Mortality prediction to hospitalized patients with influenza pneumonia: PO_2/FiO_2 combined lymphocyte count is the answer

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Abstract

Introduction: Community-acquired pneumonia (CAP) severity scores perform well in predicting mortality of CAP patients, but their applicability in influenza pneumonia is powerless.

Objectives: The aim of our research was to test the efficiency of PO_2/FiO_2 and CAP severity scores in predicting mortality and intensive care unit (ICU) admission with influenza pneumonia patients.

Methods: We reviewed all patients with positive influenza virus RNA detection in Beijing Chao-Yang Hospital during the 2009–2014 influenza seasons. Outpatients, inpatients with no pneumonia and incomplete data were excluded. We used receiver operating characteristic curves (ROCs) to verify the accuracy of severity scores or indices as mortality predictors in the study patients.

Results: Among 170 hospitalized patients with influenza pneumonia, 30 (17.6%) died. Among those who were classified as low-risk (predicted mortality 0.1%–2.1%) by pneumonia severity index (PSI) or confusion, urea, respiratory rate, blood pressure, age $\geq$65 year (CURB-65), the actual mortality ranged from 5.9 to 22.1%. Multivariate logistic regression indicated that hypoxia ($PO_2/FiO_2 \leq 250$) and lymphopenia (peripheral blood lymphocyte count $<0.8 \times 10^9$/L) were independent risk factors for mortality, with OR value of 22.483 (95% confidence interval 4.927–102.598) and 5.853 (95% confidence interval 1.887–18.152), respectively. PO_2/FiO_2 combined lymphocyte count performed well for mortality prediction with area under the curve (AUC) of 0.945, which was significantly better than current CAP severity scores of PSI, CURB-65 and confusion, respiratory rate, blood pressure, age $\geq$65 years for mortality prediction ($P < 0.001$). The scores or indices for ICU admission prediction to hospitalized patients with influenza pneumonia confirmed a similar pattern and PO_2/FiO_2 combined lymphocyte count was also the best predictor for predicting ICU admission.

Conclusion: In conclusion, we found that PO_2/FiO_2 combined lymphocyte count is simple and reliable predictor of hospitalized patients with influenza pneumonia in predicting mortality and ICU admission. When $PO_2/FiO_2 \leq 250$ or peripheral blood lymphocyte count $<0.8 \times 10^9$/L, the clinician should pay great attention to the possibility of severe influenza pneumonia.

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Abbreviations:

AUC(s)	area under the curve(s);
CAP	community-acquired pneumonia;
CRB-65	confusion, respiratory rate, blood pressure, age $\geq$65 years;
CURB-65	confusion, urea, respiratory rate, blood pressure, age $\geq$65 year;
ICU	intensive care unit;
LIS	lung injury score;
PSI	pneumonia severity index;
ROC(s)	receiver operating characteristic curve(s);
SMART-COP	systolic blood pressure, multi-lobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, arterial pH

Key words
influenza – mortality – pneumonia – severity score

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Authorship and contributorship
Bin Cao designed the study. Hui Li, Meng Liu, Fei Zhou and Bo Liu collected data. Yingmei Liu and Jiuxin Qu contributed to the providing of patients with positive influenza detection. Shujing Shi performed the study and wrote the paper.

Ethics
This research was approved by Ethic committee of Beijing Chao-Yang Hospital (the project approval number is 10-KE-49). All patients gave their informed consents.

Conflict of interest
There is no potential conflict of interest exist with any organizations.

Introduction

Three global influenza pandemics of the 20th century, ranging from Spanish flu of 1918 to the 1968 Hong Kong pandemic, proved to be disasters in the history of mankind and caused death toll more than that of the First World War (1). The recent swine origin 2009 pandemic influenza A H1N1 virus led more than 60 million laboratory confirmed cases in 214 countries and over 18 449 deaths until August 2010, resulting in substantial human admission rate and mortality (2). Most patients with severe influenza infections present with pneumonia (3–6).

As we know that, at the time of a pandemic, one of the most important decisions is to decide the appropriate site of care, which needs not only physician's clinical judgment, but also the objective severity scores or indicators to help the physicians, especially the physicians in the emergency department, to make a right decision.

