



Disease severity and clinical outcomes of community-acquired pneumonia caused by non-influenza respiratory viruses in adults: a multicentre prospective registry study from the CAP-China Network

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The high incidence of complications in non-influenza viral pneumonia and similar impact of non-influenza viruses relative to influenza virus on disease severity and outcomes suggest more attention should be given to CAP caused by non-influenza viruses <http://bit.ly/2vRTvFK>

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ABSTRACT Although broad knowledge of influenza viral pneumonia has been established, the significance of non-influenza respiratory viruses in community-acquired pneumonia (CAP) and their impact on clinical outcomes remains unclear, especially in the non-immunocompromised adult population.

Hospitalised immunocompetent patients with CAP were prospectively recruited from 34 hospitals in mainland China. Respiratory viruses were detected by molecular methods. Comparisons were conducted between influenza and non-influenza viral infection groups.

In total, 915 out of 2336 adult patients with viral infection were enrolled in the analysis, with influenza virus (28.4%) the most frequently detected virus, followed by respiratory syncytial virus (3.6%), adenovirus (3.3%), human coronavirus (3.0%), parainfluenza virus (2.2%), human rhinovirus (1.8%) and human metapneumovirus (1.5%). Non-influenza viral infections accounted for 27.4% of viral pneumonia. Consolidation was more frequently observed in patients with adenovirus infection. The occurrence of complications such as sepsis (40.1% *versus* 39.6%; $p=0.890$) and hypoxaemia (40.1% *versus* 37.2%; $p=0.449$) during hospitalisation in the influenza viral infection group did not differ from that of the non-influenza viral infection group. Compared with influenza virus infection, the multivariable adjusted odds ratios of CURB-65 (confusion, urea >7 mmol·L⁻¹, respiratory rate ≥ 30 breaths·min⁻¹, blood pressure <90 mmHg (systolic) or ≤ 60 mmHg (diastolic), age ≥ 65 years) ≥ 3 , arterial oxygen tension/inspiratory oxygen fraction <200 mmHg, and occurrence of sepsis and hypoxaemia for non-influenza respiratory virus infection were 0.87 (95% CI 0.26–2.84), 0.72 (95% CI 0.26–1.98), 1.00 (95% CI 0.63–1.58) and 1.05 (95% CI 0.66–1.65), respectively. The hazard ratio of 90-day mortality was 0.51 (95% CI 0.13–1.91).

The high incidence of complications in non-influenza viral pneumonia and similar impact of non-influenza respiratory viruses relative to influenza virus on disease severity and outcomes suggest more attention should be given to CAP caused by non-influenza respiratory viruses.

Introduction

Community-acquired pneumonia (CAP) is the leading cause of death worldwide among communicable diseases [1]. The development of molecular diagnostic techniques has markedly improved our ability to identify viruses, with numerous studies having reported a high prevalence of viral infections in patients with CAP [2]. A recent meta-analysis incorporating 31 observational studies showed that the proportion of viral infection was 24.5% in hospitalised patients with CAP, with influenza virus types A and B (IFV) most frequently identified, followed by human rhinovirus (HRV), respiratory syncytial virus (RSV) and human coronavirus (CoV) [2].

Previous studies have established the clinical features, complications and outcomes associated with influenza viral pneumonia [3, 4]. However, most data concerning non-influenza viral pneumonia were derived from case reports and case series, since non-influenza respiratory viruses were most frequently known as the cause of upper respiratory tract infections [3]. Additionally, the majority of studies focusing on non-influenza respiratory viruses in adults with pneumonia were conducted in populations with limited generalisability to CAP patients, such as immunocompromised or frail elderly patients, residents of long-term facilities, cases with underlying lung diseases, or critically ill people [5–11]. Therefore, the significance of non-influenza respiratory viruses in pneumonia and their specific impact on clinical outcomes has not been established in immunocompetent adult patients with CAP.

Here, we performed a national, prospective, multicentre study in order to evaluate the impact of non-influenza respiratory viruses compared with IFV on disease severity, proportion of patients achieving clinical stability within the first 3 days at the hospital, complications, intensive care unit (ICU) admission, length of hospital stay and 90-day mortality in immunocompetent adult patients with CAP.

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Methods

Study setting and design

The CAP-China study, a prospective multicentre observational study, was conducted in 34 hospitals from 10 provinces of mainland China (figure 1), with all of the hospitals located in urban areas (supplementary table S1). From October 1, 2015 to June 30, 2017, patients with CAP admitted to the emergency department, general wards or ICU were screened for enrolment (supplementary figure S1). Written informed consent was obtained from all patients or their caregivers before enrolment. The CAP-China study was approved by the institutional review board of the China–Japan Friendship Hospital and was registered at ClinicalTrials.gov with identifier NCT02492425.

Study population

Patients aged ≥ 14 years and hospitalised for CAP were enrolled on admission. CAP was diagnosed according to the 2007 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines [12].

Patients were excluded if one of the following criteria was met: 1) hospitalisation within the previous 90 days or enrolled in this study within the previous 30 days; 2) being immunocompromised: cancer with neutropenia (absolute neutrophil count $< 500 \text{ mm}^{-3}$), haematological malignancies, solid malignancies receiving chemotherapy during the previous 3 months, solid organ or bone marrow transplant, active graft *versus* host disease, bronchiolitis obliterans, HIV infection, immunoglobulin deficiency, using immunosuppressive agents, or current treatment with systemic corticosteroids (≥ 20 mg prednisone per day or equivalent) for > 30 continuous days before illness onset; 3) receipt of a tracheotomy, insertion of a percutaneous endoscopic gastrostomy tube or presentation of cystic fibrosis; or 4) had a clear alternative diagnosis at the end of follow-up that included lung cancer, pulmonary tuberculosis, interstitial lung disease, pulmonary embolism, pulmonary oedema or allergic bronchopulmonary aspergillosis.

2718 hospitalised CAP patients were eligible for enrolment during the study period. A total of 382 cases were excluded: refusal to consent ($n=69$), failure in sampling ($n=158$), being immunocompromised ($n=37$), final diagnosis of tuberculosis or non-pneumonia illness ($n=58$), or being lost to follow-up ($n=60$). Of the 2336 participants enrolled in the CAP-China study, 1421 were negative for viral detection. Finally, a total of 915 patients with positive viral detection were included in this analysis (figure 2).

