International Journal of Infectious Diseases 92 (2020) 208–213

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Influenza A-associated severe pneumonia in hospitalized patients: Risk factors and NAI treatments

Qianda Zou[a,b,1], Shufa Zheng[a,b,c,1], Xiaochen Wang[a,b,1], Sijia Liu[a,b,d,1], Jiaqi Bao[a,b], Fei Yu[a,b], Wei Wu[c], Xianjun Wang[e], Bo Shen[f], Tieli Zhou[g], Zhigang Zhao[h], Yiping Wang[i], Ruchang Chen[j], Wei Wang[k], Jianbo Ma[l], Yongcheng Li[m], Xiaoyan Wu[n], Weifeng Shen[o], Fuyi Xie[p], Dhanasekaran Vijaykrishna[q,r], Yu Chen[a,b,c,*]

[a] Key Laboratory of Clinical in Vitro Diagnostic Techniques of Zhejiang Province, Hangzhou, PR China
[b] Center of Clinical Laboratory, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, PR China
[c] State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation center for Diagnosis and Treatment of Infectious Diseases, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, PR China
[d] School of Laboratory Medicine and Life Sciences, Wenzhou Medical University, Wenzhou, PR China
[e] Department of Laboratory, Affiliated Hangzhou First People's Hospital, College of Medicine, Zhejiang University, Hangzhou, PR China
[f] Department of Clinical Laboratory, Taizhou Hospital of Zhejiang Province, Taizhou Enze Medical Center (Group), Linhai, PR China
[g] Department of Clinical Laboratory, First Affiliated Hospital, Wenzhou Medical University, Wenzhou, PR China
[h] Department of Clinical Laboratory, Lishui Municipal Central Hospital, Lishui, PR China
[i] Department of Clinical Laboratory, Yinzhou People's Hospital, Ningbo, PR China
[j] Medical Examination and Diagnosis Center, Yiwu Center Hospital, Yiwu, PR China
[k] Department of Clinical Laboratory, Lishui People's Hospital, the Sixth Affiliated Hospital of Wenzhou Medical University, Lishui, PR China
[l] Department of Laboratory Medicine, the Affiliated Ningbo No.2 Hospital, College of Medicine, Ningbo University, Ningbo, PR China
[m] Department of Respiratory Diseases, the First People's Hospital of Xiaoshan, Hangzhou, PR China
[n] Department of Laboratory, Second Hospital of Jiaxing, Jiaxing, PR China
[o] Department of Laboratory, First Hospital of Jiaxing, Jiaxing, PR China
[p] Clinical Laboratory, Li Huili Hospital, Ningbo Medical Center, Ningbo, PR China
[q] Department of Microbiology, Biomedicine Discovery Institute, Monash University, Victoria, Australia
[r] World Health Organization Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia

ARTICLE INFO

Article history:
Received 11 November 2019
Received in revised form 8 January 2020
Accepted 16 January 2020

Keywords:
Influenza
Severe pneumonia
Oseltamivir
Double dose

ABSTRACT

Objective: The risk factors and the impact of NAI treatments in patients with severe influenza A-associated pneumonia remain unclear.
Methods: A multicenter, retrospective, observational study was conducted in Zhejiang, China during a severe influenza epidemic in August 2017–May 2018. Clinical records of patients (>14 y) hospitalized with laboratory-confirmed influenza A virus infection and who developed severe pneumonia were compared to those with mild-to-moderate pneumonia. Risk factors related to pneumonia severity and effects of NAI treatments (monotherapy and combination of peramivir and oseltamivir) were analyzed.
Results: 202 patients with influenza A-associated severe pneumonia were enrolled, of whom 84 (41.6%) had died. Male gender (OR = 1.782; 95% CI: 1.089–2.917; $P = 0.022$), chronic pulmonary disease (OR = 2.581; 95% CI: 1.447–4.603; $P = 0.001$) and diabetes mellitus (OR = 2.042; 95% CI: 1.135–3.673; $P = 0.017$) were risk factors related to influenza A pneumonia severity. In cox proportional hazards model, severe pneumonia patients treated with double dose oseltamivir (300mg/d) had a better survival rate compared to those receiving a single dose (150 mg/d) (HR = 0.475; 95%CI: 0.254–0.887; $P = 0.019$). However, different doses of peramivir (300 mg/d vs. 600 mg/d) and combination therapy (oseltamivir-peramivir vs. monotherapy) showed no differences in 60-day mortality ($P = 0.392$ and $P = 0.658$, respectively).
Conclusions: Patients with male gender, chronic pulmonary disease, or diabetes mellitus were at high risk of developing severe pneumonia after influenza A infection. Double dose oseltamivir might be considered in treating influenza A-associated severe pneumonia.