A variety of pneumonia severity scores have been used to help the physicians to evaluate the mortality or severity of patients with community-acquired pneumonia (CAP), including pneumonia severity index (PSI) (7), confusion, urea, respiratory rate, blood pressure, age $\geq$65 year (CURB-65) (8), confusion, respiratory rate, blood pressure, age $\geq$65 years (CRB-65) (9), systolic blood pressure, multi-lobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, arterial pH (SMART-COP) (10) and lung injury score (LIS) (11). PSI and CURB-65 are valid scores in predicting 30-day mortality with CAP patients (12). SMART-COP can predict patients who might need vasopressoror ventilatory support interventions with more than 90% accuracy (10). LIS is a useful tool to diagnose acute lung injury/adult respiratory distress syndrome (13).

But current CAP severity scores (PSI, CURB-65 and CRB-65) in predicting mortality in patients with influenza pneumonia is unpersuasive. Several studies (14–16) indicated that current CAP severity scores failed to predict mortality in patients due to influenza pneumonia. Only one research pointed out that SMART-COP presented the best performance to indicate intensive care unit (ICU) admission in patients with H1N1 pneumonia (17). To our knowledge, there is no relative research about LIS in predicting mortality or severity with influenza pneumonia. The current CAP severity scores are mainly developed for CAP patients with the major pathogens of *Streptococcus pneumonia*, *Haemophilus influenza* and atypical bacterial pathogens (9, 18–20), which are different from pneumonia caused by influenza virus. As a kind of interstitial pneumonia, pathologic characteristics (21) of influenza pneumonia includes interstitial inflammation, hyaline membranes formation, intra-alveolar hemorrhage, edema and necrotizing bronchitis that affecting pulmonary diffusion function (22).

Taking these into considerations, it may be more possible that severity indices reflecting pulmonary diffusion functions may perform well in predicting prognosis with hospitalized patients due to influenza pneumonia. According to our previous study (23) and those from Korea (24), hypoxia ($PO_2/FiO_2 \leq 250$) was an independent risk factor for death in patients with influenza A (H1N1) 2009 pneumonia.

In this study, we want to test the efficiency of PO_2/FiO_2 and CAP severity scores in predicting mortality and ICU admission with influenza pneumonia patients.

Materials and methods

Study design and patients

During the 2009–2014 influenza seasons (from November to the next February in Beijing area of China), we screened patients with positive influenza virus RNA detection of respiratory specimen from the microbiology Lab in Beijing Chao-Yang Hospital. Then we excluded outpatients and inpatients with no pneumonia. Cases with unavailable data to calculate severity scores were also excluded from this analysis.

Study definitions and variables

Patients with influenza pneumonia: during the influenza seasons, patients with respiratory symptoms and a new pulmonary infiltrate on the chest radiograph, combined with positive influenza virus A RT-PCR testing and negative for other kinds of viruses as below.

Patients with bacterial co-infection: a patient who fulfilled the above criterion of influenza pneumonia, at the same time, with culture positive for bacterial pathogen from blood/sputum/bronchoalveolarlavage fluid or positive urinary antigen or positive *Mycoplasma pneumonia, Chlamydia pneumonia* RT-PCR detection before or within the initial 48 h of hospital admission.

Microbiological evaluation was performed according to our previous reports (25, 26), (i) Qualified sputum (defined as an adequate quality sputum sample with $>$25 leukocytes and $<$10 epithelial cells per $\times$ 100 magnification field) were sent for Gram staining and culture according to standard methods; (ii) urinary antigen for *Legionella pneumophila* (Binax Now *L. pneumophila* urinary antigen test; Trinity Biotech, Bray, Ireland) and urinary antigen for *S. pneumoniae*

(Binax Now *S. pneumoniae* urinary antigen test; Emergo Europe, The Netherlands); (iii) blood culture for bacteria and fungi; (iv) RT-PCR using a Seeplex RV Detection Kit (Seegene Biotechnology Inc., Seoul, Korea) according to manufacturer's instructions, including respiratory syncytial virus types A and B, influenza virus types A and B, parainfluenza virus types 1, 2, 3 and 4, rhinovirus, enterovirus, human coronavirus types 229E, NL63, OC43 and HKU1, human metapneumovirus, adenovirus and bocavirus; (5) detection of *M. pneumonia, C. pneumoniae* by RT-PCR detection kit (ZJ Bio-Tech, Shanghai, China).

