Severity and outcomes of influenza-related pneumonia in type A and B strains in China, 2013–2019

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Abstract

Background: Inconsistencies exist regarding the severity of illness caused by different influenza strains. The aim of this study was to compare the clinical outcomes of hospitalized adults and adolescents with influenza-related pneumonia (Flu-p) from type A and type B strains in China.

Methods: We retrospectively reviewed data from Flu-p patients in five hospitals in China from January 2013 to May 2019. Multivariate logistic and Cox regression models were used to assess the effects of influenza virus subtypes on clinical outcomes, and to explore the risk factors of 30-day mortality for Flu-p patients.

Results: In total, 963 laboratory-confirmed influenza A-related pneumonia (FluA-p) and 386 influenza B-related pneumonia (FluB-p) patients were included. Upon adjustment for confounders, multivariate logistic regression models showed that FluA-p was associated with an increased risk of invasive ventilation (adjusted odds ratio [aOR]: 3.824, 95% confidence interval [CI]: 2.279–6.414; P < 0.001), admittance to intensive care unit (aOR: 1.630, 95% CI: 1.074–2.473, P = 0.022) and 30-day mortality (aOR: 2.427, 95% CI: 1.568–3.756, P < 0.001) compared to FluB-p. Multivariate Cox regression models confirmed that influenza A virus infection (hazard ratio: 2.637, 95% CI: 1.134–6.131, P = 0.024) was an independent predictor for 30-day mortality in Flu-p patients.

Conclusions: The severity of illness and clinical outcomes of FluA-p patients are more severe than FluB-p. This highlights the importance of identifying the virus strain during the management of severe influenza.

Keywords: Influenza, Pneumonia, Virus type, Clinical outcome

Background

Influenza is a contagious respiratory disease that is widespread across the globe. Despite advances in medical technology, influenza causes considerable hospitalizations and mortality [1, 2]. It is estimated that each year, 1 billion cases of symptomatic influenza infection have occurred across the globe, including 3–5 million cases of severe illness and 290 000–650 000 cases of influenza-related respiratory deaths [3]. From 2010 to 2018, approximately 4.3–23 million medical visits, 140 000–960 000 hospitalizations, 18 000–96 000 influenza-related intensive care unit admissions and 12 000–79 000 deaths were associated with influenza per year in the United States of America [4]. The disease burden of influenza in Asia is similar to that of western countries [5, 6]. Influenza infection also poses an economic burden. Recent estimates place the economic burden of a moderately severe to severe pandemic at approximately USD 500 billion, or 0.6% of the global income [7]. For these reasons, influenza epidemics are regarded as the greatest threat to the public health in the twenty-first century.
Influenza presents with non-specific symptoms, including sudden onset fever, headache, a sore throat and cough. Kilbourne suggested that the disease features caused by different influenza virus subtypes are clinically indistinguishable [8]. Several studies have examined the hypothesis that the severity of illness caused by influenza is associated with causual virus types. For example, Mosnier & Irving found that the clinical symptoms and outcomes for patients with influenza A and B infections were comparable [9, 10]. Studies by Kaji and colleagues showed that influenza A infection was more severe than influenza B [11]. The outcomes of different studies have been variable in terms of sample size, study settings, populations, and the ability to control potential confounders. Despite inconsistent findings, to understand the differences of the severity and outcomes between specific influenza virus types is of great significance to arrange rational diagnostic testing, carry out prompt antiviral treatment and make other clinical decisions in the management of severe influenza.

Influenza-related pneumonia (Flu-p) is the major kind of severe influenza, which contributes to 20–50% of influenza-related hospitalizations [12]. Here, we conducted a multicenter, retrospective study aimed to evaluate the impact of virus type A and type B on the illness severity and clinical outcomes of immunocompetent, adolescents and adults hospitalized with Flu-p onset in community.

