Original Article

Distribution of the atypical pathogens of community-acquired pneumonia to disease severity

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Background: To investigate the epidemiological characteristics of 11 atypical pathogens of community-acquired pneumonia (CAP) among Chinese, and to determine whether or not there is an association between these pathogens and the severity of illness.

Methods: We conducted a surveillance study for CAP in 30 hospitals of Beijing. Epidemiological data and clinical specimens were systematically collected from enrolled CAP patients. The detection for 11 atypical pathogens [9 respiratory viruses, *Mycoplasma pneumoniae* (MP) and *Chlamydophila pneumoniae* (CP)] was performed. Risk factors of severe CAP and death in Hospital were evaluated.

Results: A total of 6,008 CAP patients [including 1,071 severe CAP (SCAP)] were enrolled. The overall detection rate of the 11 atypical pathogens was 42.4% among 1,925 child CAP (39.9% among 274 child SCAP), and 25.8% among 4,083 adult CAP (22.8% among 797 adult SCAP). The most frequent atypical pathogen among child SCAP was parainfluenza virus (10.2%) followed by respiratory syncytial virus (RSV) (8.4%). However, the most frequent atypical pathogen among adult SCAP was influenza virus (8.9%) followed by parainfluenza virus (3.8%). Multivariate analyses showed that the important predictors for SCAP were an age ≤9 years, an age ≥65 years and co-existing diseases. These factors, except an age ≤9 years, were also predictors of death in Hospital. None of these 11 atypical pathogens was included as the risk factors of SCAP or death in Hospital.

Conclusions: Although these 11 atypical pathogens were the common causes of CAP (including SCAP) among Chinese, they were not observed to increase risks for SCAP or death in Hospital.

Keywords: Community-acquired pneumonia (CAP); severe community acquired pneumonia; respiratory pathogen; atypical respiratory pathogen; surveillance

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Introduction

Community-acquired pneumonia (CAP) is a major cause of hospitalization and death worldwide. Its annual incidence ranges from 2.7–10 per 1,000 persons in European countries (1), 2.67–12 per 1,000 persons in the US (2,3) and 3.4–42.9 per 1,000 persons in Japan (2,3).

CAP can be caused by bacteria, viruses, fungi and parasites etc. (4). According to Jain's reports (5,6), virus infections in CAP patients, especially in adult cap, were more commonly than we expected. In China, there are two multiple center, population based studies that report the characteristics of bacteria, *Mycoplasma pneumoniae* (MP)

and *Chlamydophila pneumoniae* (CP) among Chinese adults with CAP (7,8). However, other existing studies on the viral characteristics of CAP are limited to single sites (8,9).

In Beijing, a Respiratory Pathogens Surveillance System (RPSS) has been established since 2014 to monitor the contagion of respiratory pathogens associated with CAP by the Beijing Center for Disease Prevention and Control (BJCDC). In this multiple center, population based, prospective surveillance study, systematic enrollment and comprehensive microbiological investigation were conducted to explore the epidemiological characteristics of nine frequent respiratory viruses, MP and CP among CAP patients in China, to find the risk factors for SCAP and death in hospital, and to determine whether or not there is an association between these pathogens and the severity of illness.

Methods

Study population

In the RPSS study, a total of 30 hospitals from all 16 districts of Beijing were recruited as sentinel hospitals (*Table S1*), which includes 12 general hospitals and 18 district level hospitals. Under the protocol of the study, approximately 10 CAP patients were required to be enrolled from each hospital every month. These 10 selected patients of each month were required to be distributed as evenly throughout the month as possible. Patients were included if they presented or were admitted to one of the 30 study hospitals and further met the following two conditions: they resided in 1 of the 16 districts in the study catchment areas, and had evidence of CAP according to Guidelines of Diagnosis and Treatment for Community Acquired Pneumonia among Adults in China (released in 2013 by Chinese Thoracic Society, Chinese Medicine Association) (10). CAP was defined as a new or aggravated infiltrate in chest radiographs obtained within 72 hours before or after presentation, which was accompanied by one of the following clinical characteristics: new cough or sputum production, aggravated underlying respiratory disease, fever (>37.8 ℃), hypothermia (<35.6 ℃), leukocytosis (>10×10^9/L), leukopenia (<4×10^9/L) or pulmonary consolidation or moist rale. The immunocompetent and immunocompromised patients with CAP were all included, immunocompromised circumstances referred to: congenital immunodeficiency syndrome, receiving chemotherapy, or anti-rejection therapy, or corticosteroid therapy, human immunodeficiency virus (HIV) infection with a CD4 cell count of >200 per cubic millimeter.

Patients were excluded if they had been hospitalized recently (<28 days for immunocompetent patients and <90 days for immunocompromised patients), had already been enrolled in the RPSS study within the previous 28 days, or had a clear alternative diagnosis of a respiratory disorder. We also excluded patients if they had lung cancer or tuberculosis, pneumoconiosis, noninfectious interstitial lung disease, pulmonary edema, pulmonary atelectasis, pulmonary thromboembolism, pulmonary infiltration with eosinophilia, or pulmonary vasculitis.

According to the Guideline on the Management of Community Acquired Pneumonia among Children in China (released in 2013 by Chinese pediatric society, Chinese Medicine Association) (11,12) . The children with CAP were identified as the SCAP cases if they had at least one of the following clinical features: severely disturbed general conditions, refusal to eat, dehydration, consciousness impairment, the respiratory rate increased to exceed the threshold level (>50 per minute for children over 1 year of age (>70 for infant less than 1 year of age), cyanosis, dyspnea, more than 2 lung lobes or more than two thirds of lung infiltrated, pleural effusion, SaO_2 >0.92, non-pulmonary complications.

According to The Guideline of Diagnosis and Treatment for Community Acquired Pneumonia among Adults in China (released in 2013 by Chinese Thoracic Society, Chinese Medicine Association) (10). Adults with CAP were identified as SCAP cases if they had at least one of the following: consciousness impairment, an increased respiratory rate exceeding the threshold level (>30 per minute), PaO_2 <60 mmHg, PaO_2/FiO_2 <300, mechanical ventilation being needed, artery systolic pressure of less than 90 mmHg, septic shock, infiltration of more than one lung lobe or an infiltrated area increased by 50% during 48 hours after admission, oliguresis (urine output <20 milliliter per hour) or acute renal failure needing dialysis. Compared to Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on Management of Community-acquired Pneumonia in Adults Version 2007 (13), the Chinese criteria of SCAP didn't include three minor criteria: leukopenia (WBC count, <4,000 mm^3), thrombocytopenia (platelet count, <1,000,000 mm^3), hypothermia (core temperature, <36 ℃).