Neoplastic disease: defined as any cancer except of basilar or squamous cell cancer of the skin that was active at the time of presentation or diagnosed within 1 year of presentation.

Liver disease: defined as a clinical or histological diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis.

Cerebrovascular disease: defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or computed tomography.

Renal disease: defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record.

Cardiac disease: defined as systolic or diastolic ventricular dysfunction documented by history, physical examination and chest radiograph, echocardiogram, multiple gated acquisition scan or left ventriculogram.

Obesity: a patient with the body mass index more than 30 kg/m^2 was considered obesity.

Mortality: the outcome variable of mortality was defined as all-cause mortality at the time of hospital discharge. According to PSI and CURB-65, we also calculated the number of deaths and actual mortality in each class or score. Predicted mortality rate was acquired from the original publications of the severity score (7, 8).

Severity scores

Severity of influenza pneumonia was evaluated using PO_2/FiO_2, PSI, CURB-65, CRB-65, SMART-COP and LIS. The severity scores or indices were calculated within 48 h of hospital admission, which were compared between deceased and survival groups.

Statistical analysis

Statistical analysis was performed using statistical software package SPSS (version 17.0). Patients were grouped as dead vs alive. Continuous variables were described as means (±standard deviation). χChi-squared[2] test or Fisher exact test was used to compare categorical variables and *t*-test for continuous variables. We used multivariate logistic regression to identify independent predictors of mortality. Receiver operating characteristic curves (ROCs) were generated to compare the total predictive accuracy of PO_2/FiO_2, PSI, CURB-65, CRB-65, SMART-COP and LIS for mortality and ICU admission, and the area under the curves (AUCs) were calculated. A P value < 0.05 was considered statistically significant, 95% confidence intervals were calculated.

Results

Study population

During the study period, 1067 patients with positive influenza virus RNA detection were screened. Five hundred fifty-eight outpatients, 322 inpatients without pneumonia and 17 patients with incomplete data were excluded. At last, a total of 170 hospitalized patients with influenza pneumonia were enrolled in the study (Fig. 1). Among 170 patients, 114 cases of H1N1, one case of H1N1+H3N2, one of H3N2 and 54 of influenza A, but not typed. Bacterial co-infection was documented in seven (4.1%) patients, with three cases of *Pseudomonas aeruginosa*, two with *Acinetobacter baumannii*, one with *Staphylococcus aureus* and one of *Klebsiella pneumonia*. All the other pathogens (including *M. pneumonia* and *C. pneumonia*, *L. pneumophila*) were negative. Mortality was 17.6% (30/170). Baseline characteristics of the hospitalized patients with influenza pneumonia were shown in Table 1.

Independent risk factors for mortality

The variables associated with mortality in hospitalized patients with influenza pneumonia were decreased lymphocyte count, decreased hemoglobin, decreased platelet, decreased albumin, decreased PO_2/FiO_2, elevated respiratory rate, elevated blood urea nitrogen, elevated lactate dehydrogenase, elevated serum glucose, multilobar infiltrates and pleural effusion. Multivariate logistic regression indicated that hypoxia ($PO_2/FiO_2 \leq 250$) and lymphopenia (peripheral blood lymphocyte count $< 0.8 \times 10^9$/L) (27) were independent risk factors for mortality, with OR value of 22.483 (95% confidence interval 4.927–102.598) and 5.853 (95% confidence interval 1.887–18.152), respectively. The result of multivariate logistic regression was showed in Table 2.

