Journal of Microbiology, Immunology and Infection 57 (2024) 184—188

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Short Communication

High mortality of patients with severe pneumonia caused by respiratory syncytial virus, August 2021—June 2023, Taiwan

Chieh-Lung Chen [a], Yu-Chao Lin [a,b], How-Yang Tseng [a], Wei-Cheng Chen [a], Shinn-Jye Liang [a], Chih-Yen Tu [a,b], Po-Ren Hsueh [c,d,e,*]

[a] *Division of Pulmonary and Critical Care, Department of Internal Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan*
[b] *School of Medicine, China Medical University, Taichung, Taiwan*
[c] *Departments of Laboratory Medicine and Internal Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan*
[d] *PhD Program for Aging, School of Medicine, China Medical University, Taichung, Taiwan*
[e] *Department of Laboratory Medicine, School of Medicine, China Medical University, Taichung, Taiwan*

Received 14 November 2023; received in revised form 5 December 2023; accepted 13 December 2023
Available online 21 December 2023

KEYWORDS
Respiratory syncytial virus;
Older adults;
Pneumonia;
Bacterial co-infection;
Mortality

Abstract Among the 14 patients with respiratory syncytial virus pneumonia, the majority (n = 8, 57.1 %) were older than 65 years and had health care-associated pneumonia (57.1 %). Over 70 % (n = 10) of them exhibited bacterial co-infection, with a high proportion (64.3 %) requiring mechanical ventilation. The hospital mortality rate was 50 %.

Introduction

Infection caused by respiratory syncytial virus (RSV) presents a considerable challenge in terms of the paediatric disease burden and public health concerns.[1—4] However, frail, elderly individuals, along with those who are immunocompromised or have underlying cardiopulmonary diseases, are also at the highest risk of developing severe and

* Corresponding author. Departments of Laboratory Medicine and Internal Medicine, China Medical University Hospital, China Medical University, No. 2, Yude Road, North District, Taichung 40447, Taiwan.
E-mail address: hsporen@gmail.com (P.-R. Hsueh).

https://doi.org/10.1016/j.jmii.2023.12.005

life-threatening illnesses due to RSV.[5] The occurrence of outbreaks in hospitals and health care facilities has brought attention to the clinical consequences of RSV infection within the adult population.[6] In May 2023, the Food and Drug Administration approved the first two vaccines, RSVPreF3 (Arexvy, GSK) and RSVpreF (Abrysvo, Pfizer), for the prevention of RSV lower respiratory tract disease for use in adults aged ≥60 years.[7] However, there remains a paucity of research on RSV infections among hospitalized older adults with pneumonia, especially among patients aged 65 years or above.[8,9]

It has been reported that pneumonia can potentially develop in up to 50 % of those requiring hospitalization.[10] Nonetheless, the absence of routine RSV evaluation in adult pneumonia may contribute to an underestimation of the clinical impact of RSV in adults. The application of BioFire® FilmArray® Pneumonia Panel (FAPP) using multiplex PCR methods has expanded the potential for rapid detection of various pathogens, including RSV, in patients with pneumonia. The FAPP was introduced into practice at China Medical University Hospital (CMUH) on August 28th, 2021. The use of FAPP was indicated for hospitalized patients with severe pneumonia, defined as pneumonia with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation, or fulfilling any three minor criteria proposed in the Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines.[11]

The epidemiology of RSV infection has changed during the coronavirus disease 2019 (COVID-19) pandemic, but the factors and mechanisms driving these changes in epidemiology are not fully understood.[12] This study aimed to investigate the clinical outcomes of pneumonia caused by RSV in adult patients in Taiwan during the COVID-19 pandemic.

Case series

Between August 28th, 2021, and June 30th, 2023, 1,065 patients were suspected to have severe pneumonia and underwent testing with the FAPP. Results from all patients receiving FAPP tests were analysed (Supplementary Figure). After excluding repeated tests in two patients and two patients lacking definitive pneumonia on chest radiographs, 14 patients (1.3 %) with their respiratory samples (sputum [n = 6], endotracheal aspirate [n = 7], or bronchoalveolar lavage [n = 1]) tested positive for RSV. The distribution of RSV cases identified on a monthly basis obtained in this study and the RSV detection trend derived from the respiratory viral surveillance database of the Taiwan Centers for Disease Control (Taiwan CDC) during the same study period are illustrated in Fig. 1A. In Taiwan, a surge of RSV cases was observed between October 2021 and February 2022.