* Corresponding author at: State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation center for Diagnosis and Treatment of Infectious Diseases, First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou, 310003, PR China.
E-mail address: chenyuzy@zju.edu.cn (Y. Chen).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ijid.2020.01.017

Introduction

Intense seasonal influenza epidemics were observed during the 2017/2018 seasons in countries around the world, leading to increased influenza-associated hospitalizations (Hammond et al., 2018). Similarly, the 2017–2018 winter epidemic in China was severe with higher levels of influenza like illness (ILI) activity, and influenza-related hospitalization exceeded the peak levels of the previous three influenza seasons (Chinese National Influenza Center, 2019). Pandemic and seasonal influenza infections can progress to severe pneumonia and cause substantial mortality (Paules and Subbarao, 2017). Patients who are elderly, obese, pregnant or with comorbidity are at high risks of hospitalization, ICU admission and mortality (Mertz et al., 2013; Zhang et al., 2019).

In severe cases, influenza virus can induce alveolar epithelium cell death, further leading to respiratory failure, acute respiratory distress syndrome (ARDS) and multiorgan disfunction (Short et al., 2014). Antiviral treatment is the primary approach against severe influenza, with neuraminidase inhibitors (NAIs) (oseltamivir and peramivir) most frequently used. The World Health Organization (WHO) recommends a standard dose of NAIs for non-complicated influenza (World Health Organization, 2010). There is substantial variation in clinical treatment courses, and it is not known whether a standard dose of NAIs is adequate for severe influenza (Hurt and Kelly, 2016). Higher dose oseltamivir treatment was observed with rapid reduction of virus load in influenza B patients (Lee et al., 2013). However, studies of double dose oseltamivir and oseltamivir-peramivir combination therapy in hospitalized and ICU patients found no improved clinical outcomes (South East Asia Infectious Disease Clinical Research Network, 2013; Noel et al., 2017; Wang et al., 2018). Nevertheless, previous observational studies were affected by small sample sizes with limited applicability to severe influenza pneumonia (Dixit et al., 2015; Lee et al., 2013).

The objective of our study was to systematically assess clinical characteristics, treatments and outcomes of hospitalized patients with influenza A-associated severe pneumonia as compared to those with mild-to-moderate pneumonia, and to evaluate the risk factors related to pneumonia severity and identify the impact of different NAI regimes.

Materials and methods

Study design

A multicenter, retrospective, observational study involving 13 teaching hospitals in Zhejiang, China between August 2017 and May 2018 was conducted. Patients (>14 years) hospitalized with influenza A infection and who developed severe pneumonia were included. Influenza A virus was confirmed by real-time polymerase chain reaction (RT-PCR) or immunofluorescence assay. We collected 202 patients from the same season with mild-to-moderate pneumonia due to influenza A, who had complete clinical records, for comparison. A team of trained physicians reviewed all medical records and collected the following data: demographics, comorbidities, clinical manifestations, laboratory and chest radiographic features on admission, treatments and clinical outcomes. Ethical approval was obtained from the research ethics committee of the First Affiliated Hospital, Zhejiang University School of Medicine, and informed consents were waived due to the non-interventional nature of our study.

Definitions

Pneumonia was defined according to the American Thoracic Society-Infectious Diseases Society of America (ATS/IDSA) guideline (Mandell et al., 2007). Classification as severe pneumonia needed to meet one of the major criteria or at least three minor criteria. Major criteria included (1) invasive mechanical ventilation, (2) septic shock with the need for vasopressors, and minor criteria were (1) respiratory rate $\geq$30 breaths per min; (2) $PaO_2/FiO_2 \leq 250$; (3) multilobar infiltrates; (4) confusion or disorientation; (5) blood urea nitrogen $\geq$20 mg/dL; (6) leucocyte count $<4 \times 10^9$cells/L; (7) platelet count $<100 \times 10^9$cells/L; (8) core temperature <36 °C; (9) hypotension requiring aggressive fluid resuscitation (Mandell et al., 2007). Patients with pneumonia that did not meet the criteria of severe pneumonia were classified as mild-to-moderate pneumonia. Septic shock was considered in patients who required a vasopressor to maintain mean arterial pressure $\geq$65 mmHg and serum lactate >2 mmol/L despite adequate fluid resuscitation (Singer et al., 2016). Secondary infection was defined as the recurrence of symptoms and signs of infection along with positive cultures of bacterial/fungal from lower respiratory tract specimens and/or blood after 48 h admission (Rothberg and Haessler, 2010).

Statistical analysis

Categorical variables were presented as percentage and compared by Chi-square test or Fisher's exact test. Continuous variables were expressed as median (interquartile ranges) and compared with *t* test or Mann-Whitney *U* test. Significant or clinically plausible variables were included in multivariate logistic regression with enter method to assess risk factors associated with influenza A pneumonia severity. Results were presented as odds ratio (OR) and 95% confidence interval (CI). A stepwise Cox proportional hazards model was used to estimate the cumulative survival rate among different doses of oseltamivir treatments in severe pneumonia group. Covariates included significant or potential clinically relevant baseline variables. Statistical analyses were carried out by SPSS (version 22.0) and a *P* value <0.05 (2-tailed) was considered significant.

