Respiratory viruses and bacterial/fungal superinfections in hospitalized adults with community-acquired pneumonia: clinical features, outcomes, and risk factors

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June 18, 2020

Abstract

Background. Bacterial/fungal superinfections are commonly reported to complicate severe influenza viral community-acquired pneumonia (CAP). However, there is limited knowledge of superinfections among patients with other respiratory viruses, especially in those with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Methods. From December 2017 to February 2020, we enrolled 255 of 528 eligible adults with viral CAP. Respiratory viruses were detected by multiplex RT-PCR. Results. Eighty-eight (34.5%) of viral CAP-associated hospitalizations had evidence of bacterial/fungal superinfection. The incidence and types of bacterial/fungal infections with non-influenza respiratory viruses were analogous to that associated with influenza, except for patients with SARS-CoV-2 infection. Superinfections complicated the clinical outcome of patients with viral pneumonia, by presenting with significantly more in-hospital mortality than those without (22.7% vs 2.4%, P < 0.0001). In the follow-up period, the incidence of death within 120 days after admission was significantly higher in patients with bacterial/fungal superinfection (HR = 9.708, P < 0.0001) than in those without. Furthermore, we found that PaO2/FiO2 < 300 (OR: 2.570, 95% CI: 1.370-4.821, P = 0.003), BUN [?] 7.1 mmol/L (OR: 4.016, 95% CI: 2.148-7.509, P < 0.001), leukocytosis (OR: 2.769, 95% CI: 1.335-5.741, P = 0.006) and lymphocytopenia (OR: 1.998, 95% CI: 1.086-3.675, P = 0.026) were independent risk factors of superinfection. Conclusions. Mixed viral-bacterial/fungal CAP was associated with a higher mortality rate than the primary viral infection. PaO2/FiO2 < 300, BUN [?] 7.1 mmol/L, leukocytosis, and lymphocytopenia were independent risk factors for superinfection.

Introduction

Viral community-acquired pneumonia (CAP) is the leading source of significant morbidity and mortality worldwide [1]. The availability of multiplex molecular-diagnostic techniques has revolutionized the interpretation of the role of respiratory viruses in pneumonia in adults [2]. The prevalence of viral CAP in hospitalized patients varies from 6% to 58% according to different populations and the proportion of CAP caused by respiratory virus climbs [3]. Moreover, the emergence of new viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and avian influenza A, has caused serious viral pneumonia with high mortality rates [4, 5], which attaches great importance to the research of viral CAP.

Little work has been done before and it is only during the pandemic of 2009 that bacterial superinfection is highlighted as a complication of viral CAP [6]. Bacterial pneumonia complicated between 25-50% of severe patients with influenza and will be the most important pathogenic cause of patient outcome [7-9], with the mortality climbing to 50-60%, even when appropriate antibiotics have been used [10]. Furthermore, dual *Aspergillus* and influenza infection is emerging and 67% mortality is linked to *Aspergillosis* highlights the concern for viral-fungal superinfection especially in patients with severe viral infection [11-13]. However, most conclusions addressing bacterial/fungal complications are from patients with influenza pneumonia admitted

to ICU[14], or have included patients without pneumonia[15] or have involved only pediatric patients[16], or from immunocompromised patients with CAP[17], all of which may lead to significant misapprehension about the impact of superinfection on the overall population of patients with viral CAP. A recent multicenter study demonstrated that complications were common in patients with non-influenza viral pneumonia and the impact of non-influenza viruses on clinical outcomes was comparable with that of influenza virus in immunocompetent adult patients [18]. It is unclear whether the risk of superinfection of non-influenza pneumonia is similar to that of influenza pneumonia, especially for SARS-CoV-2. There is also a dearth of clinical data to figure out the potential impact of superinfection on the outcome of patients with viral CAP [6].

Early implementation of treatments to limit the possibility of superinfection may reduce the mortality of patients with influenza and delaying antimicrobial medication could be associated with higher mortality [19]. Conversely, previous studies have also shown that in-hospital all-cause mortality is significantly higher among patients who continue to receive antibiotics after viral respiratory infection diagnosis without bacterial infection [20], and overuse of antibiotics is associated with the emergence of antibiotic-resistant pathogens [20], makes patients with influenza prone to*Aspergillus* infection [13]. Therefore, deciding who should be treated for bacterial/fungal superinfections has been the focus of considerable effort for hospitalized individuals with viral pneumonia [21]. Although a variety of factors such as mechanical ventilation, ICU admission, cardiovascular disease, older age, lymphocyte count have identified as the risk factors for the development of superinfection in patients with influenza [10, 22], there are few studies for patients with viral CAP, not merely with influenza, at an early stage.