Specimen and data collection

Oropharyngeal swabs were obtained from the enrolled patients as soon as possible after presentation with

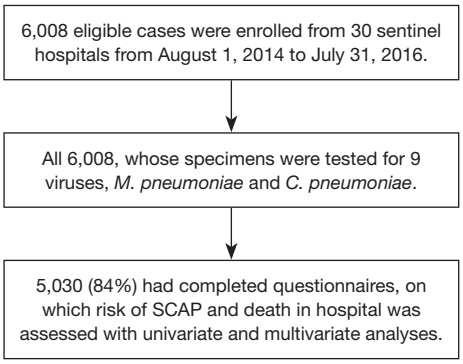

Figure 1 Flow chart of enrollment of CAP patients with radiographic evidence. CAP, community-acquired pneumonia; SCAP, severe CAP.

symptoms. In cases of patients with sputum production, sputum specimens were also obtained. Endotracheal aspirates, and bronchoalveolar-lavage specimens that were obtained for clinical care were also analyzed for the study. Only specimens obtained within 72 hours before or after admission were included. The enrolled patients, their care providers, or both were interviewed using a standardized questionnaire. The following data were collected systematically: demographic information, epidemiology information, underlying diseases, clinical symptoms and signs, laboratory findings, radiology findings, first and final diagnosis, clinical treatment and intervention measures, complications, prognosis.

Laboratory examinations

Clinical specimens were collected from the enrolled cases at each sentinel hospital and sent to BJCDC for laboratory diagnostic testing. Total nucleic acids (RNA and DNA) were extracted from the respiratory specimens (Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processors, Thermo Fisher). The testing for a panel of atypical pathogens, including respiratory viruses, MP and CP, were performed on the extracted nucleic acids. The respiratory viruses included influenza virus A and B (FLU A, FLU B), influenza virus AH1N1 2009 pandemic and AH3N2 (AH1N1 2009, AH3N2), respiratory syncytial virus (RSV), parainfluenza virus 1, 2, 3, 4 (PIV 1, 2, 3, 4), adenovirus (AdV), human rhinovirus (HRV), human metapneumovirus (HMPV), human coronavirus 229E/NL63, OC43/HKU1 (CoV 229E/NL63, OC43/HKU1), human bocavirus (HBoV), human enterovirus (EV). All atypical pathogens were tested with the use of the commercial real-time PCR based kits (Multiplex Combined Real-time PCR Detection Kit for Respiratory Viruses, Multiplex Combined Real-time PCR Detection Kit for Respiratory Bacteria, Jiangsu Uninovo Biological Technology Co. Ltd., China).

The aforementioned viral pathogens, MP and CP were determined to be present if they were detected in at least one of the specimens.

Statistical analysis

Continuous variables were summarized as medians with interquartile ranges. For categorical variables, the percentages of patients in each category were calculated. For analysis convenience, the pathogens were grouped as follows: CoV 229E/NL63, CoV OC43/HKU1 (CoV), PIV1, 2, 3 and 4(PIV), FLUA, AH1N1 2009, AH3N2, and Flu B (FLU). We used a chi-square test or Fisher's exact test, as appropriate, to compare the percentages of pathogens detected and demographic characteristics between sub groups of NSCAP and SCAP, and between sub groups of death cases (only including death in hospital) and those who recovered. We used multiple binary logistic-regression analysis to identify independent predictors of SCAP and death in hospital. The outcomes were predicted with the use of factors such as age, sex, smoke, underlying diseases (chronic lung disease, cardiovascular disease, diabetes mellitus, chronic liver diseases, chronic kidney disease, immunosuppression, neurologic disorder, and other system disease), and pathogens detected (Flu, RSV, HRV, AdV, HBoV, EV, HMPV, PIV, CoV, MP and CP). Age group was transferred to a dummy variable with 18–44 years old as reference category. Forward Stepwise method (likelihood ratio) was used for model building. Variables were included into the model as their P values less than 0.05 and removed as their P values more than 0.1. A P value of less than 0.05 (two tail) was considered to indicate statistical significance. All analyses were performed with the use of SPSS software for Windows (release 17.0).

Results

Study population

During the study period, a total of 6,008 CAP patients confirmed by radiological diagnoses were enrolled into this study from 30 hospitals in Beijing (*Figure 1*). The median

age of the patients was 52 years old (interquartile range, 7 to 75). Among the 6,008 CAP cases, 2,442 patients (40.3%) were female, 1,925 patients (32.1%) were children (with an age of <18 years old), 2,410 patients (40.1%) had underlying conditions (with chronic lung disease and cardiovascular disease as the most common), 695 patients (11.6%) required intensive care, and 168 (2.8%) died (*Table 1*).

Detection of pathogens

Of all 6,008 CAP patients enrolled, an oropharyngeal swab was obtained from 3,770 patients (62.7%), a sputum sample from 1,879 [31.3%, eligible sputum specimens from 823 (43.8%)], a bronchoalveolar-lavage specimen from 308 (5.1%), and an endotracheal aspirate from 51 (0.8%).

A pathogen was detected in 819 of all 1,925 CAP children (42.5%), as follows: ≥1 viruses in 648 (33.7%), MP/CP in 126 (6.5%) and virus-MP/CP co-detections in 45 (2.3%). However, among the 274 SCAP children, A pathogen was detected in 109 (39.8%), as follows: ≥1 viruses in 90 (32.8%), MP/CP in 12 (4.4%) and virus-MP/CP co-detections in 7 (2.6%) (*Figure 2*).

A pathogen was detected in 1,053 of all 4,083 CAP adults (25.8%), as follows: ≥1 viruses in 835 (20.5%), MP/CP in 193 (4.7%) and virus-MP/CP co-detections in 25 (0.6%). However, among the 797 SCAP adults, A pathogen was detected in 182 (22.8%), as follows: ≥1 viruses in 175 (22.0%), MP/CP in 4 (0.5%) and virus-MP/CP co-detections in 3 (0.4%) (*Figure 2*). the overall detection rates of 11 atypical pathogens among adult CAP and among adult SCAP, all decreased significantly than those of child CAP and child SCAP (42.4% *vs.* 25.8%, P<0.001; 42.4% *vs.* 25.8% , 39.9% *vs.* 22.9%, P<0.001).

Of the 1,925 CAP children, the most five frequently detected pathogens were MP (8.6%), PIV (8.4%), RSV (7.5%), flu (6.6%), HRV (6.1%). For the 274 SCAP children, the most five frequently detected pathogens were PIV (10.2%), RSV (8.4%), HRV (8%), MP (6.6%), and flu (4.0%) (*Figure 3*).

Of 4,083 CAP adults, the most five frequently detected pathogens were flu (9.0%), MP (5.0%), HRV (3.1%), PIV (2.8%), CoV (2.2%). For the 797 adults with SCAP, the most five commonly detected pathogens were flu (8.9%), PIV (3.8%), HRV (3.1%), RSV (2.4%), and CoV (2.3%). The detection rate of MP in SCAP patients was significantly lower than that in NSCAP patients (6.1% *vs.* 0.8%, P<0.001) (*Figure 3*).