Methods

Study design

Patient recruitment

We screened hospitalized patients positive for influenza virus RNA at the microbiology labs of five tertiary hospitals in China from 1 January 2013 to 31 May 2019 (Additional file 1). Patients with laboratory-confirmed Flu-p were included. Exclusion criteria were as follows: (i) Aged ≤ 14 years; (ii) not classified as community-onset pneumonia (pneumonia onset ≥ 48 h post-admission and hospitalized within the last 28 days [13]), as it was difficult to determine whether nosocomial pneumonia occurred after the onset the influenza; (iii) it has been reported that the clinical characteristics and outcomes of immunocompromised patients with influenza differ to those of immunocompetent hosts. So, those who are immunocompromised were excluded [14].

Disease and treatment definitions

Patients with influenza-related pneumonia were defined during the influenza season and manifested with respiratory symptoms and were positive for influenza virus by reverse-transcription polymerase chain reaction (RT-PCR), together with pulmonary infiltrates on chest radiographs. Early neuraminidase inhibitor (NAI) treatment was defined as any NAI (oseltamivir, zanamivir and peramivir) administered within 48 h of illness onset [15]. Systemic corticosteroid use was defined as at least one dose of any systemic corticosteroid administrated during hospitalization.

Data collection

Data were retrospectively collected and included demographic information, underlying diseases (comorbidities are defined in Additional file 1), clinical symptoms, vital signs, laboratory and radiological findings at admission, community-acquired respiratory co-infections (Additional file 1 [16]), clinical management (administration of NAIs, systemic corticosteroids, vasopressor agents, invasive and non-invasive mechanical ventilation) and outcomes (admittance to ICU, length of hospital stay and 30-day mortality). Patients with hospital stays < 30 days were followed up by phone calls to determine survival status.

Data analysis

Data were analysed for normality using a Kolmogorov–Smirnov test. Measurement data with a normal distribution are shown as the mean ± standard deviation. Those with a non-normal distribution are expressed as the median. Categorical variables were analyzed using the Chi-square or Fisher’s exact test. Continuous variables were analyzed using a Student’s t test or Mann-Whitney U test. P-values ≤ 0.05 were considered significant. All probability tests were two-tailed.

To evaluate the impact of influenza virus subtypes on illness severity and clinical outcomes (invasive ventilation, admittance to ICU and 30-day mortality) in Flu-p patients, multivariate logistic regression models were established following adjustment for age, sex, comorbidities, pregnancy, obesity, smoking history, early NAI therapy, systemic corticosteroid use, and coinfection with other pathogens. These risk factors were previously shown to be associated with the clinical outcomes of influenza patients and served as confounders [15].

According to the survival status at 30 days post-admission, patients were divided into survival and deceased groups. Baseline characteristics of these patients were then compared. To identify the risk factors for 30-day mortality in Flu-p patients, variables with P-values < 0.1 in univariate analysis and influenza virus type A were entered into the multivariate Cox regression analysis. All analyses were performed using Statistical Package for Social Science 22.0 (SPSS, Chicago, IL, USA).

Results

Screening process

We screened 3190 patients that were influenza RNA positive. A total of 693 laboratory-confirmed FluA-p
patients and 386 FluB-p patients were included (Fig. 1). Amongst the FluA-p patients, 38.1% (264/693) were infected with A (H1N1) pdm09 and 11.0% (76/693) were infected with A (H3N2). In total, 50.9% (353/693) of patients were infected with an unclassified subtype.

**Clinical characteristics of Flu-p patients**

The median age of the Flu-p patients was 61.0 years old. Males accounted for 54.1% (584/1079) of Flu-p patients. More than 50% had at least one underlying disease, including cardiovascular disease 24.0% (259/1079), diabetes mellitus 11.8% (127/1079) and cerebrovascular disease 9.0% (97/1079). In total, 29% (313/1079) of patients had a history of smoking. Axillary temperatures \( \geq 38^\circ C \) (75.4%, 814/1079) and cough/sputum (98.2%, 1060/1079) were the most common symptoms. Confusion and respiratory rates \( \geq 30 \text{ beats/min} \) were observed in 13.9% (150/1079) and 13.5% (146/1079) of patients, respectively. Only 1.4% (15/1079) of patients showed systolic blood pressure < 90 mmHg at admission. In total, 46.8% (480/1025) of patients had PO\(_2\)/FiO\(_2\) < 300 mmHg and 73.6% (794/1079) showed multilobar infiltrates on chest radiology (Table 1).