In this study, we conducted a 2-year observational study to investigate the incidence and impact of bacterial/fungal complications in patients hospitalized with viral pneumonia and to identify predictors for the development of superinfection at an early stage.

Materials and methods

Study design and populations

A consecutive 2-year prospective study from December 2017 to February 2020 was conducted in 2 tertiary hospitals in China: Beijing Tongren Hospital and the First People's Hospital of Lianyungang City. During the study period, all patients aged [?] 18 years with CAP admitted to the emergency department, general wards, or ICUs were screened for enrollment and selected with a positive multiplex PCR result within the 72 hours following their admission. Patients were diagnosed with pneumonia according to the guideline published by the American Thoracic Society (ATS) in 2007 [23]. Patients were excluded if one of the following criteria was met: 1) aspiration pneumonia; 2) had a clear alternative final diagnosis at the end of follow-up as lung cancer or other non-pneumonia illness; 3) long hospitalization $>$ 90 days before death. The study protocol was approved by the medical ethical committees of the hospitals. The requirement for written informed patient content was waived because all data were anonymous and the observational nature of the study.

During the study period, 528 hospitalized CAP patients were eligible for enrollment, and 272 of them had initial positive RT-PCR results. A total of 17 cases were excluded for final diagnosis of non-pneumonia illness (N = 8), age $<$ 18 years (N = 4), or being lost to follow-up (N = 3), or aspiration pneumonia (N = 2). Finally, a total of 255 pneumonia patients with positive viral detection were included in this analysis (Supplementary Figure 1).

Data collection

Data were collected on admission with demographic information, comorbidities, clinical manifestations, vital signs, laboratory results, microbiology data, chest radiography, antimicrobial use, complications, and outcomes collected using a standardized case-report form. The information was double-checked before entering into an MS Excel sheet. During a 120-day follow up period, all-cause death was recorded by a phone call.

Microbiological evaluation

Viral infections due to influenza A (Flu A), influenza B (Flu B), human rhinovirus (HRV), adenovirus (AdV), bocavirus, coronavirus (CoV), parainfluenza (PIV), respiratory syncytial virus (RSV), enterovirus(EV) and human metapneumovirus (HMPV) were confirmed using the xTAG Respiratory Viral Panel (Luminex Molecular Diagnostics Corporation, Toronto, ON, Canada) [24] via qualified sputum (defined as >25 leukocytes and <10 epithelial cells per 100× magnified field [18]), endotracheal aspirate (ETA), bronchoalveolar lavage fluid (BALF) samples, or nasopharyngeal (NP) swabs. If there was discordance between two tests, the result was confirmed by monoplex PCR. Since Jan 22, 2020, SARS-CoV-2 was further detected in respiratory specimens by real-time PCR methods (Zhijiang, Shanghai, China).

Low respiratory tract specimens and pleural fluid underwent routine Gram staining and quantitative culture for bacterial pathogens. Blood cultures were obtained from patients with temperature 38.5 within 48 h on admission. A bacterial pathogen was determined to be present if detected in a blood sample, sputum, ETA, BALF, or pleural fluid through culture or PCR assay (Seegene Inc. Seoul, Korea), selected bacteria were considered to be contaminants or colonization [25]; if *C. pneumonia* or *M. pneumonia* or *L. pneumophila* was detected in low respiratory tract specimens using PCR assay; or if *L. pneumophila* or *S. pneumonia* was detected in urine employing antigen detection (Binax now, Trinity Biotech, Bray, Ireland) [26].