Data collection and quality control

Before study initiation, all local principal investigators and study staff received extensive training on the protocol. Trained staff interviewed patients (or their caregivers) within 24 h after enrolment, with

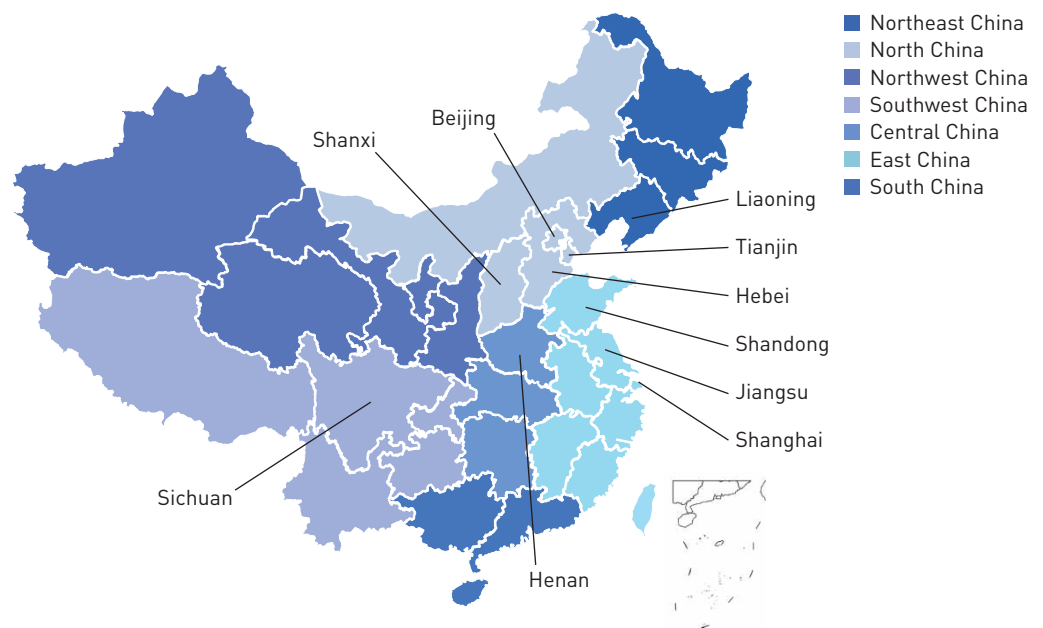


FIGURE 1 Patients were enrolled from five of the seven geographical locations in mainland China, including Beijing, Tianjin, Hebei and Shanxi provinces in North China; Shanghai, Shandong and Jiangsu provinces in East China; Henan province in Central China; Sichuan province in Southwest China; and Liaoning province in Northeast China.

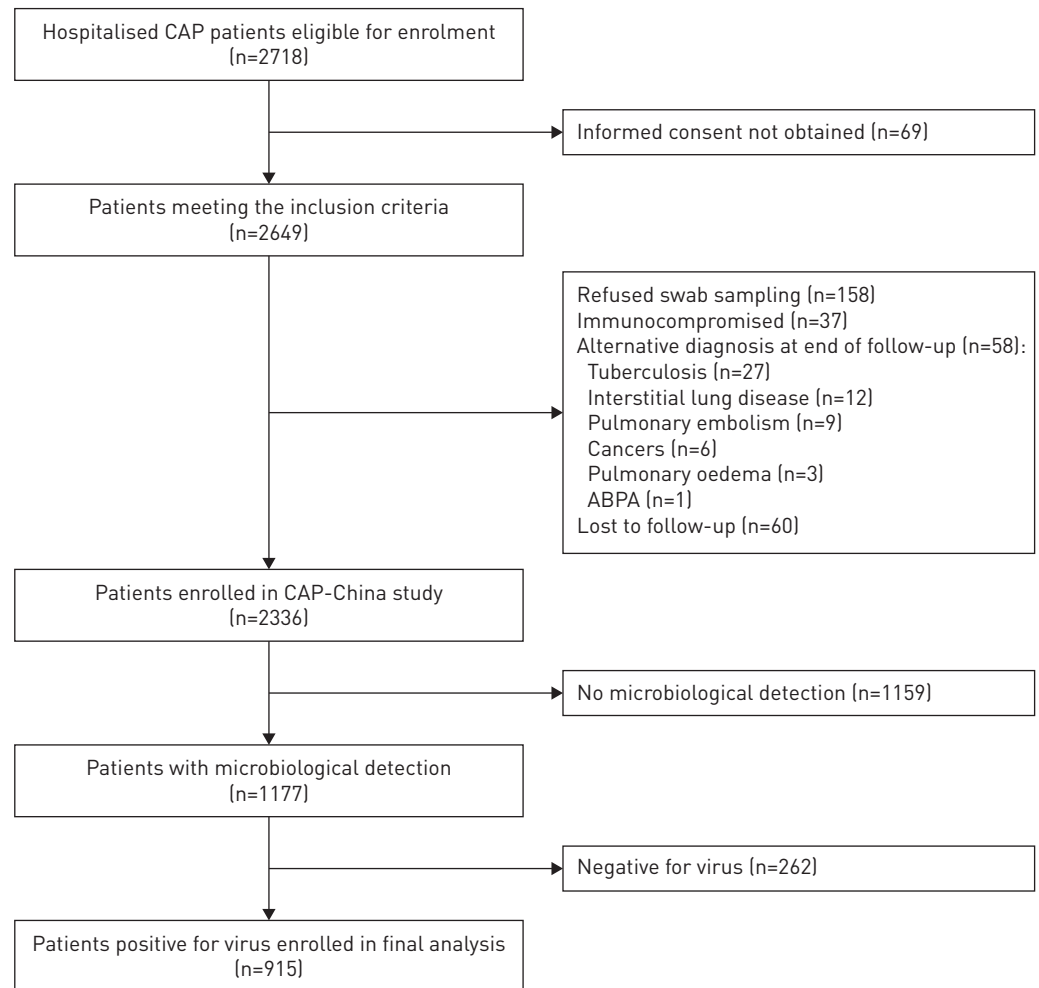


FIGURE 2 Study flowchart. CAP: community-acquired pneumonia; ABPA: allergic bronchopulmonary aspergillosis.

demographic information, comorbidities, clinical manifestations, vital signs, laboratory results and microbiology data, antimicrobial use, complications, and outcomes collected using a standardised case report form. During a 90-day follow-up period, all-cause death was recorded by telephone interview. All information was uploaded into an electronic database (www.chinapneumonia.cn) by trained clinical research coordinators and systematic data checks were performed automatically online in order to detect logical errors or extremes. For each case, 10% of the data were selected at random and checked against the original medical records by clinical research associates in order to confirm accuracy and completeness.