Other community-acquired pathogens were present in 34.0% (367/1079) of Flu-p patients. *Klebsiella pneumoniae* (31.6%, 116/367) was the most common, followed by *Streptococcus pneumoniae* (29.7%, 109/367) and *Staphylococcus aureus* (19.3%, 71/367) (Additional File 1).

The clinical management and outcomes of Flu-p patients are shown in Table 2. All received antibiotics and NAI, with early NAI administrated to 35.7% (385/1079) of patients. In total, 24.3% (262/1079) of patients received systemic corticosteroids during hospitalization, whilst 23.1% (249/1079), 24.6% (265/1079) and 4.9% (53/1079) developed respiratory failure, heart failure and septic shock, respectively. In total, 17.9% (193/1079) of

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**Fig. 1** Screening algorithm of patients hospitalized with Flu-p in China, 2013–2019. 3190 patients with influenza RNA positive were screened. Totally, 693 laboratory-confirmed FluA-p patients and 386 FluB-p patients were included into the study.
patients received invasive ventilation and 22.4% (242/1079) were admitted to the ICU. The 30-day mortality rates were 19.3% (208/1079).

### Comparison of patients hospitalized with FluA-p and FluB-p

Compared to patients with FluB-p, FluA-p patients were younger and predominantly male. In FluA-p patients, cerebrovascular disease, diabetes mellitus and smoking history were frequent, whilst cardiovascular disease was less common. FluA-p patients more frequently showed axillary temperatures ≥38 °C, confusion, arterial hydrogen ion index (pH) < 7.35, PO2/FiO2 < 300 mmHg and multilobar infiltrates compared to FluB-p patients. More FluA-p patients had coinfections (Table 1).

A larger number of FluB-p patients received early NAI, systemic corticosteroid therapy and developed complications such as heart failure during hospitalization. Invasive ventilation was more frequent in FluA-p patients. The length of stay in hospital was significantly longer in FluA-p patients compared to FluB-p patients. The 30-day mortality rates were similar between the two groups (Table 2).

### Impact of virus type on the severity of illness and clinical outcomes of flu-p patients

Univariate logistic analysis showed that influenza A virus infection was associated with an increased risk of

| Variable                                      | Total (n = 1079) | FluA-p (n = 693) | FluB-p (n = 386) | P-value |
|-----------------------------------------------|------------------|------------------|------------------|---------|
| Age (years, median, IQR)                      | 61.0 (49.0–78.0) | 61.0 (36.0–73.0) | 67.0 (55.0–80.0) | < 0.001 |
| Male (n, %)                                   | 584 (54.1)       | 461 (66.5)       | 123 (31.9)       | < 0.001 |
| Days from disease onset to admission (median, IQR) | 3.0 (2.0–4.0)   | 3.0 (2.0–4.0)    | 3.0 (2.0–4.3)    | 0.082   |
| Comorbidities (n, %)                          |                  |                  |                  |         |
| Cardiovascular disease                        | 259 (24.0)       | 136 (19.6)       | 123 (31.9)       | < 0.001 |
| Cerebrovascular disease                       | 97 (9.0)         | 72 (10.4)        | 25 (6.6)         | 0.031   |
| Diabetes Mellitus                             | 127 (11.8)       | 92 (13.3)        | 35 (9.1)         | 0.040   |
| COPD                                          | 91 (8.4)         | 40 (5.8)         | 51 (13.2)        | < 0.001 |
| Asthma                                        | 33 (3.0)         | 19 (2.7)         | 14 (3.6)         | 0.418   |
| Chronic kidney disease                        | 30 (2.8)         | 16 (2.3)         | 14 (3.6)         | 0.207   |
| Solid Malignant tumor                         | 24 (2.2)         | 16 (2.3)         | 8 (2.1)          | 0.801   |
| Obesity                                       | 76 (7.0)         | 48 (6.9)         | 28 (7.3)         | 0.840   |
| Pregnancy                                     | 8 (0.7)          | 8 (1.2)          | 0 (0.0)          | 0.080   |
| Smoking history                               | 313 (29.0)       | 243 (35.1)       | 70 (18.1)        | < 0.001 |
| Baseline clinical and radiologic features (n, %) |                  |                  |                  |         |
| Axillary temperature ≥ 38 °C                  | 814 (75.4)       | 661 (95.4)       | 153 (39.6)       | < 0.001 |
| Cough/sputum                                  | 1060 (98.2)      | 679 (98.0)       | 381 (98.7)       | 0.386   |
| Confusion                                     | 150 (13.9)       | 32 (4.6)         | 118 (30.6)       | < 0.001 |
| Respiratory rates ≥ 30 beats/min              | 146 (13.5)       | 121 (17.5)       | 25 (6.5)         | < 0.001 |
| SBP < 90 mmHg                                 | 15 (1.4)         | 8 (1.2)          | 7 (1.8)          | 0.375   |
| Leukocytes > 10 × 10⁹/L                       | 283 (26.2)       | 118 (17.0)       | 165 (42.7)       | < 0.001 |
| Lymphocytes < 0.8 × 10⁹/L                     | 480/1063 (45.2)  | 299/677 (44.2)   | 181 (46.9)       | 0.390   |
| HB < 100 g/L                                 | 240 (22.2)       | 69 (10.0)        | 171 (44.3)       | < 0.001 |
| ALB < 35 g/L                                 | 187/1025 (18.2)  | 58/639 (9.1)     | 129 (33.4)       | < 0.001 |
| BUN > 7 mmol/L                               | 446/1071 (41.6)  | 183/685 (26.7)   | 263 (68.1)       | < 0.001 |
| Arterial pH < 7.35                            | 171/1025 (16.7)  | 120/639 (18.8)   | 51 (12.7)        | 0.021   |
| PO2/FiO2 < 300 mmHg                           | 480/1025 (46.8)  | 340/639 (53.2)   | 140 (36.3)       | < 0.001 |
| Multilobar infiltrates                        | 794 (73.6)       | 546 (78.8)       | 248 (64.2)       | < 0.001 |
| Coinfections (n, %)                           | 367 (34.0)       | 265 (38.2)       | 102 (26.4)       | < 0.001 |