Detection of viral pathogens among CAP patients decreased steadily with age (*Figure 4*). Flu was more frequently detected among persons ≥10 years old than in younger children (8.9% *vs.* 6.7%, P=0.005). RSV was more commonly detected among children <5 years old than older persons (10.0% *vs.* 2.0%, P<0.001). MP was more commonly detected among patients between the ages of 5–44 years old than other age groups (17.2% *vs.* 2.4%, P<0.001). PIV and HRV were more frequently detected among children than among adults (PIV: 8.4% *vs.* 2.8%, P<0.001; HRV: 6.1% *vs.* 3.1%, P<0.001). For the SCAP patients, the similar findings were observed, but, as compared to the NSCAP, the detection of MP in adults aged 18–44 years old decreased significantly (17.4% *vs.* 3.2%, P=0.038) (*Figure 4*, *Table S2*).

Seasonality

The overall detection rate of the viral pathogens among CAP patients was increased during winter and spring, and hit a minor peak between August and September. The detection rate of RSV peaked in winter, and those of FLU and HMPV were increased during winter and spring. In contrast, the detection rate of PIV rose from the spring, was high through the summer and fell in autumn. The detection rate of MP rose from the summer, remained high through the fall and fell in winter. There is no strong seasonal pattern in HRV; it was detected during the whole year (*Figure 5*).

Risk factors of SCAP and death in hospital

Of 6,008 CAP patients, only 5,030 (84%) have completed their questionnaires as required, and were assessed for risk factors of SCAP and death in hospital. The univariate analyses showed that the independent predictive factors for SCAP were female, an age of 45 years or older, an age of 17 years or younger, chronic lung disease, cardiovascular disease, diabetes mellitus, chronic kidney disease, neurologic disorder, immunosuppression, MP and other system diseases. None of the nine viruses (Flu, RSV, HRV, AdV, HBoV, EV, HMPV, PIV, and CoV) or CP were included into the predictors (*Table S3*). However, multivariate analysis showed that the most important independent risk factors were an age of 45 years or older (especially an age of 65 years or older), an age of 17 years or younger (especially an age of 9 years or younger), neurologic disorder, chronic renal disease and immunosuppression. Female gender was excluded from the multivariate logistic regression model

Table 1 Demographic and clinical characteristics of 6,008 patients with community-acquired pneumonia in the study

Characteristic	Value
Age	
Median [interquartile range], years	52 [7–75]
Sub group (years), n (%)	
0–1	449 (7.5)
2–4	748 (12.5)
5–9	510 (8.5)
10–17	218 (3.6)
18–44	805 (13.4)
45–64	1,085 (18.1)
65–79	1,190 (19.8)
≥80	1,003 (16.7)
Female sex, n (%)	2,422 (40.3)
Smoke, n (%)	
Current smoker[1]	549 (9.1)
Non smoker	4,601 (76.6)
Undocumented	858 (14.3)
Underlying disease[2], n (%)	
Any	2,410 (40.1)
Chronic lung disease	987 (16.4)
Cardiovascular disease	1,081 (18.0)
Chronic renal disease	679 (11.3)
Neurologic disorder	417 (6.9)
Chronic liver disease	81 (1.3)
Diabetes mellitus	679 (11.3)
Immunosuppression	112 (1.9)
Other system disease	485 (8.1)
Undocumented	978 (16.3)
Maximum body temperature (℃), n (%)	
<36	27 (0.4)
36–37.2	932 (15.5)
37.3–38	1,071 (17.8)
38.1–39	2,419 (40.3)
≥39.1	1,424 (23.7)
Undocumented	135 (2.2)
Symptom, n (%)	
Cough	5,425 (90.3)
Chest pain	422 (7.0)
Dyspnea or tachypnea	1,629 (27.1)
Moist rales	2,549 (42.4)
Radiographic findings, n (%)	
Consolidation or infiltrate	2,107 (35.1)
Pleural effusion	447 (7.4)
Other[3]	3,454 (57.5)
Severity of pneumonia, n (%)	
NSCAP	4,937 (82.2)
SCAP	1,071 (17.8)
Hospital treatment, n (%)	
Intensive care unit admission	695 (11.6)
Invasive mechanical ventilation	617 (10.3)
Extracorporeal membrane oxygenation	71 (1.2)
Oxygen therapy	2,331 (38.8)
Death in hospital	168 (2.8)
Patients with eligible SFLRT[4]	1,182 (19.7)
Age median [interquartile range], years	59 [29–76]
Underlying disease, n (%)	588 (49.7)
SCAP, n (%)	252 (21.3)
Patients without eligible SFLRT	4,826 (80.3)
Age Median [interquartile range], years	49 [6–74]
Underlying disease, n (%)	1,822 (37.8)
SCAP, n (%)	819 (17.0)

[1], smoker was defined as a person who smoked at least once a day, and this condition lasted for more than 6 months. [2], any underlying medical condition included chronic lung diseases (asthma, reactive airway diseases, chronic obstructive pulmonary disease, or obstructive sleep apnea), chronic heart disease (i.e., congenital heart disease for children, coronary artery disease or congestive heart failure, but not hypertension), immunosuppression (either due to chronic condition or medication, cancer, or HIV infection with a CD4 cell count of >200 per cubic millimeter), diabetes mellitus, chronic kidney disease (with or without dialysis), chronic liver disease (hepatitis, cirrhosis, or hepatic failure), neurologic disorder (epilepsy, cerebral palsy, dementia, Parkinson's disease, or history of stroke), and other system disease that affected less than 1% of patients. Categories were not mutually exclusive and therefore do not sum to 100%. [3], denote those cases who had radiographic diagnosis of CAP, but no detailed radiographic findings provided in their questionnaires. [4], SFLRT indicates specimen obtained from lower respiratory tract, including eligible sputum, bronchoalveolar-lavage, endotracheal aspirate. There are significant differences in age media ($P<0.001$), underlying disease rate ($P<0.001$) and SCAP percentage ($P<0.001$) between the group with eligible SFLRT and the group without eligible SFLRT. Notably, those cases with the missing values of underlying diseases were not included into calculation for underlying disease rates.

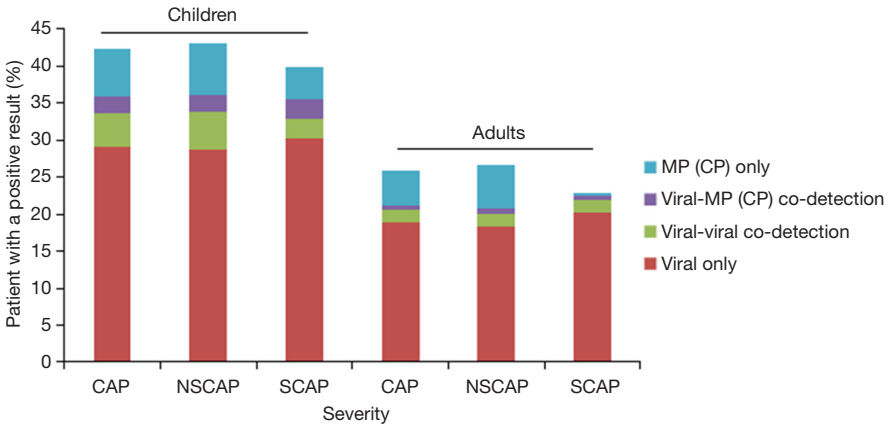

Figure 2 Distribution of infection types among CAP patients by age group and illness severity. This figure shows the results among 6,008 CAP consisting of 4,937 patients with NSCAP, and 1,071 SCAP obtained from August 1, 2014, through July 31, 2016. CAP, community-acquired pneumonia; NSCAP, non-severe CAP; SCAP, severe CAP.

