Infectious Disease Modelling 10 (2025) 989–1001

Contents lists available at ScienceDirect

Infectious Disease Modelling

journal homepage: www.keaipublishing.com/idm

Characteristics and risk factors for outcomes in patients with *Mycoplasma pneumoniae* mono- and coinfections: A multicenter surveillance study in Wuhan, China, 2023

Banghua Chen [a, 1], Jie Pan [b, 1], Ying Peng [a], Yuanyuan Zhang [a], Yunan Wan [a], Hongjie Wei [b], Kangguo Li [b], Wentao Song [b], Yunkang Zhao [b], Kang Fang [b], Huiming Ye [c], Jiali Cao [c], Jia Rui [b, 2, *], Zeyu Zhao [b, 2, **], Tianmu Chen [b, 2, ***]

[a] *Wuhan Center for Disease Control and Prevention, People's Republic of China*
[b] *State Key Laboratory of Vaccines for Infectious Diseases, Xiang An Biomedicine Laboratory, National Innovation Platform for Industry-Education Integration in Vaccine Research, School of Public Health, Xiamen University, Xiamen 361102, People's Republic of China*
[c] *Department of Laboratory Medicine, Fujian Key Clinical Specialty of Laboratory Medicine, Women and Children's Hospital, School of Medicine, Xiamen University, People's Republic of China*

ARTICLE INFO

Article history:
Received 19 February 2025
Received in revised form 17 April 2025
Accepted 24 April 2025
Available online 30 April 2025
Handling Editor: Dr Yiming Shao

Keywords:
Respiratory tract disease
Coinfection
Multifactorial analysis
Outcome

ABSTRACT

Objectives: *Mycoplasma pneumoniae* (MP) is a key cause of community-acquired pneumonia, and coinfections lead to varied patient outcomes. A comprehensive understanding of the outcome characteristics and associated etiologies of coinfections in MP patients is lacking.

Methods and results: We analyzed 121,357 MP cases from 522,292,680 visits in Wuhan, China, in 2023 (the final year of the COVID-19 pandemic). Children aged 1–10 years had the highest incidence, whereas those over 60 years had elevated hospitalization, severe infection, and fatality rates. Coinfection patterns differed by age, with bacterial-viral-*Chlamydia pneumoniae* (*C. pneumoniae*) / other pathogens prevalent in infants, bacterial-viral pathogens prevalent in preschoolers, and viral-viral pathogens prevalent in school-aged children. Bacterial coinfections were most common in MP-infected patients, especially those who were hospitalized. Coinfection, especially with *C. pneumoniae*, *Pseudomonas aeruginosa* (*P. aeruginosa*), *Haemophilus influenzae* (*H. influenzae*), and *Streptococcus pneumoniae* (*S. pneumoniae*), increased hospitalization rates. The most severe outcomes and deaths occurred in patients coinfected with *C. pneumoniae*-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza A-parainfluenza virus (PIV) or adenovirus-PIV. Logistic regression analysis demonstrated that male sex and adult age (particularly ≥40 years) were significantly associated with adverse outcomes in MP monoinfection. For coinfections, significantly higher hospitalization rates were reported among very young children (0–5 years) and adults aged ≥40 years, whereas adults presented an increased risk of severe disease. Coinfection outcomes were significantly associated with seasons of the year (winter, spring, and summer), specific age groups (3–5 years, 18–39 years, 40–50 years, and 60 years and over), gender (male), and longer onset-

* Corresponding author. School of Public Health, Xiamen University, Xiamen City, 361102, Fujian Province, People's Republic of China.
** Corresponding author. School of Public Health, Xiamen University, Xiamen City, 361102, Fujian Province, People's Republic of China.
*** Corresponding author. School of Public Health, Xiamen University, Xiamen City, 361102, Fujian Province, People's Republic of China.
E-mail addresses: ruijia5345@163.com (J. Rui), 381597586@qq.com (Z. Zhao), chentianmu@xmu.edu.cn, 13698665@qq.com (T. Chen).
Peer review under the responsibility of KeAi Communications Co., Ltd.
[1] These authors contributed equally to this study.
[2] These authors are joint senior authors and contributed equally to this work.

https://doi.org/10.1016/j.idm.2025.04.006

to-diagnosis periods. Middle-aged and elderly patients, coinfection, spring and summer, gender (male), and longer onset-to-diagnosis periods were significantly associated with increased hospitalization and serious illness risk. Coinfection, winter, older (adult) age, and gender (male) were significantly associated with an increased risk of death.

Conclusions: Compared with adults, children with MP have a greater morbidity risk, whereas middle-aged and older adults face greater risks of hospitalization, serious illness, and death. Coinfection with other pathogens heightens hospitalization and death risks. These insights are crucial for etiological screening, diagnosing multiple pathogens, and preventing and treating infections.

1. Introduction

Community-acquired pneumonia (CAP) is a significant global health issue with high morbidity and mortality. The disease burden of CAP is unevenly distributed due to geographical, seasonal, and demographic factors (Ferreira-Coimbra et al., 2020; Tsoumani et al., 2023). This variation is pronounced in China, where a vast area and large population lead to disparate morbidity and severity among different regions and populations (Sun et al., 2020). Mono- or polypathogen infections primarily cause the spatiotemporal heterogeneity of CAP observed in children (Tramper-Stranders, 2018). Among these pathogens, *Mycoplasma pneumoniae* (MP) is prevalent for CAP across all age groups (Mycoplasma pneumoniae carriage in children; Jain et al., 2015; Metlay et al., 2019; Meyer Sauteur & Beeton, 2023). MP is estimated to account for 10 %–30 % of CAP cases in China.

While MP monoinfection typically poses a low risk of severe disease and death, but coinfections with other pathogens significantly increase the risk of severe pneumonia (Chen, Lin, et al., 2024; Li et al., 2022). Approximately 1 %–2 % of severe CAP cases are caused by coinfections with other pathogens in MP-infected patients (Liu et al., 2023). Such coinfections exacerbate the inflammatory response in the lungs, thereby increasing the risk of complications. Furthermore, coinfections in MP-infected patients can increase the risk of severe disease by 0.5-fold (Li et al., 2024).

Over the past decade, there has been a paucity of large-scale epidemiological studies using representative samples to characterize the pattern of coinfections and their prevalence in MP-infected patients. Though some studies have explored the role of factors such as multipathogen infections and age in severe pneumonia, but few have investigated the combined effects of these factors on coinfection stages, including disease onset, hospitalization, disease severity, and death (Gao et al., 2020; Li et al., 2024). Since January 2024, there has been a marked rise in mono- or coinfections with pathogens such as MP, RSV, and pertussis in China, highlighting the need for in-depth analysis of coinfections and associated outcomes (National Overview of Statutory Communicable, 2024).

To address this research gap, we leveraged data from a big data research center established in Wuhan city, which compiled surveillance information from 52.23 million outpatient and emergency visits and 3.55 million hospitalizations in 2023. We analyzed these data, covering 163,634 MP patients from 194 hospitals, to determine the incidence, hospitalization, severe infection, and case fatality rates (CFRs) for MP infection and coinfection. We aimed to establish associations among age, season, and other factors and these indicators to inform policymakers on effective prevention and control strategies for patients with MP coinfection.

2. Methods

2.1. Data sources and case definitions

In 2023, the Wuhan Municipal Health Commission established an infectious disease surveillance and early warning system. This system collates electronic medical record (EMR), hospital information management system (HIS), laboratory information system (LIS), and picture archiving and communication system (PACS) data from 294 healthcare institutions in a uniform, standardized format. In 2023, the system included 52.23 million outpatient and emergency room visits and 3.55 million hospitalizations. From this pool, we extracted data, including demographic and case information, on patients diagnosed with MP infection for analysis.

The inclusion criteria were positive results from laboratory tests such as MP culture, IgM antibody assay (colloidal gold method, enzyme immunoassay, or granulocyte agglutination test), DNA assay, RNA assay, serologic test (agglutination method), and antibody titer test (titer ratio of 1:80 or more).

Patients with simple infections were defined as patients with laboratory-confirmed MP infection and either negative tests for other respiratory pathogens or no additional pathogen testing.

Patients with coinfection were defined as patients with laboratory-confirmed MP infection and concurrent detection of one or more additional respiratory pathogens.