Fungal pathogens were determined per clinical guidelines [27]. We used culture and microscopic morphological characteristics to distinguish different types of fungal pathogens. A "probable" fungal diagnosis was based on the presence of acute pulmonary infiltrates of the lungs with the positive determination of galactomannan (GM) antigen in the serum or BALF and/or filamentous fungi isolates in BALF, but not necessarily need the presence of immunocompromised disorder [11]. Filamentous fungi isolate in respiratory samples but the absence of newly pulmonary infiltrates or with a negative GM test was described as colonization.*Pneumocystis jirovecii* was determined to be present if detected microscopically in sputum, ETA, or BALF using conventional or immunofluorescence staining or PCR assay (Zhuochenghuisheng, Beijing, China) [28], and supplemented by 1,3-β-D-glucan tests (G tests) in the serum or BALF. *Candida spp.* isolated from low respiratory tract specimens were not considered to be contaminants rather than pathogens.

Definition

Fever was defined as an axillary temperature of 37.3°C or higher. Hypoxemia was defined as PaO_2/FiO_2 < 300 mmHg [18]. Acute respiratory distress syndrome (ARDS) was diagnosed according to ARDS Berlin definition, i.e. severe hypoxemia (PaO_2/FiO_2[?] 300 mmHg with PEEP [?] 5 cmH2O), associated with bilateral opacities on chest X-ray, which could not be fully explained by cardiac failure or fluid overload [29]. Obesity was considered if patients with a body mass index of more than 28 kg/m^2. Pneumonia severity was assessed by CURB-65 [30] and the Pneumonia Severity Index (PSI) [31]. Severe pneumonia was according to modified ATS criteria [23]. Viral and bacterial/fungal superinfection was defined as the detection of both viruses and bacteria/fungi [13, 18]. Mixed viral infection was defined as concurrent detection of both virus detection of [?] 2 viruses. Leukocytosis: leukocyte count > 10,000/mm^3. Neutrophilopenia: neutrophilic granulocyte count < 1500/mm^3. Lymphocytopenia: lymphocyte count < 1000/mm^3. Anemia: hemoglobin <120 g/L for men and <110 g/L for women. Thrombocytopenia: platelet count < 150,000/mm^3.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQR), and categorical variables were presented as numbers and frequencies with percentages to describe the populations, as appropriate. The two-group comparison was done by the Mann-Whitney-U test, and Kruskal-Wallis H nonparametric test was used for multiple comparisons between different groups. A χ^2 test or Fisher exact test was used to compare categorical variables, as appropriate. Actuarial survival rates were analyzed by the Kaplan-Meier method and survival was measured in days from diagnosis to death or the last review. The log-rank test was applied for comparisons between groups. Univariate and multivariate logistic regression was performed to explore the association of clinical characteristics and laboratory parameters and the risk for superinfection. A stepwise backward conditional method was used to select variables entering the multivariate model.

Strongly correlated variables were excluded from multivariate analyses. Multi-collinearity was checked before determining the final model. We assessed goodness of fit with the Hosmer-Lemeshow (HL) test. Data analysis was performed with MedCalc and SPSS 24.0 for Windows software (SPSS Inc. Chicago). For all tests, a two-sided $P < 0.05$ was considered as statistically significant.

Results

Patient characteristics

In this study, 148 (58.0%) of 255 patients with viral pneumonia were male with a median age of 67.0 (54.0-81.0) years (Table 1). One hundred and eight (42.4%) patients had a smoking history. A total of 201 (85.5%) patients had one or more coexisting illnesses. Hypertension, cardiovascular diseases, diabetes, and COPD were the most common coexisting conditions. Cough, fever, and sputum production were the most common symptoms. Chest pain/tightness was reported in 24.3% of the patients. On admission, the leukocyte count was normal or slightly increased in most patients. Elevated levels of C-reactive protein (CRP) were observed in most patients. Hypoxemia ($PaO_2/FiO_2 < 300$ mmHg) was found in 97 (38.0%) of the patients. All patients underwent chest radiography on admission, 180 (70.6%), and 72 (28.2%) of patients had findings of multi-lobular infiltration and pleural effusion, respectively. Generally, 79 (31.0%) patients had a bacterial infection, and 9 (3.6%) had a fungal infection. Common complications included respiratory failure (68 [26.7%] of patients), followed by acute cardiac injury and acute kidney injury. There were 136 (57.9%) patients who had received antiviral medication, and 211 (89.8%) were administrated with antibiotic treatment. Additionally, 59 (25.1%) patients were given systemic corticosteroids. Eighty-eight (34.5%) patients were diagnosed with severe pneumonia. The median length of hospital stay was 13.0 (8.0-21.0) days, and the 120-day mortality was 11.0%.