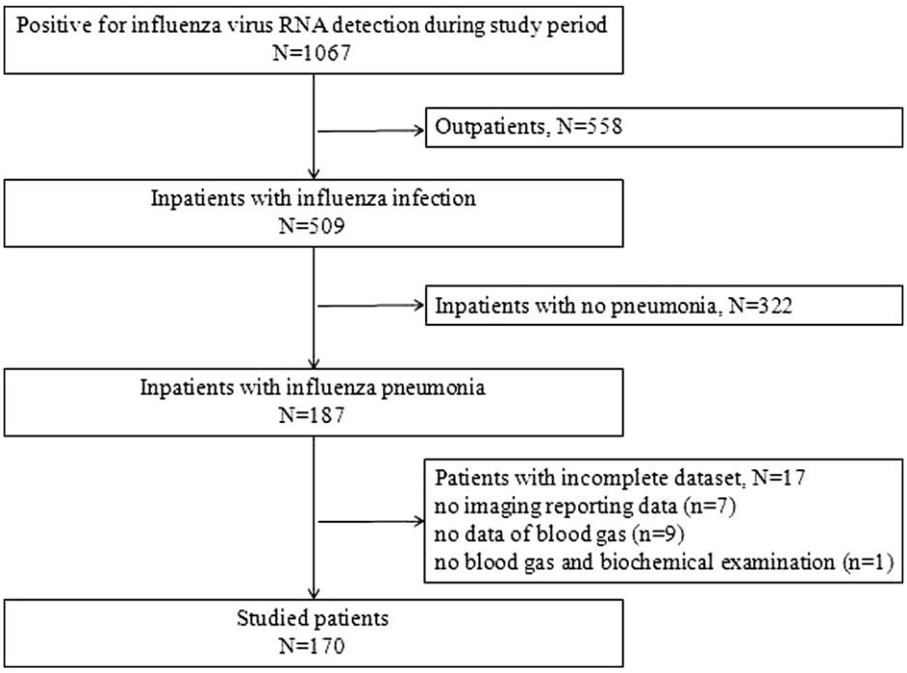

Figure 1. Flowchart of enrolled patients.

Current CAP severity scores underestimate mortality with low-risk patients

The deceased patients and the total number of patients stratified by PSI and CURB-65 with their actual and predicted mortality rates were shown in Table 3. Predicted mortality in the range of 0.1%–2.1% was defined as low risk. According to PSI and CURB-65, low risk was determined in 130 (76.5%) patients and 136 (80%) patients, respectively, which accounted for a majority part of hospitalized patients with influenza pneumonia. The actual mortality in these patients ranged from 5.9 to 22.1%. That was to say, PSI and CURB-65 underestimated the mortality in a significant number of hospitalized patients with influenza pneumonia.

Comparison of severity scores or indices for mortality prediction

As we mentioned above, lymphopenia was also an independent risk factor for mortality. So, we finally used eight severity scores or indices (PSI, CURB-65, CRB-65, SMART-COP, LIS, PO_2/FiO_2, lymphocyte count and PaO_2/FiO_2 combined lymphocyte count) to compare AUCs for mortality prediction in hospitalized patients with influenza pneumonia (Table 4). The ROCs for mortality prediction was shown in Supporting Information e-Fig. 1.

PaO_2/FiO_2 combined lymphocyte count performs best in mortality prediction with hospitalized patients due to influenza pneumonia with AUC of 0.945 (95% confidence interval, 0.910–0.979), and the AUC of PO_2/FiO_2 was 0.916 (95% confidence interval, 0.869–0.962), which was lower than PaO_2/FiO_2 combined lymphocyte count. The AUCs of PSI, CURB-65 and CRB-65 were less than 0.70. PaO_2/FiO_2 combined lymphocyte count was significantly better than current CAP severity scores of PSI, CURB-65 and CRB-65 ($P < 0.001$). The AUCs of LIS, SMART-COP and lymphocyte count were respectively 0.892 (95% confidence interval, 0.823–0.961), 0.808 (95% confidence interval, 0.728–0.889) and 0.827 (95% confidence interval, 0.750–0.905), which were all less than the AUC of PaO_2/FiO_2 combined lymphocyte count.

Comparison of severity scores or indices for ICU admission prediction

The AUCs of the eight severity scores or indices for ICU admission prediction in hospitalized patients with influenza pneumonia confirmed a similar pattern to mortality prediction (Table 5). The ROCs for predicting ICU admission was shown in Supporting Information e-Fig. 2.

