.1)	59 (4.1)	0.220
Vomiting, n (%)	174 (6.8)	72 (6.5)	102 (7.0)	0.622
Laboratory findings, median (IQR)				
Oxygen saturation, %	94.0 (91.0, 97.0)	93.0 (90.0, 97.0)	94.0 (91.0, 98.0)	0.104
Leukocyte count, $\times10^9$/L	12.3 (10.1, 14.9)	13.8 (11.0, 16.7)	11.1 (9.5,13.9)	< 0.001
NLR	3.9 (3.1, 5.3)	4.2 (3.5, 6.2)	3.6 (2.8, 5.0)	< 0.001
$CD4^+$ /$CD8^+$ T cell ratio	1.2 (0.9, 1.6)	1.2 (0.8, 1.5)	1.2 (1.0, 1.7)	0.621
ESR, mm/H	17.0 (15.0, 23.0)	21.0 (14.0, 29.0)	16.0 (14.0, 22.0)	0.195
CRP, mg/L	11.7 (8.0, 17.9)	12.3 (8.9, 19.6)	9.8 (4.7, 17.2)	0.009
PCT, ng/mL	0.4 (0.1, 1.1)	0.4 (0.1, 1.2)	0.4 (0.2, 1.1)	0.418
IL-6, pg/mL	18.2 (10.3, 27.8)	19.5 (12.4, 32.8)	16.5 (10.2, 27.3)	0.007
ALT, U/L	25.0 (20.0, 37.0)	24.0 (19.0, 33.0)	25.0 (21.0, 39.0)	0.110
AST, U/L	27.0 (20.0, 35.0)	26.0 (19.0, 35.0)	28.0 (22.0, 35.0)	0.322
LDH, U/L	390.6 (350.7, 509.0)	398.6 (351.2, 568.9)	387.0 (349.6, 505.8)	0.175
Cr, umol/L	29.5 (24.9, 37.8)	31.6 (26.3, 38.2)	29.2 (23.9, 37.6)	0.382
Urea, mmol/L	3.2 (2.2, 4.7)	3.0 (2.1, 4.5)	3.2 (2.2, 4.7)	0.510
CK-MB, U/L	48.1 (39.3, 55.0)	51.0 (41.4, 60.8)	46.3 (39.0, 53.6)	0.139
Co-infection, n (%)	957 (37.5)	439 (39.8)	518 (35.7)	0.032

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; Cr, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; IQR, interquartile ranges; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin

Table 3 Outcome measures of patients in the pre- and post-COVID-19 groups

Characteristics	Total (*n* = 2553)	Post-COVID-19 group (*n* = 1102)	Pre-COVID-19 group (*n* = 1451)	*P* value
SLRTI, n (%)	483 (18.9)	239 (21.7)	244 (16.8)	0.002
Mechanical ventilation, n (%)	156 (6.1)	86 (7.8)	70 (4.8)	0.002
ICU admission, n (%)	210 (8.2)	101 (9.2)	109 (7.5)	0.132
LOS, days, median (IQR)	5.0 (4.0, 7.0)	6.0 (4.0, 8.0)	5.0 (4.0, 7.0)	< 0.001

ICU, intensive care unit; IQR, interquartile ranges; LOS, length of hospital stay; SLRTI, severe lower respiratory tract infection

Table 4 Co-infection of patients in the pre- and post-COVID-19 groups

Characteristics	Post-COVID-19 group (*n* = 439)	Pre-COVID-19 group (*n* = 518)	*P* value
Dual infection, n (%)	299 (68.1)	412 (79.5)	< 0.001
Triple infection, n (%)	98 (22.3)	80 (15.4)	0.006
Quadruple infection, n (%)	42 (9.6)	26 (5.0)	0.006
Main combinations of co-infection, n (%)			
RSV + IAV	60 (13.7)	35 (6.8)	< 0.001
RSV + HRV	38 (8.7)	73 (14.1)	0.009
RSV + HPIV	24 (5.5)	61 (11.8)	0.001
RSV + HMPV	7 (1.6)	69 (13.3)	< 0.001
RSV + *M. pneumoniae*	47 (10.7)	33 (6.4)	0.016

HMPV, human metapneumovirus; HPIV, human parainfluenza virus; HRV, human rhinovirus; IAV, influenza A virus; *M. pneumoniae*, *mycoplasma pneumoniae*; RSV, respiratory syncytial virus

proportion than that in the post-COVID-19 group [79.5% (412/518) vs. 68.1% (299/439), $P<0.001$]; whereas the proportions of triple and quadruple infections were significantly lower than those in the post-COVID-19 group [15.4% (80/518) vs. 22.3% (98/439), $P=0.006$; 5.0% (26/518) vs.9.6% (42/439), $P=0.006$)]. The top three combinations of co-infections in the pre-COVID-19 group in order were RSV + HRV [73 (14.1%)], RSV + HMPV [69 (13.3%)], and RSV + HPIV [61 (11.8%)].

