

# FluA-p score: a novel prediction rule for mortality in influenza A-related pneumonia patients

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## Research

**Keywords:** influenza, pneumonia, mortality, Prediction rule

**Posted Date:** February 17th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.23663/v1>

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**Version of Record:** A version of this preprint was published at Respiratory Research on May 8th, 2020.  
See the published version at <https://doi.org/10.1186/s12931-020-01379-z>.

# Abstract

## Background

The pneumonia severity index (PSI) and the CURB-65 (confusion, urea, respiratory rate, blood pressure, age  $\geq$  65 years) score have been shown to predict mortality in community-acquired pneumonia. Their ability to predict influenza-related pneumonia, however, is less well-established.

## Methods

A total of 693 laboratory-confirmed FluA-p patients diagnosed between Jan 2013 and Dec 2018 and recruited from five teaching hospitals in China were included in the study. The sample included 494 patients in the derivation cohort and 199 patients in the validation cohort. The prediction rule was established based on independent risk factors for 30-day mortality in FluA-p patients from the derivation cohort.

## Results

The 30-day mortality of FluA-p patients was 19.6% (136/693). The FluA-p score was based on a multivariate logistic regression model designed to predict mortality. Results indicated the following significant predictors (regression statistics and point contributions toward total score in parentheses): blood urea nitrogen  $> 7$  mmol/L (OR 1.604, 95% CI 1.150-4.492,  $p = 0.040$ ; 1 points),  $\text{pO}_2 / \text{FiO}_2 \leq 250$  mmHg (OR 2.649, 95% CI 1.103-5.142,  $p = 0.022$ ; 2 points), cardiovascular disease (OR 3.967, 95% CI 1.269-7.322,  $p < 0.001$ ; 3 points), arterial PH  $< 7.35$  (OR 3.959, 95% CI 1.393-7.332,  $p < 0.001$ ; 3 points), smoking history (OR 5.176, 95% CI 2.604-11.838,  $p = 0.001$ ; 4 points), lymphocytes  $< 0.8 \times 10^9 / \text{L}$  (OR 8.391, 95% CI 3.271-16.212,  $p < 0.001$ ; 5 points), and early neurominidase inhibitor therapy (OR 0.567, 95% CI 0.202-0.833,  $p = 0.005$ ; -2 points). Seven points was used as the cut-off value for mortality risk stratification. The model showed a sensitivity of 0.941, a specificity of 0.762, and overall better predictive performance than the PSI risk class (AUROC = 0.908 vs 0.560,  $p < 0.001$ ) and the CURB-65 score (AUROC = 0.908 vs 0.777,  $p < 0.001$ ).

## Conclusions

Our results showed that a FluA-p score was easy to derive and that it served as a reliable prediction rule for 30-day mortality in FluA-p patients. The score could also effectively stratify FluA-p patients into relevant risk categories and thereby help treatment providers to make more rational clinical decisions.

## Background

Influenza is a common contagious respiratory disease and influenza-related epidemics and pandemics have occurred all over the world [1–2]. Despite advances in medical technology and greater economic development in many countries, influenza still causes numerous hospitalizations and is associated with considerable mortality [3–5]. Each year, 10–20% of the global population experiences symptomatic

influenza, including 3–5 million cases of severe illness and 290–650 thousand deaths [6]. For these reasons, influenza is regarded by some experts as the greatest threat to global health in the 21st century [7].

Patients infected with influenza may exhibit a broad spectrum of clinical symptoms, ranging from self-limited upper respiratory tract illness to severe pneumonia [8–9]. Influenza-related pneumonia (Flu-p), including primary viral pneumonia and secondary bacterial pneumonia, is the major cause of influenza-associated hospitalizations and deaths [10]. When the diagnosis of pneumonia is confirmed, the first priority is to assess the degree of disease severity. Several prediction rules have been established to help clinicians predict the mortality rate of patients with pneumonia. Scores on the CURB-65 (confusion, urea, respiratory rate, blood pressure, age  $\geq$  65 years) and the pneumonia severity index (PSI) are the most widely used indices to predict 30-day mortality rates for patients diagnosed with community-acquired pneumonia [11–12]. However, the validity of these two measures for use with Flu-p patients is questionable [13–14]. Some variables that might be more useful in predicting severe influenza include  $PO_2/FiO_2$  and lymphocyte counts [15–16]. But to our knowledge, standard decision rules using these (and perhaps other) variables to predict the extent of Flu-p severity have yet to be developed.