Table 1. Baseline characteristics of hospitalized patients with influenza pneumonia by mortality

Variables	Total ($N = 170$)	Dead ($n = 30$)	Alive ($n = 140$)	P value
Patient characteristics				
Age (year)	55.4 ± 17.7	54.9 ± 19.3	55.5 ± 17.4	0.883
Male, No.	104 (61.2)	23 (76.7)	81 (57.9)	0.055
Time interval from onset to admission (day)	6.6 ± 3.9	7.8 ± 5.0	6.3 ± 3.6	0.113
Comorbidities, no.				
Neoplastic disease	5 (2.9)	2 (6.7)	3 (2.1)	0.462
Cardiac disease	23 (13.5)	6 (20.0)	17 (12.1)	0.397
Liver disease	3 (1.8)	0 (0)	3 (2.1)	0.964
Kidney disease	9 (5.3)	4 (13.3)	5 (3.6)	0.086
Cerebrovascular disease	10 (5.9)	4 (13.3)	6 (4.3)	0.138
Pulmonary disease	38 (22.4)	3 (10.0)	35 (25.0)	0.074
COPD	20 (11.8)	2 (6.7)	18 (12.9)	0.520
Bronchiectasis	11 (6.5)	0 (0)	11 (7.9)	0.239
Asthma	7 (4.1)	1 (3.3)	6 (4.3)	1.000
Diabetes	26 (15.3)	8 (26.7)	18 (12.9)	0.104
Obesity	27 (20.9)	3 (17.6)	24 (21.4)	0.970
Laboratory and image				
WBC ($\times 10^9$/L)	7.03 ± 4.19	6.78 ± 3.98	7.09 ± 4.27	0.720
Neutrophil ($\times 10^9$/L)	6.05 ± 7.15	6.08 ± 3.69	6.04 ± 7.71	0.981
Lymphocyte ($\times 10^9$/L)	1.00 ± 0.63	0.50 ± 0.30	1.11 ± 0.63	<0.001*
Hemoglobin (g/L)	125.5 ± 23.7	116.6 ± 26.2	127.4 ± 22.8	0.023*
Platelet ($\times 10^9$/L)	196.8 ± 104.2	146.0 ± 72.0	207.7 ± 107.0	0.003*
Albumin (g/L)	27.8 ± 5.6	24.0 ± 5.6	28.7 ± 5.2	<0.001*
BUN (mmol/L)	5.75 ± 4.61	8.89 ± 8.18	5.08 ± 3.05	0.017*
Scr (μmmol/L)	84.8 ± 71.4	120.1 ± 152.7	77.3 ± 31.8	0.137
Creatine kinase (U/L)	276.3 ± 476.2	331.7 ± 499.0	264.0 ± 472.1	0.483
LDH (U/L)	386.4 ± 256.8	566.7 ± 304.2	347.3 ± 228.3	<0.001*
Serum-glucose (mmol/L)	7.66 ± 3.99	10.09 ± 6.94	7.12 ± 2.73	0.028*
Blood pH	7.43 ± 0.57	7.43 ± 0.439	7.43 ± 0.05	0.864
PaO_2/FiO_2	270.4 ± 114.6	132.7 ± 63.9	300.0 ± 100.7	<0.001*
Multilobar infiltrates, no.	120 (81.6)	28 (96.6)	92 (78.0)	0.021*
Pleural effusion, no.	42 (28.6)	14 (48.3)	28 (23.7)	0.009*
Bacterial co-infection	7 (4.1)	2 (6.7)	5 (3.8)	0.789
Vital signs				
HR (beats/min)	90.5 ± 16.5	92.8 ± 16.6	90.0 ± 16.5	0.404
RR (breath/min)	24.1 ± 6.0	27.9 ± 7.5	23.3 ± 5.2	0.003*

*$P < 0.05$.

Data are presented as mean ± standard deviation or No. (%) unless indicated otherwise. COPD, chronic obstructive pulmonary disease; BUN, blood urea nitrogen; Scr, serum creatinine; LDH, lactate dehydrogenase; HR, heart rate; RR, respiratory rate.

PaO_2/FiO_2 combined lymphocyte count was also a good predictor for ICU admission prediction with AUC of 0.857 (95% confidence interval 0.797–0.917), which was higher than PaO_2/FiO_2 alone. The AUC of PaO_2/FiO_2 combined lymphocyte count was also greater than current CAP severity scores of PSI, CURB-65 and CRB-65 ($P < 0.05$). The AUC of LIS, SMART-COP and lymphocyte count were all less than that of PaO_2/FiO_2 combined lymphocyte count.