Independent risk factors for RSV-associated SLRTI

As shown in Tables 5 and 239 (21.7%) cases in the post-COVID-19 group and 244 (16.8%) cases in the pre-COVID-19 group were classified into respective severe subgroups. Patients' characteristics of severe and non-severe subgroups in both pre- and post-COVID-19 groups were summarized in Tables 5, 6 and 7. Variables with significant differences between severe and non-severe subgroups were included into logistic regression analysis. Finally, age, low birthweight, preterm birth, personal history of atopy, underlying condition, NLR, and IL-6 were identified as the shared independent risk factors of SLRTI in both pre- and post-COVID-19 groups, whereas seizures and co-infection were independently associated with SLRTI only in the post-COVID-19 group (Fig. 3).

Discussion

Based on multicenter data, this study assessed children hospitalized for RSV infection during the pre- (2018–2019) and post-COVID-19 eras (2023) in Yunnan, China, to clarify the differences in characteristics of pediatric RSV infection between the two periods.

Before the COVID-19 pandemic, the RSV activities generally followed a predictable seasonal pattern with epidemic peaks from October to April of the following year in the Northern Hemisphere [5]. Consistent with this knowledge, in the pre-COVID-19 group of our study, the RSV-associated hospitalizations occurred

Table 5 General characteristics of patients in the respective severe and non-severe subgroups

Characteristics	Post-COVID-19 group		*P* value	Pre-COVID-19 group		*P* value
	Severe (*n* = 239)	Non-severe (*n* = 863)		Severe (*n* = 244)	Non-severe (*n* = 1207)	
Age, months, median (IQR)	11.2 (9.3, 17.9)	17.3 (14.1, 22.5)	< 0.001	2.2 (1.0, 5.1)	5.8 (2.3, 12.4)	< 0.001
Male, n (%)	139 (58.2)	489 (56.7)	0.679	151 (61.9)	713 (59.1)	0.422
Low birthweight, n (%)	48 (20.1)	107 (12.4)	0.002	42 (17.2)	133 (11.0)	0.007
Preterm birth, n (%)	40 (16.7)	96 (11.1)	0.020	44 (18.0)	156 (13.8)	0.035
Personal history of atopy, n (%)	69 (28.9)	180 (20.9)	0.009	63 (25.8)	242 (20.0)	0.044
Family history of atopy, n (%)	45 (18.8)	123 (14.3)	0.082	45 (18.4)	149 (12.3)	0.011
Non-EBF, n (%)	116 (48.5)	389 (45.1)	0.342	107 (43.9)	545 (45.2)	0.709
Underlying condition, n (%)	51 (21.3)	112 (13.0)	0.001	46 (18.9)	152 (12.6)	0.009
Duration of symptoms prior to admission, days, median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	0.581	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.880

IQR, interquartile ranges; Non-EBF, non-exclusively breastfeeding

Table 6 Clinical and laboratory characteristics of patients in the respective severe and non-severe subgroups