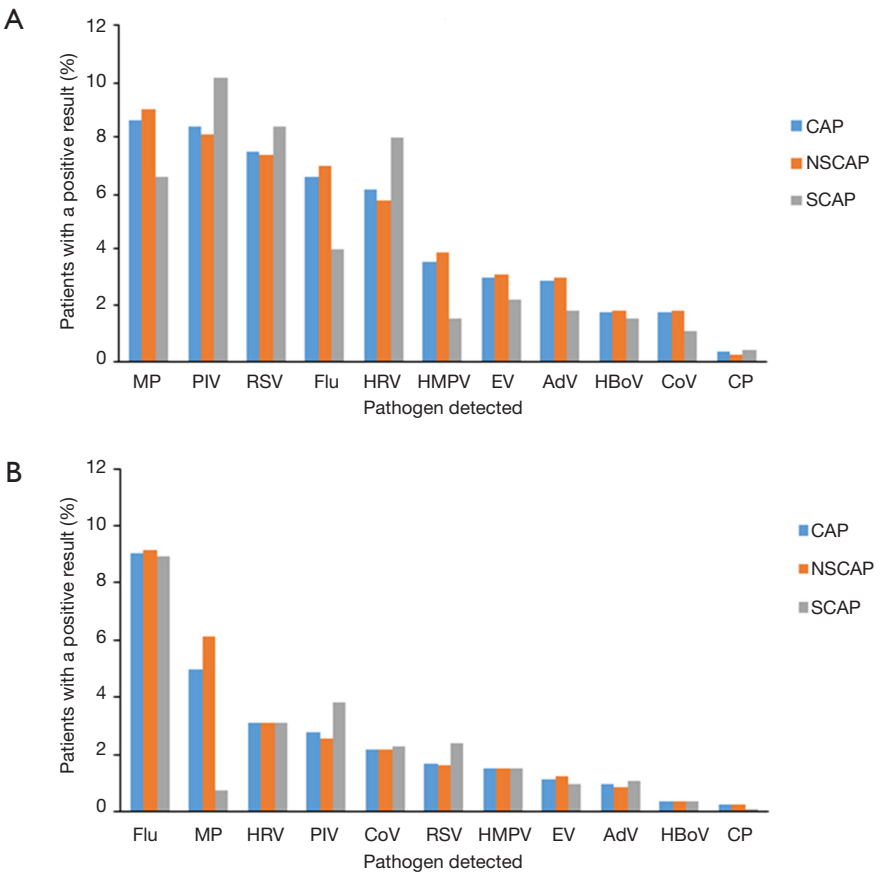

Figure 3 Percentages of the pathogens detected among (A) child patients and (B) adult patients. Among 6,008 CAP patients who had tests for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and viral pathogens. CAP, community-acquired pneumonia; AdV, adenovirus; CoV, coronavirus; Flu, influenza A or B virus; HMPV, human metapneumovirus; HRV, human rhinovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; HBoV, human bocavirus; EV, enterovirus; MP, *Mycoplasma pneumoniae*; CP, *Chlamydophila pneumoniae*.