IQR Interquartile range, COPD Chronic obstructive pulmonary disease; SBP Systolic blood pressure, HB Haemoglobin, ALB Albumin, BUN Blood urea nitrogen, pH Hydrogen ion index, PO2/FiO2 Arterial pressure of oxygen/fraction of inspiration oxygen
invasive ventilation \( (OR: 2.811, 95\% \text{ CI: } 1.905–4.167, \ P < 0.001) \) and admittance to the ICU \( (OR: 1.651, 95\% \text{ CI: } 1.204–1.204, \ P = 0.002) \), but did not correlate with 30-day mortality \( (OR: 1.065, 95\% \text{ CI: } 0.775–1.463, \ P = 0.698) \) in Flu-p patients (Table 3).

Following adjustment for age, sex, comorbidities, pregnancy, obesity, smoking history, early NAI treatment and systemic corticosteroid use, and coinfections, multivariate logistic regression models revealed that influenza A virus infection was associated with an increased risk of invasive ventilation \( (OR: 3.824, 95\% \text{ CI: } 2.279–6.414, \ P < 0.001) \), ICU admission \( (OR: 1.630, 95\% \text{ CI: } 1.074–2.473, \ P = 0.022) \) and 30-day mortality \( (OR: 2.427, 95\% \text{ CI: } 1.568–3.756, \ P < 0.001) \) in Flu-p patients (Table 3).

The forest plots of the impact of influenza virus A on invasive ventilation, admittance to the ICU and 30-day mortality in Flu-p patients after and prior to adjusting for confounders are shown in Fig. 2.

### Risk factors for 30-day mortality in flu-p patients

Logistic regression analysis allowed us to explore the factors for 30-day mortality in Flu-p patients. All potential factors screened in the univariate analysis with \( P < 0.1 \) and influenza A virus infection were added to the Cox regression model (Additional file 1).