Characteristics	Post-COVID-19 group		*P* value	Pre-COVID-19 group		*P* value
	Severe (*n* = 239)	Non-severe (*n* = 863)		Severe (*n* = 244)	Non-severe (*n* = 1207)	
Clinical symptoms						
Fever, n (%)	136 (56.9)	446 (51.7)	0.152	127 (52.0)	575 (47.6)	0.209
Fever peak, °C, median (IQR)	38.1 (37.7, 39.2)	37.8 (37.1, 38.3)	0.018	38.4 (37.2, 39.1)	37.6 (37.0, 38.0)	0.008
Cough, n (%)	219 (91.6)	774 (89.7)	0.373	212 (86.9)	1071 (88.7)	0.411
Rhinorrhea, n (%)	115 (48.1)	380 (44.0)	0.261	115 (47.1)	507 (42.0)	0.140
Nasal congestion, n (%)	103 (43.1)	349 (40.4)	0.460	112 (45.9)	522 (43.2)	0.446
Wheezing, n (%)	111 (46.4)	337 (39.0)	0.039	127 (52.0)	524 (43.4)	0.013
Acute otitis media, n (%)	66 (27.4)	218 (25.3)	0.461	52 (21.3)	217 (18.0)	0.222
Seizure, n (%)	41 (17.2)	90 (10.4)	0.004	17 (7.0)	54 (4.5)	0.100
Poor appetite, n (%)	79 (33.1)	272 (31.5)	0.652	93 (38.1)	394 (32.6)	0.099
Diarrhea, n (%)	11 (4.6)	45 (5.2)	0.703	12 (4.9)	47 (3.9)	0.460
Vomiting, n (%)	17 (7.1)	55 (6.4)	0.682	19 (7.8)	83 (6.9)	0.612
Laboratory findings, median (IQR)						
Oxygen saturation, %	91.0 (88.0, 95.0)	93.0 (90.0, 98.0)	0.072	93.0 (91.0, 95.0)	94.0 (91.0, 98.0)	0.274
Leukocyte count, $\times 10^9$/L	16.4 (13.2, 19.8)	12.9 (10.7, 15.6)	< 0.001	14.5 (11.3, 17.9)	11.0 (9.2, 13.4)	< 0.001
NLR	5.6 (3.9, 8.8)	4.0 (3.3, 5.9)	< 0.001	5.3 (3.3, 7.9)	3.5 (2.7, 4.8)	< 0.001
$CD4^+$ /$CD8^+$ T cell ratio	1.1 (0.7, 1.3)	1.2 (1.0, 1.6)	0.063	1.1 (0.7, 1.6)	1.3 (1.0, 1.8)	0.037
ESR, mm/H	23.0 (16.0, 33.0)	20.0 (13.0, 27.0)	0.182	20.0 (15.0, 26.0)	16.0 (13.0, 21.0)	0.167
CRP, mg/L	16.3 (14.8, 22.5)	11.4 (8.1, 14.3)	< 0.001	15.1 (12.5, 22.7)	9.3 (4.5, 16.7)	< 0.001
PCT, ng/mL	0.5 (0.3, 1.6)	0.4 (0.2, 0.9)	0.032	0.5 (0.5, 1.3)	0.4 (0.2, 0.9)	0.076
IL-6, pg/mL	22.8 (18.1, 36.7)	17.9 (11.2, 30.5)	0.002	21.7 (17.0, 34.1)	15.5 (9.9, 25.5)	< 0.001
ALT, U/L	24.0 (20.0, 41.0)	24.0 (19.0, 32.0)	0.416	28.0 (24.0, 41.0)	24.0 (20.0. 37.0)	0.461
AST, U/L	28.0 (20.0, 38.0)	26.0 (19.0, 34.0)	0.337	30.0 (24.0, 38.0)	27.0 (20.0, 33.0)	0.215
LDH, U/L	402.7 (369.1, 577.2)	395.8 (346.3, 552.1)	0.146	401.1 (365.5, 521.0)	379.4 (347.5, 491.3)	0.387
Cr, umol/L	34.5 (29.3, 41.2)	30.4 (25.7, 36.9)	0.484	34.1(26.2, 39.4)	28.5 (21.6, 35.3)	0.109
Urea, mmol/L	3.1 (2.6, 4.8)	3.0 (2.0, 4.4)	0.391	3.5 (3.0, 6.9)	3.0 (2.0, 4.4)	0.175
CK-MB, U/L	54.7 (44.1, 69.6)	50.2 (40.5, 58.3)	0.307	51.0 (46.2, 57.8)	45.0 (37.1, 52.3)	0.692
Co-infection, n (%)	110 (46.0)	329 (38.1)	0.027	97 (39.8)	421 (34.9)	0.147

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; Cr, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; IQR, interquartile ranges; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin

Table 7 Outcome measures of patients in the respective severe and non-severe subgroups

Characteristics	Post-COVID-19 group		*P* value	Pre-COVID-19 group		*P* value
	Severe (*n* = 239)	Non-severe (*n* = 863)		Severe (*n* = 244)	Non-severe (*n* = 1207)	
Mechanical ventilation, n (%)	86 (36.0)	0	< 0.001	70 (28.7)	0	< 0.001
ICU admission, n (%)	101 (42.3)	0	< 0.001	109 (44.7)	0	< 0.001
LOS, days, median (IQR)	7.0 (6.0, 9.0)	6.0 (4.0, 7.0)	< 0.001	6.0 (5.0, 8.0)	5.0 (4.0, 7.0)	0.002

ICU, intensive care unit; LOS, length of hospital stay

more frequently during January- April and October-December in both 2018 and 2019. Whereas the post-COVID-19 group showed a pronounced off-season RSV endemic from April to September 2023, suggesting a significant seasonal shift in RSV prevalence during the post-COVID-19 era compared to the pre-COVID-19 era. Similar phenomena were also observed in multiple countries and regions, such as Japan and Italy [18, 19]. In addition, it should be noted, as we mentioned earlier, that RSV activity was barely recorded worldwide during the COVID-19 pandemic due to the strict implementation of COVID-19-related NPIs. Therefore, it may be difficult to determine the actual epidemiological and clinical features of RSV during the pandemic period. This is also the main reason why this study did not collect RSV data from the pandemic period for comparison and analysis.