Results

Prevalence of influenza A-associated severe pneumonia

During the study period between August 2017 and May 2018, 4468 hospitalized patients from 13 hospitals in Zhejiang were infected with influenza A virus and 202 (4.5%) developed severe pneumonia. Of 202 severe cases, 84 (41.6%) had died. Our study included a small number of the severe pneumonia cases (n = 16) from August to September 2017 along with a majority collected during the peak (n = 183) between January and February 2018 (Figure 1).

Clinical characteristics and outcomes

The proportion of patients aged $\geq$65 years old was significantly higher in the severe pneumonia group (P = 0.022) (Table 1). Comorbidities including hypertension, chronic pulmonary disease, diabetes mellitus, immunosuppression and symptoms including fever, sputum, chest distress and hemoptysis were more

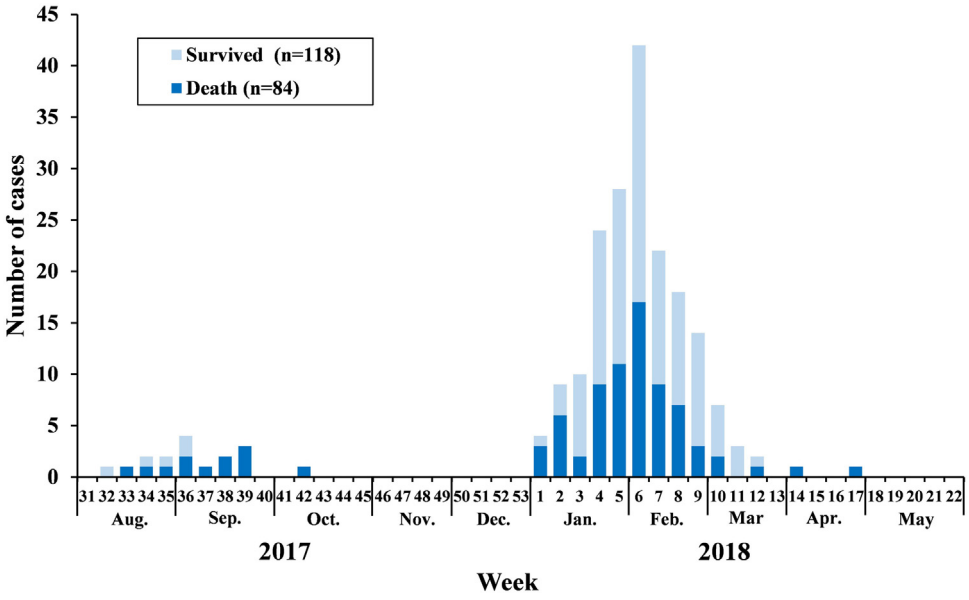

Figure 1. Influenza A-associated severe pneumonia patients in Zhejiang, China, through August 2017 to May 2018. Weekly number of patients that were hospitalized.

Table 1
Clinical characteristics of 404 patients with influenza A-associated pneumonia according to disease severity.