Multivariate Cox regression models confirmed that influenza A virus infection \( (\text{hazard ratio } [HR]: 2.637, 95\% \text{ CI: } 1.134–6.131, \ P = 0.024) \), age \( (HR: 1.055, 95\% \text{ CI: } 1.033–1.077, \ P < 0.001) \), cardiovascular disease \( (HR: 7.683, 95\% \text{ CI: } 3.175–18.58, \ P < 0.001) \), smoking history \( (HR: 3.137, 95\% \text{ CI: } 1.417–7.124, \ P < 0.001) \), lymphocytes \( < 0.8 \times 10^9/L \), hemoglobin \( < 100 \text{ g/L} \), blood urea nitrogen (BUN) \( > 7 \text{ mmol/L} \) \( (HR: 3.170, 95\% \text{ CI: } 1.449–6.935, \ P = 0.004) \) and arterial pH \( < 7.35 \) \( (HR: 3.037, 95\% \text{ CI: } 1.552–5.945, \ P = 0.001) \) were independent risk factors for 30-day mortality in Flu-p patients (Table 4).

The survival curve shows that the 30-day mortality of FluA patients was higher than that of FluB-p patients after adjusting for confounders (age, cardiovascular disease, chronic kidney disease, smoking history, confusion, lymphocytes \( < 0.8 \times 10^9/L \), hemoglobin \( < 100 \text{ g/L} \), BUN \( > 7 \text{ mmol/L} \), arterial pH \( < 7.35 \), \( \text{PO}_2/\text{FiO}_2 < 300 \text{ mmHg} \), coinfections and systemic corticosteroid use) (Fig. 3).

### Table 2 The comparison of clinical management and outcomes between patients hospitalized with FluA-p and FluB-p in China, 2013–2019

| Variable                          | Total (n = 1079) | FluA-p (n = 693) | FluB-p (n = 386) | P-value |
|-----------------------------------|-----------------|-----------------|-----------------|---------|
| Early NAI therapy (n, %)          | 385 (35.7)      | 232 (33.5)      | 153 (39.6)      | 0.043   |
| Systemic corticosteroid use       | 262 (24.3)      | 132 (19.0)      | 130 (33.7)      | < 0.001 |
| Length of stay in hospital (n)    |                 |                 |                 |         |
| Vasopressor use (n, %)            |                 |                 |                 |         |
| Septic shock (n, %)               |                 |                 |                 |         |
| Acute renal failure (n, %)        |                 |                 |                 |         |
| Bloodstream infection (n, %)      |                 |                 |                 |         |
| Noninvasive ventilation (n, %)    |                 |                 |                 |         |
| Invasive ventilation (n, %)       |                 |                 |                 |         |
| Admittance to ICU (n, %)          |                 |                 |                 |         |
| Length of stay in hospital (days, median, IQR) | 10.0 (8.0–14.0) | 12.0 (7.0–14.5) | 10.0 (8.0–17.0) | < 0.001 |
| 30-day mortality (n, %)           | 208 (19.3)      | 136 (19.6)      | 72 (18.7)       | 0.698   |

\* NAI: neuraminidase inhibitor, ICU: intensive care unit; IQR: interquartile range

### Table 3 The impact of influenza virus type A on the illness severity and outcomes of patients hospitalized with flu-p in China, 2013–2019

| Variable                  | Univariate logistic analysis | Multivariate logistic analysis |
|---------------------------|------------------------------|-------------------------------|
|                           | OR (95% CI)                  | OR (95% CI)                   |
| Invasive ventilation      | 2.811 (1.905–4.167)          | 3.824 (2.279–6.414)           |
| Admittance to ICU         | 1.651 (1.204–1.204)          | 1.630 (1.074–2.473)           |
| 30-day mortality          | 1.065 (0.775–1.463)          | 2.427 (1.568–3.756)           |

\* OR: Odd ratio, CI: Confidence interval, ICU: Intensive care unit. \*: adjusted for age, sex, comorbidities, pregnancy, obesity, smoking history, early NAI treatment and systemic corticosteroid, and coinfection with other pathogens.
Discussion

This large-sample cohort study showed that illness severity and clinical outcomes were poorer in patients hospitalized with FluA-p as opposed to FluB-p after adjusting for potential confounders, suggesting a direct impact of influenza virus types on the characteristics and outcomes of influenza related pneumonia.