Most baseline characteristics, mixed bacterial/fungal infections, complications, risk assessment, and clinical outcomes were comparable among influenza, non-influenza, and mixed viral pneumonia. Patients with influenza had the highest rate of antiviral use (111, 68.1%) and the shortest length of hospital stay (12, IQR 7-17 days) compared to the remainder. Other significant differences were summarized in Table 1.

Pathogens distribution

Low respiratory tract specimens for viral identification were obtained in 238 (93.3%) patients (117 for sputum, 53 for ETA, and 68 for BALF respectively). Among all viral patients, Flu A was the first ranking viral pathogen by the detection rate of 49% (126/255), followed by Flu B, 15%; SARS-CoV-2, 8%; HRV, 7%; PIV and CoV, 4%; AdV, 3%; RSV, 2%; HMPV, 1%. No bocavirus was detected. Mixed viral infections were observed in 18 (7%) cases (Figure 1). Approximately forty percent of patients had bacterial/fungal superinfection (ranging from 38%-50%), except for patients with HMPV and SARS-CoV-2 (5%). Notably, there were no significant differences in the rate of bacterial/fungal infection by the viral pathogen (χ^2=11.490, $P = 0.244$).

For the 88 (34.5%) patients involving mixed bacterial/fungal infection, the diagnosis was confirmed with blood culture (in 6 cases), pleural fluid (3 cases), low respiratory specimens culture or PCR (91 cases). Especially, the detection rate of specific bacteria/fungi etiology were similar among influenza, non-influenza and mixed viral infection group (Table S1). A total of 129 strains of pathogens were isolated from 88 patients, and 27 cases of superinfection were caused by dual or more pathogens.*P. aeruginosa* (20.5%, 18/88) and *K. pneumonia* (19.3%, 17/88) were the most commonly detected pathogens, followed by *A. baumannii* (18.2%) and *H. influenza* (17.0%). Of note, fungal infections were documented 9 (10.2%) patients (Figure 2). Up to 75% (6/8) of *S. aureus* were methicillin-resistant, 53% (9/17) of *K. pneumonia* resistant to β-lactam antibiotics, including third-generation cephalosporins and carbapenems, 33% (6/18) of *P. aeruginosa* and 31% (5/11) of*A. baumannii* resistant to carbapenem. Other details were shown in Figure 2. Furthermore,

58.1% (18/31) of antibiotic-resistant bacteria were documented from patients with ventilation, 83.9% (26/31) from patients with severe pneumonia, and 48.4% (15/31) from those who died in 120-days after admission.

Severe clinical outcome of bacterial/fungal superinfection

Clinical and laboratory parameters were compared between hospitalizations involving viral infection alone to those with mixed viral-bacterial/fungal infections. A battery of clinical features was profoundly different between the two groups as indicated in Table 2. Patients with mixed viral-bacterial/fungal infections had more males, higher rates of coexisting illness, especially for hypertension, liver disease, and cancer. These individuals also had a higher incidence of cough, dyspnea and rales, higher respiratory rate, worse laboratory findings, more common abnormalities on chest CT of multi-lobular infiltration and pleural effusion, and worse clinical admission characteristics. Immune examinations between two groups demonstrated that serum levels of T cells were decreased in the bacterial/fungal superinfection group (P = 0.003), and the subset of $CD8^+$ T cells declined further (P = 0.005). There were no differences in antiviral or antibiotic treatments between patients with or without bacterial/fungal superinfection. However, patients with bacterial/fungal superinfection revealed a dramatic increase in the use of antifungal drugs, systematic corticosteroids and mechanical ventilation, incidence of complications, and length of hospital stay as compared with those who suffered viral infection alone (Table 3). The in-hospital mortality was strikingly higher in patients with mixed viral-bacterial/fungal infections than in those without (22.7% vs 2.4%, P < 0.001), especially when they came from non-ICU wards (non-ICU: 15.8% vs 1.3%, P < 0.001; ICU: 45.2% vs 17.6%, P = 0.057, Figure 3). The Kaplan-Meier survival curves for patients with and without bacterial/fungal superinfection showed that the incidence of death within 120 days after admission was significantly higher in patients with bacterial/fungal superinfection (HR = 9.708 P < 0.0001) than in those without.