We screened 163,634 MP infection cases reported by 194 healthcare organizations. Of these, 121,357 (74.2 %) were eligible for the study. The study excluded patients with onset dates other than 2023, patients with illogical values, patients with garbled value data, patients with missing data or patients without a laboratory-confirmed diagnosis. This filtering resulted in the exclusion of 42,277 ineligible patients. Among the 121,357 eligible patients, 107,368 patients had simple MP infection and 13,989 patients had coinfection with any other pathogen (11.5 %), including 12,189 patients with a single coinfection and 1800 patients with multiple coinfections (Fig. 1).

2.2. Procedures for pathogen detection

The dataset for this study included demographic details, diagnostic information, admission records, clinical manifestations, laboratory test results, and clinical outcomes. These were collected from medical records and entered into a standardized database by clinicians trained in data entry. Blood, urine, and sputum samples were tested for various pathogenic bacteria, including pertussis, rhinovirus (RhV), human bocavirus (HBoV), enterovirus (EV), *Klebsiella pneumoniae* (*K. pneumoniae*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Chlamydia pneumoniae* (*C. pneumoniae)*, parainfluenza virus (PIV), SARS-CoV-2, respiratory syncytial virus (RSV), influenza A, *Haemophilus influenzae* (*H. influenzae*), *Legionella pneumophila*, *Pseudomonas aeruginosa* (*P. aeruginosa*), adenovirus, and influenza B. All tests conducted for pertussis were performed in accordance with the standard operating procedures established by the Chinese Center for Disease Control and Prevention.

Viral pathogens were detected via RT–PCR, antigen detection, and antibody detection. Bacterial pathogens were detected through nucleic acid testing and culture methods, whereas *C. pneumoniae* was detected via IgM antibody testing. Importantly,

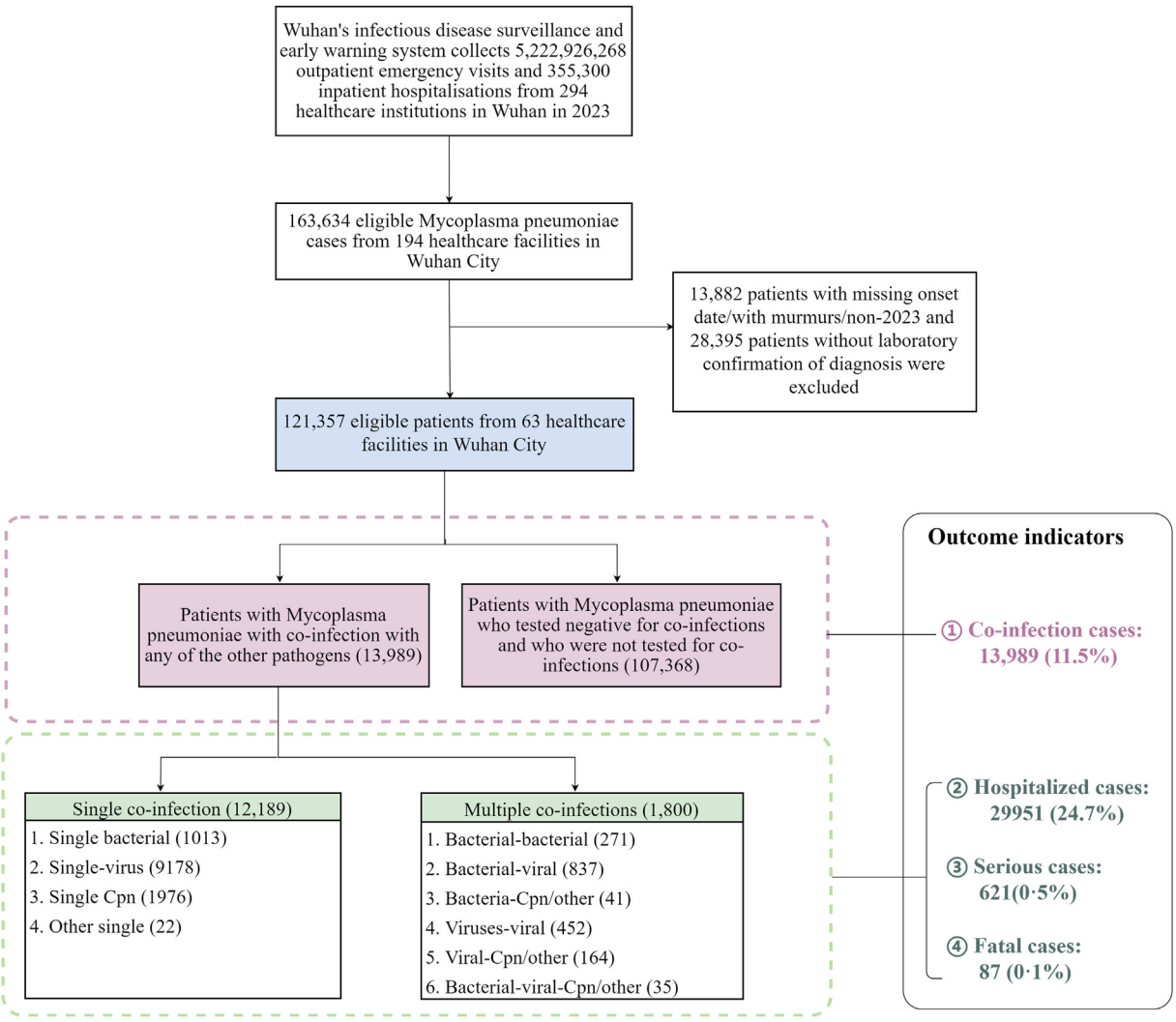

Fig. 1. Data handling process diagram.

there were no discrepancies in sample collection or testing strategies between patients with simple MP infection and those with MP coinfection. Each positive test result was reviewed by at least one infectious disease physician. Coinfection was defined as a positive result for the detection of more than one respiratory pathogen.

2.3. Outcomes

We evaluated the pattern of coinfections of MP with various pathogens, including viruses, bacteria and chlamydia. A multifactorial analysis of four outcome indicators, namely, the coinfection rate, hospitalization rate, severe infection rate and CFR, was performed.

2.4. Statistical analysis

We analyzed the data using descriptive statistics and compared groups via the chi-square test or Fisher's exact test. For interval estimates, we applied binomial and generalized additive models. We used multiple logistic regression models to assess variables associated with simple pulmonary branch infections and coinfections, including sex, age, season (categorized into spring, summer, autumn, and winter), and time from illness onset to consultation. Logistic regression was also used to explore the relationships between coinfection type, demographic factors, and outcomes (hospitalization, critical illness, death) in MP-infected patients. All variables were evaluated via multivariate analyses, with $p < 0.05$ indicating significance. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated using the maximum likelihood method.

R version 4.3.2 served as the platform for all the statistical analyses.

3. Results

3.1. Epidemiology and clinical characteristics

A total of 121,357 patients from 63 hospitals (Table S1) with MP infection were enrolled in this study from January 1, 2023 to December 31, 2023, of whom 13,989 (11.5 %) had coinfections, 29,951 (24.7 %) were hospitalized, 621 (0.5 %) had serious illness, and 87 (0.1 %) died of the disease. The patients included 60,591 males and 60,766 females with a median age of 7 years (interquartile spacing: 4–11 years). High rates of coinfection relative to no coinfection were detected in males (52.2 % vs. 49.6 %), adults aged 18–39 years (10.8 % vs. 8.4 %), middle-aged adults aged 40–59 years (3.1 % vs.2.9 %), elderly individuals aged more than 60 years (5.9 % vs. 3.3 %), spring (17.2 % vs. 11.8 %), winter (36.1 % vs. 24.8 %), hospitalization (45.5 % vs. 22 %), and death (0.3 % vs. 0.0 %). No coinfection was diagnosed in less than 1 day in 49.5 % of patients, which was much greater than the proportion of coinfected patients (37.5 %) (Table S2). The proportion of coinfection was greater than that of no coinfection in patients who presented with clinical symptoms of fever (59.8 % vs. 40.8 %), cough (65.1 % vs. 58.7 %), sore throat (11.3 % vs. 8.4 %), fatigue (6.9 % vs. 4 %), headache (7.2 % vs. 4.1 %), or nausea (29.5 % vs. 29 %). For all these results, $p < 0.001$ (Table S3).