There was an increase in age of patients in the post-COVID-19 group than those in the pre-COVID-19 group. It was well known that younger children, especially those under one year of age, were the main RSV-susceptible population in the past [20]. In our study, the pre-COVID-19 group showed a median age of 5.5 months, which was quite close to that reported in the previous literature [21, 22]. However, a significantly older median age (15.1 months) was found in the post-COVID −19 group. Similarly, Australia, one of the earliest

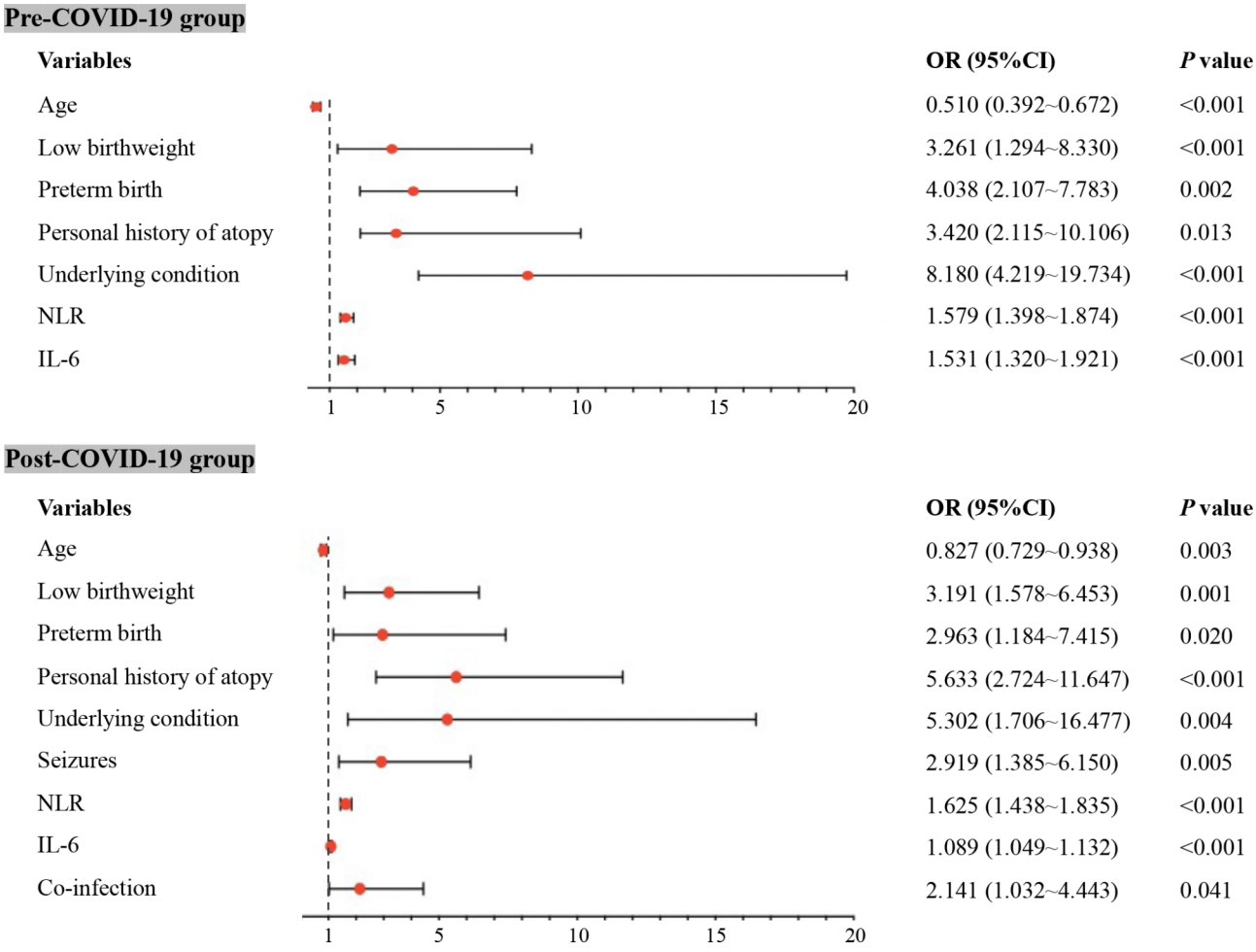

Fig. 3 The independent risk factors of RSV-related SLRTI in the pre- and post-COVID-19 groups. CI, confidence interval; NLR neutrophil-lymphocyte ratio; OR, odd ratio; RSV, respiratory syncytial virus; SLRTI, severe lower respiratory tract infection

countries suffering from the out-of-season RSV outbreak after easing of COVID-19 containment, reported that RSV patients during the post-COVID-19 period had a median age of 16.4 months, which was more than twice that observed before the emergence of COVID-19 pandemic (8.1 months) [12]. Jiang et al. [23] recently demonstrated the immunity debt due to the absent seasonal RSV circulation mainly caused by NPIs. The levels of RSV-specific antibody among children were significantly declined during the COVID-19 pandemic compared to those in the pre-pandemic period, and the changes of antibody levels presented marked variability across different age groups, with a more prominent decrease identified in older children. This might partially explain the trend towards increasing age of children with RSV infection in the post-COVID-19 era.