In an effort to remedy this situation we conducted a multicenter, retrospective study with the principal aim being to develop an easy-to-use and accurate severity assessment tool to predict the 30-day mortality rate of patients with influenza A-related pneumonia (FluA-p).

## Methods

### Study design and patient recruitment

Hospitalised patients who tested positive for influenza A virus RNA at the Microbiology Labs of five tertiary hospitals in China from 1st Jan 2013 to 31st Dec 2018 were screened for inclusion (the information for the participating centers is contained in Supplementary material 1). Patients with laboratory-confirmed Flu-p were included. Exclusion criteria for the patients were as follows [17]: (i) Younger than 14 years old; (ii) pneumonia whose onset was not in the community (i.e., pneumonia onset  $\geq$  48 h after admission and hospitalised within the last 28 days); and (iii) immunocompromised status.

### Disease And Treatment Definitions

Patients with influenza-related pneumonia experienced disease onset during the influenza season and manifested with respiratory symptoms along with newly developed pulmonary infiltrates on chest radiographs. In addition, patients with influenza-related pneumonia tested positive for influenza virus RNA by reverse-transcription polymerase chain reaction (RT-PCR). The biological samples subjected to RT-PCR were respiratory specimens (i.e., nasal/nasopharyngeal swabs, sputum, bronchial aspirates or bronchoalveolar lavage fluid). Community-acquired respiratory co-infections resulting from coinfecting pathogens were identified using standard microbiologic procedures within the first 48 hours after

admission [18]. Early neuraminidase inhibitor (NAI) treatment was defined as any NAI (oseltamivir, zanamivir or peramivir) administered within 48 h after illness onset [19]. Systemic corticosteroid use was defined as at least one dose of any systemic corticosteroid administered during hospitalisation.

## Data Collection

Data were retrospectively collected and included demographic information, chronic medical conditions (Supplementary material 2), baseline clinical characteristics (clinical symptoms, vital signs, laboratory and radiological findings), illness severity of pneumonia on admission (CURB-65 and PSI scores), community-acquired respiratory coinfections (Supplementary material 3), clinical management (administration of NAI, systemic corticosteroid use, invasive and non-invasive mechanical ventilation, admittance to the intensive care unit (ICU) ), and 30-day mortality rate.

## Statistical analysis

Six hundred and ninety-three FluA-p patients were divided into a derivation cohort (494 patients from 2013 to 2016) and a validation cohort (199 patients from 2017 to 2018). The derivation cohort was used to establish the statistical model, and the validation cohort was used to validate the model.

According to the survival status at 30 days post-admission, the 693 patients were divided into surviving and deceased groups. Baseline characteristics of these two groups were compared. Variables with  $p$ -values  $< 0.1$  in the univariate analyses were entered into a backward stepwise logistic regression model to explore risk factors for 30-day mortality. For pragmatic reasons, the score for each predictor was assigned an integer value relative to the regression coefficient ( $\beta$ ). A cut-off point was designated following Youden's index from the receiver operating characteristic (ROC) curve. A Kaplan-Meier analysis was performed to compare the difference in 30-day mortality rates between the low-risk and high-risk groups according to the designated cut-off value. Performance of the cut-off score was assessed by measuring the area under the ROC curve (AUROC) and by calculating measures of sensitivity and specificity.

The data were analysed for normality using a Kolmogorov–Smirnov test. In presenting our results, variables with a normal distribution are shown as the mean  $\pm$  SD. Those variables with a non-normal distribution are expressed as medians. Categorical variables were analysed using either the Chi-square test or Fisher's exact test. Continuous variables were analysed using either Student's  $t$  test or the Mann–Whitney  $U$  test. For all analyses, a two-tailed  $P$ -value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using either SPSS version 22.0 or MedCalc version 19.0.

## Results

### Screening process

We screened 2,187 hospitalised patients who tested positive for influenza A RNA. Overall, 693 immunocompetent adult and adolescent patients hospitalised with FluA-p were included in the final analysis (Fig. 1). Among these patients, 38.1% (264/693) were infected with A(H1N1)pdm09 and 11.0% (76/693) were infected with A(H3N2). In addition, 50.9% (353/693) of patients were infected with an unclassified influenza subtype.