In this study, the 30-day mortality was 19.6%, which was accordant with the 5–50% reported in previous reports [17–19]. The median age was 61.0 years and over 50% of patients had co-morbidities, delayed NAI therapy and systemic corticosteroid (70 and 25% of patients respectively), which may explain the high mortality rates. The proportion of patients requiring invasive ventilation and ICU admission were higher for FluB-p patients. Although the death rates between the two groups were comparable. Significant differences in the 30-day mortality were observed after controlling for confounders.

Our data were consistent with Wang et al. [20] that included 369 patients with flu A infection and 205 patients with flu B infection. After adjustment for age, sex, heart disease, malignancies and time from illness onset to antiviral

Table 4 The risk factors for 30-day mortality of patients hospitalized with Flu-p in China, 2013–2019

| Variable                     | P-value | aHR (95% CI)          |
|------------------------------|---------|-----------------------|
| Influenza virus A infection  | 0.024   | 2.637 (1.134–6.131)   |
| Age                          | < 0.001 | 1.055 (1.033–1.077)   |
| Cardiovascular disease       | < 0.001 | 7.683 (3.175–18.589)  |
| Smoking history              | < 0.001 | 3.137 (1.417–7.124)   |
| Lymphocytes < 0.8 × 10⁹/L    | < 0.001 | 10.473 (5.033–21.792) |
| BUN > 7 mmol/L               | 0.004   | 3.170 (1.449–6.935)   |
| Arterial pH < 7.35           | 0.001   | 3.037 (1.552–5.945)   |

aHR: adjusted hazard ratio, CI: Confidence interval, BUN: Blood urea nitrogen

Fig. 2 Forrest plot of the impact of influenza virus type on the illness severity and outcomes of patients hospitalized with Flu-p in China, 2013–2019. Before adjusting for confounders, influenza A virus infection was associated with an increased risks of invasive ventilation and admittance to intensive care unit (ICU), but did not correlate with 30-day mortality. After adjusting for confounders, influenza A virus infection was associated with an increased risks of invasive ventilation, ICU admission and 30-day mortality in Flu-p patients.

Fig. 3 Survival rate of patients hospitalized with FluA-p and FluB-p in China, 2013–2019 (censored at 30 d after admission). The 30-day mortality of FluA patients was higher than that of FluB-p patients after adjusting for confounders.
treatment, logistic regression models showed a higher probability of clinical improvement (HR: 1.266, 95% CI: 1.019–1.573) and weaning oxygen supplementation (HR: 1.285, 95% CI: 1.030–1.603) in flu B patients. The in-hospital mortality of flu A patients was marginally higher than flu B patients (11.4% vs 6.8%; P = 0.078), which might be due to the relatively small number of deaths (56 in total). Similarly, Chaves and colleagues [21] performed a retrospective study using population-based influenza hospitalization surveillance data. They found that A (H1N1) pdm09 infection was an independent predictor for illness severity both in children (aOR: 2.19, 95% CI: 1.11–4.33) and adults (aOR: 2.21, 95% CI: 1.66–2.943) compared to flu B infection.

In ferret models, A (H1N1) pdm09 strains led to more severe clinical symptoms and histopathology, followed by A (H3N2) strains, whilst Flu B strains had a milder illness [22]. Although the specific pathogenesis governing these effects has not been elucidated, some mechanisms have been postulated. Hemagglutinin (HA) of influenza B virus strains is heavily glycosylated [23]. Since glycosylated HA binds collagenous lectins in lung surfactants, it is easily cleared from the lungs. HA of human influenza B viruses also preferentially bind to α-2,6-linked sialic acids present in the human upper respiratory tract, whilst A (H1N1) pdm09 viruses bind both α-2,6-linked and α-2,3-linked sialic acids [24]. Influenza B viruses are therefore restricted to the upper respiratory tract, whilst A (H1N1) pdm09 viruses are more prevalent in the lower respiratory tract [25]. Compared to influenza A viruses, influenza B has lower receptor-binding affinity due to the presence of a Phe-95 versus a Tyr-98 in the HA protein, resulting in a loss of hydrogen bonds [26]. The innate IFN response is also more rapidly initiated following influenza B as opposed to influenza A virus infection. This leads to more rapid viral clearance and lower viral titers [27]. In vivo, both influenza A and B viruses downregulate the surface expression of major histocompatibility complex-I (MHC-I). A more pronounced reduction in surface MHC-I expression was observed in influenza B patients, leading to milder immunologic reactions, followed by significantly lower levels of inflammatory cytokines and lung tissue injury [28].