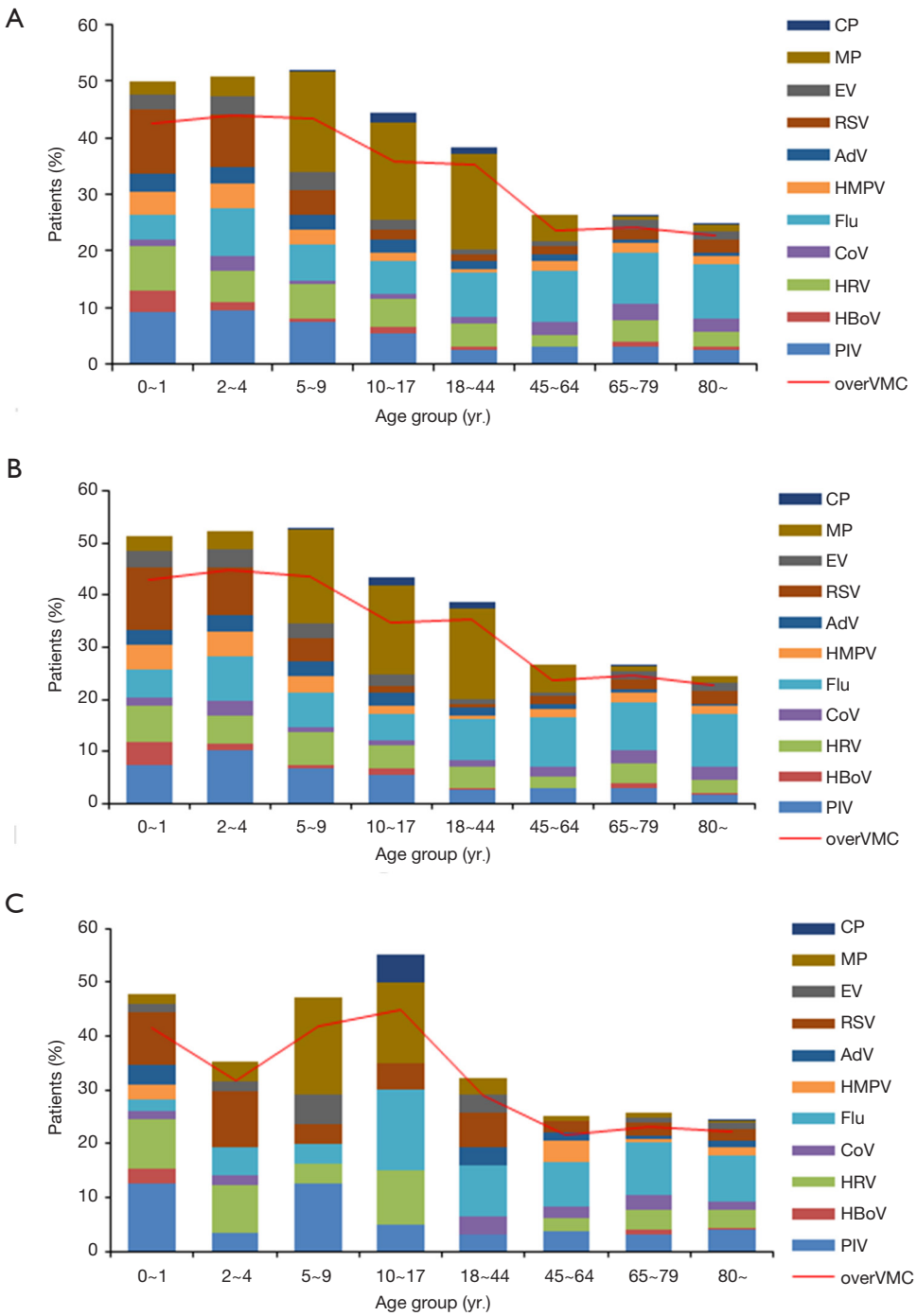

Figure 4 Spectrum of pathogens by age group among (A) all CAP patients, (B) NSCAP patients and (C) SCAP patients. Bars indicate the detection yield of each pathogen; line indicates the detection yield of pathogens together. Over VMC stands for the overall positive rate of respiratory viruses, MP and CP, It means the rate of the patients with at least one of 9 respiratory viruses, MP and CP detected. CAP, community-acquired pneumonia; NSCAP, non-severe CAP; SCAP, severe CAP.

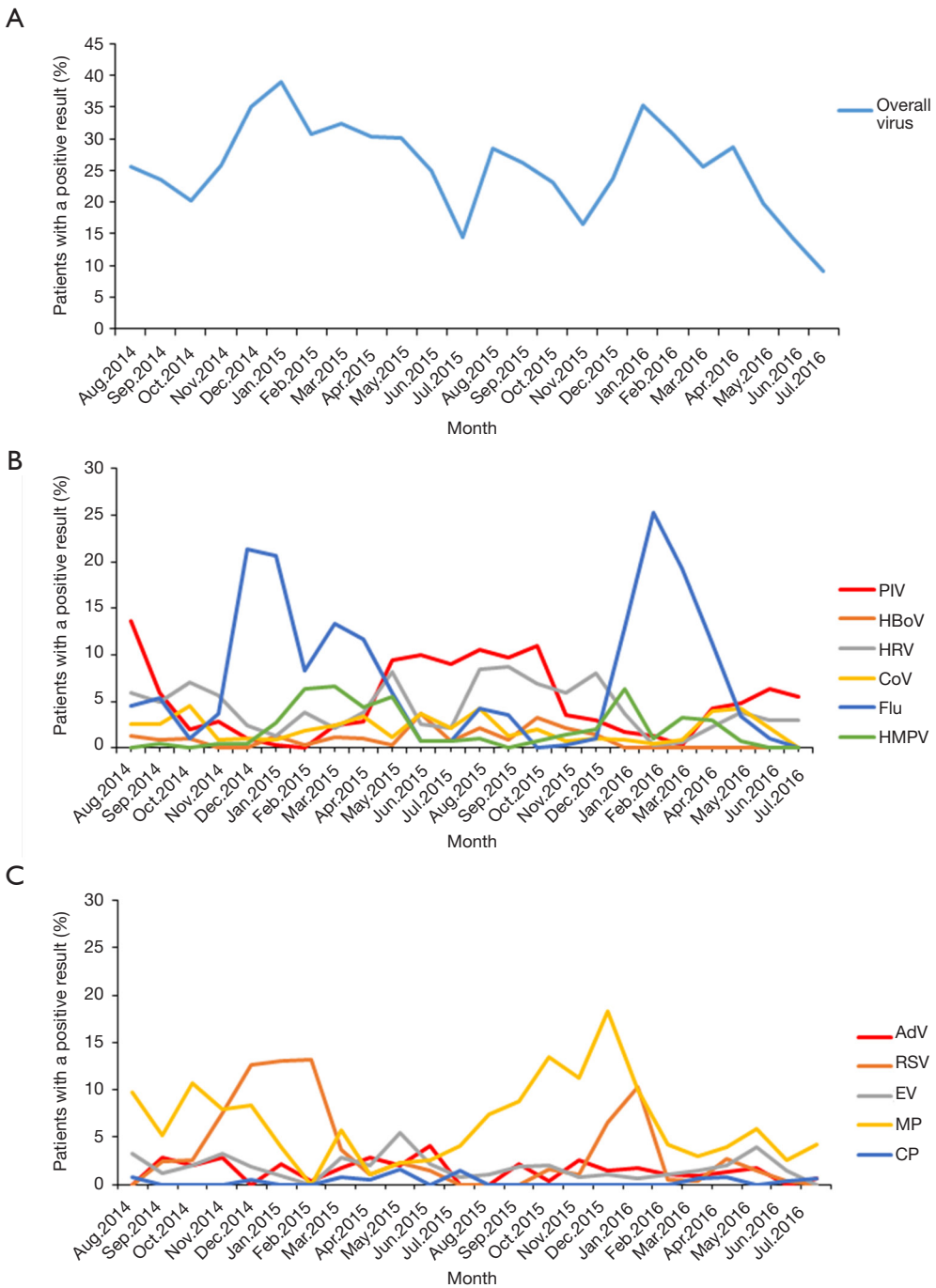

Figure 5 Monthly detection of pathogens among the CAP patients detected from August 1, 2014 to July 31, 2016. (A) Monthly detection rate of 9 viruses together among all CAP patients; (B) the frequency of patients in whom parainfluenza virus, human bocavirus, human rhinovirus, coronavirus, influenza virus, and human metapneumovirus were detected; (C) the frequency of patients in whom adenovirus, respiratory syncytial virus, enterovirus, *M. pneumoniae*, and *C. pneumoniae* were detected. Note the difference in scale of the y axis for each line graph. CAP, community-acquired pneumonia.

Table 2 Multivariate analysis of risk factors for SCAP and death in Hospital of 5,030 CAP patients

Risk factors	Odds ratio (95% CI)	P value
SCAP as outcome		
Age group* (years)		
0–1	10.80 (7.06–16.54)	<0.001
2–4	1.90 (1.20–3.01)	0.006
5–9	3.03 (1.91–4.83)	<0.001
10–17	2.29 (1.27–4.14)	0.006
45–64	2.06 (1.36–3.14)	0.001
65–79	3.50 (2.33–5.25)	<0.001
≥80	4.39 (2.91–6.63)	<0.001
Chronic lung disease	1.74 (1.45–2.09)	<0.001
Cardiovascular disease	1.55 (1.29–1.85)	<0.001
Diabetes mellitus	1.55 (1.27–1.90)	<0.001
Chronic kidney disease	2.52 (1.80–3.53)	<0.001
Immunosuppression	2.41 (1.59–3.67)	<0.001
Neurologic disorder	3.19 (2.54–4.01)	<0.001
Other system disease	1.29 (1.02–1.63)	0.033
Mycoplasma pneumoniae	0.61 (0.38–0.96)	0.031
Constant	0.05	<0.001
Death in hospital as outcome		
Age group* (years)		
0–1	0 (0–0)	0.994
2–4	0 (0–0)	0.992
5–9	0 (0–0)	0.993
10–17	0.78 (0.09–7.08)	0.828
45–64	2.68 (0.90–8.01)	0.078
65–79	7.85 (2.83–21.83)	<0.001
≥80	10.09 (3.62–28.06)	<0.001
Diabetes mellitus	1.44 (1.01–2.06)	0.005
Chronic kidney disease	2.06 (1.25–3.41)	<0.001
Immunosuppression	6.52 (4.00–10.62)	0.023
Neurologic disorder	1.57 (1.06–2.33)	<0.001
Constant	0	0.994

*, age group was transferred to dummy variables with 18–45 years as the reference category. CAP, community-acquired pneumonia; SCAP, severe CAP.