## Overview Of FluA-p Patients

Overall, 39.2% (272/693) of patients were above 65 years old and 66.5% (461/693) of patients were male. 35.1% (243/693) of patients had a history of smoking. Cardiovascular disease (19.6%), diabetes mellitus (13.3%) and cerebrovascular disease (10.4%) were the most common chronic medical conditions. Respiratory rates  $\geq 30$  beats/min and altered mental status could be seen in 17.5% (121/693) and 4.6% (32/693) of patients, respectively. Only 1.2% (8/693) of patients had SBP  $< 90$  mmHg. 26.9% (172/639) of patients had  $pO_2/FiO_2 \leq 250$  mmHg (Table 1).

Table 1  
Comparison of clinical features between deceased and survival patients

Variable	Total (n = 693)	Deceased group (n = 136)	Survival group (n = 557)	p- value
Male (n, %)	461 (66.5)	92 (67.6)	369 (66.2)	0.757
Age ≥ 65 years (n, %)	272 (39.2)	60 (44.1)	212 (38.1)	0.195
Obesity (n, %) #	48 (6.9)	0 (0.0)	48 (8.6)	< 0.001
Pregnancy (n, %)	8 (1.2)	0 (0.0)	8 (1.4)	0.338
Smoking history (n, %) #	243 (35.1)	68 (50.0)	175 (31.4)	< 0.001
Comorbidities (n, %)				
Cardiovascular disease#	136 (19.6)	48 (35.3)	88 (15.8)	< 0.001
Diabetes mellitus	92 (13.3)	14 (10.3)	78 (14.0)	0.253
Cerebrovascular disease	72 (10.4)	10 (7.4)	62 (11.1)	0.195
COPD #	40 (5.8)	3 (2.2)	37 (6.6)	0.047
Asthma	19 (2.7)	2 (1.5)	17 (3.1)	0.222
Chronic kidney disease	16 (2.3)	6 (4.4)	10 (1.8)	0.139
Malignant solid tumor	16 (2.3)	0 (0.0)	16 (2.9)	0.193
Clinical and radiologic characteristics (n, %)				
Respiratory rates ≥ 30 times/min	121 (17.5)	25 (18.4)	96 (17.2)	0.752
Confusion#	32 (4.6)	32 (23.5)	0 (0.0)	< 0.001
SBP < 90 mmHg	8 (1.2)	0 (0.0)	8 (1.4)	0.338
Leukocytes > 10 × 10 <sup>9</sup> /L #	118 (17.0)	42 (30.9)	76 (13.6)	< 0.001

COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; Hb: hemoglobin; ALB: albumin; BUN: blood urea nitrogen; BG: blood glucose; pO<sub>2</sub>/FiO<sub>2</sub>: arterial pressure of oxygen/fraction of inspiration oxygen; NAi: neuraminidase inhibitor. #: variables cited in the table above were the candidates which were entered into the multivariate logistic regression model. The bolded values are p-values < 0.05, which represented significant differences between survival group and deceased group.

Variable	Total (n = 693)	Deceased group (n = 136)	Survival group (n = 557)	p- value
Lymphocytes < 0.8 × 10 <sup>9</sup> /L #	299/677 (44.2)	120 (88.2)	179/541 (33.1)	< 0.001
Hb < 100 g/L #	69 (10.0)	34 (25.0)	35 (6.3)	< 0.001
ALB < 35 g/L #	58/639 (9.1)	12/131 (9.2)	46/508 (9.1)	0.970
BUN > 7 mmol/L #	183/685 (26.7)	97 (71.3)	86/549 (15.7)	< 0.001
BG > 14 mmol/L	8 (1.2)	0 (0.0)	8 (1.4)	0.288
Arterial PH < 7.35 #	120/639 (18.8)	60 (44.1)	60/503 (11.9)	< 0.001
pO <sub>2</sub> /F <sub>i</sub> O <sub>2</sub> ≤ 250 mmHg #	172/639 (26.9)	28 (20.6)	144/503 (28.6)	0.061
Multilobar infiltrates#	546 (78.8)	120 (88.2)	426 (76.5)	0.003
Pleural effusion #	120 (17.3)	36 (26.5)	84 (15.1)	< 0.001
Coinfections (n, %) #	265 (38.2)	84 (61.8)	181 (32.5)	< 0.001
Early NAI use (n, %) #	232 (33.5)	60 (43.4)	172 (30.9)	0.003
Systemic corticosteroid use (n, %) #	132 (19.0)	60 (44.1)	72 (12.9)	< 0.001
Noninvasive ventilation (n,%)	159 (22.9)	71 (52.2)	88 (15.8)	< 0.001
Invasive ventilation (n,%)	158 (22.8)	86 (63.2)	72 (12.9)	< 0.001
Admittance to ICU (n,%)	176 (25.4)	92 (67.6)	84 (15.1)	< 0.001
<p>COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; Hb: hemoglobin; ALB: albumin; BUN: blood urea nitrogen; BG: blood glucose; pO<sub>2</sub>/F<sub>i</sub>O<sub>2</sub>: arterial pressure of oxygen/fraction of inspiration oxygen; NAI: neuraminidase inhibitor. #: variables cited in the table above were the candidates which were entered into the multivariate logistic regression model. The bolded values are p-values &lt; 0.05, which represented significant differences between survival group and deceased group.</p>				