Besides, more frequent clinical manifestations (fever, acute otitis media, seizures), elevated inflammatory indicators (NLR, CRP, IL-6), higher proportion of SLRTI, increased requirement of mechanical ventilation, and longer LOS were observed in the post-COVID-19 group compared to those in the pre-COVID-19 group, suggesting a greater clinical severity of RSV infection in the post-COVID-19 group. The discrepancy of clinical severity between the two groups was probably linked to two factors: immunity debt caused by NPIs and immune dysregulation associated with prior SARS-CoV-2 infection [24]. First, the absence of RSV seasonal exposure due to the implementation of NPIs during COVID-19 pandemic was confirmed to generate immunity debt [8, 23], which might exacerbate the clinical course of RSV infection. Second, previous studies revealed that compared with healthy individuals, patients who had overcome acute SARS-CoV-2 infection for over two months showed significant impairment of T, NKT, and NKT-like cells [25]. Meanwhile, the absence of naive T and B cells could still be found in some recovered patients at eight months after acute SARS-CoV-2 infection [26]. Altogether, these findings implied that immune dysregulation might persist for months following the recovery from

acute SARS-CoV-2 infection, potentially causing harmful effects on the immune system. Given the ultra-high prior infection rate of SARS-CoV-2 in China [27], potential immune dysregulation could be a non-negligible factor affecting RSV severity in the post-COVID-19 era. Of course, we also cannot ignore that the increased severity of symptoms observed in the post-COVID-19 group might also be attributed to an increased likelihood of encountering severe cases, given the intensified RSV circulation and its associated hospitalization burden worldwide. Consistent with this, in our study, the number of inpatients in the post-COVID-19 group (1102 cases) was indeed greater than that in any single year of the pre-COVID-19 group (658 cases in 2018 and 793 cases in 2019). Therefore, although the severity evaluation of RSV was performed based on multiple aspects (inflammatory indicators, proportion of severe case, requirement of mechanical ventilation, LOS) in this study, we must acknowledge the potential that the increase in hospitalized cases could have led to a higher likelihood of observing severe cases. In addition, it was recently proposed that conditions associated with the COVID-19 pandemic perhaps favored the emergence of more virulent or contagious RSV strains [24], but the current findings do not support this perspective [28, 29] and more reliable evidence is required.

In addition, one noteworthy phenomenon was that compared to the pre-COVID-19 group, the post-COVID-19 group showed a significantly increased incidence of seizures (11.9% vs. 4.9%), which might serve as the vital evidence suggesting the association between COVID-19 pandemic and the heightened clinical severity of RSV infection during the post-pandemic period. Combined with previous studies [27, 30–33], the reactivation of residual SARS-CoV-2 virus among the recovered individuals and/or the current co-infection with Omicron variant might partially account for the raised incidence of seizures in pediatric RSV infection. Furthermore, even before the COVID-19 pandemic, RSV infection itself could lead to fatal neurological damage in children [34], so attention to neurological complications is particularly needed in the clinical management of pediatric RSV infection during the post-COVID-19 period. Another significant clinical alteration of RSV infection in the post-COVID-19 era was the decreased proportion of wheezing (44.9% and 40.7% in pre- and post-COVID-19 groups, respectively), which was one of the most common symptoms of children with RSV infection in the past. This change implied that clinicians also should pay sufficient attention to RSV patients without wheezing during the post-COVID-19 era, in order to avoid missed diagnosis and misdiagnosis.

Moreover, in this study, the post-COVID-19 group showed a higher proportion of co-infections (39.8% vs. 35.7%), with more frequent multiple infections (triple infection: 22.3% vs. 15.4%; quadruple infection: 9.6% vs. 5.0%), compared to the pre-COVID-19 group. This phenomenon might also be relevant to the NPIs-induced immunity debt, which affected not only RSV but also other pathogens. Variable degrees of resurgences in multiple pathogens, such as influenza viruses and *M. pneumoniae*, have been reported after the easing of NPIs [8, 35]. This perhaps represented a potential cause underlying the increased co-infections, especially multiple infections, during the post-COVID-19 era. Simultaneously, increased co-infection might be one of reasons why the RSV infection in the post-COVID-19 group displayed a greater clinical severity than the traditional seasonal RSV infection, because numerous studies have shown that mixed infections tended to be closely linked to more severe clinical outcomes [36]. Furthermore, significant differences in the pathogen spectrum of co-infections were observed between the two groups. In the post-COVID-19 group, the top three combinations of co-infections were RSV+IAV, RSV+*M. pneumoniae*, and RSV+HRV, while they were RSV+HRV, RSV+HMPV, and RSV+HPIV in the pre-COVID-19 group. Particularly, it is important to mention that incidences of RSV+IAV and RSV+*M. pneumoniae* in the post-COVID-19 group were significantly higher than those in the pre-COVID-19 group. Haney et al. [37]. have confirmed that the co-infection of RSV and IAV forms hybrid virus particles (HVPs), which can utilize RSV fusion glycoprotein to escape antiviral neutralizing antibodies, thus enhancing viral infection and transmission among cells. This interaction between RSV and IVA might affect virus pathogenesis by expanding virus tropism and enabling immune escape. This experimental finding may well explain the clinical observation that co-infection of RSV/IVA is associated with more severe outcomes [38, 39]. A similar trend was reported in individuals concurrently infected with RSV and *M. pneumoniae*, where the clinical severity was significantly higher in those with co-infection compared to those with single RSV infection [40]. Therefore, the changes in pathogen spectrum of mixed infections might also be one of the potential factors causing the variation in clinical characteristics and severity of RSV infection between pre- and post-COVID-19 groups.