In Wuhan city, during 2023, we analyzed data from 121,357 eligible patients who met our inclusion and exclusion criteria (as detailed in Fig. 1). The weekly reported counts for MP infection morbidity, hospitalization, and severity among these eligible patients fluctuated but overall tended to increase, peaking at the end of the year. Conversely, mortality counts showed a decreasing trend, with a peak at the start of the year. The highest number of morbidities 28,545) and hospitalizations (Mycoplasma pneumoniae carriage in children) were reported in the 6–17 age group during autumn, and elderly individuals accounted for the most severe cases (109). In winter, the highest CFR (49) was reported among older individuals. Patients with coinfections exhibited morbidity and hospitalization trends that mirrored those of the overall patient cohort, with a significant peak in morbidity documented in December. Notably, coinfected patients were underrepresented among critically ill patients throughout the year, with the exception of December. Importantly, during the early months of the year, coinfections were present in a substantial proportion of fatal outcomes (Fig. 2).

The distributions of the incidence rate, severe infection rate, hospitalization rate, and CFR differed significantly across age groups. The estimated incidence rate for the entire population was 0.9 % (95 % CI: 0.9 %–0.9 %), with notable differences between age groups. The prevalence of MP infection was highest among children aged 0–10 years (5.6 %, 95 % CI: 5.6–5.6 %) and decreased to less than 0.5 % in those aged 15 years and older. The hospitalization rate among MP-infected patients was estimated to be 24.7 % (95 % CI: 24.4 %–24.9 %), showing a decreasing trend with age and then increasing significantly after the age of 15 years. The severe infection rate among MP-infected patients was 0.5 % (95 % CI: 0.5 %–0.6 %). The severe infection rate was generally less than 1 % in children under 10 years of age but increased progressively with age. The estimated mortality rate for MP-infected patients was 0.1 % (95 % CI: 0.1 %–0.1 %), with deaths predominantly occurring in patients over 45 years of age. Patients $\geq$60 years of age had increased hospitalization rates (84.0 %, 95 % CI: 82.9 %–85.1 %), severe infection rates (6.7 %, 95 % CI: 66 %–7.5 %), and CFRs (1.7 %, 95 % CI: 1.4 %–2.2 %) (Fig. 3).

Analyses of 16 pathogens revealed that influenza A (34 %), *C. pneumoniae* (13.6 %), and adenovirus (8.4 %) were the most common coinfection pathogens among MP-infected patients. Hospitalized patients were most frequently coinfected with *H. influenzae* (14.4 %), RhV (14.1 %), or influenza A (13.8 %). Severely infected patients were most commonly coinfected with influenza A (36.5 %), other pathogens (20.6 %), or RhV (12.7 %) (Fig. S1).

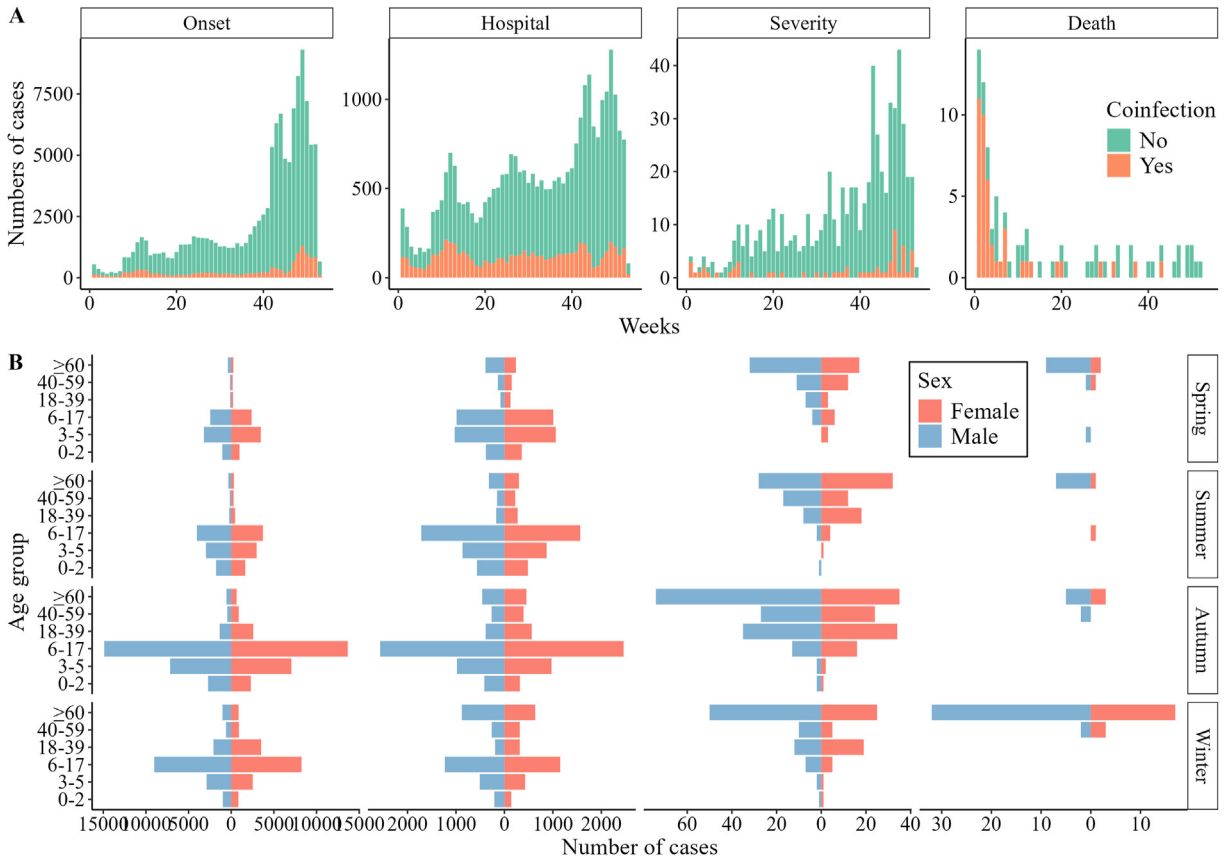

Fig. 2. Epidemiological characteristics of MP-infected patients with four outcomes (A) Epidemic trends for morbidity, hospitalization, severity, and the CFR associated with MP infection, both monoinfections and coinfections, during 2023. (B) Distribution of MP infection patients across sex, age, and season groups.

3.2. Characteristics of coinfections

Among the 121,357 MP-infected patients, males accounted for the highest proportion (62.9 %) of bacterial-viral-*C. pneumoniae*/other pathogen coinfections, whereas females predominantly had viral *C. pneumoniae*/other pathogen coinfections (53.7 %). Among the various age groups, the bacterial-viral-*C. pneumoniae*/other pathogen coinfections were most common in patients aged 0–2 years (42.9 %), bacterial–viral coinfections were most common in patients aged 3–5 years (48.7 %), and bacterial–bacteria coinfections were most common in patients aged 6–17 years (55.7 %). The proportions of MP-infected patients aged 18–39 years, 40–59 years, and older than 60 years were the highest for single viral (13.8 %), single other pathogen (9.1 %), and single *C. pneumoniae* coinfections (22.5 %), respectively. During the peak season, the greatest proportion of MP-infected patients without coinfections occurred in autumn (47.9 %), whereas a greater proportion of MP-infected patients with single viral coinfections occurred in winter (44.7 %). Approximately 50.5 % of patients with *C. pneumoniae* coinfections are diagnosed within one day. A total of 40.2 % of patients with single pathogen infections were diagnosed within the first day of illness, whereas only 14.2 % of patients with multipathogen infections were diagnosed within 1 day. A greater proportion of hospitalized MP infection patients had bacterial–viral coinfections (93.2 %), whereas coinfection with *C. pneumoniae* was more prevalent (1.9 %) among MP infection patients who died (Table S4).

MP-infected patients with coinfections presented the highest positive test rate for *H. influenzae* (24.7 %), followed by *S. pneumoniae* (21 %), *K. pneumoniae* (20.4 %), influenza A (13.8 %), and RhV (13.4 %). The primary coinfecting pathogens, predominantly bacteria, varied with age. Pertussis had the highest positivity rate (57.1 %) in infants and children aged 0–2 years, whereas *S. pneumoniae* was most common in preschoolers aged 3–5 years (33.3 %). The highest positivity rate for *S. pneumoniae* was detected in schoolchildren aged 6–17 years (29.6 %). Among young adults aged 18–39 years, influenza A accounted for the highest proportion (20.6 %). In the middle-aged population (40–59 years), *S. pneumoniae* was most prevalent (19.2 %). For the population aged 60 years and older, SARS-CoV-2 had the highest positivity rate (17.89 %) (Fig. 4A).