Specimen collection and testing

Two nasopharyngeal swabs were obtained from all patients (n=2332) immediately upon entry to the emergency department, general wards or ICU. One swab was collected for rapid influenza antigen testing on site; the other swab was placed in universal transport medium and stored at -80°C for PCR analysis in the central laboratory (National Clinical Research Center of Respiratory Diseases, China–Japan Friendship Hospital, Beijing, China). On-site urine antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed in all patients within 24 h after admission. Blood for cultures was obtained from 610 patients with a temperature $\geq 38.5^{\circ}\text{C}$ within 48 h of admission, with 73.4% of them having received empirical antibiotics treatment. A total of 1229 patients had qualified sputum or endotracheal aspirate collected within 48 h after admission, with 868 of these patients having already received empirical CAP antibiotics. On-site Gram staining and bacterial cultures were performed according to routine microbiological guidance. Sputum, endotracheal aspirate and bronchoalveolar lavage fluid (BALF) samples were stored at -80°C until PCR testing in the central laboratory.

Pathogen detection

Viral aetiology was considered positive if one of the following criteria was met: 1) detection of respiratory virus in sputum, endotracheal aspirate, BALF or nasopharyngeal swabs by real-time PCR (TaqMan Array Microfluidic Cards; Applied Biosystems, Foster City, CA, USA) [13], including RSV, IFV, parainfluenza virus (PIV), HRV, CoV, human metapneumovirus (HMPV) and adenovirus (AdV); or 2) positive antigen for IFV (Clearview Exact Influenza A&B; Alere, Waltham, MA, USA).

Bacterial or atypical pathogens were considered positive if one of the following criteria was met: 1) positive bacterial culture from blood or pleural fluid; 2) positive urinary antigen for *L. pneumophila* (Binax Now; Trinity Biotech, Bray, Ireland) or *S. pneumoniae* (Binax Now; Emergo Europe, Amsterdam, The Netherlands); 3) detection of *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* in sputum, BALF, endotracheal aspirate or nasopharyngeal swabs by real-time PCR (Shanghai Zhijiang Bio-Tec, Shanghai, China) [14]; 4) detection of *L. pneumophila* in sputum, BALF or endotracheal aspirate by real-time PCR (Shanghai Zhijiang Bio-Tec) [14]; or 5) bacteria with moderate to heavy growth (graded as >3+ growth) in qualified sputum or endotracheal aspirate, or quantified culture in BALF of $\geq 10^4$ CFU·mL⁻¹. In this study, qualified samples were defined as more than 25 leukocytes and less than 10 epithelial cells per magnified field (at $\times 100$ magnification).

Definitions

Hypoxaemia was defined as arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) <300 mmHg [15]. Sepsis was diagnosed based on the revised criteria defined by SINGER *et al.* [16], *i.e.* Sequential Organ Failure Assessment score ≥ 2 . Pneumonia severity was assessed by CURB-65 (confusion, urea >7 mmol·L⁻¹, respiratory rate ≥ 30 breaths·min⁻¹, blood pressure <90 mmHg (systolic) or ≤ 60 mmHg (diastolic), age ≥ 65 years) [17] and P_{aO_2}/F_{IO_2} . Clinical stability was defined according to the 2007 IDSA/ATS guidelines [12]. Viral and bacterial co-infection was defined as detection of both viruses and bacteria [18]. Viral and *M. pneumoniae/C. pneumoniae* co-infection was defined as detection of both viruses and atypical pathogens. Mixed viral infection was defined as detection of two or more viruses.

Statistical analysis

Viral CAP patients were classified into three groups: influenza viral infection group, non-influenza viral infection group and mixed viral infection group. For the influenza or non-influenza viral infection group, only one virus was detected. Clinical features, CURB-65 ≥ 3 and P_{aO_2}/F_{IO_2} <200 mmHg on admission, 24 and 72 h clinical stability, hypoxaemia and sepsis during hospitalisation, ICU admission, invasive ventilation, and 90-day mortality were compared between the influenza and non-influenza viral infection groups. Further comparisons were performed in different viral infection groups (IFV, CoV, HMPV, HRV, AdV, PIV, RSV and mixed viral infection). Continuous variables are presented as median (interquartile range (IQR)) and categorical variables are presented as number (percentage). The normality of data distribution was assessed and a Mann–Whitney U-test was used for non-normally distributed variables. A Chi-squared test was used to compare categorical variables. Univariate logistic regression analysis was used to estimate the odds ratios and 95% confidence intervals of underlying diseases, clinical features, laboratory findings, severe disease, complications and mortality for the non-influenza viral infection group compared with the influenza viral infection group. A multivariable adjusted logistic regression model was used to estimate the effect of different viruses on disease severity (CURB-65 ≥ 3 and P_{aO_2}/F_{IO_2} <200 mmHg on admission) and complications (sepsis and hypoxaemia during hospitalisation). Multivariable adjusted Cox regression was conducted to estimate the association between viral aetiology and 90-day mortality. All data were analysed with SPSS version 19.0 (SPSS, Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant. Bonferroni correction was used for multiple comparisons.

Results

Patient characteristics

The median (IQR) age of the 915 patients with viral infection was 59.0 (36.0–72.0) years and 55.2% were male (table 1). A total of 426 (46.6%) patients had comorbidities, with cardiovascular disease the most commonly observed (31.3%), followed by diabetes (14.6%) and chronic obstructive pulmonary disease (COPD) (4.5%). The most common symptoms of patients with viral infection were cough (93.0%), fever (81.3%) and sputum (81.3%), and ~33% of patients had dyspnoea. 151 patients had received antiviral therapy in the emergency department or on admission, among which 98.7% represented empirical treatment. Neuraminidase inhibitors were the most commonly used antivirals (86%), followed by ganciclovir (9%), acyclovir (7%) and ribavirin (2%). The median (IQR) length of hospital stay in patients with viral infection was 10 (8–14) days and the 90-day mortality was 3.1%.