To better facilitate the understanding and early recognition of RSV-associated SLRTI, we identified and further compared the independent risk factors of SLRTI between the pre- and post-COVID-19 groups. The result showed that age, low birthweight, preterm birth, personal history of atopy, underlying condition, NLR, and IL-6 were independently associated with occurrence of RSV-associated SLRTI in both pre- and post-COVID-19 groups. This was not unexpected, because these factors have been widely reported and recognized as the effective

predictors for severe RSV infection in previous research [21, 41, 42]. However, an interesting finding in our study was that in addition to the seven shared risk factors, seizures and co-infection were identified as the risk factors of SLRTI only in the post-COVID-19 group. This again suggested that more frequent seizures and co-infection were likely to be significant characteristics of RSV infection in the post-COVID-19 era and played important roles in the progression of RSV infection, reflecting the potential impact of COVID-19 pandemic on RSV infection. Therefore, strengthening the evaluation of these above indicators, especially seizures and co-infections, are essential for the early recognition of RSV-associated SLRTI in the post-COVID-19 era.

The present study has several limitations that should be considered. First, there were inherent biases due to the retrospective nature of study. Second, only inpatients were included in this study. To better explore epidemic dynamics of RSV, outpatients should be enrolled in future research. Another limitation is that only one year of post-pandemic RSV data was collected and analyzed, so it might not be able to fully reflect the dynamic changes of RSV during this period. In addition, the present study did not classify underlying condition in detail, which resulted in the failure to fully explain the influence of different comorbidities on the occurrence of RSV-associated SLRTI, despite identifying underlying condition as an independent risk factor. Finally, we did not analyze the circulating RSV strains at the genomic level to assess possible discrepancy between the pre- and post-COVID-19 periods.

Conclusions

This multicenter retrospective study indicated an out-of-season RSV endemic in Yunnan, China, during the post-COVID-19 era, with a peak period of pediatric RSV hospitalization from April to September 2023. Children hospitalized for RSV infection in the post-pandemic era showed a trend towards older age, different clinical features, and increased severity. Meanwhile, in addition to seven shared risk factors (age, low birthweight, preterm birth, personal history of atopy, underlying condition, NLR, IL-6) for RSV-associated SLRTI in both pre- and post-COVID-19 groups, seizures and co-infection were independently associated with SLRTI among patients only in the post-COVID-19 group. It is essential for clinicians to be aware of these changes and differences between the two periods, in order to optimize the clinical management of such patients and reduce the occurrence of RSV-related SLRTI and deaths.

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
CK	MB-Creatine kinase-MB
Cr	Creatinine
CRP	C-reactive protein
EBF	Exclusively breastfeeding
ESR	Erythrocyte sedimentation rate
HAdV	Human adenovirus
HMPV	Human metapneumovirus
HPIV	Human parainfluenza virus
HRV	Human rhinovirus
HVPs	Hybrid virus particles
IAV	Influenza A virus
IBV	Influenza B virus
ICU	Intensive care unit
IL	6-Interleukin 6
IQR	Interquartile range
LDH	Lactate dehydrogenase
LOS	Length of hospital stay
M. pneumoniae	Mycoplasma pneumoniae
NLR	Neutrophil-to-lymphocyte ratio
NPIs	Non-pharmaceutical interventions
PCT	Procalcitonin
RSV	Respiratory syncytial virus
SLRTI	Severe lower respiratory tract infection

Acknowledgements

Not applicable.

Author contributions

L.H.F. contributed to conceptualization, formal analysis, funding acquisition, and writing–original draft. W.Y.Y., Z.X.Z., and L.H.Y. were involved in methodology, formal analysis, and supervision. X.M., L.R., L.C.Y., L.W., F.Q.L., G.Y.J., and H.R.W. performed data extraction and visualization. F.H.M. contributed to conceptualization, methodology, project administration, funding acquisition, supervision, writing–review and editing. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (grant numbers: 81960021 and 82360025) and the Yunnan Provincial Department of Education Science Research Fund Project (grant number: 2023Y0790).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committees of Kunming Children's Hospital Affiliated to Kunming Medical University (the lead institution of this study) (2023-05-012-K01), who also waived the informed consent due to the retrospective design of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pulmonary and Critical Care Medicine, Yunnan Key Laboratory of Children's Major Disease Research, Yunnan Medical Center for Pediatric Diseases, Kunming Children's Hospital, Kunming Medical University, No. 28, Shulin Street, Xishan District, Kunming 650034, China
[2]Department of Pediatrics, The People's Hospital of Dali, The Third Affiliated Hospital of Dali University, Dali 671000, China
[3]Department of Pediatrics, The People's Hospital of Lincang, Lincang 677000, China
[4]Department of Pediatrics, The First People's Hospital of Zhaotong, Zhaotong Hospital, Affiliated to Kunming Medical University, Zhaotong 657000, China