The detailed clinical information of the 14 patients with severe pneumonia is shown in Supplementary Table. Among the 14 patients, seven (50 %) were male, eight (57.1 %) were older than 65 years. Six (42.9 %) patients had community-acquired pneumonia, four (28.6 %) had healthcare-associated pneumonia, and four (28.6 %) had hospital-acquired/ventilator-associated pneumonia (Table 1 and Fig. 1B). Four patients developed nosocomial RSV pneumonia, as defined by a positive laboratory-confirmed RSV test in conjunction with a ≥48-h time frame between hospital admission and the onset of respiratory symptoms. The levels of inflammatory markers, including C-reactive protein, procalcitonin, and monocyte distribution width, were not obviously elevated. Four (28.6 %) of the 14 patients tested positive for FAPP results only for RSV, while two tested positive for other viruses (human rhinovirus/enterovirus and/or parainfluenza virus) as well as bacteria. Notably, over 70 % (n = 10) of the 14 patients exhibited bacterial co-infection, with a high proportion (64.3 %) requiring mechanical ventilation. More than one-third (n = 5) of patients had acute respiratory distress syndrome (ARDS), but septic shock (n = 2, 14.3 %) was uncommon. In addition to the other viral pathogens concomitantly detected by the FAPP, the most common bacteria detected were *Pseudomonas aeruginosa* (n = 5), followed by *Acinetobacter calcoaceticus-baumannii* complex (n = 3), *Staphylococcus aureus* (n = 2), *Klebsiella pneumoniae* group (n = 2), *Enterobacter cloacae* complex (n = 2), *Serratia marcescens* (n = 1), and *Streptococcus pneumoniae* (n = 1). Furthermore, several antibiotic resistance-related genes (*mec*A and genes encoding CTX-M and *K. pneumoniae* carbapenemase) were also detected. Overall, the hospital mortality rate was 50 %, and the median hospital length of stay was 26 days (interquartile range 16.5—36.5 days). Kaplan—Meier curves demonstrated that bacterial co-infection was associated with early mortality (Fig. 1C).

Discussion

In this study, we reported a case series of 14 patients with severe RSV pneumonia who were tested positive with FAPP during the COVID-19 pandemic. Although a substantial number of patients required mechanical ventilation and treatment in the intensive care unit (ICU), we observed only slight increases in serum inflammatory markers. This observation is consistent with the results of a cohort study conducted in Korea.[10] Together with the relatively low occurrence of septic shock, we can infer that RSV predominantly triggers severe pulmonary inflammation rather than a systemic inflammatory response, thereby acting as the primary driver of disease progression. There were four patients who acquired severe nosocomial RSV pneumonia, and one (25 %) of them died. However, an investigation into a possible nosocomial outbreak was not conducted, despite these patients contracting RSV infections at different times over several months. Aichinger et al. reported 56 nosocomial RSV infection cases identified between November 2011 and January 2012.[13] Of these cases, 36 were laboratory-confirmed and outbreak-related. Among these cases, 23 (64 %) presented with pneumonia, and 11 (31 %) had died while hospitalized.[13]

Lee et al. documented a 30-day mortality rate of 15 % among patients with RSV-associated pneumonia.[14] In a separate study, Jeannnoël et al. reported a hospital mortality rate of 25.9 %.[8] In our patient cohort, the hospital mortality rate was 50 %, representing a considerable increase in comparison to the results of the previous studies.[5,14,15] Notably, our patients exhibited a considerable