Among the 915 patients, influenza viral infection, non-influenza viral infection and mixed viral infection was found in 581, 240 and 94 cases, respectively. The baseline characteristics of age, symptoms, underlying

TABLE 1 Demographic characteristics, underlying diseases, clinical features and laboratory findings of hospitalised community-acquired pneumonia patients with viral infections

	Viral infection	Influenza viral infection [#]	Non-influenza viral infection [¶]	Mixed viral infection ⁺	p-value
Patients	915	581	240	94	
Age years	59.0 (36.0–72.0)	58.0 (36.0–72.5)	59.0 (34.3–72.8)	59.0 (37.0–72.0)	0.866
Male	505 (55.2)	312 (52.7)	136 (56.7)	57 (60.6)	0.438
Underlying diseases					
Cardiovascular disease	286 (31.3)	181 (31.2)	77 (32.1)	28 (29.8)	0.794
Diabetes	134 (14.6)	82 (14.1)	38 (15.8)	14 (14.9)	0.526
COPD	45 (4.5)	27 (4.6)	13 (5.4)	5 (5.3)	0.641
Chronic renal failure	41 (4.5)	29 (5.0)	9 (3.8)	3 (3.2)	0.441
Asthma	30 (3.3)	20 (3.4)	6 (2.5)	4 (4.3)	0.483
Solid malignancy [§]	23 (2.5)	14 (2.4)	6 (2.5)	3 (3.2)	0.939
Liver disease	16 (1.7)	12 (2.1)	2 (0.8)	2 (2.1)	0.345
Symptoms					
Fever	744 (81.3)	482 (83.0)	190 (79.2)	72 (76.6)	0.200
Cough	851 (93.0)	535 (92.1)	227 (94.6)	89 (94.7)	0.207
Sputum	744 (81.3)	471 (81.1)	196 (81.7)	77 (81.9)	0.841
Haemoptysis	48 (5.2)	27 (4.6)	10 (4.2)	11 (11.7)	0.763
Myalgia	364 (39.8)	240 (41.3)	91 (37.9)	33 (35.1)	0.368
Chill	352 (38.5)	228 (39.2)	87 (36.2)	37 (39.4)	0.423
Dyspnoea	303 (33.1)	195 (33.6)	70 (29.2)	38 (40.4)	0.220
Chest pain	147 (16.1)	99 (17.0)	29 (12.1)	19 (20.2)	0.075
Diarrhoea	40 (4.4)	26 (4.5)	11 (4.6)	3 (3.2)	0.946
Laboratory findings on admission					
Leukocytosis ^f	175/907 (19.3)	92/575 (16.0)	60/238 (25.2)	23 (24.5)	0.002
Granulocytopenia ^{##}	44/907 (4.9)	29/575 (5.0)	11/238 (4.6)	4 (4.3)	0.800
Lymphocytopenia ^{¶¶}	188/907 (20.7)	120/575 (20.9)	47/238 (19.7)	21 (22.3)	0.719
Anaemia ⁺⁺	184/907 (20.3)	114/575 (19.8)	46/238 (19.3)	24 (25.5)	0.871
Thrombocytopenia ^{§§}	193/907 (21.3)	130/575 (22.6)	47/238 (19.7)	16 (17.0)	0.368
ALT >40 U·L ⁻¹	199/896 (22.2)	135/567 (23.8)	48/237 (20.3)	16/92 (17.4)	0.273
LDH >250 U·L ⁻¹	224/844 (26.5)	194/544 (27.4)	59/218 (27.1)	16/82 (19.5)	0.927
BUN >7 mmol·L ⁻¹	131/903 (14.5)	82/571 (14.4)	35/238 (14.7)	14 (4.6)	0.899
PCT ng·mL ⁻¹					
<0.25	568/812 (70.0)	365/509 (71.7)	141/216 (65.3)	62/87 (71.3)	0.520
0.25–0.50	70/812 (8.6)	39/509 (7.7)	22/216 (10.2)	9/87 (10.3)	
0.50–1.00	66/812 (8.1)	40/509 (7.9)	22/216 (10.2)	4/87 (4.6)	
≥1.00	108/812 (13.3)	65/509 (12.8)	31/216 (14.4)	12/87 (3.8)	
CRP ≤100 mg·L ⁻¹	68/528 (87.1)	45/344 (86.9)	18/122 (85.2)	5/62 (7.4)	0.642
PaO ₂ /F _I O ₂ <300 mmHg	327/855 (38.2)	204/534 (38.2)	86/234 (36.8)	37/87 (42.5)	0.703
Initial radiographic findings					
Consolidation	395/759 (52.0)	241/478 (50.4)	112/210 (53.3)	42/71 (59.2)	0.481
Ground-glass opacity	542/759 (71.4)	351/478 (73.4)	141/210 (67.1)	50/71 (70.4)	0.092
Diffuse bilateral pulmonary infiltration	225/759 (29.6)	176/478 (36.8)	29/210 (13.8)	20/71 (28.2)	<0.001
Pleural effusion	36/579 (4.7)	24/478 (5.0)	8/210 (3.8)	4/71 (5.6)	0.487
Received antibiotic treatment before enrolment	705 (77.7)	461 (79.3)	178 (74.2)	66 (70.2)	0.104
Received antiviral treatment before enrolment	151 (16.5)	107 (18.4)	31 (12.9)	13 (13.8)	0.055
Received antibiotic treatment during hospitalisation	904 (98.8)	575 (99.0)	235 (97.9)	94 (100.0)	0.234
Received antiviral treatment during hospitalisation	130 (14.2)	97 (16.7)	23 (9.6)	10 (10.6)	0.009
Viral–bacterial co-infection^{ff}	66 (7.2)	38 (6.5)	15 (6.2)	13 (13.8)	0.878
Viral–<i>M. pneumoniae</i>/<i>C. pneumoniae</i> co-infection	130 (14.2)	87 (15.0)	31 (12.9)	12 (12.8)	0.445

Data are presented as n, median (interquartile range) or n/N (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; PCT: procalcitonin; CRP: C-reactive protein; PaO₂: arterial oxygen tension; F_IO₂: inspiratory oxygen fraction; *M. pneumoniae*: *Mycoplasma pneumoniae*; *C. pneumoniae*: *Chlamydia pneumoniae*. #: only influenza virus with or without co-infection; ¶: any non-influenza virus with or without co-infection; +: any two or more viruses; §: including n=6 lung cancer, n=5 colon cancer, n=4 stomach cancer, n=4 liver cancer, n=2 thyroid cancer, n=1 breast cancer and n=1 cervical cancer; f: leukocyte count >10 000 mm⁻³; ##: neutrophil count <1500 mm⁻³; ¶¶: lymphocyte count <800 mm⁻³; ++: haemoglobin <120 g·L⁻¹ for males and <110 g·L⁻¹ for females; §§: platelet count <150 000 mm⁻³; ff: includes typical bacteria and viruses co-infection (n=57) and *L. pneumophila* and viruses co-infection (n=9). p-values are for the influenza viral infection group versus the non-influenza viral infection group.