Variables	Mild-to-moderate pneumonia (n = 202)	Severe pneumonia (n = 202)	*P* values
Demographics			
Age (median [IQR]) (yr)	61 (48–72.3)	66 (50.8–76)	**.041**
Age ≥65y, n (%)	84 (41.6)	107 (53.0)	**.022**
Male gender, n (%)	118 (58.4)	141 (69.8)	**.017**
Smoking history, n (%)	63 (31.2)	70 (34.7)	.459
Comorbidities, n (%)			
Any comorbidity	120 (59.4)	139 (68.8)	**.049**
Hypertension	67 (33.2)	87 (43.1)	**.040**
Chronic pulmonary disease[a]	24 (11.9)	50 (24.8)	**.001**
Diabetes mellitus	22 (10.9)	42 (20.8)	**.006**
Malignancy	10 (5.0)	8 (4.0)	.630
Coronary heart disease	11 (5.4)	12 (5.9)	.830
Chronic liver disease	6 (3.0)	13 (6.4)	.100
Chronic renal disease	6 (3.0)	12 (5.9)	.148
Immunosuppression[b]	1 (0.5)	14 (6.9)	**.001**
Clinical manifestations, n (%)			
Fever	178 (88.1)	190 (94.1)	**.036**
Cough	184 (91.1)	190 (94.1)	.255
Sputum	160 (79.2)	178 (88.1)	**.015**
Chest distress	55 (27.2)	150 (74.3)	<**0.001**
Gastrointestinal	24 (11.9)	26 (12.9)	.763
Hemoptysis	5 (2.5)	14 (6.9)	**.034**
Laboratory results on admission			
Leukocyte count (median [IQR]) (mm^3)	6 (4–8.9)	7.2 (4.5–10.1)	**.015**
Lymphocyte count (median [IQR]) (mm^3)	0.9 (0.6–1.3)	0.5 (0.3-0.7)	<**0.001**
Hemoglobin (median [IQR]) (g/L)	125 (112–138)	123 (102–137.8)	.307
Platelet count (median [IQR]) (mm^3)	165 (125–231)	143 (105–211)	**.013**
Creatine kinase (median [IQR]) (UI/L)	83 (43–192.3)	143 (51.8–358.8)	**.001**
Aspartate transaminase (median [IQR]) (UI/L)	29 (21.3–43)	51 (30–93)	<**0.001**
Creatinine (median [IQR]) (μmol/L)	73 (61–88)	77 (61–102)	.066
Lactate dehydrogenase (median [IQR]) (UI/L)	247 (191–324)	429 (277.8–710.8)	<**0.001**
D-dimer (median [IQR]) (mg/L)	0.52 (0.31–0.91)	1.52 (0.77–3.08)	<**0.001**
PaO_2(median [IQR]) (mmHg)	79 (64–103)	62.8 (50.1–81.9)	<**0.001**
K^+ (median [IQR]) (mmol/L)	3.9 (3.6–4.3)	3.9 (3.5–4.3)	.673
C-reactive protein (median [IQR]) (mg/L)	48.2 (21–99.1)	90 (42.9–148)	<**0.001**
Procalcitonin (median [IQR]) (ng/mL)	0.12 (0.05–0.4)	0.7 (0.2–3)	<**0.001**
Chest radiographic features on admission			
Infiltrations involving bilateral lungs, n (%)	78 (38.6)	188 (93.1)	<**0.001**

IQR, interquartile range.
[a] Chronic pulmonary diseases include chronic obstructive pulmonary disease, asthma and bronchiectasis.
[b] Immunosuppression includes receiving radiotherapy, chemotherapy or corticosteroid therapy within one month before symptom onset.

Table 2
Treatment and clinical outcomes of 404 patients with influenza A-associated pneumonia according to disease severity.

Variables	Mild-to-moderate pneumonia (n = 202)	Severe pneumonia (n = 202)	P values
Treatments			
Invasive mechanical ventilation, n (%)	0 (0)	140 (69.3)	<**0.001**
Extracorporeal membrane oxygenation, n (%)	0 (0)	13 (6.4)	<**0.001**
Continuous renal replacement therapy, n (%)	0 (0)	11 (5.4)	**.001**
Antibiotic treatment, n (%)	199 (98.5)	200 (99.0)	.653
Corticosteroid treatment, n (%)	67 (33.2)	159 (78.7)	<**0.001**
NAIs treatment, n (%)	192 (95.0)	191 (94.6)	.823
NAIs administered ≤48 h from illness onset, n (%)	23 (11.4)	17 (8.4)	.318
Duration of NAIs treatment (median [IQR]) (d)	6 (4–9.8)	7 (5–10)	<**0.001**
Clinical outcomes			
Septic Shock, n (%)	0 (0)	39 (19.3)	<**0.001**
Secondary bacterial infection, n (%)	1 (0.5)	57 (28.2)	<**0.001**
ICU admission, n (%)	0 (0)	135 (66.8)	<**0.001**
60-day mortality, n (%)	0 (0)	84 (41.6)	<**0.001**
Length of stay in hospital (median [IQR]) (d)	9 (6–13.3)	16 (10–24)	<**0.001**

IQR, interquartile range; NAI, neuraminidase inhibitor; ICU, intensive care unit.

commonly seen in the severe pneumonia group. Among laboratory results on admission, higher levels of leukocyte count, creatine kinase, aspartate transaminase, lactate dehydrogenase, D-dimer, C-reactive protein, procalcitonin and lower levels of lymphocyte count, platelet count and PaO_2 were observed in severe pneumonia group. The chest image of 188 (93.1%) patients in the severe pneumonia group showed infiltrations involving bilateral lungs, which was significantly higher than those in mild-to-moderate pneumonia group ($P < 0.001$) (Table 1).

Supportive therapies provided for the severe pneumonia group include invasive mechanical ventilation (69.3%), extracorporeal membrane oxygenation (6.4%) and continuous renal replacement therapy (5.4%). A higher percentage of corticosteroid treatment was observed in the severe pneumonia group (78.7% vs. 33.2%, $P < 0.001$), but no difference in treatments using antibiotics and NAIs between the two groups. The proportion of NAIs administered ≤48 h from illness onset in mild-to-moderate pneumonia group was higher than the severe pneumonia group, although no statistical difference was found (11.4% vs. 8.4%, $P = 0.318$). Patients with severe pneumonia had significantly higher rates of septic shock ($P < 0.001$) and secondary infection ($P < 0.001$) comparing to mild-to-moderate pneumonia. 135 (66.8%) patients in the severe pneumonia group were admitted into the ICU and 84 (41.6%) had died (Table 2).