(*Table 2*).

The univariate analyses showed that the risk factors of death in Hospital were an age of 45 years or older and an age of 17 years or younger; chronic lung disease, cardiovascular disease, diabetes mellitus, chronic kidney disease, neurological disorder, immunosuppression and MP. Almost all aforementioned pathogens except MP were excluded (*Table S4*). However, multivariate analysis showed that the independent risk factors only included an age of 65 years or older, chronic kidney disease, neurologic disorder immunosuppression (*Table 2*).

Discussion

This study was one of the largest multiple center surveillance projects on the etiology of CAP among the Chinese to date, and mainly investigated infections of viruses, MP and CP associated with CAP.

In this study, the most five commonly detected viruses were PIV (8.4%), RSV (7.5%), flu (6.6%), HRV (6.1%) and HMPV (3.6%) among children, and flu (9.0%), HRV (3.1%), PIV (2.8%), CoV (2.2%) and RSV (1.7%) among adults. However, Jain *et al.* (5,6) reported the top five frequently detected viruses were RSV (28.0%), HRV (27.3%), HMPV (12.8%), AdV (11.2%) and PIV (6.8%) among children with CAP requiring hospitalization; and HRV (8.4%), flu (5.7%), HMPV (3.8%), RSV (2.9%), PIV (2.9%) among adults with CAP requiring hospitalization in USA between 2010–2013. Xie *et al.* (9) reported that the most three commonly detected viruses were RSV (4.5–50.9%), HRV (12.9–36.2%), PIV (3.9–17.8%) among children younger than 15 years old with acute lower respiratory tract infection from 2007 to 2010. The detection rates of pathogens of this study were obviously lower than those of Jain's (except for PIV among CAP children), but consistent to Xie's findings (except for HRV among CAP children). The difference in inclusion criteria of study populations may be one of the important reasons for the different detection rates. Both CAP inpatient and CAP outpatient were enrolled in our study, but only CAP inpatients were included in Jain's study. Furthermore geographic difference between America and China should also be considered. Our findings indicated that PIV and HRV, which were usually considered as the common pathogens of the patients with acute upper respiratory tract infection, were also the important pathogens of the patients with CAP in China, and should be paid more attention to.

Our results showed that *M. Pneumoniae* was the most

frequently detected pathogen in CAP children (8.6%) and the second in CAP adults (5.0%). Liu *et al.* (7) reported that *M. pneumoniae* was detected among 13.4% of CAP adults in China in 2004. Tao *et al.* (8) reported that *M. pneumoniae* was detected among 31.1% of CAP adults in China from 2004 to 2005. Although the detection rates of *M. pneumoniae* varied considerably among these studies, likely due to a difference in testing methods and study populations, all of the studies indicated that *M. pneumoniae* was one of the very common pathogens of CAP patients in China, as was one of the important characteristics of CAP in China (10). Notably, *M. Pneumoniae* was more commonly detected among patients between the ages of 5–44 years old than other age groups, and the detection rate of *M. Pneumoniae* in adult SCAP was significantly lower than that in adult NSCAP, which indicate that *M. Pneumoniae* infection seems more likely to occur in more "healthy" population. The reason behind this finding is unclear and needs the further research.

The multivariate analyses show that the most important risk factors for SCAP were an age of 45 years or older (especially an age of 65 years or older), an age of 17 years or younger (especially an age of 9 years or younger), chronic renal disease, neurological disorder and immunosuppression. None of respiratory viruses, MP and CP was included. The independent predictors of death in hospital were an age of 65 years or older, chronic kidney disease, neurologic disorders and immunosuppression. However, an age of 9 years or younger, which was one of the important risk factors of SCAP, was not included. Zhang *et al.* (14) also found that fatality of child SCAP among Chinese was associated with congenital heart disease, trisomy 21 syndrome, cerebral palsy, and immune deficiency, and no relationship was noted between fatality and specific pathogens. Their findings were consistent to ours. Wang *et al.* (15) reported that HRV was associated with severe adult CAP in Chinese; Yu *et al.* (16) reported that human adenovirus 7 type caused higher fatality rate (28.6%) of Chinese child acute respiratory infectious disease than other types. However, their conclusions were almost drew from univariate analyses, and some confounding factors, such as underlying disease, should be excluded.

Despite our maximum effort, there were still some limitations in this study.

First, bacterial pathogens were not tested, though they are very important to the etiology of CAP, especially in adult patients. This lack of bacterial testing results, not only led to an incomplete study on the etiology of CAP, but also made it impossible to determine whether or not there is an association between bacterial pathogens and SCAP.

Second, as some studies reported (5), many respiratory viruses identified in patients with CAP might just be colonisation other than the causative pathogens. However, respiratory virus colonisation is not so common as respiratory bacteria. According to the Guideline on the Management of Community Acquired Pneumonia among Children in China (released in 2013 by Chinese pediatric society, Chinese Medicine Association), virus identified from respiratory specimen could be thought as the causative pathogen of the respiratory infection.

Finally, the study population in this study was from Beijing, one of the most developed areas of China, which made it difficult to apply all conclusions of this study to China, as a whole, given the big difference in characteristics of people, culture, economy, geography and climate among the different areas of China.

Conclusions

In conclusion, the above mentioned 11 atypical pathogens were the common causes of CAP (including SCAP) among Chinese, however, among those patients who were exposed to these 11 atypical respiratory pathogens (influenza virus H5N1, influenza virus H7N9 and coronavirus SARS not included), the increase of the risk for SCAP was not observed. The important risk factors for SCAP were an age of 9 years or younger, an age of 65 years or older and co-existing disease (immunosuppression, neurologic disorders and cardiovascular disease). These factors, except for having an age of 9 years or younger, were significantly associated with death in hospital. These findings suggest that the patient's health condition may play a more important role during the SCAP development process than these 11 atypical pathogens.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The ethics approvals for the protocol of this study were obtained from the Ethics Committee of Beijing Center for Disease Prevention and Control. Before enrollment, the nature, purpose, procedures, potential healthy impact and benefits of this study were explained carefully to each patient or their care providers, and written informed consents were obtained. Patients themselves were required to provide assents when their age and medical condition were appropriate.