Among hospitalized MP-infected patients, the highest positivity rate was observed for *H. influenzae* (24.8 %), followed by *K. pneumoniae* (21 %) and *S. pneumoniae* (20.8 %). The positivity rate in hospitalized patients exhibited an age-specific trend similar to that in all patients (Fig. 4B).

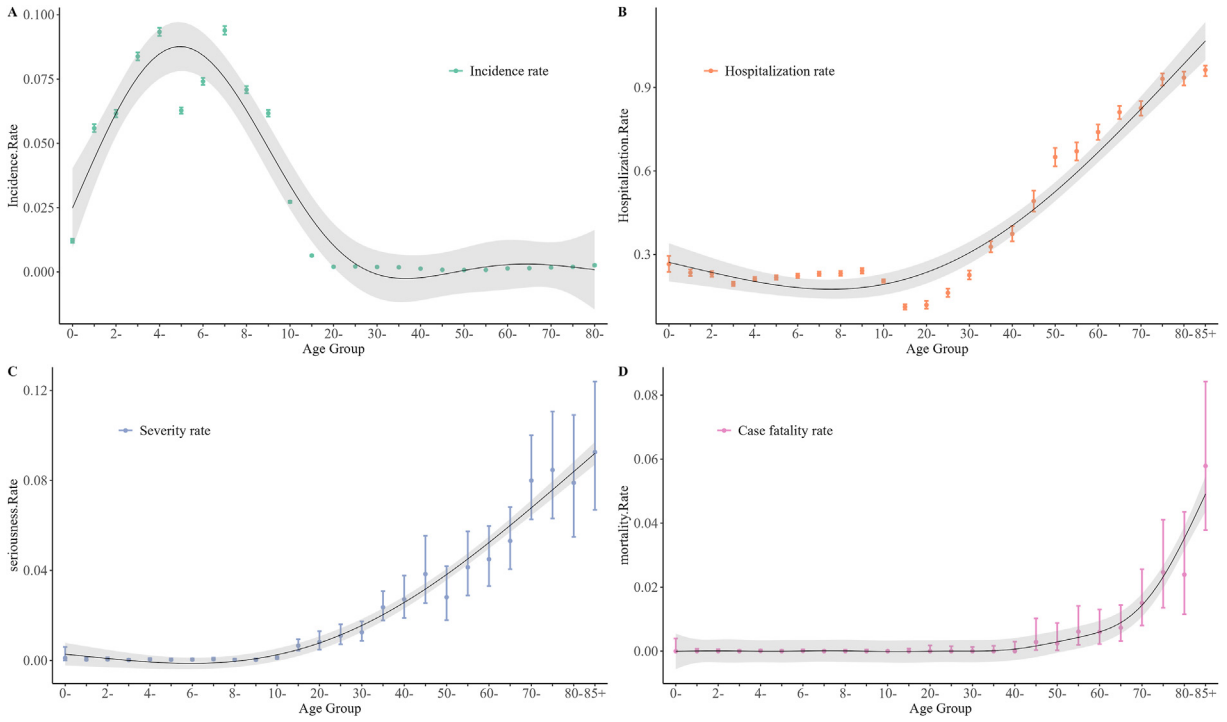

Fig. 3. Estimation of the incidence rate, hospitalization rate, severe infection rate and CFR across different age groups (A) Incidence rate (number of morbidities in the age group/population in the age group), (B) hospitalization rate (number of hospitalizations in the age group/number of cases in the age group), (C) severe infection rate (number of serious illnesses in the age group/number of cases in the age group), and (D) case fatality rate (number of deaths in the age group/number of cases in the age group). The points and intervals in each subplot correspond to the calculated rates for each age group and the 95 % CI estimated by the binomial distribution. Locally weighted regression was applied to the rates for each age group, with the resulting fitted curves and confidence bands depicted.

Severe MP infection patients presented the highest EV positivity rate (50.0 %), predominantly in the 3–5 years age group. The positivity rates for other pathogens were less than 11 %. The pathogens with the highest positivity rates varied by age group, whereas *K. pneumoniae* had the highest positivity rate (42.9 %) in patients over 60 years (Fig. 4C).

Among the patients who died from MP infection, SARS-CoV-2 (50.0 %) or *C. pneumoniae* (46.4 %) had the highest positivity rates. SARS-CoV-2 (50.0 %) and *C. pneumoniae* (49.3 %) were most prevalent in patients older than 60 years (Fig. 4D).

The most prevalent coinfecting pathogens in MP-infected patients varied by season. In spring, *H. influenzae* (32 %), *K. pneumoniae* (31.8 %), and pertussis (22.2 %) were most common. In summer, *H. influenzae* (26.2 %), *K. pneumoniae* (20.1 %), and *S. pneumoniae* (15.8 %) were the most prevalent. In autumn, *S. pneumoniae* (22.6 %), *H. influenzae* (20 %), and *K. pneumoniae* (15.2 %) were the most common pathogens, whereas in winter, *S. pneumoniae* (23.9 %), *H. influenzae* (23.2 %), and *SARS-CoV-2* (20 %) were the most common coinfecting pathogens (Table S5).

Our study revealed that among all hospitalized MP-infected patients, the proportions of those with single bacterial coinfections (14.8 %), bacterial–viral coinfections (12.3 %), bacterial–bacterial coinfections (3.8 %), and viral–viral coinfections (4.9 %) exceeded those of nonhospitalized patients. Compared with nonhospitalized adults, hospitalized adult patients presented a significantly greater percentage of *C. pneumoniae* coinfections (44.3 %) and single bacterial coinfections (10.8 %). In severe MP-infected patients, the proportions of viral-viral coinfections (5 %), *C. pneumoniae* coinfections (21.7 %), and single bacterial coinfections (10 %) were greater than those in nonsevere MP-infected patients. Among the deceased MP-infected patients, the most prevalent coinfection pathogen was *C. pneumoniae* (88.37 %) (Fig. 5A).

The most common coinfections in all MP-infected patients were bacterial-bacterial infections, specifically *H. influenzae-S. pneumoniae* (7.7 %) and *H. influenzae-K. pneumoniae* (7.4 %). Viral–viral coinfections primarily involved RhV-EV (3.3 %), whereas viral–bacterial coinfections mostly involved RhV-*H. influenzae* (3.2 %). Most MP-infected patients with coinfections, such as coinfections with pathogens such as *C. pneumoniae, P. aeruginosa*, *H. influenzae*, and *S. pneumoniae*, had a high percentage of hospitalization (Fig. 5B). Both *C. pneumoniae*-SARS-CoV-2(11.1 %), influenza A-PIV (5.6 %) and adenovirus-PIV(5.6 %) coinfections were most common in severely ill MP-infected patients and those who died (Fig. 5C). The largest proportion of severe MP-infected patients were coinfected with influenza A-PIV (5.6 %) and adenovirus-PIV (5.6 %) (Fig. S2A), whereas the greatest proportion of deceased patients with lung complications were coinfected with C. pneumoniae-SARS-CoV-2 (11.1 %) and influenza A-PIV (2.8 %) (Fig. S2B).