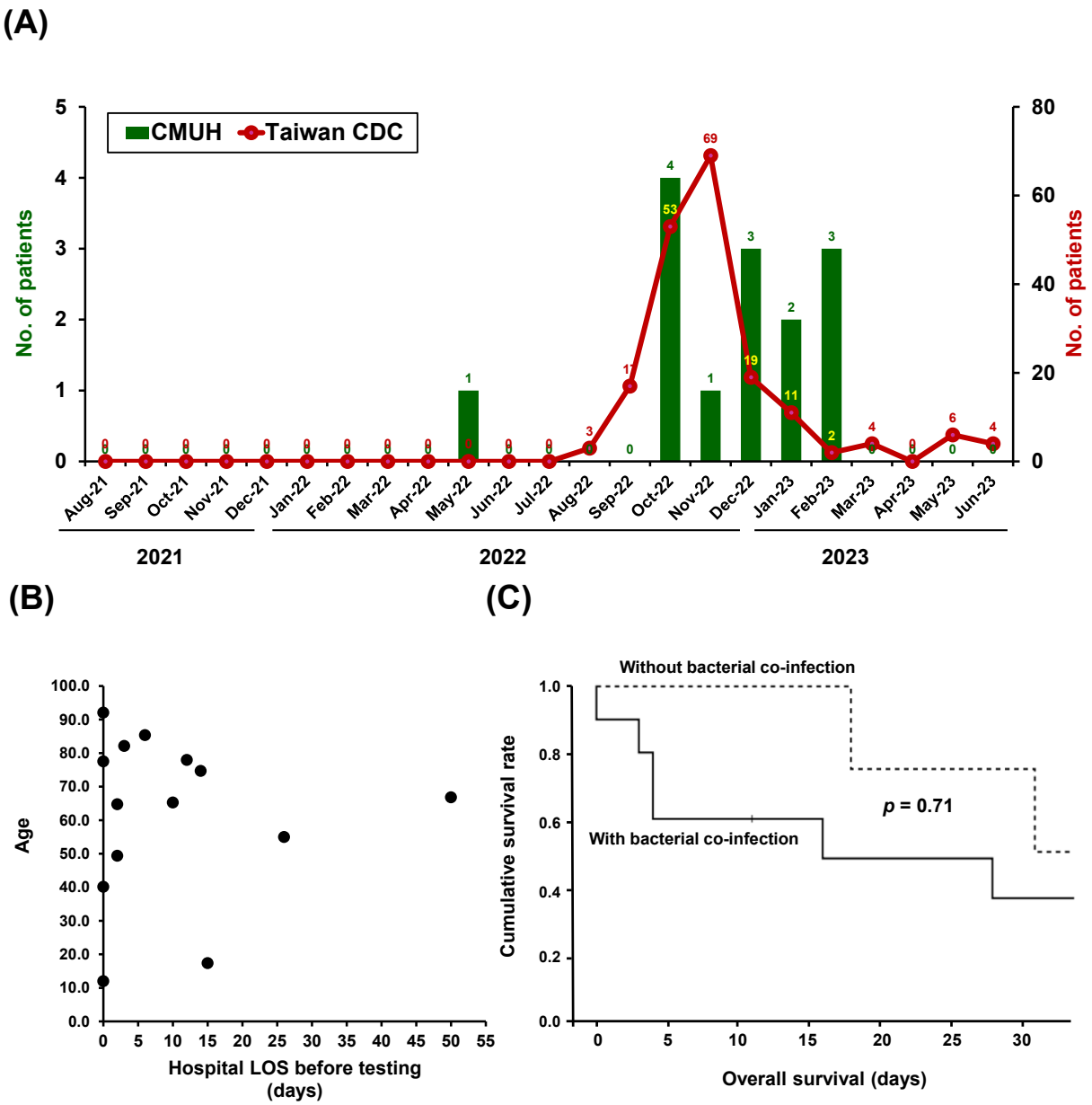

Figure 1. (A) Monthly distribution of respiratory syncytial virus (RSV) detected throughout the study period. Green bars indicate the case numbers in this study. The red line indicates the trend of RSV infection surveillance by the Taiwan Centers for Disease Control (Taiwan CDC). This figure was modified according to the database from the Taiwan CDC website (https://nidss.cdc.gov.tw/). (B) Age distribution and timing of FilmArray® Pneumonia Panel testing among patients with detected RSV infections. (C) The impact of bacterial coinfection on 30-day mortality among hospitalized patients with pneumonia who tested positive for RSV.

prevalence of comorbidities, which have been well recognized as a poor prognostic factor for RSV infection, coupled with a high frequency of respiratory failure necessitating mechanical ventilator support, along with a substantial incidence of ARDS. Furthermore, it is essential to emphasize that our RSV cases were identified using the FAPP. Currently, this diagnostic method is primarily employed for patients with more severe conditions, leading to an inevitable selection bias and subsequently higher observed mortality rates.

S. pneumoniae, *S. aureus*, and *Haemophilus influenzae* have been found in up to 30 % of patients with RSV infection, although the role of bacterial coinfection with RSV has not been well studied.[5] Recent studies have indicated an increased occurrence of *P. aeruginosa* and Enterobacterales coinfection among patients with RSV infection.[8,13,14] In our cohort, a substantial subset (5/14, 35.7 %) showed *P. aeruginosa* isolates and the identification of antibiotic resistance genes (4/14, 25.6 %). These results should be interpreted cautiously due to the limited sample size. However, the development of antibiotic-resistant bacterial coinfection following RSV infection remains an aspect that needs continuous monitoring in the future.