Risk factors for influenza A-associated pneumonia severity

In the multivariate regression analysis, risk factors associated with influenza A-associated pneumonia severity were as follows: male gender (OR = 1.782; 95% CI: 1.089-2.917; $P = 0.022$), chronic pulmonary disease (OR = 2.581; 95% CI: 1.447–4.603; $P = 0.001$) and diabetes mellitus (OR = 2.042; 95% CI :1.135–3.673; $P = 0.017$), whereas age, smoking history and hypertension were not the independent risk factors (Table 3).

NAIs treatment on influenza A-associated severe pneumonia

Of 191 NAI-administered patients in the severe pneumonia group, 122 (63.9%) received oseltamivir monotherapy, 40 (20.9%) received peramivir monotherapy and 29 (15.2%) received oseltamivir-peramivir combination therapy. Demographic information showed that patients treated with double dose oseltamivir (300 mg/d) were younger ($P < 0.001$) and had less comorbidities ($P = 0.002$) compared to those with single dose (150mg/d) treatment (Table S1). In adjusted Cox regression survival analysis, double dose oseltamivir (300mg/d) recipients had a higher cumulative survival rate compared to single dose (150mg/d) recipients (HR = 0.475, 95%CI: 0.254–0.887, $P = 0.019$; Figure 2). However, there were no significant differences in 60-day mortality between patients who received double dose (300 mg/d) and single dose (600 mg/d) peramivir treatment ($P = 0.392$) (Table S2), and among oseltamivir-peramivir combination therapy, oseltamivir monotherapy and peramivir monotherapy ($P = 0.658$) (Table S3).

Table 3
Multivariate analysis for risk factors associated with influenza A pneumonia severity.

Factors	OR	95% CI	P values
Age	1.000	0.986–1.013	.967
Male gender	1.782	1.089–2.917	**.022**
Smoking history	0.780	0.470–1.293	.335
Chronic pulmonary disease	2.581	1.447–4.603	**.001**
Diabetes mellitus	2.042	1.135–3.673	**.017**
Hypertension	1.283	0.811–2.030	.287

OR, odds ratio; CI, confidence interval.

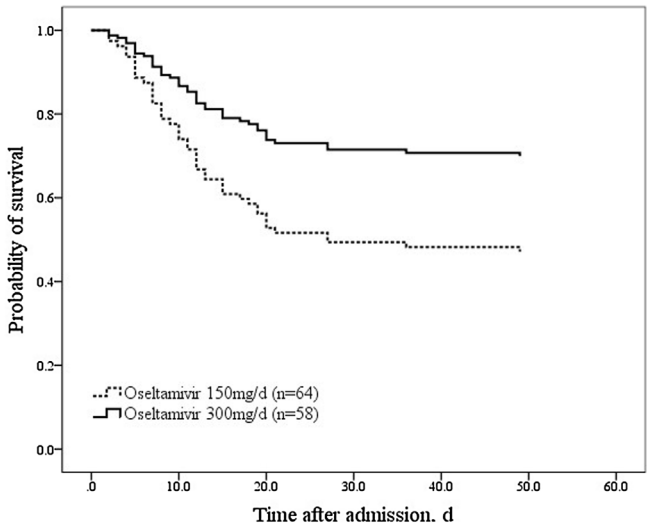

Figure 2. Survival plot classified by oseltamivir treatments in patients with influenza A-associated severe pneumonia. Cox regression for adjusted survival in patients treated with 150 mg/d and 300 mg/d oseltamivir. Covariates included oseltamivir treatment (300 mg/d vs. 150 mg/d; HR = 0.475, 95%CI: 0.254–0.887, P = 0.019), age, sex, any comorbidity, oseltamivir initial time and SOFA score. SOFA: sequential organ failure assessment.

Discussion

Our study found that 4.5% (202/4468) of inpatients had influenza A-associated severe pneumonia and 1.9% (84/4468) of them died during the 2017–2018 influenza season. The overall in-hospital mortality during 2017–2018 was marginally higher than the 1.2% in-hospital mortality of seasonal influenza during 2011–2017 in China (Fu et al., 2019), although consistent with a global report of 1.5% in-hospital mortality of influenza respiratory tract infection in 2017 (GBD 2017 Influenza Collaborators, 2019). Fatality due to influenza A-associated severe pneumonia was substantially higher (84/202, 41.6%) than fatality reported among ICU admitted patients during 2009–2016 (26.4∼20.6%) (Shah et al., 2015; Alvarez-Lerma et al., 2016; Chao et al., 2017). The high mortality of influenza A-associated pneumonia observed in our study suggests that more effective treatments toward this certain population are urgently warranted.