Table 2  
AUC for mortality predictions in FluA-p patients

Variable	AUC	SE	95% CI	Z statistic	p value
FluA-p score	0.908	0.016	0.881–0.931	--	Reference
PSI risk class	0.560	0.035	0.518–0.602	10.875	< 0.001
CURB-65 score	0.777	0.020	0.740–0.811	6.041	< 0.001
AUC: area under the curve; SE: standard error; CI: confidence interval.					

Almost forty percent (38.2%, 265/693) of patients were coinfecting with other community-acquired pathogens. *Streptococcus pneumoniae* (33.2%) was the most common coinfection, followed by *Klebsiella pneumoniae* (30.6%) and *Staphylococcus aureus* (20.4%) (Supplementary material 4).

All patients received antibiotic treatment within 48 hours after admission (Supplementary material 5), and NAI therapy during the course of the disease. Early NAI therapy and systemic corticosteroid use were administered in 33.5% (232/693) and 19.0% (132/693) of patients, respectively. 22.8% (158/693) of patients received invasive ventilation, 25.4% (176/693) of patients were admitted to the ICU, and the 30-day mortality rate was 19.6% (136/693) (Table 1).

There were no significant differences in the demographic characteristics, clinical features, approach to clinical management, and treatment outcomes between patients in the derivation and validation cohorts (Supplementary material 6).

## Predicted and actual mortality in FluA-p patients stratified by CURB-65 score and PSI risk class

Supplemental material 7 shows the actual and predicted mortality rates stratified by PSI risk class and CURB-65 scores. For the 136 deceased patients, the proportions of patients with PSI risk I–IV were 38.2% (52/136), 8.8% (12/136), 5.9% (8/136), 47.1% (64/136) and 0% (0/136), respectively; the proportions of patients with CURB-65 scores 0–5 were 0% (0/136), 66.9% (91/136), 12.5% (17/136), 0% (0/136) and 0% (0/136), respectively.

## Risk Factors For 30-day Mortality

Following the procedures described in the Statistical Analysis section, the following variables were entered into a backward stepwise logistic regression analysis: obesity, smoking history, cardiovascular disease, chronic pulmonary disease (COPD), confusion, leukocytes  $> 10 \times 10^9/L$ , lymphocytes  $< 0.8 \times 10^9/L$ , hemoglobin (Hb)  $< 100 \text{ g/L}$ , albumin (ALB)  $< 35 \text{ g/L}$ , blood urea nitrogen (BUN)  $> 7 \text{ mmol/L}$ , arterial

PH < 7.35, pO<sub>2</sub>/FiO<sub>2</sub> ≤ 250 mmHg, multilobar infiltrates, pleural effusion, early NAI therapy, systemic corticosteroid use, and coinfections.

A multivariate logistic regression model indicated that the following variables were significantly associated with 30-day mortality (see Fig. 2): BUN > 7 mmol/L (OR 1.604, 95% CI 1.150–4.492, p = 0.040), pO<sub>2</sub>/FiO<sub>2</sub> ≤ 250 mmHg (OR 2.649, 95% CI 1.103–5.142, p = 0.022), cardiovascular disease (OR 3.967, 95% CI 1.269–7.322, p < 0.001), arterial PH < 7.35 (OR 3.959, 95% CI 1.393–7.332, p < 0.001), smoking history (OR 5.176, 95% CI 2.604–11.838, p < 0.001), lymphocytes < 0.8 × 10<sup>9</sup>/L (OR 8.391, 95% CI 3.271–16.212, p < 0.001) and early NAI therapy (OR 0.567, 95% CI 0.202–0.833, p = 0.001).