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Supplementary

Table S1 Thirty sentinel hospitals from all of 16 districts in Beijing, China

Districts	Sentinel hospitals
Dongcheng district	Tiantan Hospital, Tongren Hospital, Beijing No. 6 Hospital, Dongzhimen Hospital
Xicheng district	Peking University People's Hospital, Beijing Children' Hospital, Jianggong Hospital
Chaoyiang district	The First Hospital of Qsinghua University, China-Japan friendship Hospital, Chuiyangliu Hospital
Haidian district	Aerospace Center Hospital, Beijing Shijitan Hospital, Haidian Hospital
Shijingshan district	Shijinshan Hospital, Peking University Shougang Hospital, Jingxi Court of Chuiyangliu Hospital
Miyun district	Miyun Hospital
Daxin district	Daxing Hospital
Mentougou district	Beijing Jingmei Group General Hospital
Changping district	Changping Hospital
Huairou district	Huairou First Hospital
Fengtai district	Dongfang Hospital
Fangshan district	Liangxiang Hospital
Shunyi district	Shunyi Hospital
Tongzhou district	Luhe Hospital
Pinggu district	Pinggu Hospital
Yanqing district	Yianqing Hospital

Table S2 Number (percentage) of patients with a positive result by illness severity and age group

Illness severity	Age group (years)	Cases	Patients with a positive result (%)											
			PIV	HBoV	HRV	CoV	Flu	HMPV	AdV	RSV	EV	MP	CP	Over
CAP (n=6,008)	0–1	449	41 (9.1)	17 (3.8)	35 (7.8)	6 (1.3)	20 (4.5)	18 (4.0)	14 (3.1)	51 (11.4)	12 (2.7)	11 (2.4)	0 (0)	191 (42.5)
	2–4	748	72 (9.6)	10 (1.3)	42 (5.6)	20 (2.7)	62 (8.3)	34 (4.5)	22 (2.9)	69 (9.2)	25 (3.3)	27 (3.6)	0 (0)	328 (43.9)
	5–9	510	37 (7.3)	4 (0.8)	30 (5.9)	4 (0.8)	32 (6.3)	14 (2.7)	14 (2.7)	21 (4.1)	17 (3.3)	91 (17.8)	1 (0.2)	222 (43.5)
	10–17	218	12 (5.5)	2 (0.9)	11 (5.0)	2 (0.9)	13 (6.0)	3 (1.4)	5 (2.3)	4 (1.8)	4 (1.8)	37 (17)	4 (1.8)	78 (35.8)
	18–44	805	21 (2.6)	4 (0.5)	32 (4.0)	10 (1.2)	63 (7.8)	5 (0.6)	13 (1.6)	8 (1.0)	8 (1.0)	136 (16.9)	10 (1.2)	283 (35.2)
	45–64	1,085	32 (2.9)	1 (0.1)	23 (2.1)	24 (2.2)	100 (9.2)	20 (1.8)	12 (1.1)	16 (1.5)	8 (0.7)	51 (4.7)	0 (0)	256 (23.6)
	65–79	1,190	37 (3.1)	9 (0.8)	45 (3.8)	33 (2.8)	110 (9.2)	19 (1.6)	7 (0.6)	23 (1.9)	19 (1.6)	10 (0.8)	1 (0.1)	287 (24.1)
	≥8yr	1,003	26 (2.6)	3 (0.3)	28 (2.8)	22 (2.2)	96 (9.6)	16 (1.6)	7 (0.7)	23 (2.3)	15 (1.5)	9 (0.9)	1 (0.1)	227 (22.6)
	Total	6,008	278 (4.6)	50 (0.8)	246 (4.1)	121 (2.0)	496 (8.3)	129 (2.1)	94 (1.6)	215 (3.6)	108 (1.8)	372 (6.2)	17 (0.3)	1,872 (31.2)
NSCAP (n=4,937)	0–1	307	23 (7.5)	13 (4.2)	22 (7.2)	4 (1.3)	17 (5.5)	14 (4.6)	9 (2.9)	37 (12.1)	10 (3.3)	8 (2.6)	0 (0)	132 (43)
	2–4	691	70 (10.1)	10 (1.4)	37 (5.4)	19 (2.7)	59 (8.5)	34 (4.9)	22 (3.2)	63 (9.1)	24 (3.5)	25 (3.6)	0 (0)	310 (44.9)
	5–9	455	30 (6.6)	4 (0.9)	28 (6.2)	4 (0.9)	30 (6.6)	14 (3.1)	14 (3.1)	19 (4.2)	14 (3.1)	81 (17.8)	1 (0.2)	199 (43.7)
	10–17	198	11 (5.6)	2 (1.0)	9 (4.5)	2 (1.0)	10 (5.1)	3 (1.5)	5 (2.5)	3 (1.5)	4 (2.0)	34 (17.2)	3 (1.5)	69 (34.8)
	18–44	774	20 (2.6)	4 (0.5)	32 (4.1)	9 (1.2)	60 (7.8)	5 (0.6)	12 (1.6)	6 (0.8)	7 (0.9)	135 (17.4)	10 (1.3)	274 (35.4)
	45–64	952	27 (2.8)	1 (0.1)	20 (2.1)	21 (2.2)	89 (9.3)	15 (1.6)	10 (1.1)	13 (1.4)	8 (0.8)	50 (5.3)	0 (0)	227 (23.8)
	65–79	887	27 (3.0)	7 (0.8)	34 (3.8)	24 (2.7)	81 (9.1)	17 (1.9)	5 (0.6)	16 (1.8)	16 (1.8)	7 (0.8)	1 (0.1)	217 (24.5)
	≥80	673	12 (1.8)	2 (0.3)	17 (2.5)	17 (2.5)	68 (10.1)	11 (1.6)	3 (0.4)	16 (2.4)	11 (1.6)	8 (1.2)	0 (0)	153 (22.7)
	Total	4,937	220 (4.5)	43 (0.9)	199 (4.0)	100 (2.0)	414 (8.4)	113 (2.3)	80 (1.6)	173 (3.5)	94 (1.9)	348 (7.0)	15 (0.3)	1,581 (32)
SCAP (n=1,071)	0–1	142	18 (12.7)	4 (2.8)	13 (9.2)	2 (1.4)	3 (2.1)	4 (2.8)	5 (3.5)	14 (9.9)	2 (1.4)	3 (2.1)	0 (0)	59 (41.5)
	2–4	57	2 (3.5)	0 (0)	5 (8.8)	1 (1.8)	3 (5.3)	0 (0)	0 (0)	6 (10.5)	1 (1.8)	2 (3.5)	0 (0)	18 (31.6)
	5–9	55	7 (12.7)	0 (0)	2 (3.6)	0 (0)	2 (3.6)	0 (0)	0 (0)	2 (3.6)	3 (5.5)	10 (18.2)	0 (0)	23 (41.8)
	10–17	20	1 (5.0)	0 (0)	2 (10.0)	0 (0)	3 (15.0)	0 (0)	0 (0)	1 (5.0)	0 (0)	3 (15.0)	1 (5.0)	9 (45.0)
	18–44	31	1 (3.2)	0 (0)	0 (0)	1 (3.2)	3 (9.7)	0 (0)	1 (3.2)	2 (6.5)	1 (3.2)	1 (3.2)	0 (0)	9 (29.0)
	45–64	133	5 (3.8)	0 (0)	3 (2.3)	3 (2.3)	11 (8.3)	5 (3.8)	2 (1.5)	3 (2.3)	0 (0)	1 (0.8)	0 (0)	29 (21.8)
	65–79	303	10 (3.3)	2 (0.7)	11 (3.6)	9 (3.0)	29 (9.6)	2 (0.7)	2 (0.7)	7 (2.3)	3 (1.0)	3 (1.0)	0 (0)	70 (23.1)
	≥80	330	14 (4.2)	1 (0.3)	11 (3.3)	5 (1.5)	28 (8.5)	5 (1.5)	4 (1.2)	7 (2.1)	4 (1.2)	1 (0.3)	1 (0.3)	74 (22.4)
	Total	1,071	58 (5.4)	7 (0.7)	47 (4.4)	21 (2.0)	82 (7.7)	16 (1.5)	14 (1.3)	42 (3.9)	14 (1.3)	24 (2.2)	2 (0.2)	291 (27.2)