Improved survival requires the identification of factors associated with severe pneumonia following influenza infection and timely treatments, with host factors and treatment regiments being key drivers of severity. Previous studies reported underlying chronic medical conditions of the host, such as cardiac disease, chronic pulmonary disease, immunosuppression, diabetes mellitus, obesity and pregnancy, were major factors associated with influenza severity (Chow et al., 2019). Similarly, our study found patients with comorbidities including chronic pulmonary disease and diabetes mellitus had a higher predisposition to critical influenza (Mertz et al., 2013; Zhang et al., 2019). Decreased lung compliance is related to persistent viral RNA detection, which contribute to the higher risk of progression to severe disease in these patients (Chow et al., 2019). In our study, male gender was an independent risk factor related to pneumonia severity, which might be attributed to the higher frequency of comorbidities and intense immune states observed in males (Bonmarin et al., 2015; Shah et al., 2015). Virus factors driving enhancing disease severity in patients may include virus type/subtype and key genetic mutations (Kash and Taubenberger, 2015). Regrettably, few hospitals in our study subtyped the influenza A virus, therefore we were unable to assess the basis for routine influenza subtyping for patients with severe pneumonia. According to national surveillance reports, influenza A(H3N2) virus was predominant during July to October 2017 in Southern China, and influenza A (H1N1)pdm09 and B (Yamagata lineage) viruses gradually showed up and became dominant between January and February 2018 (Chinese National Influenza Center, 2019).

NAIs are the predominant countermeasure available for influenza infection (Chow et al., 2019). In this study, we mainly focused on different NAI treatments for patients with influenza A-associated severe pneumonia. NAIs are most beneficial when commenced within 48 h from illness onset when viral replication is active (Lee et al., 2009). However, only a few patients (9.9%) had received NAIs within 48 h of illness onset in our study. A higher rate of NAI treatment within 48 h was observed in the mild-to-moderate pneumonia group, indicating the importance of prompt diagnosis and NAIs treatment following infection.

The WHO guideline recommends a higher dose of oseltamivir (e.g. 300 mg/d in adults) to treat critically ill patients. However, whether a higher dose could provide additional protection against severe influenza remains controversial due to the implications in stockpile (Hurt and Kelly, 2016). Studies conducted in avian influenza A(H7N9) infected patients (Wang et al., 2018), ICU-admitted patients with untyped influenza infection (Noel et al., 2017) and pediatric patients with severe influenza (South East Asia Infectious Disease Clinical Research Network, 2013) showed that double dose oseltamivir (300 mg per day) did not present additive effects on clinical outcomes (duration of mechanical ventilation day, length of hospitalization, length of ICU stay or mortality) compared with the standard dose. In our study, after adjusting for covariates, double dose oseltamivir was correlated with improved survival in patients with influenza A-associated severe pneumonia, whereas different doses of peramivir and combination therapy of oseltamivir-peramivir showed no differences in survival.

Higher viral loads and prolonged viral shedding are observed in patients with severe influenza (Li et al., 2010), and an increased dose of oseltamivir in animal models has shown correlation with decreased mortality (Govorkova et al., 2007). Lee et al observed a faster RNA decline rate in influenza B virus infected inpatients (n = 10) who were treated with 300 mg/d oseltamivir (Lee et al., 2013), while Kumar et al. found that a triple dose oseltamivir in ICU patients (n = 18) was associated with better virus clearance, but observed no differences in clinical outcomes (Kumar, 2013). These observational studies were small with a few ICU patient populations, while our study focused on patients with community acquired influenza A-associated severe pneumonia, a well-defined population and a substantially larger sample size than previous studies. In addition, our study was conducted in the same influenza season during the predominant circulation of A(H1N1)pdm09 subtype, therefore virus variations would have limited influence on the potency of NAIs. Our study urges further research on virus clearance and pharmacokinetics of different dose oseltamivir treatments in influenza A-associated severe pneumonia.

Peramivir is an intravenous NAI favored for seriously ill patients or those unable to tolerate oral antivirals (Wester and Shetty, 2016). Reduction of mortality was insignificant between treatment of 300 mg or 600 mg peramivir once daily, which was congruent with other studies in severe influenza (de Jong et al., 2014; Ison et al., 2014). This might be potentially explained by the high-dose treating preference towards more severe patients, however the group size in our study was small (n = 43). In addition, our study found no significant difference in 60-day mortality among monotherapy and oseltamivir-peramivir combination therapy. Similarly, studies of A(H7N9) hospitalized patients comparing oseltamivir-peramivir combination to monotherapy found no additional benefits in virologic or clinical outcomes (Wang et al., 2018; Zhang et al., 2016). Research on seasonal influenza and A(H1N1)pdm09 infection also showed no synergistic effect between oseltamivir-zanamivir bitherapy and monotherapy (Duval et al., 2010; Escuret et al., 2012). Due to the similarity in chemical structure, NAIs combination treatment might not exert a greater antiviral effect (Duval et al., 2010). Novel antiviral drugs such as Baloxavir Marboxil (Hayden et al., 2018) with different mechanisms would be an option for potential combination therapy.