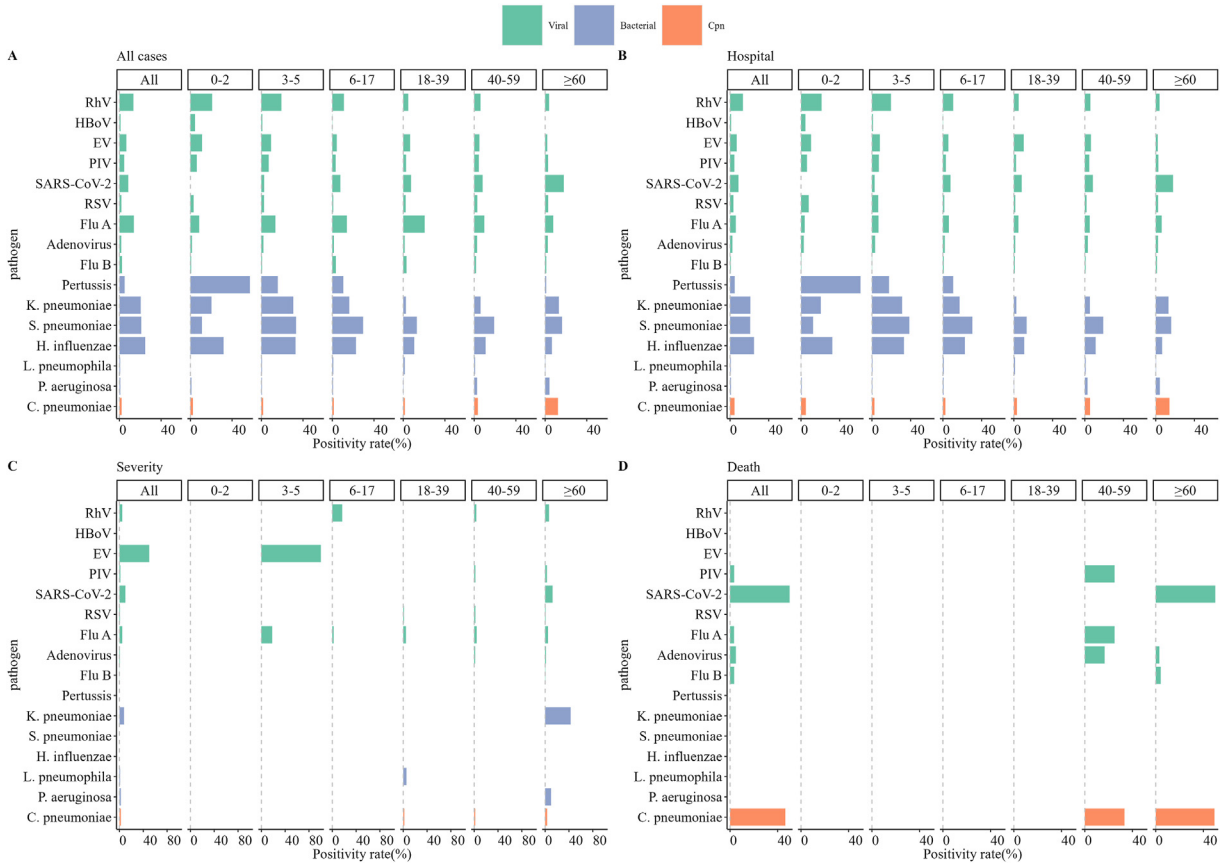

Fig. 4. Positivity rates for each pathogen for patients with different outcomes (A) Positive rate in all patients. (B) Positive rate in hospitalized patients. (C) Positive rate in severely ill patients. (D) Positive rate in patients who died due to MP infection.

3.3. *Multivariate analysis of different outcomes*

Logistic regression analysis revealed significant associations between the outcomes of hospitalization, serious illness, and death and factors such as sex, age, season of onset, and time from onset to diagnosis in the singly infected or coinfected population.

Among patients with simple pulmonary mycoplasma infection, the risk of hospitalization was greater in males than in females (OR: 1.05, 95 % CI: 1.02–1.09). Hospitalization risk was significantly greater in spring (OR: 3.09, 95 % CI: 2.95–3.24) and summer (OR: 3.06, 95 % CI: 2.93–3.18) than in autumn. When analyzed by age, hospitalization risk was significantly greater in patients aged 18–39 years (OR: 1.33, 95 % CI: 1.26–1.41), 40–59 years (OR: 5.03, 95 % CI: 4.66–5.43), and ≥60 years (OR: 22.48, 95 % CI: 20.50–24.64) −17 years. Additionally, each additional day from symptom onset to diagnosis was associated with a 5 % increase in hospitalization risk (OR: 1.05, 95 % CI: 1.05–1.06) (Fig. 6A).

For severe disease risk in patients with simple pulmonary infection, males were at greater risk than females (OR: 1.56, 95 % CI: 1.31–1.85). The risk of severe illness was significantly greater in spring (OR: 1.40, 95 % CI: 1.08–1.82) and summer (OR: 1.40, 95 % CI: 1.12–1.77) than in autumn. Age analysis revealed substantially increased risk in patients aged 18–39 years (OR: 19.54, 95 % CI: 14.07–27.12), 40–59 years (OR: 43.69, 95 % CI: 31.21–61.14), and ≥60 years (OR: 89.36, 95 % CI: 65.79–121.36) compared with the risk in the 6–17 years age group. Each additional day from onset to diagnosis was associated with a 5 % increase in severe illness risk (OR: 1.05, 95 % CI: 1.02–1.08) (Fig. 6B).

The mortality risk among patients with simple pulmonary infection was significantly greater in males than in females (OR: 2.02, 95 % CI: 1.07–3.84). Compared with that in autumn, the risk of death was significantly greater in both spring (OR: 2.76, 95 % CI: 1.02–7.49) and winter (OR: 2.44, 95 % CI: 1.03–5.82). The risk of death was markedly greater in the 40–59 years age group (OR: 59.38, 95 % CI: 6.60–534.32) and ≥60 years age group (OR: 411.25, 95 % CI: 55.95–3022.80) than in the 6–17 years age group (Fig. 6C).

Among patients with coinfection, hospitalization risk was significantly greater in spring (OR: 1.76, 95 % CI: 1.59–1.94), summer (OR: 6.85, 95 % CI: 6.04–7.76), and autumn (OR: 1.76, 95 % CI: 1.59–1.94) than in winter. Hospitalization risk was significantly greater in the 0–2 years age group (OR: 1.47, 95 % CI: 1.29–1.69), 3–5 years age group (OR: 1.18, 95 % CI:

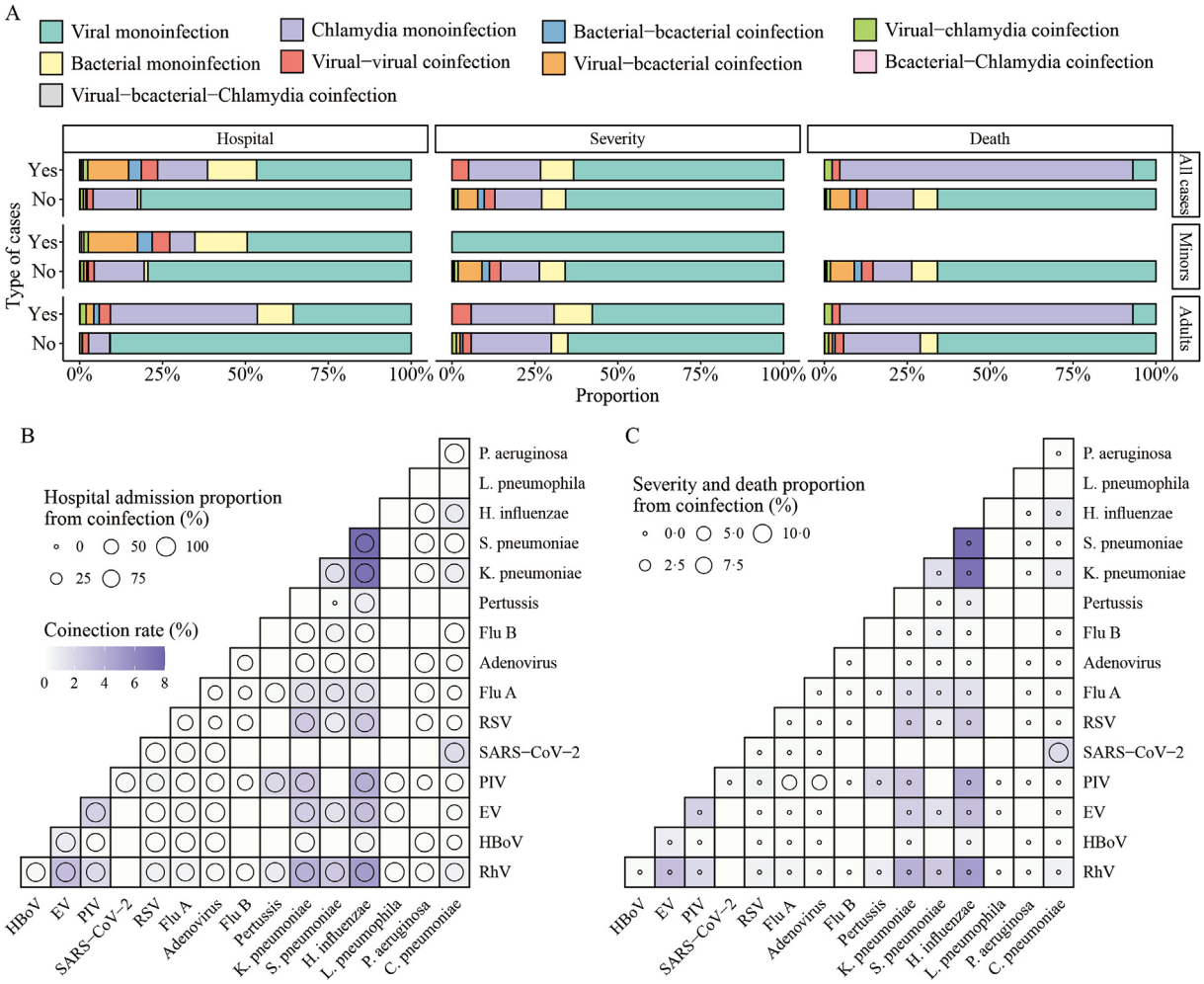

Fig. 5. Distribution of infection types and matrix of pathogen coinfection rates in MP infection patients (A) The proportions of various infection types among pediatric and adult MP infection patients according to hospitalization, severe infection, and death rates. (B) The coinfection rates of different pathogens and their proportions among hospitalized MP infection patients. (C) The coinfection rates of different pathogens and their proportions among severe MP infection patients. The color gradient represents the coinfection rate between any two pathogens among MP-infected patients, with darker shading indicating higher coinfection rates. The size of the dots corresponds to the percentage of patients with two coinfecting pathogens for hospitalization, severe infection and death; larger dots denote a greater percentage of such patients with two coinfections.

1.07–1.29), 40–59 years age group (OR: 5.05, 95 % CI: 4.06–6.28), and ≥60 years age group (OR: 31.86, 95 % CI: 24.77–40.98) than in the 6–17 years age group. Each additional day from onset to diagnosis was associated with a 16 % increase in hospitalization risk (OR: 1.16, 95 % CI: 1.15–1.18) (Fig. 6D).

For coinfected patients, the risk of serious illness was significantly greater in autumn (OR: 3.06, 95 % CI: 1.65–5.68) than in winter. The risk of serious illness was significantly greater in patients aged 18–39 years (OR: 9.63, 95 % CI: 3.25–28.54), 40–59 years (OR: 28.63, 95 % CI: 9.48–86.49), and ≥60 years (OR: 60.56, 95 % CI: 23.00–159.42) −17 years (Fig. 6E).

In terms of hospitalization outcomes, the coinfected population of patients with MP had a greater risk of hospitalization in the 0–2 years and 3–5 years age groups than in the 6–17 years age group, which was not the case for patients with single infection. In terms of the three outcomes of hospitalization, serious illness, and death, males with MP infection alone had a greater risk of poor outcomes than females did; however, this was not the case for coinfected patients.

Logistic regression analysis revealed significant associations between coinfections and factors such as sex, age, season of onset, and time from onset to diagnosis. Males had a greater risk of coinfection than females did (OR: 1.13, 95 % CI: 1.09–1.17). The risk of coinfection was notably greater in spring (OR: 2.32, 95 % CI: 2.19–2.45), summer (OR: 1.54, 95 % CI: 1.46–1.63), and winter (OR: 2.29, 95 % CI: 2.19–2.39) than in autumn. The 3–5 years age group (OR: 1.06, 95 % CI: 1.02–1.11), 18–39 years age group (OR: 1.34, 95 % CI: 1.26–1.42), 40–59 years age group (OR: 1.13, 95 % CI: 1.02–1.26), and ≥60 years age group(OR: 1.82, 95 % CI: 1.68–1.98) had a higher coinfection risk than did the 6–17 years age group. Furthermore, each additional day from onset to diagnosis increased the coinfection risk by 7 % (OR: 1.07, 95 % CI: 1.06–1.07) (Fig. 7A).

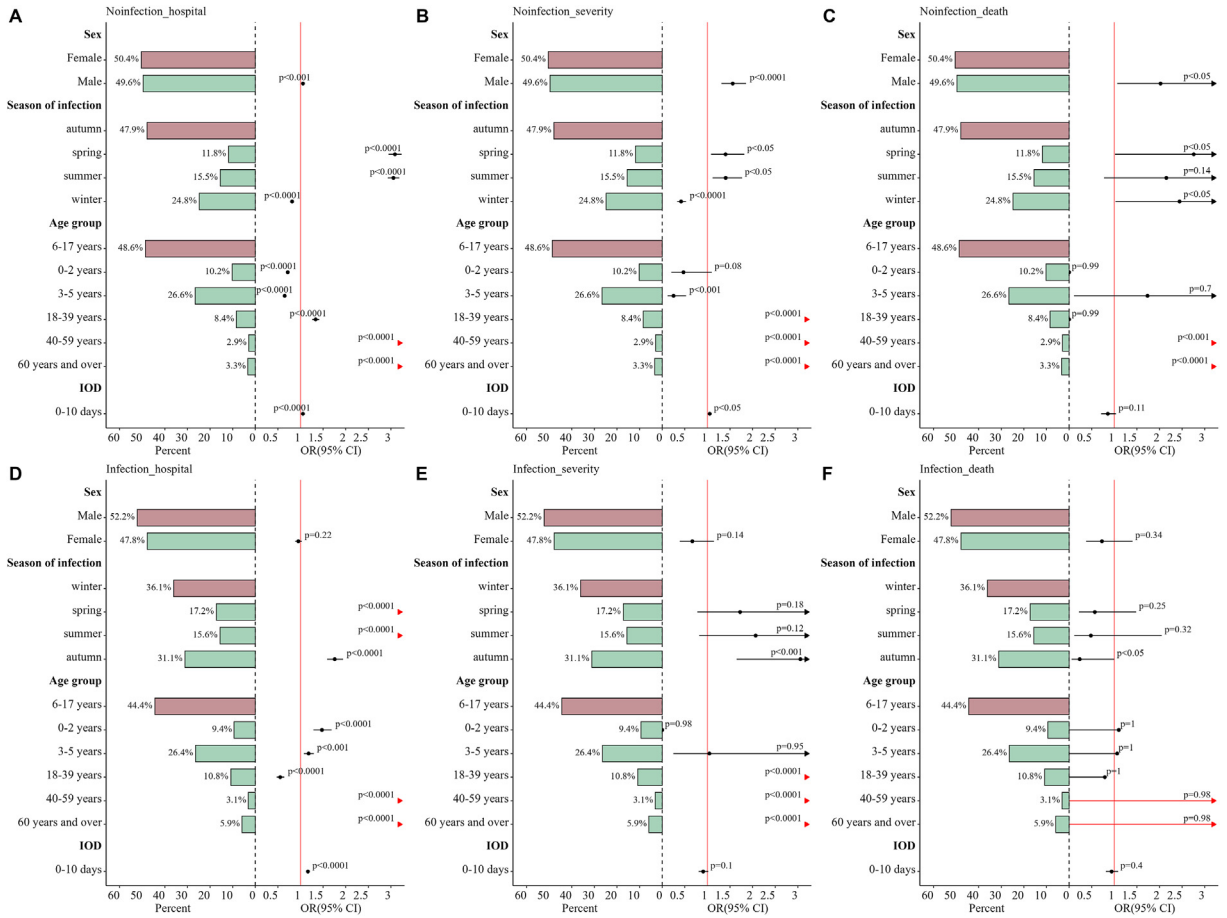

Fig. 6. Logistic regression analysis of clinical outcomes in patients with MP monoinfection versus those with coinfection (A) Hospitalization status of patients with simple infections. (B) Disease severity of patients with simple infections. (C) Mortality status of patients with simple infections. (D) Hospitalization status of patients with coinfections. (E) Disease severity of patients with coinfections. (F) Mortality status of patients with coinfections. The bars on the left depict the percentage of MP infection patients in various characteristic subgroups, whereas those on the right display the ORs alongside their 95 % CIs for the logistic regression outcomes. Red bars indicate the reference variables used in the logistic regression analysis. The black arrows indicate that the upper limit of the variable's OR and 95 % CI is out of range, and the red arrows suggest that the variable's OR is out of range. "IOD" denotes the number of days from onset to diagnosis.