TABLE 2 Patients with positive virus detection

Viral detection only	
One viral infection	645
Influenza A/B	452
Adenovirus	45
Respiratory syncytial virus	45
Human coronavirus	29
Parainfluenza virus 1–4	28
Human rhinovirus	24
Human metapneumovirus	22
Mixed viral infection	68
Viral–bacterial co-infection[#]	66
Viral–<i>M. pneumoniae</i>/<i>C. pneumoniae</i> co-infection	130
Viral–bacterial–<i>M. pneumoniae</i>/<i>C. pneumoniae</i> co-infection[¶]	6

Data are presented as n. *M. pneumoniae*: *Mycoplasma pneumoniae*; *C. pneumoniae*: *Chlamydia pneumoniae*.
[#]: includes typical bacteria and viruses co-infection (n=57) and *L. pneumophila* and viruses co-infection (n=9); [¶]: includes viruses, typical bacteria and *M. pneumoniae*/*C. pneumoniae* co-infection.

diseases and laboratory findings were similar between the influenza and non-influenza viral infection groups, except that leukocytosis was more common in the non-influenza viral infection group (25.2% versus 16.0%; OR 1.77, 95% CI 1.23–2.56; p=0.002) and diffuse bilateral pulmonary infiltration was more common in the influenza viral infection group (36.8% versus 13.8%; OR 0.28, 95% CI 0.18–0.42; p<0.001) (table 1 and supplementary table S2).

Pathogen detection

Among 2336 hospitalised patients with CAP, IFV (28.4%) was the most frequently detected virus, followed by RSV (3.6%), AdV (3.3%) and CoV (3.0%); mixed viral infection was observed in 68 patients (table 2). AdV infection was found in 4.6%, 4.2%, 1.8%, 1.2% and 1.6% of patients aged 14–24, 25–44, 45–64, 65–84 and ≥85 years, respectively (p=0.002), with the positive rate of other respiratory viruses similar in different age groups (supplementary table S3). Influenza viral infection was more common in patients admitted to the ICU than patients in general wards (32.9% versus 24.3%; OR 1.52, 95% CI 1.06–2.18; p=0.023) (supplementary table S4). Typical bacteria were detected in 72 patients with viral infection, with *S. pneumoniae* and *Klebsiella pneumoniae* most commonly detected (supplementary table S5).

Comparison of illness severity, complications and clinical outcomes between the influenza and non-influenza viral infection groups

Among 915 patients with viral infection, the proportions of patients with CURB-65 ≥3 (4.9% versus 3.8%; OR 0.76, 95% CI 0.35–1.64; p=0.486) and $P_{aO_2}/F_{iO_2} < 200$ mmHg (8.6% versus 5.1%; OR 0.57, 95% CI 0.30–1.10; p=0.092) on admission, and incidence of sepsis (40.1% versus 39.6%; OR 0.98, 95% CI 0.72–1.33; p=0.890) and hypoxaemia (40.1% versus 37.2%; OR 0.89, 95% CI 0.65–1.22; p=0.449) during hospitalisation in the influenza viral infection group did not significantly differ from those in the non-influenza viral infection group (table 3 and supplementary table S6). Additionally, there was no significant difference in ICU admission (8.3% versus 5.4%; OR 0.64, 95% CI 0.34–1.20; p=0.157), 90-day mortality (3.8% versus 1.7%; OR 0.43, 95% CI 0.15–1.26; p=0.174) and length of hospital stay (10 versus 10 days; p=0.986) between the two groups.

Compared with the influenza viral infection group, the multivariable adjusted odds ratios of CURB-65 ≥3 and $P_{aO_2}/F_{iO_2} < 200$ mmHg on admission, and occurrence of sepsis and hypoxaemia during hospitalisation for the non-influenza viral infection group were 0.87 (95% CI 0.26–2.84), 0.72 (95% CI 0.26–1.98), 1.00 (95% CI 0.63–1.58) and 1.05 (95% CI 0.66–1.65), respectively. The hazard ratio of 90-day mortality was 0.51 (95% CI 0.13–1.91) (table 4). Additionally, diabetes and elevated procalcitonin (PCT) were associated with a higher proportion of CURB-65 ≥3 and sepsis (supplementary table S7).

Relationship between viral aetiology and disease severity, complications and outcomes

On admission, the proportions of patient with CURB-65 ≥3 (p=0.803) and $P_{aO_2}/F_{iO_2} < 200$ mmHg (p=0.476) were similar in the different viral infection groups (IFV, CoV, HMPV, HRV, AdV, PIV, RSV and two or more viruses) (figure 3). No significant difference was found in terms of demographic characteristics, underlying diseases, respiratory symptoms, C-reactive protein or PCT between the influenza viral infection group and any of the different non-influenza viral infection groups following Bonferroni correction. Higher proportions of consolidation on chest radiography (83.7% versus 50.4%; OR

TABLE 3 Disease severity, complications and outcomes in the influenza and non-influenza viral infection groups

	Influenza viral infection [#]	Non-influenza viral infection [¶]	Mixed viral infection [*]	p-value
Patients	581	240	94	
CURB-65 ≥ 3 on admission	28/571 [4.9]	9/238 [3.8]	3 [3.2]	0.486
$P_{aO_2}/F_{iO_2} < 200$ mmHg on admission	46/534 [8.6]	12/234 [5.1]	4/87 [4.6]	0.092
Complications during hospitalisation				
Sepsis	233 [40.1]	95 [39.6]	39 [41.5]	0.890
Hypoxaemia [§]	214/534 [40.1]	87/234 [37.2]	39/87 [44.8]	0.449
ICU admission	48 [8.3]	13 [5.4]	2 [2.1]	0.157
Invasive mechanical ventilation	30 [5.2]	5 [2.1]	1 [1.1]	0.056
Length of hospital stay days	10.0 [8.0–14.0]	10.0 [7.0–14.0]	11.0 [8.0–14.3]	0.986
In-hospital mortality	16 [2.8]	1 [0.4]	1 [1.1]	0.062
90-day mortality	22 [3.8]	4 [1.7]	2 [2.1]	0.174

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. CURB-65: confusion, urea >7 mmol·L⁻¹, respiratory rate ≥ 30 breaths·min⁻¹, blood pressure <90 mmHg (systolic) or ≤ 60 mmHg (diastolic), age ≥ 65 years; P_{aO_2} : arterial oxygen tension; F_{iO_2} : inspiratory oxygen fraction; ICU: intensive care unit. [#]: only influenza virus with or without co-infection; [¶]: any non-influenza respiratory viruses with or without co-infection; ^{*}: any two or more viruses; [§]: $P_{aO_2}/F_{iO_2} < 300$ mmHg. p-values are for the influenza viral infection group *versus* the non-influenza viral infection group.