Risk factors of bacterial/fungal superinfection

To explore the risk factors associated with superinfection, we initially evaluated each variable that displayed statistical significance with P < 0.05 in the difference between patients with and without superinfection using univariate analysis, and candidate variables were shown in Table 2. Considering the total number of patients with superinfection (N = 88) in our study and to avoid overfitting in the model, ten variables were chosen for further multivariable analysis based on previous findings and clinical constraints, namely PaO_2/FiO_2, BUN, leukocytosis, lymphocytopenia, ICU admission within 24 h after hospitalization, need for mechanical ventilation on admission, comorbidity, D-dimer, rales, and age. Finally, $PaO_2/FiO_2 < 300$ (OR: 2.570, 95% CI: 1.370-4.821, P = 0.003), BUN [?] 7.1 mmol/L (OR: 4.016, 95% CI: 2.148-7.509, P < 0.001), leukocytosis (OR: 2.769, 95% CI: 1.335-5.741, P = 0.006) and lymphocytopenia (OR: 1.998, 95% CI: 1.086-3.675, P = 0.026) were independent risk factors of superinfection (Table 4).

Discussion

Very few prospective studies were performed for bacterial/fungal complications of viral CAP in hospitalized adults. In this present study, the incidence, outcome, and risk factors of bacterial/fungal complications were investigated on prospective analysis of two consecutive years' data from patients hospitalized with viral pneumonia. Using comprehensive microbiological tests, our data indicated that 34.5% of viral CAP-associated hospitalizations had evidence of bacterial/fungal superinfection. Apart from illness severity and clinical outcome, the incidence and types of bacterial/fungal infections with non-influenza respiratory viruses were also analogous to that associated with influenza, except for patients with SARS-CoV-2 infection. The high rate of superinfection complicated the clinical outcome of patients with viral pneumonia, while patients with superinfection presented significantly more in-hospital mortality than those without (22.7% vs 2.4%), especially when they came from non-ICU wards. In the follow-up period, the incidence of death within 120 days after admission was significantly higher in patients with bacterial/fungal superinfection than in

those without. Furthermore, we found that $PaO_2/FiO_2 < 300$, BUN [?] 7.1 mmol/L, leukocytosis, and lymphocytopenia were independent risk factors of superinfection.

With the development of multiplex PCR assays for viruses, recent etiology studies have demonstrated an elevated proportion of viral infection (varies from 6% to 58%) and a declined detection of bacterial infection (7.8-24.8%)[2, 18, 32]. Flu was the first ranking viral pathogen, which was in line with other studies [5, 18]. Non-influenza viruses constituted exceeding one-quarter of the patients with viral pneumonia. Mixed viral infection was diagnosed in approximately one out of ten patients, indicating that virus co-infection may be the common phenomenon in viral pneumonia cases, and multiplexing of molecular assays could facilitate the identification of those patients [33]. In contrast to secondary bacterial infections, these mixed viral infections were not associated with a more severe disease course. Most studies published to date in viral CAP have included only one influenza season [5, 14]. The present consecutive 2-year prospective study demonstrated a regular seasonality profile in viral pneumonia, with a peak time in the period of November to March. In accordance with previous studies, we found comparable clinical characteristics among influenza, non-influenza, and mixed viral infection groups [18, 34]. Yet, patients with influenza had a higher rate of antiviral medication, and so perhaps the shorter length of hospital stay.

In our cohort, the severity of diseases, complications, and clinical outcomes of non-influenza pneumonia was analogous to that of influenza pneumonia, which were in line with previous studies [18, 35]. Accumulating evidence reported the notorious complication of bacterial/fungal superinfection followed by influenza infection [9], however, there were few clinical data on whether the risk of bacterial/fungal superinfection of non-influenza pneumonia was similar to that of influenza pneumonia. Our data demonstrated that 34.5% of patients had bacterial/fungal superinfection (ranging from 38%-50% by different viruses), except for SARS-CoV-2 infection. It was consistent with reports in previous studies patients with respiratory tract viral illness [15]. There was limited data on superinfection among patients with SARS-CoV-2 infection [36]. In our study, 5% of patients with SARS-CoV-2 had bacterial superinfection, which was relatively low compared to other respiratory viral infections. The immune system lacks the preexistence of a clonally expanded population of antigen-specific lymphocytes during the first year of the SARS-CoV-2 pandemic, the new virus may trigger an exacerbated inflammatory response that makes superinfection difficult to occur [37]. Notably, there were no significant differences in the rate of bacterial/fungal infection by a viral pathogen ($\chi 2 = 11.490$, $P = 0.244$). This finding is original, since previous works that studied bacterial/fungal complications of viral CAP patients did not make any comparison between influenza and non-influenza viruses. These findings suggested equal attention should be given to pneumonia caused by non-influenza viruses.