The duration of hospitalization for MP infection correlated with sex, age, season of onset, coinfection type, and time from onset to diagnosis. Males had a greater hospitalization risk than females did. The risk was greater in spring (OR: 3.17, 95 % CI: 3.04–3.41) and summer (OR: 3.11, 95 % CI: 2.99–3.23) than in autumn. Compared with the 6–17 year group, the 18–39 year (OR: 1.17, 95 % CI: 1.11–1.23), 40–59 year (OR: 5.09, 95 % CI: 4.74–5.47) and ≥60 year groups (OR: 23.7, 95 % CI: 21.74–25.85) had a greater risk. Multiple pathogen coinfections increased the risk. Each additional day from onset to diagnosis increased the risk of hospitalization by 7 % (OR: 1.07, 95 % CI: 1.06–1.07) (Fig. 7B).

MP infection severity correlated with sex, age, season of onset, coinfection type, and time from onset to diagnosis. Males had a greater risk of severe disease risk than females did. The risk was greater in spring (OR: 1.28, CI: 1.00–1.64) and summer (OR: 1.34, CI: 1.07–1.67) but lower in winter. The ≥60 years group had higher risks than the other years group did. Each additional day from onset to diagnosis increased the risk by 4 % (OR: 1.04, 95 % CI: 1.01–1.07) (Fig. 7C).

Death in MP-infected patients was associated with sex, age, season of onset, coinfection type, and time from onset to diagnosis. The risk was greater in males and in the winter. The ≥60 years group had a significantly greater risk than the other years group did. Coinfections increased the risk of death (OR: 3.79, 95 % CI: 2.43–5.91) (Fig. 7D).

4. Discussion

In this large-scale study of 121,357 MP infection patients from 63 hospitals, we examined the etiological and epidemic characteristics of various outcomes, including coinfections, hospitalization, infection severity, and death. We analyzed trends and case compositions across multiple dimensions and investigated associations between multifactorial indicators, providing an important basis for clinical management.

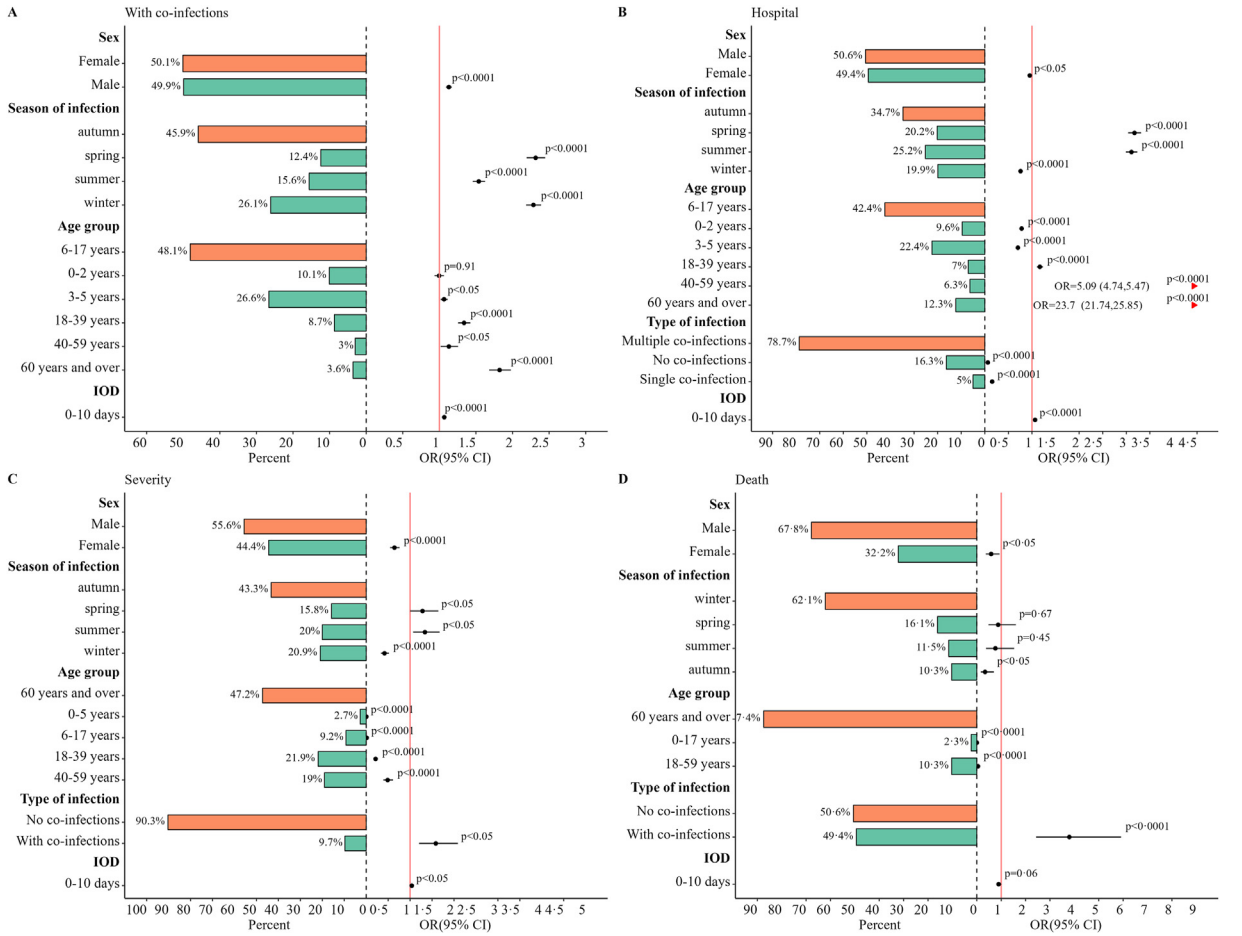

Fig. 7. Logistic regression analysis of different outcomes (A) Coinfection status of patients. (B) Hospitalization status of patients. (C) Disease severity of patients. (D) Mortality status of patients. The bars on the left depict the percentage of MP infection patients in various characteristic subgroups, whereas those on the right display the ORs alongside their 95 % CIs for the logistic regression outcomes. Red bars indicate the reference variables used in the logistic regression analysis. The black arrows indicate that the upper limit of the variable's OR and 95 % CI is out of range, and the red arrows suggest that the variable's OR is out of range. "IOD" denotes the number of days from onset to diagnosis.

We observed notable increases in MP infection morbidity, hospitalization, and severity by the end of 2023, which aligns with previous findings (Chen et al., 2024; WHO statement on reported clusters). MP has been identified as a leading cause of community-onset pneumonia and severe pneumonia in adolescents, with age-specific differences in morbidity and severity (Liu et al., 2023). Notably, MP infections predominantly affect male children and adolescents, whereas severe infections are more common in elderly individuals. Although the incidence was higher in children and adolescents, the rates of hospitalization, severe infections, and mortality were higher in the elderly population, which may be due to increased susceptibility due to decreased immunity in elderly individuals (Bartleson et al., 2021; Calder, 2021; Glynn & Moss, 2020). This finding has important implications for optimizing the allocation of healthcare resources and suggests that the frequency of surveillance and the intensity of interventions for elderly patients should be increased during disease epidemics.

Nonpharmacologic interventions implemented during the COVID-19 pandemic not only provided protection against SARS-CoV-2 infection but also reduced the transmission of other respiratory pathogens, such as MP. Since MP, similar to SARS-CoV-2, is transmitted primarily via droplet transmission, these preventive and control measures undoubtedly influence the epidemiologic dynamics of MP in the population. This temporary suppression of transmission may have led to a generalized decrease in MP antibody titers and increased susceptibility in the population, which in turn may have triggered a large-scale epidemic of MP in 2023 (Waldeck et al., 2025). The unusually high number of coinfection deaths observed in early 2023 may be related to coinfections with MP and COVID-19, revealing a complex association between the major COVID-19 wave that occurred in China in late 2022 (after the relaxation of zero-COVID policies) and the subsequent MP epidemic patterns. The first peak of MP infections observed in early 2023 closely followed the major COVID-19 wave (Fig. S3), suggesting that recent COVID-19 infection may have altered population susceptibility to MP, potentially through immune system perturbations or respiratory epithelial damage that facilitated MP infection. This temporal relationship between COVID-19 and MP epidemics

provides an important perspective on post-pandemic respiratory disease dynamics. This phenomenon suggests that we should establish a continuous surveillance system after the control of a large-scale epidemic to predict the possible rebound of other respiratory pathogens and to develop prevention strategies accordingly.