5.04, 95% CI 2.31–10.98; $p < 0.001$) but lower rates of diffuse bilateral pulmonary infiltration (4.1% *versus* 36.8%; OR 0.07, 95% CI 0.02–0.30; $p < 0.001$) were found in the AdV group compared with the IFV group (supplementary table S8).

Although more patients with AdV infection had a temperature $>37.8^\circ\text{C}$, the proportion of patients achieving clinical stability within 24 h ($p = 0.205$) and 72 h ($p = 0.230$) after hospitalisation was similar irrespective of viral aetiology (figure 4).

During hospitalisation, the frequency of hypoxaemia was 45.1% in the influenza viral infection group and was similar among the different viral infection groups ($p = 0.416$). Although the proportion of sepsis was lower in the RSV group than that in the IFV (24.6% *versus* 40.1%; OR 0.49, 95% CI 0.26–0.91; $p = 0.022$), AdV (24.6% *versus* 44.6%; OR 0.40, 95% CI 0.18–0.90; $p = 0.025$), HMPV (24.6% *versus* 46.4%; OR 0.38, 95% CI 0.14–0.97; $p = 0.036$) and CoV (24.6% *versus* 48.3%; OR 0.43, 95% CI 0.14–0.98; $p = 0.042$) groups, the difference was not significant following Bonferroni correction. Additionally, no significant difference in 90-day mortality ($p = 0.953$) or length of hospital stay ($p = 0.185$) was found between the different viral infection groups (figure 3).

Multivariable analysis showed no significant difference in the impact of different non-influenza respiratory viruses on risk of CURB-65 ≥ 3 or $P_{aO_2}/F_{iO_2} < 200$ mmHg on admission, and occurrence of sepsis or hypoxaemia during hospitalisation, and 90-day mortality was not significantly different from that of influenza viral infection, after adjustment for confounding factors ($p > 0.05$ for all) (table 4).

Discussion

Here, we performed a large multicentre prospective observational study (conducted in 34 hospitals) in mainland China to systemically investigate the impact of non-influenza respiratory viruses in the adult immunocompetent population, relative to that of IFV. Our results indicated that the effect of non-influenza respiratory viruses on illness severity, complications and outcomes in immunocompetent patients with CAP is similar to that associated with IFV-related respiratory diseases.

In the GLIMP [19] and EPIC studies [20], viral CAP diagnosis was 37.2% in Asia and 23% in the USA, similar to our results (39.2%). Studies of adult CAP in China from 2001 and 2005 showed that bacterial aetiology (atypical and other bacteria) was much higher than viral causes (30.3–53.1% *versus* 10.6–19.0%) [21–25], whereas recent CAP aetiology studies from 2009 and 2016 in China revealed an increased detection of viral infections (21.1% *versus* 34.9%) and a decline of bacterial infections (7.8–24.8%) [14, 26–29], similar to the trends reported in European countries and the USA [30]. The use of new molecular diagnostic methods rather than paired serum antibody titres might explain the higher rate of viral detection. According to the recent epidemic surveillance data, with the exception of IFV, the primary causes of non-influenza viral pneumonia in China were AdV, RSV, CoVs, PIV, HRV and HMPV, with these viruses representing the main focus of this study [14, 26, 29, 31–34].

Non-influenza respiratory viruses accounted for nearly a third of the patients with viral pneumonia in this study. However, HRV was uncommon compared with the EPIC study, where it was the most common

TABLE 4 Association of different viruses with CURB-65 ≥ 3 and arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) < 200 mmHg on admission, occurrence of hypoxaemia and sepsis during hospitalisation, and 90-day mortality in multivariable analysis[#]

Virus	CURB-65 ≥ 3 on admission		P_{aO_2}/F_{IO_2} < 200 mmHg on admission		Sepsis during hospitalisation		Hypoxaemia during hospitalisation		90-day mortality	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	HR (95% CI)	p-value
IFV	Reference		Reference		Reference		Reference		Reference	
Non-IFV[¶]	0.87 (0.26–2.84)	0.811	0.72 (0.26–1.98)	0.519	1.00 (0.63–1.58)	0.993	1.05 (0.66–1.65)	0.842	0.51 (0.13–1.91)	0.314
CoV	0.51 (0.04–6.64)	0.600	0.36 (0.02–5.78)	0.469	1.25 (0.46–3.40)	0.659	1.38 (0.52–3.66)	0.514	3.33 (0.30–36.80)	0.327
HMPV	0.88 (0.08–9.31)	0.916	0.75 (0.07–8.05)	0.810	1.63 (0.64–4.19)	0.307	1.45 (0.57–3.67)	0.436	7.39 (0.54–10.16)	0.135
HRV	3.74 (0.24–17.42)	0.344	2.33 (0.22–24.75)	0.483	1.86 (0.64–5.40)	0.257	1.81 (0.64–5.13)	0.265	NA	
AdV	0.87 (0.11–6.71)	0.892	1.29 (0.29–5.79)	0.742	0.82 (0.37–1.80)	0.629	0.89 (0.40–2.00)	0.779	0.10 (0.04–2.62)	0.170
PIV	2.37 (0.23–24.05)	0.464	NA		1.40 (0.53–3.71)	0.493	1.14 (0.43–3.03)	0.786	NA	
RSV	0.59 (0.06–5.77)	0.653	1.11 (0.19–6.36)	0.905	0.56 (0.23–1.39)	0.209	0.55 (0.22–1.38)	0.204	4.60 (0.36–58.65)	0.240
≥ 2 viruses	0.66 (0.10–4.27)	0.661	0.62 (0.15–2.64)	0.618	1.08 (0.52–2.22)	0.838	1.14 (0.57–2.28)	0.713	0.16 (0.01–2.50)	0.190

CURB-65: confusion, urea > 7 mmol·L⁻¹, respiratory rate ≥ 30 breaths·min⁻¹, blood pressure < 90 mmHg (systolic) or ≤ 60 mmHg (diastolic), age ≥ 65 years; IFV: influenza virus types A and B; CoV: human coronavirus; HMPV: human metapneumovirus; HRV: human rhinovirus; AdV: adenovirus; PIV: parainfluenza virus; RSV: respiratory syncytial virus; NA: not available. [#]: co-infection, fever, elevated procalcitonin, leukocytosis, lobar consolidation and all other variables with $p < 0.2$ in the univariate analysis were included in the multivariable regression model; the variables included in the multivariable adjusted regression analysis are shown in supplementary table S7; [¶]: non-influenza respiratory viruses including CoV, HMPV, HRV, AdV, PIV and RSV.