Table 2. Multivariate logistic regression of risk factors for hospitalized patients with influenza pneumonia

Variables	OR (95% CI)	P value
Hypoxia ($PaO_2/FiO_2 \leq 250$)	22.483 (4.927–102.598)	<0.001
Lymphopenia (lymphcyte count $<0.8 \times 10^9$/L)	5.853 (1.887–18.152)	0.002

OR, odds ratio; CI, confidence interval.

Discussion

This study demonstrated that PO_2/FiO_2 combined lymphocyte count is simple and reliable severity predictor of hospitalized patients with influenza pneumonia, which is significantly better than current CAP

Table 3. Predicted and actual mortality rates among hospitalized patients with influenza pneumonia stratified by common use severity scores

Risk stratification	Patients, no.	Deaths, no	Actual mortality, %	Predicted mortality, % (7, 8)
PSI				
I	43	4	9.3	0.1
II	54	7	13.0	0.6
III	33	5	15.2	0.9
IV	37	11	26.2	9.3
V	3	3	100	27.0
CURB-65				
0	68	4	5.9	0.7
1	68	15	22.1	2.1
2	29	11	40.0	9.2
3	5	0	0	14.5
4	-	-	-	40
5	-	-	-	14

PSI class of I, II, or III and CURB-65 score of 0 or 1 are classified as low risk (predicted mortality 0–1.5%).

Table 4. AUC for mortality prediction in hospitalized patients with influenza pneumonia

Scores or indices	AUC	95% confidence interval	*P* value
PO_2/FiO_2 combined lymphocyte	0.945	0.910–0.979	Reference
PO_2/FiO_2	0.916	0.869–0.962	0.324
LIS	0.892	0.823–0.961	0.173
Lymphocyte	0.827	0.750–0.905	0.007*
SMART-COP	0.808	0.728–0.889	0.002*
CURB-65	0.675	0.574–0.776	<0.001*
PSI	0.666	0.549–0.784	<0.001*
CRB-65	0.607	0.500–0.714	<0.001*

*$P < 0.05$.

Table 5. AUC for ICU admission prediction in hospitalized patients with influenza pneumonia

Scores or indices	AUC	95% confidence interval	*P* value
PO_2/FiO_2 combined lymphocyte	0.857	0.797–0.917	Reference
PO_2/FiO_2	0.844	0.780–0.908	0.774
LIS	0.793	0.707–0.880	0.234
Lymphocyte	0.737	0.649–0.825	0.028*
SMART-COP	0.787	0.704–0.869	0.180
CURB-65	0.700	0.597–0.804	0.011*
PSI	0.697	0.588–0.807	0.012*
CRB-65	0.679	0.575–0.783	0.004*

*$P < 0.05$.

severity scores of PSI, CURB-65 and CRB-65. When $PO_2/FiO_2 \leq 250$ or peripheral blood lymphocyte count $<0.8 \times 10^9$/L, the clinician should pay great attention to the possibility of severe influenza pneumonia. Moreover, PO_2/FiO_2 and lymphocyte count are easy to calculate and very suitable for clinical application in busy emergency department and in admission units at the time of a pandemic.

Commons and Denholm (28) investigated 105 patients of H1N1 influenza infection and found that the common used CAP severity scores (PSI and CURB-65) had insufficient predictive ability to low-risk patients in ICU admission. Other researches (29–31) also showed that routine prediction rules underestimated severity of influenza A 2009 (H1N1) Pneumonia, but no effective severity score had been put forward. In our study, PSI and CURB-65 underestimated a significant number of hospitalized patients. But the influenza pneumonia patients with high risk (PSI class of V and CURB-65 score of 3–5) are scarce, so the conclusion is inadequate and we need to increase the sample size in our further research.

The severity scores of PSI and CURB-65 heavily weight on advanced age and complication (7, 8), but 2009 H1N1 influenza A virus infection has been reported to occur in young, previously healthy individuals (32–35), which may be one reason that the scores fail to predict mortality. Another possible explanation may be due to the facts that current CAP severity scores are mainly developed for CAP patients with the typical bacterial and atypical bacterial pneumonia.