Table 1 Baseline and demographic information of the 14 patients with pneumonia caused by respiratory syncytial virus (RSV).

Characteristic	No. (% or range) of patients (n = 14)
Age, median (IQR)	66.1 (47.1—79)
Age ≥65 years (%)	8 (57.1 %)
Male/female (%)	7/7 (50 %/50 %)
BW, median (IQR)	65 (53.8—72.4)
BMI, median (IQR)	23.4 (21.0—25.0)
Charlson Comorbidity Index, median (IQR)	6 (2.8—7.5)
Comorbidities	
Chronic lung diseases[a]	3 (21.4 %)
Cardiovascular disease	4 (28.6 %)
Diabetes	7 (50 %)
ESRD	4 (28.6 %)
Liver cirrhosis	2 (14.3 %)
Solid tumour	4 (28.6 %)
Haematologic malignancies	1 (7.1 %)
Pneumonia type	
CAP	6 (42.8 %)
HCAP	4 (28.6 %)
HAP/VAP	4 (28.6 %)
Respiratory sample tested by the FAPP	
Sputum	6 (42.9 %)
Endotracheal aspirate	7 (50 %)
Bronchoalveolar lavage	1 (7.1 %)
Infection pattern	
Single RSV infection	4 (28.6 %)
Bacterial coinfection	8 (57.1 %)
Multiple viral and bacterial coinfection	2 (14.3 %)
Inflammatory markers	
CRP (mg/dL)	5.4 (1.0—14.9)
PCT (ng/mL)	1.6 (0.4—19.5)
MDW (U)	25.4 (21.4—35.0)
SOFA score	8.5 (5—14)
Mechanical ventilation	9 (64.3 %)
ARDS	5 (35.7 %)
Septic shock	2 (14.3 %)
Hospital LOS	26 (16.5—36.5)
Hospital mortality	7 (50 %)

[a] Includes old pulmonary tuberculosis, chronic obstructive pulmonary disease, asthma, and bronchiectasis.
ARDS, acute respiratory distress syndrome; BMI, body mass index; BW, body weight; CAP, community-acquired pneumonia; CRP, C-reactive protein; FAPP, FilmArray® Pneumonia Panel; HCAP, healthcare-associated pneumonia; HAP, hospital-acquired pneumonia; IQR, interquartile range; LOS, length of stay; MDW, monocyte distribution width; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment; VAP, ventilator-associated pneumonia.

While the burden of bacterial coinfection and its impact on outcomes has been extensively described among patients with viral respiratory infections, only a limited number of studies have investigated this aspect among individuals with RSV-related acute respiratory infection. Jeannnoël et al. reported that bacterial coinfection resulted in increased ICU hospitalization and longer lengths of hospital stay.[8] Godefroy et al. demonstrated that among elderly patients (>65 years old) with RSV-related acute respiratory infection, bacterial coinfection was associated with higher mortality.[15] In our study, out of the 10 patients who experienced bacterial coinfection, an early and significant hospital mortality rate of 60 % was observed.

While RSV exhibits two serotypes, serotypes A and B, syndromic PCR and viral culture cannot distinguish between them. Nonetheless, there is controversy regarding whether serotype variability impacts the clinical course and outcomes of RSV infection among children and infants.[16,17] A previous study did not reveal prognostic differences between the two serotypes in adults.[9]

The main limitation of this study is the possibility of selection bias in the study population, wherein the severity of pneumonia prompted the use of the FAPP for pathogen identification, subsequently leading to RSV detection. This situation could potentially result in an overestimation of severe RSV cases.

In conclusion, the potential underestimation of the disease burden related to RSV and the impact of bacterial co-infection on prognosis should be noted, as these co-infection could elevate the risk of mortality. Given the increasing availability of diagnostic tools, clinicians should diligently and systematically test for both RSV and bacterial co-infection in hospitalized adult patients with acute respiratory infections, especially in populations susceptible to life-threatening infections, such as frail and elderly individuals and those with comorbidities. Moreover, greater attention should be directed towards the incidence of co-infection involving multidrug-resistant bacteria.

Author contributions

All the authors contributed significantly to this manuscript. Chieh-Lung Chen and Yu-Chao Lin performed data entry and analysis and wrote the first draft, and How-Yang Tseng, Wei-Cheng Chen, Shinn-Jye Liang, Chih-Yen Tu, and Po-Ren Hsueh reviewed the manuscript. All the authors reviewed and approved the final submission.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The institutional review board of China Medical University Hospital waived the requirement for written informed consent because the study involved minimal risk to the patients (IRB number: CMUH112-REC3-041).