This study revealed significant age and sex differences in the pattern of coinfections in patients with MP infections, which were greater in preschoolers, young adults, and older adults and were more common in males than in females, peaking in spring and summer. Coinfections were more likely to occur in patients who were seen more than one day after the onset of symptoms, suggesting the importance of early diagnosis in the management and treatment of patients at risk of serious illness and death due to coinfections (Cilloniz et al., 2022). On the basis of these findings, we recommend the establishment of rapid testing and referral systems, especially for high-risk populations, to reduce diagnostic delays.

The type and distribution of coinfections also showed age-related patterns. Bacteria, viruses, and *C. pneumoniae* were prevalent in infants with pulmonary involvement, with pertussis being the most common. A relatively high proportion of viral coinfections, especially *S. pneumoniae*, were found in school-aged children. Single coinfections were more common in adults, which may be related to their well-developed immune system and reduced exposure to pathogens (Lloyd & Saglani, 2023). Increased social interactions among school-aged children may lead to increased rates of viral coinfections (Glass & Glass, 2008), whereas the maturity and stability of the adult immune system may lead to increased rates of single coinfections (Brodin & Davis, 2017). These age-specific patterns should influence clinical management decisions, including empirical antibiotic selection and prioritization of ancillary tests.

Coinfection with respiratory viruses, which are prevalent in MP infection patients, tends to exacerbate the disease burden (Haney et al., 2022). Our analysis revealed that patients coinfected with *C. pneumoniae*-SARS-CoV-2, influenza A-PIV, or adenovirus-PIV presented increased risks of severe illness and death, which may be associated with an exacerbated inflammatory response, tissue damage, and immunosuppression (Chen et al., 2017). Specifically, *C. pneumoniae* and SARS-CoV-2 coinfection may amplify viral pathogenicity, whereas coinfection with influenza A and PIV could lead to more extensive respiratory inflammation and severe respiratory failure. These findings underscore the interactive and additive effects among respiratory pathogens, offering insights for improved prevention and treatment strategies for MP coinfections. Early intensive anti-inflammatory therapy and more intensive respiratory support should be considered for high-risk coinfected patients, along with more rigorous prognostic assessment criteria.

Using Wuhan's surveillance system, we analyzed MP infection outcomes in a large patient database. Sex and age differences in clinical outcomes suggest the need for targeted management. Among patients with MP infection alone, males had a greater risk of adverse outcomes than females did; adult patients had a greater risk of hospitalization and severe illness than minor patients did; and patients over 40 years of age had a significantly greater risk of death than did patients under 40 years of age. In contrast, among patients with MP coinfection, the risk of hospitalization was significantly greater in the 0–5- and ≥40-year-old age groups than in the 6–17-year-old age group, and the risk of severe illness was greater in adult patients than in minor patients. These differences may be related to the fact that coinfections alter the host intracellular environment, affecting drug metabolism and therapeutic efficacy, as well as the immune vulnerability of different age groups to multipathogen infections (Guo et al., 2022; Khojandi et al., 2019; Quiros-Roldan et al., 2024). On the basis of these findings, we recommend a multipathogen testing strategy for patients aged 0–5 years and 40 years and older, with attention to drug–drug interactions and potential toxicity, especially in young children and older patients. In addition, as simple infections exhibit more pronounced sex differences, enhanced health promotion during the epidemic season to reduce the risk of transmission and a more intensive follow-up program for male patients to monitor disease progression could be considered. In addition, these findings provide important clues for further research on host susceptibility factors for MP infection.

Seasonal factors also significantly influenced infection outcomes, with the risk of coinfection being highest in winter and spring, hospitalization and serious illness peaking in spring and summer, and disease and death rates being highest in winter. These seasonal differences may be related to climatic factors influencing pathogen–host interactions and environmental condition (Clementi et al., 2021). Examples include crowded indoor activities, vitamin D deficiency due to reduced sunlight exposure, and cold temperatures that increase viral stability. Notably, patients with coinfections, especially those with multiple pathogens, presented a significantly greater risk of hospitalization and death, which is consistent with findings from other studies (Krumbein et al.; Liu et al., 2021). These findings also emphasize the importance of early recognition and management of coinfections to improve MP outcomes (Liu et al., 2021). This seasonal model can be used to guide the seasonal allocation of public health resources to increase the readiness of the healthcare system in advance of high-incidence seasons, including planning for bed capacity and training healthcare worker.

Our findings also prompted us to reflect on the adaptability of current clinical management strategies for MP infections. On the basis of the risk profiles of different populations, we suggest the development of stratified treatment regimens, including: intensive surveillance and early intervention strategies for high-risk elderly patients, rapid multipathogen screening and targeted treatment for children and adolescents, and prevention strategies and healthcare resource allocation adapted to seasonal and epidemiologic characteristics.

This study has several limitations. First, not all patients were tested for the same wide range of pathogens, and the extent and depth of testing may have varied significantly due to resource constraints, differences in clinical judgment, or the timing of the patient's visit. This uneven testing pattern may lead to bias in two ways: for one, we could not completely exclude the possibility that patients categorized as having “simple MP infection” might carry other pathogens that were not detected; for another, the determination of coinfections did not take into account that patients with MP infection were infected with undetected pathogens, which may lead to an underestimation of the actual rate of coinfections. Additionally, while our data

shows a temporal relationship between the COVID-19 wave in late 2022 and subsequent MP infection patterns, we acknowledge limitations in establishing direct causality. Our study lacks individual-level COVID-19 infection history for all patients in the cohort, particularly from the transition period when testing protocols changed dramatically during China's shift away from zero-COVID policies. Furthermore, while the data encompassed nearly all individuals seeking medical care in Wuhan, this population might not fully represent the city's entire population of MP infection patients. Future studies should consider a wider range of assays, more representative sample collection strategies, and research specifically designed to track individual infection histories across multiple respiratory pathogens to validate our findings and confirm potential pathogen interactions while elucidating the immunological mechanisms involved.

This study, which utilized a substantial sample size, mapped the distribution of outcomes for monoinfections and coinfections in MP-infected patients, revealing their etiological links. This study provides robust epidemiological data on 16 respiratory pathogens in a major Chinese city, elucidating how season, age, and coinfection affect disease progression. Our results indicate that healthcare providers should account for age, sex, season, and coinfection type when managing MP infections. This understanding can inform better prevention, treatment, and prognosis strategies, potentially lowering the incidence of community-acquired pneumonia (CAP). These findings have important implications for public health policy and clinical practice worldwide, especially in the context of potentially significant changes in respiratory infection patterns in the postepidemic era.

CRediT authorship contribution statement

Banghua Chen: Writing – original draft, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jie Pan:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation. **Ying Peng:** Writing – original draft, Visualization, Investigation, Data curation. **Yuanyuan Zhang:** Writing – original draft, Resources, Investigation, Data curation. **Yunan Wan:** Writing – original draft, Validation, Formal analysis. **Hongjie Wei:** Writing – original draft, Validation, Formal analysis. **Kangguo Li:** Writing – review & editing, Validation. **Wentao Song:** Writing – review & editing, Methodology. **Yunkang Zhao:** Writing – original draft, Visualization. **Kang Fang:** Writing – original draft, Validation. **Huiming Ye:** Writing – original draft, Methodology. **Jiali Cao:** Writing – original draft, Visualization. **Jia Rui:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Zeyu Zhao:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Tianmu Chen:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

Declarations

Ethics approval and consent to participate and consent for publication

This observational study received ethical approval from the Wuhan CDC Ethics Review Board (WHCDCIRB-K-2023043). The process of data collection from hospitals was incorporated into the routine surveillance duties of the Wuhan Centers for Disease Control and Prevention. Given the anonymized nature of the data and its exclusive use for scientific research, the requirement for informed consent was deemed unnecessary.

Availability of data and materials

All the data and the R code used for the statistical analysis are available at the GitHub repository (https://github.com/xmupamo/MP-figures-code).

Funding

This research was supported by Guangzhou Laboratory (Grant No. SRPG22-007), Major Project of Guangzhou National Laboratory (Grant No. GZNL2024A01004) and The National Natural Science Foundation of China (Grant No. 82341034).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank all the participants and their families, the collaborating clinicians, the Wuhan Center for Disease Control and Prevention Acute Respiratory Infection Etiology Surveillance Study Group, and the 294 participating hospitals for their valuable contributions to fieldwork, administrative coordination, and data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2025.04.006.

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