## Comparison Of Severity Scores For Mortality Prediction

In order to develop a simple and useful clinical predicting tool, relative weights were assigned according to the regression coefficient ( $\beta$ ) of each categorical variable. Supplementary material 8 shows that the AUROC of the derivation cohort was 0.934 (95% CI 0.906–0.957), which was higher than the CURB-65 score (AUC = 0.813, 95% CI 0.772–0.850, p < 0.001) and the PSI risk class (AUC = 0.577, 95% CI 0.527–0.625, p < 0.001) (Supplemental Fig. 1). Supplementary material 9 shows that the AUROC of the validation cohort was 0.846 (95% CI 0.781–0.897), which was higher than the CURB-65 score (AUC = 0.681, 95% CI 0.604–0.752, p < 0.001) and the PSI risk class (AUC = 0.525, 95% CI 0.445–0.604, p < 0.001) (Supplemental Fig. 2). For the full sample of 693 patients, the AUROC was 0.908 (95% CI 0.881–0.931), which was higher than the CURB-65 score (AUC = 0.777, 95% CI 0.740–0.811, p < 0.001) and the PSI risk class (AUC = 0.560, 95% CI 0.518–0.602, p < 0.001) (Table 3). Table 4 shows the sensitivity, specificity and actual mortality associated with the FluA-p score (in the full sample of 693 patients). In accordance with the cut-score approach described earlier, patients were divided into high-risk and low-risk groups based on a cut-off value of 7. The Kaplan-Meier survival curves showed that 30-day mortality was significantly higher in patients with high-risk than for patients at low-risk (52.9% vs 2.1%, log rank test, p < 0.001) (Fig. 3).

Table 3  
FluA-p score and actual mortality

Score	Actual 30-day Mortality (% <i>, n</i> )	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
0	0 (0/120)	100.00	97.3–100.0	0.00	0.0–0.8	1.00	
1	50.0 (8/16)	100.00	97.3–100.0	25.05	21.2–29.2	1.33	0.00
2	0 (0/237)	94.12	88.7–97.4	26.72	22.8–30.9	1.28	0.22
3	24.4 (20/82)	94.12	88.7–97.4	76.20	72.1–79.9	3.95	0.077
4	25.0 (8/32)	79.41	71.6–85.9	89.14	86.0–91.8	7.32	0.23
5	71.4 (40/56)	73.53	65.3–80.7	94.15	91.7–96.1	12.58	0.28
6	100 (8/8)	44.12	35.6–52.9	97.49	95.7–98.7	17.61	0.57
7	81.3 (52/64)	38.24	30.0–47.0	97.49	95.7–98.7	15.26	0.63
8	NA	0.00	0.0–2.7	100.00	99.2–100.0		1.00

+LR: positive likelihood ratio; -LR: negative likelihood ratio.

## Discussion

Our study not only assessed several risk factors, but also developed a simple and reliable prediction tool for predicting mortality in patients with FluA-p. Our method showed greater predictive validity than did the common pneumonia severity scores of PSI and CURB-65.

PSI and CURB-65 scores are recommended by the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) and the British Thoracic Society (BTS) for the assessment of disease severity of CAP. Numerous studies have found that PSI and CURB-65 scores accurately predict the 30-day mortality rates of CAP and are applicable for use in many clinical settings [20–22]. Recently, however, some studies suggested that they were insufficient for predicting mortality in settings involving influenza pneumonia. Our results likewise suggested that PSI and CURB-65 scores underestimated the mortality of FluA-p patients. More than half of the deceased patients were classified as low death risk (CURB-65 score 0–2 and PSI risk class I–III). Both CURB-65 and PSI were heavily weighted by age and comorbidities. But many Flu-p patients were young and previously healthy individuals. In our study cohort, 60% of patients were younger than 65 years of age. During the H1N1 influenza A pandemic in 2009, a large proportion of severe cases were young patients who experienced acute respiratory failure [23–24]. Another issue to consider is that the current severity tool that relies on PSI and CURB-65 scores was derived from patients diagnosed primarily with bacterial pneumonia rather than influenza pneumonia. In fact, Guo et al reported that CURB-65 scores were not powerful predictors of mortality in the context of viral pneumonia [25].