CAP, community-acquired pneumonia; NSCAP, non-severe CAP; SCAP, severe CAP; HBoV, human bocavirus; HRV, human rhinovirus; CoV, coronavirus; Flu, influenza A or B virus; HMPV, human metapneumovirus; AdV, adenovirus; RSV, respiratory syncytial virus; PIV, parainfluenza virus; EV, enterovirus; MP, *Mycoplasma pneumoniae*; CP, *Chlamydophila pneumoniae.*

Table S3 Univariate analysis of risk factors for SCAP of 5,030 CAP patients

Variable	NSCAP [3,974], n (%)	SCAP [1,056], n (%)	P value
Female sex	1,607 (40.4)	391 (37.0)	0.044
Age (years)			<0.001
0–1	230 (5.8)	136 (12.9)	
2–4	583 (14.7)	56 (5.3)	
5–9	379 (9.5)	54 (5.1)	
10–17	176 (4.4)	20 (1.9)	
18–44	560 (14.1)	31 (2.9)	
45–64	731 (18.4)	130 (12.3)	
65–79	759 (19.1)	301 (28.5)	
≥80	556 (14.0)	328 (31.1)	
Current smoker*	441 (12.3)	106 (10.9)	0.248
Chronic lung disease	654 (16.5)	333 (31.5)	<0.001
Cardiovascular disease	686 (17.3)	395 (37.4)	<0.001
Diabetes mellitus	437 (11.0)	242 (22.9)	<0.001
Chronic kidney disease	82 (2.1)	92 (8.7)	<0.001
Chronic liver disease	59 (1.5)	22 (2.1)	0.170
Immunosuppression	62 (1.6)	50 (4.7)	<0.001
Neurologic disorder	210 (5.3)	207 (19.6)	<0.001
Other system disease	348 (8.8)	137 (13.0)	<0.001
HBoV	38 (1.0)	7 (0.7)	0.368
HRV	155 (3.9)	45 (4.3)	0.594
CoV	96 (2.4)	21 (2.0)	0.413
Flu	329 (8.3)	81 (7.7)	0.521
HMPV	92 (2.3)	15 (1.4)	0.073
AdV	65 (1.6)	14 (1.3)	0.472
RSV	153 (3.9)	41 (3.9)	0.961
PIV	192 (4.8)	58 (5.5)	0.380
EV	88 (2.2)	14 (1.3)	0.069
MP	295 (7.4)	23 (2.2)	<0.001
CP	11 (0.3)	2 (0.2)	0.876

*, only 4573 of 5,030 cases have full information on smoke history. CAP, community-acquired pneumonia; NSCAP, non-severe CAP; SCAP, severe CAP; HBoV, human bocavirus; HRV, human rhinovirus; CoV, coronavirus; Flu, influenza A or B virus; HMPV, human metapneumovirus; AdV, adenovirus; RSV, respiratory syncytial virus; PIV, parainfluenza virus; EV, enterovirus; MP, *Mycoplasma pneumoniae*; CP, *Chlamydophila pneumoniae*.

Table S4 Univariate analysis of risk factors for death in hospital of 5,030 CAP patients

Variable	Death [168], n (%)	Recovery [4,862], n (%)	P value
Female sex	63 (37.5)	1,935 (39.8)	0.549
Age (years)			
0–1	0 (0)	366 (7.5)	<0.001
2–4	0 (0)	639 (13.1)	
5–9	0 (0)	433 (8.9)	
10–17	1 (0.6)	195 (4.0)	
18–44	4 (2.4)	587 (12.1)	
45–64	18 (10.7)	843 (17.3)	
65–79	68 (40.5)	992 (20.4)	
≥80	77 (45.8)	807 (16.6)	
Current smoker*	18 (11.3)	529 (12.0)	0.778
Chronic lung disease	69 (41.1)	918 (18.9)	<0.001
Cardiovascular disease	79 (47.0)	1,002 (20.6)	<0.001
Diabetes mellitus	52 (31.0)	627 (12.9)	<0.001
Chronic kidney disease	23 (13.7)	151 (3.1)	<0.001
Chronic liver disease	5 (3.0)	76 (1.6)	0.263
Immunosuppression	27 (16.1)	85 (1.7)	<0.001
Neurologic disorder	39 (23.2)	378 (7.8)	<0.001
Other system disease	21 (12.5)	464 (9.5)	0.202
HBoV	1 (0.6)	44 (0.9)	0.998
HRV	10 (6.0)	190 (3.9)	0.182
CoV	2 (1.2)	115 (2.4)	0.464
Flu	18 (10.7)	392 (8.1)	0.217
HMPV	0 (0)	107 (2.2)	0.095
AdV	0 (0)	79 (1.6)	0.177
RSV	3 (1.8)	191 (3.9)	0.156
PIV	3 (1.8)	247 (5.1)	0.053
EV	3 (1.8)	99 (2.0)	1.000
MP	0 (0)	318 (6.5)	0.001
CP	0 (0)	13 (0.3)	1.000

*, only 4,573 of 5,030 cases have full information on smoke history. CAP, community-acquired pneumonia; HBoV, human bocavirus; HRV, human rhinovirus; CoV, coronavirus; Flu, influenza A or B virus; HMPV, human metapneumovirus; AdV, adenovirus; RSV, respiratory syncytial virus; PIV, parainfluenza virus; EV, enterovirus; MP, *Mycoplasma pneumoniae*; CP, *Chlamydophila pneumoniae.*