Declarations of competing interest

The authors have no competing interests to declare.

References

1. Atamna A, Babich T, Froimovici D, Yahav D, Sorek N, Ben-Zvi H, et al. Morbidity and mortality of respiratory syncytial virus infection in hospitalized adults: comparison with seasonal influenza. *Int J Infect Dis* 2021;**103**:489—93.
2. Chang TH, Liu YC, Lin SR, Chiu PH, Chou CC, Chang LY, et al. Clinical characteristics of hospitalized children with community-acquired pneumonia and respiratory infections: using machine learning approaches to support pathogen prediction at admission. *J Microbiol Immunol Infect* 2023;**56**(4):772—81.
3. Lin TY, Chi H, Kuo CY, Tsai HP, Wang JR, Liu CC, et al. Outbreak of respiratory syncytial virus subtype ON1 among children during COVID-19 pandemic in Southern Taiwan. *J Microbiol Immunol Infect* 2022;**55**(6 Pt 2):1168—79.
4. Hsu HT, Huang FL, Ting PJ, Chang CC, Chen PY. The epidemiological features of pediatric viral respiratory infection during the COVID-19 pandemic in Taiwan. *J Microbiol Immunol Infect* 2022;**55**(6 Pt 1):1101—7.
5. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. *Clin Microbiol Rev* 2000;**13**:371—84.
6. Begley KM, Monto AS, Lamerato LE, Malani AN, Lauring AS, Talbot HK, et al. Prevalence and clinical outcomes of respiratory syncytial virus vs influenza in adults hospitalized with acute respiratory illness from a prospective multicenter study. *Clin Infect Dis* 2023;**76**(11):1980—8.
7. Melgar M, Britton A, Roper LE, Talbot HK, Long SS, Kotton CN, et al. Use of respiratory syncytial virus vaccines in older adults: recommendations of the Advisory Committee on Immunization Practices - United States, 2023. *MMWR Morb Mortal Wkly Rep* 2023;**72**(29):793—801.
8. Jeannoel M, Lina G, Rasigade JP, Lina B, Morfin F, Casalegno JS. Microorganisms associated with respiratory syncytial virus pneumonia in the adult population. *Eur J Clin Microbiol Infect Dis* 2019;**38**(1):157—60.
9. Kim T, Huh JW, Hong SB, Jung J, Kim MJ, Chong YP, et al. Epidemiology and characteristics of respiratory syncytial virus pneumonia in critically ill adults. *Open Forum Infect Dis* 2023;**10**(4):ofad131.
10. Park SY, Kim T, Jang YR, Kim MC, Chong YP, Lee SO, et al. Factors predicting life-threatening infections with respiratory syncytial virus in adult patients. *Inf Disp* 2017;**49**(5):333—40.
11. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;**44**(Suppl 2):S27—72. Suppl 2.
12. Abu-Raya B, Viñeta Paramo M, Reicherz F, Lavoie PM. Why has the epidemiology of RSV changed during the COVID-19 pandemic? *EClin Med* 2023;**61**:102089.
13. Aichinger E, Schnitzler P, Heeg K, Dederer W, Benz MA, Buda S, et al. Contributing and terminating factors of a large RSV outbreak in an adult hematology and transplant unit. *PLoS Curr* 2014;**6**. ecurrents.outbreaks.3bc85b2a508d205ecc4a5534ecb1f9be.
14. Lee N, Lui GC, Wong KT, Li TC, Tse EC, Chan JY, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. *Clin Infect Dis* 2013;**57**(8):1069—77.
15. Godefroy R, Giraud-Gatineau A, Jimeno MT, Edouard S, Meddeb L, Zandotti C, et al. Respiratory syncytial virus infection: its propensity for bacterial coinfection and related mortality in elderly adults. *Open Forum Infect Dis* 2020;**7**(12):ofaa546.
16. Vandini S, Biagi C, Lanari M. Respiratory syncytial virus: the influence of serotype and genotype variability on clinical course of infection. *Int J Mol Sci* 2017;**18**(8):1717.
17. Redlberger-Fritz M, Springer DN, Camp JV, Aberle JH. Respiratory syncytial virus surge in 2022 caused by lineages already present before the COVID-19 pandemic. *J Med Virol* 2023;**95**(6):e28830.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.12.005.