There are several limitations in this study. First, as an observational and retrospective study, certain biases, such as the lost information of patients with incomplete records, unstandardized disease course on patients' admission, and physician's treatment preference, are difficult to completely rule out. Secondly, our study had a small sample size, and it is underpowered to evaluate the effects of different NAIs treatments in subgroups. Our result regarding the benefit of double dose oseltamivir treatment in influenza A-associated severe pneumonia must be interpreted carefully and within the limitation of the study design. In addition, the virologic response is a direct indicator in evaluating the effects of different NAI regimens. However, we were unable to assess the daily changes of viral RNA concentrations due to the retrospective nature of our study.

Conclusions

A high rate of mortality due to influenza A-associated severe pneumonia was observed among hospitalized patients in China during a peak infection in the 2017–2018 season. Patients who developed influenza A-associated pneumonia were more likely to

be of male gender, with chronic pulmonary disease and diabetes mellitus. Our study urges closer attention to this high-risk group during influenza season, offering a chance for prompt NAIs treatment, preventing progressing into severe pneumonia. We also provided supportive evidence for double dose oseltamivir in treating patients with influenza A-associated severe pneumonia.

Declaration of interest

None.

Authors contributions

Yu Chen and Shufa Zheng designed the study and reviewed the manuscript. Qianda Zou conducted data analysis and drafted the manuscript. Xiaochen Wang and Sijia Liu involved data collection, data analysis and manuscript revising. Jiaqi Bao and Fei Yu conceived the study and interpreted data. Wei Wu, Xianjun Wang, Bo Shen, Tieli Zhou, Zhigang Zhao, Yiping Wang, Ruchang Chen, Wei Wang, Jianbo Ma, Yongcheng Li, Xiaoyan Wu, Weifeng Shen and Fuyi Xie contributed in data collection from each hospital. Dhanasekaran Vijaykrishna reviewed the manuscript. All authors read and approved the final manuscript.

Financial supports

Supported by the China National Mega-Projects for Infectious Diseases (grants 2018ZX10101001, 2017ZX10103008 and 2017ZX10103008008); and the National Natural Science Foundation of China (grants 81672014 and 81702079). D.V. is supported by contract HHSN272201400006C from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services.

Acknowledgments

The authors thank Ian Barr and Aeron Hurt from World Health Organization Collaborating Centre for Reference and Research on Influenza for their immense advices and comments on the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.01.017.

References

Alvarez-Lerma F, Marin-Corral J, Vila C, Masclans JR, Gonzalez de Molina FJ, Martin Loeches I, et al. Delay in diagnosis of influenza A (H1N1)pdm09 virus infection in critically ill patients and impact on clinical outcome. Crit Care. 2016;20(1):337.

Bonmarin I, Belchior E, Bergounioux J, Brun-Buisson C, Megarbane B, Chappert JL, et al. Intensive care unit surveillance of influenza infection in France: the 2009/10 pandemic and the three subsequent seasons. Euro Surveill. 2015;20(46) pii=30066.

Chinese National Influenza Center. Chinese influenza surveillance report. Available from: http://www.chinaivdc.cn/cnic/zyzx/lgzb/201802/t20180202_158647/ accessed 27 October 2019.

Chao CM, Lai CC, Chan KS, Cheng KC, Chou W, Yuan KS, et al. Outcomes of patients with severe influenza infection admitted to intensive care units: a retrospective study in a medical centre. J Med Microbiol 2017;66(10):1421–8.

Chow EJ, Doyle JD, Uyeki TM. Influenza virus-related critical illness: prevention, diagnosis, treatment. Crit Care. 2019;23(1):214.

de Jong MD, Ison MG, Monto AS, Metev H, Clark C, O'Neil B, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. Clin Infect Dis. 2014;59(12):e172–85.

Dixit R, Khandaker G, Hay P, McPhie K, Taylor J, Rashid H, et al. A randomized study of standard versus double dose oseltamivir for treating influenza in the community. Antivir Ther. 2015;20(7):689–98.

Duval X, van der Werf S, Blanchon T, Mosnier A, Bouscambert-Duchamp M, Tibi A, et al. Efficacy of oseltamivir-zanamivir combination compared to each monotherapy for seasonal influenza: a randomized placebo-controlled trial. Plos Med. 2010;7(11)e1000362.