A prospective study from France et al. [29] included 556 patients with influenza, of which 30% had pneumonia, showed that the admittance to the ICU, not the virus type, was the main risk factor for death. They further confirmed that prior chronic respiratory disease was associated with ICU admission in multivariate logistic regression models. The proportion of chronic respiratory disease patients was significantly higher in flu A compared to flu B patients. However, the association of virus types with ICU admission were not assessed.

Several studies have compared the mortality rates between patients according to virus type, but many failed to control for confounders [9, 10, 30–32]. Recently, a systematic review suggested the A (H1N1) pdm09 during the post-pandemic period was more related to poor outcomes (secondary bacterial pneumonia, ICU admission, and death) than influenza B viruses [33].

To our knowledge, this is the first real-world cohort study (with a large population of adolescents and adults admitted to general hospital wards or ICUs) that focused on the association of influenza viruses types with illness severity and clinical outcomes of laboratory-confirmed influenza-related pneumonia patients. Methods were taken to reduce selection bias and control confounders, but some limitations should be noted. First, due to the retrospective nature of the study, potential selection bias may have influenced the data. For example, during each influenza season, patients with influenza-like illness (such as fever, sore throat or cough) were assessed through influenza RNA tests by the subjective judgement of attending physicians in the five hospitals. It was possible that more severe (or milder) patients were tested for influenza. Not all respiratory cases were eligible for swabbing and some selection bias occurred. Secondly, due to the retrospective design, the impact of vaccination on disease severity could not be evaluated, and the inclusion of incomplete data may have lowered the accuracy of our results. Thirdly, there is evidence of different severities of influenza A virus subtypes [11, 32]. However, over 50% of patients were not tested for subtypes in our study. Further work is required to compare the clinical features according to subtype. Finally, our study population were immunocompetent, adolescent and adult hospitalized patients. The conclusions should be assessed prudently prior to similar assessments in immunocompromised patients, pediatrics and outpatients.

Conclusions
The clinical outcomes of FluA-p are worse than FluB-p, highlighting the importance of influenza virus strain testing in the management of severe influenza. As influenza A virus infection is a predictor for poor outcomes in patients with influenza-related pneumonia, regardless of their ages and chronic underlying conditions, the clinicians should pay more attention to patients with FluA-p. Also, it suggests the priority of vaccination covered influenza virus type A strains in certain populations is rational.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s40249-020-00655-w.

Additional file 1: Appendix 1. Details of participating centers.
Appendix 2. Definition of underlying diseases of patients hospitalized.
with Flu-p in China, 2013–2019. Definition of microbiological criteria of coinfection with other pathogens in patients hospitalized with Flu-p in China, 2013–2019. Appendix 3. Coinfection with other community-acquired pathogens in patients hospitalized with Flu-p in China, 2013–2019. Appendix 4. Univariate analysis on risk factors for 30-day mortality of patients hospitalized with Flu-p in China, 2013–2019.

Abbreviations
BUN: Blood urea nitrogen; CI: Interval confidence; Flu-p: Influenza-related pneumonia; HR: Hazard ratio; ICU: Intensive care unit; IQR: Interquartile range; NA: Neuraminidase inhibitor; OR: Odds ratio; pH: Hydrogen ion index; pO2/FiO2: Arterial pressure of oxygen/fraction of inspiration oxygen; RCT: Randomized controlled trial; RT-PCR: Reverse transcription polymerase chain reaction

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Authors’ contributions
Study concept and design: LC, XdH. Data acquisition: LC, XdH, YL, CxZ, XqX. Statistical analysis: LC. Drafting of the manuscript: LC. Critical revision of the manuscript for intellectual content: XdH, XqX. All authors agreed with the article submission. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article and supplementary information.

Ethics approval and consent to participate
The study design was approved by the Ethics Committee of Beijing Jishuitan Hospital (No. 201911–15). Given the retrospective nature of the study, the Ethics Committee determined that an informed consent was not required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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