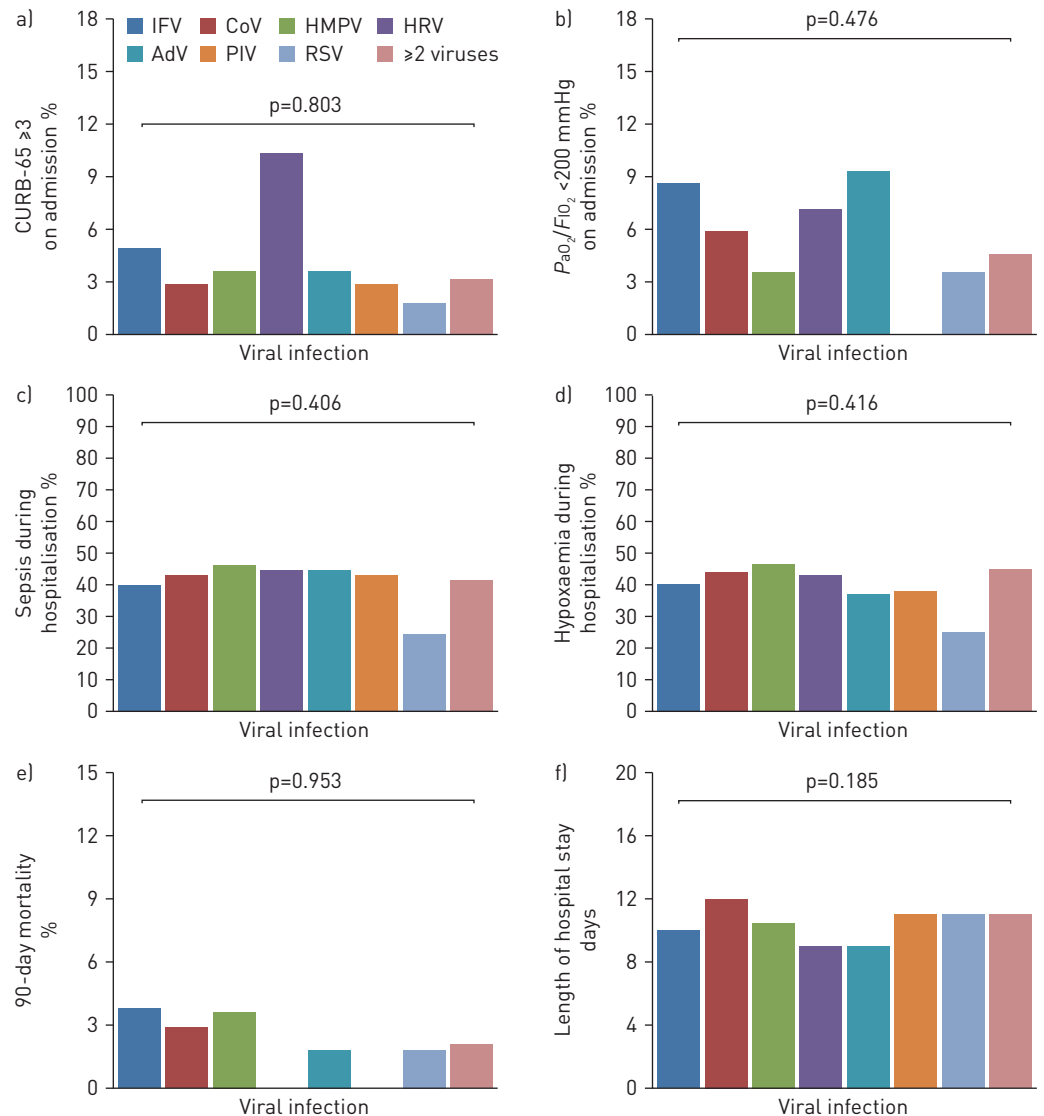


FIGURE 3 a, b) Illness severity on admission, c, d) complications during hospitalisation and e, f) outcomes of hospitalised community-acquired pneumonia patients with viral infections. CURB-65: confusion, urea >7 mmol·L⁻¹, respiratory rate ≥ 30 breaths·min⁻¹, blood pressure <90 mmHg (systolic) or ≤ 60 mmHg (diastolic), age ≥ 65 years; P_{aO_2} : arterial oxygen tension; F_{iO_2} : inspiratory oxygen fraction; IFV: influenza virus types A and B; CoV: human coronavirus; HMPV: human metapneumovirus; HRV: human rhinovirus; AdV: adenovirus; PIV: parainfluenza virus; RSV: respiratory syncytial virus. On admission, the proportions of patients with a) CURB-65 ≥ 3 ($p=0.803$) and b) $P_{aO_2}/F_{iO_2} < 200$ mmHg ($p=0.476$) were comparable in the different viral infection groups. During hospitalisation, no differences in the incidence of c) sepsis ($p=0.406$) and d) hypoxaemia ($p=0.416$) were found among the different viral infection groups. e) 90-day mortality ($p=0.953$) and f) length of hospitalisation ($p=0.185$) showed no statistically significant differences among the different viral infection groups.

viral pathogen [20]. According to recent research and meta-analysis, HRV was the most common virus isolated from patients with COPD, with detection in 23.0% of exacerbated cases [35, 36]. However, only 5.1% (120 out of 2336) of the patients in our cohort had COPD compared with 42% (968 out of 2320) in the EPIC study [20] and 26% (759 out of 3149) in the GLIMP study [19]. This difference might be due to the younger age (median 59.0 *versus* 69.0 years) and fewer current/ex-smokers (31.3% *versus* 42.3%) among our patients [19]. Additionally, RADOVANOVIC *et al.* [19] found a higher prevalence of HRV in North America relative to other continents, including Asia, Europe, Africa and Oceania (26.7% *versus* 2.8%; $p<0.001$), suggesting that climate, geographical position and local epidemiological trends might also influence the prevalence of viruses.