Influenza infection may facilitate the nasopharyngeal colonization of opportunistic pathogens (such as *A. baumannii* , *K. pneumoniae* , *Pseudomonas* species or *C. striatum*) that can gain better access to the lower respiratory tract by chemotaxis and cell motility genes and cause severe secondary infection [38] [39] [40]. It has reported that influenza-infected patients co-infected with *P. aeruginosa* and *Aspergillus spp.* were correlated with a significant mortality [37]. Among antibiotic-resistant microorganisms from patients in ICU, infection with *K. pneumonia* ,*A. baumannii,* and *S. aureus* was independently associated with a higher risk of death vs infection with another microorganism [41-44]. In the present study, the most frequent pathogen identified in the two years was *P.aeruginosa* and*K. pneumonia* , followed by*A. baumannii* and *H. influenza* , which was similar to the trend reported in a multicenter study [14]. Of note, fungal infection were documented 9 (9/255, 3.5%) patients. Up to 75% of*S. aureus* were methicillin-resistant, 53% of *K. pneumonia*resistant to β-lactam antibiotics, including third-generation cephalosporins and carbapenems, 33% of MDR *P. aeruginosa* and 31% of *A. baumannii* resistant to carbapenem, which may explain the higher mortality of patients with superinfection.

In CAP, viral-bacterial infection has been associated with a more complicated and worse outcome (e.g., a higher rate of hospital mortality or mechanical ventilation for > 7 days) than infections with viruses only, bacteria only, or no identified etiology [14, 45]. However, these conclusions are drawn from patients admitted to the ICU, few prospective studies were performed for the impact of bacterial/fungal complications on the overall population of patients with viral CAP. Our study clearly demonstrated that patients with

bacterial/fungal superinfection had worse clinical outcomes as opposed to those without, whereas the case-fatality rate was found to be similar between patients with viral CAP and viral-bacterial CAP in patients from conventional wards in a recent study [16]. Such a gap probably owed to the older age and higher frequency of comorbidities of our cohort. Accumulating experimental data demonstrate that viral infection predisposes to bacterial superinfection by augmented bacterial adherence and dysregulation of the immune response [15, 46]. Unexpectedly, Martin-Loeches et al. [14] found the lack of association between appropriate antibiotic treatment and the outcome of viral-bacterial infection, partly underlining the major role of the immune response in the physiopathology of patients with severe influenza infection. In fact, respiratory viruses with both severe and mild disease courses such as influenza, RSV, and HRV may induce immunosuppression. Type I interferons productions are shown to increase after respiratory virus infection, which inhibits the phagocytosis of macrophages, decrease the recruitment of leukocyte to the lung, and increase levels of anti-inflammatory cytokines. For adaptive T cells, $CD8^{+}$T cells are important in recovery from virulent influenza infections [47]. In our study, we found a profoundly higher leukocyte count, lower platelet count, and lymphocyte count. Of note, $CD8^{+}$ T cells were decreased in the superinfection group indicating inadequate adaptive immune responses. These effects all may then contribute to the susceptibility toward various superinfections [48].

Given the incidence and worse outcome of superinfection in viral CAP, some predictors should be identified to determine the initiation of antimicrobial treatment. In patients with severe influenza pneumonia, PCT is shown to be a reasonably accurate marker for the detection of bacterial pneumonia. However, it might not be sufficient as a stand-alone marker for withholding antibiotic treatment [49, 50]. More complementary and simple-to-use markers are needed. Previously, some data suggest that the superinfection rate increased progressively with higher admission BUN levels among 12, 363 patients [51]. The current study confirmed that BUN [?] 7.1 mmol/L was an important independent predictor of mixed viral-bacterial/fungal infection. We also found that hypoxemia might be a good predictor for superinfection, and reflect the state of alveolar ventilation dysfunction. Further research is needed to investigate the pathogenesis of hypoxemia in superinfection. Similar to study in adult patients with respiratory tract viral illness, leukocytosis was indecently associated with superinfection in patients with viral CAP. Respiratory virus-induced type I interferons mediate dysfunction of leukocytes that contributes to the increased susceptibility of various superinfections [48]. At the same time, we also found that lymphocytopenia were independent risk factors of superinfection. Animal model research indicated that lymphocyte deficiency would deactivate neutrophil and macrophages, resulting in impaired bacterial clearance [52]. Data from patients with influenza indicated that lymphopenia on admission was associated with the occurrence of nosocomial infection, which partially favored our result [10].