Escuret V, Cornu C, Boutitie F, Enouf V, Mosnier A, Bouscambert-Duchamp M, et al. Oseltamivir-zanamivir bitherapy compared to oseltamivir monotherapy in the treatment of pandemic 2009 influenza A(H1N1) virus infections. Antiviral Res. 2012;96(2):130–7.

Fu X, Zhou Y, Wu J, Liu X, Ding C, Huang C, et al. Clinical characteristics and outcomes during a severe influenza season in China during 2017–2018. BMC Infect Dis. 2019;19(1):668.

GBD 2017 Influenza Collaborators. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 2019;7(1):69–89.

Govorkova EA, Ilyushina NA, Boltz DA, Douglas A, Yilmaz N, Webster RG. Efficacy of oseltamivir therapy in ferrets inoculated with different clades of H5N1 influenza virus. Antimicrob Agents Chemother. 2007;51(4):1414–24.

Hammond A, Schafer HL, Marsland M, Besselaar T, Fitzner J, Vandemaele K, et al. Review of 2017-18 influenza season in the northern hemisphere. Weekly Epidemiological Record. 2018;93(34):429–44.

Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, Hurt AC, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. N Engl J Med. 2018;379(10):913–23.

Hurt AC, Kelly H. Debate regarding Oseltamivir use for seasonal and pandemic influenza. Emerg Infect Dis. 2016;22(6):949–55.

Ison MG, Fraiz J, Heller B, Jauregui L, Mills G, O'Riordan W, et al. Intravenous peramivir for treatment of influenza in hospitalized patients. Antivir Ther. 2014;19(4):349–61.

Kash JC, Taubenberger JK. The role of viral, host, and secondary bacterial factors in influenza pathogenesis. Am J Pathol. 2015;185(6):1528–36.

Kumar A. ROSII Study Investigators. Viral clearance with standard or triple dose oseltamivir therapy in critically ill patients with pandemic (H1N1) 2009 influenza. Programs and abstracts of the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Denver). Washington, DC: American Society for Microbiology; 2013. p. 1470.

Lee N, Chan PK, Hui DS, Rainer TH, Wong E, Choi KW, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis. 2009;200(4):492–500.

Lee N, Hui DS, Zuo Z, Ngai KL, Lui GC, Wo SK, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza A and B infections. Clin Infect Dis 2013;57(11):1511–9.

Li CC, Wang L, Eng HL, You HL, Chang LS, Tang KS, et al. Correlation of pandemic (H1N1) 2009 viral load with disease severity and prolonged viral shedding in children. Emerg Infect Dis 2010;16(8):1265–72.

Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.

Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ. 2013;347:f5061.

Noel ZR, Bastin MLT, Montgomery AA, Flannery AH. Comparison of high-dose versus standard dose Oseltamivir in critically ill patients with influenza. J Intensive Care Med. 2017;32(10):574–7.

Paules C, Subbarao K. Influenza. Lancet 2017;390(10095):697–708.

Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med 2010;38(4 Suppl):e91–7.

Shah NS, Greenberg JA, McNulty MC, Gregg KS, Riddell J, Mangino JE, et al. Severe influenza in 33 US hospitals, 2013-2014: complications and risk factors for death in 507 patients. Infect Control Hosp Epidemiol. 2015;36(11):1251–60.

Short KR, Kroeze E, Fouchier RAM, Kuiken T. Pathogenesis of influenza-induced acute respiratory distress syndrome. Lancet Infect Dis. 2014;14(1):57–69.

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–10.

South East Asia Infectious Disease Clinical Research Network. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. BMJ 2013;346:f3039.

Wang Y, Guo Q, Yan Z, Zhou D, Zhang W, Zhou S, et al. Factors associated with prolonged viral shedding in patients with avian influenza A(H7N9) virus infection. J Infect Dis. 2018;217(11):1708–17.

Wester A, Shetty AK. Peramivir injection in the treatment of acute influenza: a review of the literature. Infect Drug Resist. 2016;9:201–14.

World Health Organization. WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and Other Influenza Viruses. Geneva, Switzerland: World Health Organization; 2010 Available from: http://www.ncbi.nlm.nih.gov/books/NBK138515/ accessed 27 October 2019.

Zhang Y, Gao H, Liang W, Tang L, Yang Y, Wu X, et al. Efficacy of oseltamivir-peramivir combination therapy compared to oseltamivir monotherapy for Influenza A (H7N9) infection: a retrospective study. BMC Infect Dis. 2016;16:76.

Zhang ZXZ, Mar Kyaw W, Ho HJ, Tay MZ, Huang H, Aung Hein A, et al. Seasonal influenza-associated intensive care unit admission and death in tropical Singapore, 2011-2015. J Clin Virol. 2019;117:73–9.