Consistent with previous studies, we observed similar clinical features among the different viral infection groups [37]. Although diffuse bilateral infiltrates were more common in IFV infection cases, further

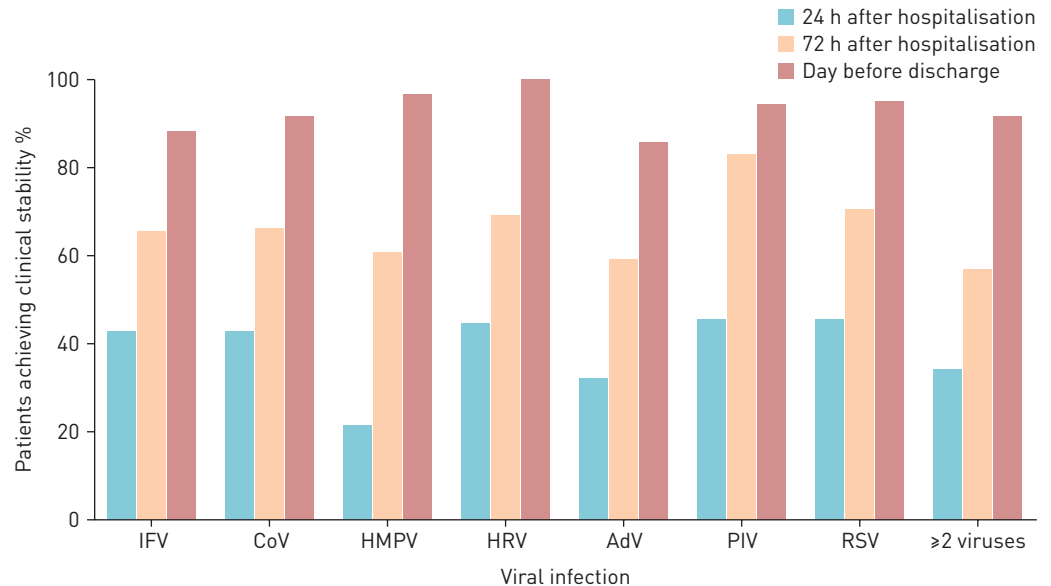


FIGURE 4 Proportion of patients achieving clinical stability 24 and 72 h after hospitalisation and the day before discharge. IFV: influenza virus types A and B; CoV: human coronavirus; HMPV: human metapneumovirus; HRV: human rhinovirus; AdV: adenovirus; PIV: parainfluenza virus; RSV: respiratory syncytial virus. The proportions of patients that achieved clinical stability were similar irrespective of viral aetiology within 24 h ($p=0.205$) and 72 h ($p=0.230$) after hospitalisation.

analysis showed that the difference only remained significant between IFV and AdV infection groups following Bonferroni correction. As previously reported, AdV infection was more commonly observed in young adults and more frequently appeared as consolidation than other viruses [38, 39]. The high rate of elevated lactate dehydrogenase associated with AdV infection might reflect the possibility of hepatitis [40]. Moreover, we found a high proportion of hypoxaemia associated with HMPV and HRV infection. However, none of the clinical factors was specific enough to reliably discriminate between pneumonia caused by IFV and other viral pathogens.

Our data showed that the severity of pneumonia caused by non-influenza respiratory viruses was similar to that caused by IFV, which agrees with reports by GILCA *et al.* [41] and BJARNASON *et al.* [42]. Previous studies had reported that the spread of virus into the bronchial epithelium could induce respiratory airway injury and release of cytokines. Although the induced cytokine profiles might vary by virus, they converge on a common end pathway and result in similar diffuse alveolar damage [43, 44]. In the present study, we found that comorbidities but not the type of viruses were independently associated with sepsis and hypoxaemia in patients with viral pneumonia. For elderly hospitalised patients with respiratory symptoms, RSV, HMPV and PIV were even associated with a higher mortality and more complications compared with IFV [45–49].

The impact of bacterial co-infection on disease severity and mortality had been reported in patients with viral infections [18, 49, 50]. However, detecting all of the concomitant bacterial infection was difficult due to the limitations in traditional methods, the few molecular diagnostic tests approved for bacteria identification [51] and the high rate of pre-sampling antibiotic use. According to a previous study, a PCT threshold of ≥ 0.5 ng·mL⁻¹ resulted in a specificity of 72.5% for bacterial identification [52]. Additionally, fever, leukocytosis and lobar consolidation have also been used to predict bacterial pneumonia [30]. After adjusting for viral–bacterial co-detection, elevated PCT, leukocytosis, fever and lobar consolidation in multivariate analysis, the non-influenza viral infection group was still confirmed to be comparable with the influenza viral infection group regarding disease severity, complications and mortality.

Our study offers critical insights into and recognition of non-influenza respiratory viruses among patients requiring admission to the hospital and potentially the ICU. In some randomised controlled trials and observational studies, rapid recognition of viruses was not associated with reducing the proportion of antibiotic use, early de-escalation or decreased hospital stay [53–58]. However, the duration of antibiotic use was reduced in patients with influenza-like illness, asthma and infective exacerbation of COPD [53, 55]. We recently completed a randomised controlled trial study (ClinicalTrials.gov identifier NCT03391076) which demonstrated that timely virus detection *via* PCR contributes to a decreased duration of antibiotics treatment in hospitalised CAP patients [59]. Furthermore, success has been achieved in patients with a

decreased antibiotic prescription rate along with increased antiviral use following detection of IFV by rapid point-of-care testing [60]. Recognising the role of non-influenza respiratory viruses will promote the rapid development of antivirals, along the same lines as anti-influenza drug development (e.g. balozavir [61], pimodivir [62] and favipiravi [63]). Additionally, more novel antivirals are currently undergoing pre-clinical trials, including DAS181 for influenza [64], HMPV [65] and PIV [66], GS5806, ALS-8176 and AK0529 for RSV [67], and cidofovir for AdV [68]. Timely diagnosis of viral aetiology might help clinicians to optimise the use of antivirals and antibiotics in the era of targeted therapy.

There were some limitations in our study. First, viruses identified from nasopharyngeal swabs cannot easily differentiate lower and upper respiratory tract infections. In this study, only patients with radiologically confirmed pneumonia were enrolled and those with only upper respiratory tract infection had been excluded. Second, bacterial aetiology (atypical and other bacteria) was lower than that reported in previous studies (30.3–53.1%) [21–25] in China from 2001 to 2005 [69]. This might be explained by increased pre-sampling antibiotic use, the relatively lower prevalence of comorbidities and less severe disease, resulting in lower bacterial detection in our study. Third, the PCR test was not used to detect typical bacterial pathogens, as it has not been recommended by the IDSA/American Society for Microbiology guidelines [51]. Fourth, we did not include immunosuppressed patients in this study and therefore our results cannot be generalised to that patient subset.

Conclusions

These findings suggest that complications were common in patients with non-influenza viral pneumonia and the impact of non-influenza respiratory viruses on clinical outcomes was comparable with that of IFV in immunocompetent adult patients with CAP. The increasing recognition of the significant role of non-influenza respiratory viruses might promote the development of CAP management procedures for immunocompetent adult patients.

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