This study has some limitations. First, PCR detection of viruses in the NP swabs did not indicate the real pathogen of infection. However, low respiratory tract specimens for viral identification were obtained in 238 (93.3%) in our study, indicated that the causation was believable. Second, the diagnosis of bacterial infection was largely based on routine culture methods. The widely empirical use of antibiotics would result in underestimating the incidence of bacterial superinfection. Third, the nasopharyngeal microbiota may play a critical role in viral respiratory infection[39]. Because the background nasopharyngeal microbiota of these patients with viral CAP before hospitalization was unknown, it was hard to trace the isolated bacterial/fungal strains were due to nosocomial infection or the invading downward of existing colonizing strains [40]. Longitudinal studies are needed to address this issue.

In conclusion, superinfections may make up a significant proportion of total viral CAP cases, and the incidence and types of bacterial/fungal infections with non-influenza respiratory viruses were also analogous to that associated with influenza. These findings suggested equal attention should be given to pneumonia caused by non-influenza viruses. Mixed viral-bacterial/fungal infections were associated with a higher mortality rate than primary viral infection. An aggressive microbiological diagnostic approach should be initiated for those with a high risk of superinfection, and clinicians should consider the epidemiology of bacterial pathogens in this setting and consider empiric treatment for those who are critically ill.

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Financial support. This work was supported by the Chinese National Major Project for Infectious Diseases Control (No. 2014ZX10004005), National Science and Technology Major Project for Control and Prevention of Major Infectious Diseases of China (2017ZX10103004).

Potential conflicts of interest. All authors: No reported conflicts.

Acknowledgments: LW and XL conceived of the project and performed the analysis; LW, SL, and JZ collected the data; LW and QZ did the experiments; LW drafted the paper, and all authors critically revised the manuscript; XL takes full responsibility for the data and analysis.

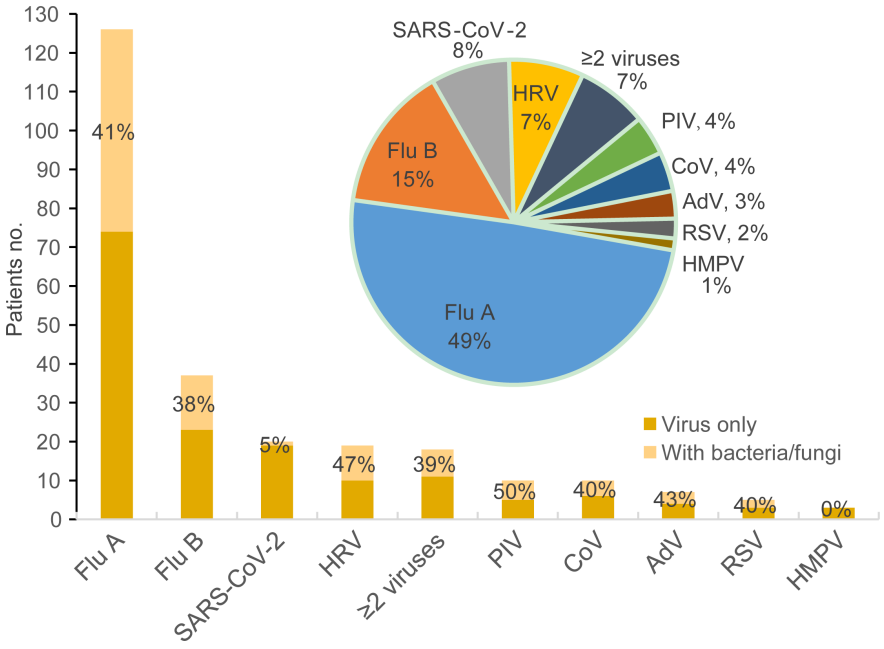
We appreciate all the clinicians and nurses who participated in treating the patients with viral CAP.