[5]Department of Pediatrics, The People's Hospital of Honghe, Mengzi 651400, China
[6]Department of Pediatrics, The People's Hospital of Wenshan Zhuang & Miao Autonomous Prefecture, Wenshan 663000, China
[7]Department of Pediatrics, The People's Hospital of Baoshan, Baoshan 678000, China
[8]Department of Pediatrics, The People's Hospital of Guandu District, The Fifth People's Hospital of Kunming, Kunming 650200, China

Received: 13 March 2024 / Accepted: 21 August 2024
Published online: 19 September 2024

References

1. O'Brien KL, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Higdon MM, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019;394(10200):757–79.
2. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399(10340):2047–64.
3. Cevigney R, Leary C, Gonik B. Adjustable algorithmic tool for assessing the effectiveness of maternal respiratory syncytial virus (RSV) vaccination on infant mortality in developing countries. Infect Dis Obstet Gynecol. 2021, 2021:5536633.
4. Laudanno SL, Sánchez Yanotti CI, Polack FP. RSV lower respiratory tract illness in infants of low- and middle-income countries. Acta Med Acad. 2020;49(2):191–7.
5. Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health. 2019;7(8):e1031–45.
6. Oh KB, Doherty TM, Vetter V, Bonanni P. Lifting non-pharmaceutical interventions following the COVID-19 pandemic - the quiet before the storm? Expert Rev Vaccines. 2022;21(11):1541–53.
7. Treggiari D, Pomari C, Zavarise G, Piubelli C, Formenti F, Perandin F. Characteristics of respiratory syncytial virus infections in children in the post-COVID Seasons: A Northern Italy hospital experience. Viruses. 2024;16(1):126.
8. Cohen R, Pettoello-Mantovani M, Somekh E, Levy C. European pediatric societies call for an implementation of regular vaccination programs to contrast the immunity debt associated to coronavirus disease-2019 pandemic in children. J Pediatr. 2022;242:260–e261263.
9. Piedra PA, Jewell AM, Cron SG, Atmar RL, Glezen WP. Correlates of immunity to respiratory syncytial virus (RSV) associated-hospitalization: establishment of minimum protective threshold levels of serum neutralizing antibodies. Vaccine. 2003;21(24):3479–82.
10. Steff AM, Monroe J, Friedrich K, Chandramouli S, Nguyen TL, Tian S, et al. Pre-fusion RSV F strongly boosts pre-fusion specific neutralizing responses in cattle pre-exposed to bovine RSV. Nat Commun. 2017;8(1):1085.
11. Zhu L, Luo T, Yuan Y, Yang S, Niu C, Gong T, et al. Epidemiological characteristics of respiratory viruses in hospitalized children during the COVID-19 pandemic in southwestern China. Front Cell Infect Microbiol. 2023;13:1142199.
12. Foley DA, Phuong LK, Peplinski J, Lim SM, Lee WH, Farhat A, et al. Examining the interseasonal resurgence of respiratory syncytial virus in Western Australia. Arch Dis Child. 2022;107(3):e7.
13. Hatter L, Eathorne A, Hills T, Bruce P, Beasley R. Respiratory syncytial virus: paying the immunity debt with interest. Lancet Child Adolesc Health. 2021;5(12):e44–5.
14. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N. Resurgence of respiratory syncytial virus infections during COVID-19 pandemic, Tokyo, Japan. Emerg Infect Dis. 2021;27(11):2969–70.
15. Perk Y, Özdil M. Respiratory syncytial virüs infections in neonates and infants. Turk Pediatri Ars. 2018;53(2):63–70.
16. Rodrigues CMC, Groves H. Community-Acquired Pneumonia in children: the challenges of microbiological diagnosis. J Clin Microbiol. 2018;56(3):e01318–17.
17. Brent B, Obonyo N, Akech S, Shebbe M, Mpoya A, Mturi N, et al. Assessment of myocardial function in Kenyan children with severe, acute malnutrition: the cardiac physiology in malnutrition (CAPMAL) study. JAMA Netw Open. 2019;2(3):e191054.
18. McNab S, Ha Do LA, Clifford V, Crawford NW, Daley A, Mulholland K, et al. Changing epidemiology of respiratory syncytial virus in Australia-delayed re-emergence in Victoria compared to Western Australia/New South Wales (WA/NSW) after prolonged lock-down for coronavirus disease 2019 (COVID-19). Clin Infect Dis. 2021;73(12):2365–6.
19. Ozeki S, Kawada JI, Yamashita D, Yasufuku C, Akano T, Kato M, et al. Impact of the coronavirus disease 2019 pandemic on the clinical features of pediatric respiratory syncytial virus infection in Japan. Open Forum Infect Dis. 2022;9(11):ofac562.