Concerning on PaO_2/FiO_2 and the prognosis of influenza pneumonia, a study in Washington (36) identified different mean PaO_2/FiO_2 values in survivors (230) and non-survivors (91) ($P = 0.005$) in patients with influenza pneumonia. Ho *et al.* (37) indicated that PaO_2/FiO_2 was a useful parameter in predicting mortality with influenza pneumonia, but the study only evaluated 38 cases and there was no comparison with other severity scores.

The pathologic changes of influenza pneumonia are characterized by diffused alveolar damage and altered pulmonary diffusion function (21, 22). The clinical and radiological characteristics of CAP caused by influenza A 2009 (H1N1) differed markedly from CAP caused by bacterial agents, with high frequency of dyspnea, hemoptysis and bilateral interstitial infiltrate (29). These above features of influenza pneumonia are closely associated with low PO_2/FiO_2. Therefore, there was no surprise that the index of PO_2/FiO_2 performed so well in predicting mortality of hospitalized patients with influenza pneumonia.

And it is also understandable that severity prediction scores including the variable of PaO_2/FiO_2, such as SMART-COP and LIS, presented better performance than PSI, CURB-65 and CRB-65, which have no variables associated with PaO_2/FiO_2. But the severity scores of LIS and SMART-COP are more complex to calculate, and some variables (e.g. respiratory system compliance) in the scores are difficult to obtain, which confine its application.

Our study also found that decreased lymphocyte count was an independent predictor of mortality. Previous studies pointed out that lymphopenia were an early and reliable laboratory finding of adult severe influenza A infection (27, 38, 39). Concerning on the mechanism of lymphopenia, it needs further research.

Some limitations of this study should be noted. First, our study only included 170 patients from one centre, the conclusion generalized to be widely used still need a large-scale clinical validation. Second, our study consists of only hospitalized patients with influenza pneumonia, we are not able to define severity scores or indices in ambulatory patients.

Despite the above limitations, we believe that our study has shown important and novel findings about the death prediction in hospitalized patients with influenza pneumonia. To our knowledge, this is the first study that compared PO_2/FiO_2 and lymphocyte count with current CAP severity scores. Our findings that PO_2/FiO_2 combined lymphocyte count is a useful predictor for severity of influenza pneumonia may help clinicians more accurately predict prognosis, and triage place to improve outcome.

In conclusion, we found that PO_2/FiO_2 combined lymphocyte count is simple and reliable predictor of hospitalized patients with influenza pneumonia in predicting mortality and ICU admission. When $PO_2/FiO_2 \leq 250$ or peripheral blood lymphocyte count $<0.8 \times 10^9$/L, the clinician should pay great attention to the possibility of severe influenza pneumonia.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure 1(e-Fig 1). The ROCs for mortality prediction in hospitalized patients with influenza pneumonia PaO_2/FiO_2 combined lymphocyte count performs best in mortality prediction with hospitalized patients due to influenza pneumonia with AUC of 0.945 (95% confidence interval, 0.910–0.979), and the AUC of PO_2/FiO_2 was 0.916 (95% confidence interval, 0.869–0.962), which was lower than PaO_2/FiO_2 combined lymphocyte count. The AUCs of PSI, CURB-65 and CRB-65 were less than 0.70. PaO_2/FiO_2 combined lymphocyte count was significantly better than current CAP severity scores of PSI, CURB-65 and CRB-65

($P < 0.001$). The AUCs of LIS, SMART-COP and lymphocyte count were, respectively, 0.892 (95% confidence interval, 0.823–0.961), 0.808 (95% confidence interval, 0.728–0.889) and 0.827 (95% confidence interval, 0.750–0.905), which were all less than the AUC of PaO_2/FiO_2 combined lymphocyte count.

Figure 2(e-Fig 2). The ROCs for predicting ICU admission in hospitalized patients with influenza pneumonia PaO_2/FiO_2 combined lymphocyte count was also a good predictor for ICU admission prediction with AUC of 0.857 (95% confidence interval 0.797–0.917), which was higher than PaO_2/FiO_2 alone. The AUC of PaO_2/FiO_2 combined lymphocyte count was also greater than current CAP severity scores of PSI, CURB-65 and CRB-65 ($P < 0.05$). The AUC of LIS, SMART-COP and lymphocyte count were all less than that of PaO_2/FiO_2 combined lymphocyte count.