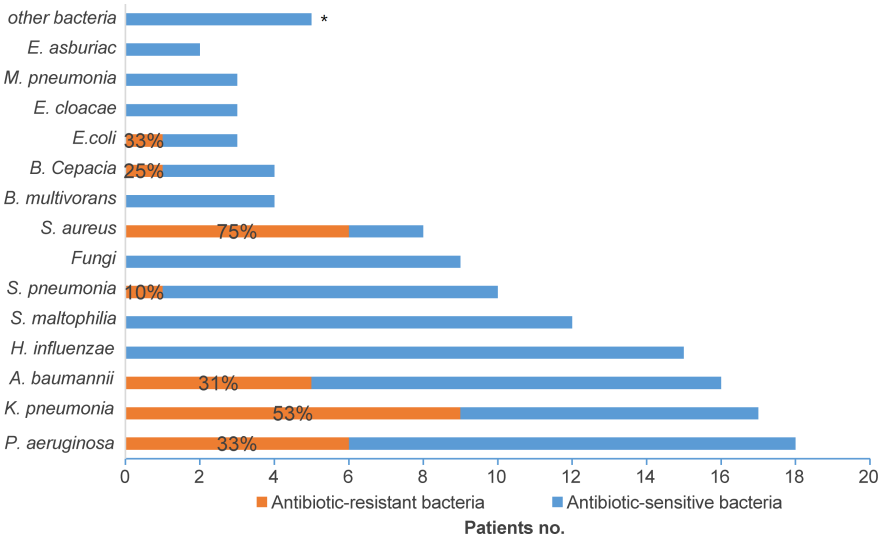
Supplementary Figure 1. Study flow chart. CAP, community-acquired pneumonia. RT-PCR: reverse-transcription polymerase chain reaction.

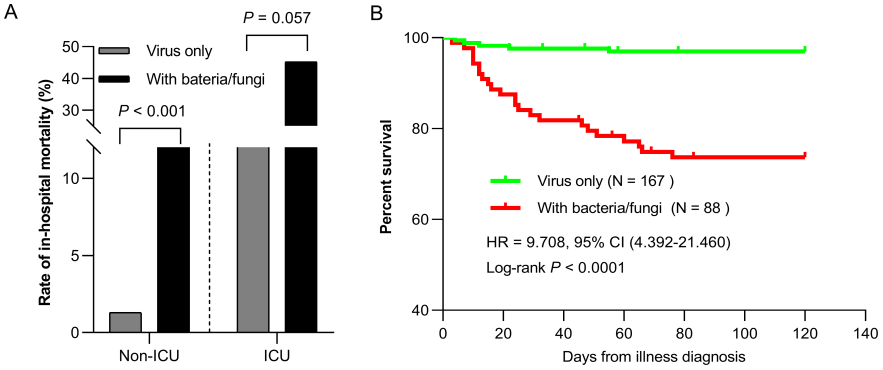
Figure 1. Pathogen detection and monthly distribution of single virus detected among hospitalized adults with viral pneumonia, 2017-2020. Patients' numbers of a specific virus detected were showed. Numbers in the bars represented the percentages of bacterial/fungal co-infection. The proportions of influenza A (Flu A), influenza B (Flu B), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human rhinovirus (HRV), adenovirus (AdV), coronavirus (CoV), parainfluenza (PIV), respiratory syncytial virus (RSV), human metapneumovirus (HMPV) and mixed viral infection () were indicated in the pie chart.

Figure 2. Numbers of specific bacterial/fungal identified in patients hospitalized with viral pneumonia. *, other bacteria included 1*Proteus mirabilis* , 1 *Chlamydophila pneumonia* , and 1*Cupriavidus paucula* isolated from low respiratory specimens. 1*Peptostreptococcus anaerobius* and 1 *S. gallolyticus*isolated from blood. Numbers in the bar represented the percentage of antibiotic-resistance.

Figure 3. Survival of viral pneumonia patients between virus alone and mixed viral-bacterial/fungal groups. The mixed viral-bacterial/fungal group had significantly poorer survival rates compared to the virus group in hospital (A) or in the follow-up period (B). HR, hazard ratio.







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