20. Faraguna MC, Lepri I, Clavenna A, Bonati M, Vimercati C, Sala D, et al. The bronchiolitis epidemic in 2021–2022 during the SARS-CoV-2 pandemic: experience of a third level centre in Northern Italy. Ital J Pediatr. 2023;49(1):26.
21. Anderson J, Oeum M, Verkolf E, Licciardi PV, Mulholland K, Nguyen C, et al. Factors associated with severe respiratory syncytial virus disease in hospitalised children: a retrospective analysis. Arch Dis Child. 2022;107(4):359–64.
22. Hassan MZ, Islam MA, Haider S, Shirin T, Chowdhury F. Respiratory syncytial virus-associated deaths among children under five before and during the COVID-19 pandemic in Bangladesh. Viruses. 2024;16(1):111.
23. Jiang W, Xu L, Wang Y, Hao C. Exploring immunity debt: dynamic alterations in RSV antibody levels in children under 5 years during the COVID-19 pandemic. J Infect. 2024;88(1):53–6.
24. Abu-Raya B, Viñeta Paramo M, Reicherz F, Lavoie P. Why has the epidemiology of RSV changed during the COVID-19 pandemic? EClinicalMedicine. 2023;61:102089.
25. Liu J, Yang X, Wang H, Li Z, Deng H, Liu J, et al. Analysis of the long-term impact on cellular immunity in COVID-19-Recovered individuals reveals a profound NKT cell impairment. mBio. 2021;12(2):e00085–21.
26. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol. 2022;23(2):210–6.
27. Fu D, He G, Li H, Tan H, Ji X, Lin Z, et al. Effectiveness of COVID-19 vaccination against SARS-CoV-2 Omicron variant infection and symptoms - China, December 2022-February 2023. China CDC Wkly. 2023;5(17):369–73.
28. Goya S, Sereewit J, Pfalmer D, Nguyen TV, Bakhash S, Sobolik EB, et al. Genomic characterization of respiratory syncytial virus during 2022-23 outbreak, Washington, USA. Emerg Infect Dis. 2023;29(4):865–8.
29. Adams G, Moreno GK, Petros BA, Uddin R, Levine Z, Kotzen B, et al. Viral lineages in the 2022 RSV surge in the United States. N Engl J Med. 2023;388(14):1335–7.
30. Liu HF, Lu R, Yang J, Xiang M, Ban D, Yang JW, et al. Evaluation of febrile seizures in children infected with SARS-CoV-2 Omicron variant in Yunnan, China: a multi-center, retrospective observational study. Front Pediatr. 2023;11:1223521.
31. Callaway E. COVID's future: mini-waves rather than seasonal surges. Nature. 2023;617(7960):229–30.
32. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21(3):133–46.
33. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, et al. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature. 2022;612(7941):758–63.
34. Xu L, Gao H, Zeng J, Liu J, Lu C, Guan X, et al. A fatal case associated with respiratory syncytial virus infection in a young child. BMC Infect Dis. 2018;18(1):217.
35. Leung C, Konya L, Su L. Postpandemic immunity debt of influenza in the USA and England: an interrupted time series study. Public Health. 2024;227:239–42.
36. Li Y, Pillai P, Miyake F, Nair H. The role of viral co-infections in the severity of acute respiratory infections among children infected with respiratory syncytial virus (RSV): a systematic review and meta-analysis. J Glob Health. 2020;10(1):010426.
37. Haney J, Vijayakrishnan S, Streetley J, Dee K, Goldfarb DM, Clarke M, et al. Coinfection by influenza a virus and respiratory syncytial virus produces hybrid virus particles. Nat Microbiol. 2022;7(11):1879–90.
38. Meskill SD, Revell PA, Chandramohan L, Cruz AT. Prevalence of co-infection between respiratory syncytial virus and influenza in children. Am J Emerg Med. 2017;35(3):495–8.
39. Zhang Y, Zhao J, Zou X, Fan Y, Xiong Z, Li B, et al. Severity of influenza virus and respiratory syncytial virus coinfections in hospitalized adult patients. J Clin Virol. 2020;133:104685.
40. Wu SH, Chen XQ, Kong X, Yin PL, Dong L, Liao PY, et al. Characteristics of respiratory syncytial virus-induced bronchiolitis co-infection with

Mycoplasma pneumoniae and add-on therapy with montelukast. World J Pediatr. 2016;12(1):88–95.
41. Kaler J, Hussain A, Patel K, Hernandez T, Ray S. Respiratory syncytial virus: a comprehensive review of transmission, pathophysiology, and manifestation. Cureus. 2023;15(3):e36342.
42. Shi T, Balsells E, Wastnedge E, Singleton R, Rasmussen ZA, Zar HJ, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. J Glob Health. 2015;5(2):020416.

Publisher's note