Several studies have reported lymphocytopenia in severe influenza [26–28]. Shi et al suggested that lymphocytopenia was an early and reliable predictor of mortality in patients diagnosed with influenza A(H1N1)pdm09 pneumonia [27]. Although the mechanisms of lymphocytopenia in severe influenza are not well elucidated, it is believed that the reduction of T lymphocytes (including CD8 + T effector and central memory cells, CD4 + T, and/or NK cells), rather than B lymphocytes, in the peripheral blood might be the causes of lymphocytopenia [29–31]. Lymphocytopenia also plays a role in suppressive cellular immunity and the delayed clearance of viruses [32].

Smoking history was another predictor of FluA-p mortality in our study, which is a finding commensurate with some previous reports [33–35]. Wong and colleagues, for example, found that influenza-related mortality for all-causes and for cardiovascular and respiratory diseases was greater in current and ex-smokers than in never smokers [33]. A case-control study by Hennessy et al found that smoking (OR 3.03, 95% CI 1.01–9.23) was a significant risk factor for death in patients with A(H1N1)pdm09 [34]. Although the precise nature of the association between smoking and influenza-related mortality has yet to be determined, some potential mechanisms suggest the possibility of biological associations. Smoking could disrupt the normal defenses of the respiratory tract by causing peribronchiolar inflammation, slowing mucociliary clearance, and/or damaging respiratory epithelial cells [36]. Animal studies using mouse models have shown that smoking induces inflammatory mediators and suppresses innate immunity against influenza infection [37]. Smoking could increase viral replication by directly suppressing epithelial antiviral pathways, facilitating cytokine release in mucosal innate immunity and increasing deoxyribonucleic acid (DNA) methylation for viral infection [38].

BUN,  $pO_2/FiO_2$ , and arterial PH were parameters in calculating PSI and/or CURB-65 scores. Our study showed that these parameters were valuable predictors of mortality in FluA-p patients. Early administration of NAI therapy is associated with better outcomes in severe influenza [39–40]. Old age and chronic medical conditions, such as COPD, diabetes mellitus, and chronic kidney disease, have been associated with poorer outcomes in patients with influenza [41–43]. However, in our study only cardiovascular disease was identified as a risk factor for mortality in FluA-p patients. Other studies have shown that coinfections can worsen illness severity and increase mortality in severe influenza [44–45]. In our univariate analyses, coinfections were associated with increased mortality for FluA-p patients, but coinfections were not significant predictors in the multivariate analysis.

FluA-p score is a very simple severity assessment tool containing only seven parameters and it serves as a reliable prediction rule. ROC showed better predictive validity compared to PSI risk class and the CURB-65 score. Specifically, using a cutoff value of 7, the new score could stratify patients into two groups with significantly different death risks. We believe this novel assessment tool is suitable for use in clinical settings with FluA-p patients.

Some limitations of our study should be noted. First, despite our respectable sample size and comprehensive statistical approach, the retrospective research design (along with some missing data) may have affected our results. Second, due to the retrospective study design, we were unable to retrieve

and evaluate vaccination data. Finally, some studies have suggested that the clinical characteristics and prognosis of immunocompromised patients with influenza is not the same as that for immunocompetent hosts [46–47]. Thus, it is important to further assess our influenza prediction model in immunocompromised patients.

## Conclusions

We developed a simple and reliable prediction rule for 30-day mortality in patients hospitalised with FluA-p. The prediction rule could help clinicians to more accurately assess influenza disease severity. Our recommendation is that clinicians should pay particular attention to patients with FluA-p scores  $\geq 7$ , as such individuals have an increased risk for death.

## Abbreviations

Flu-p: Influenza-related pneumonia; FluA-p: Influenza A-related pneumonia; PSI: Pneumonia severity index; CURB-65: Confusion, urea, respiratory rate, blood pressure, age  $\geq 65$  years; NAI: Neuraminidase inhibitor; OR: Odds ratio; IC: Interval confidence; ROC: Receiver operating characteristic; AUROC: Area under the ROC curve; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; Hb: Hemoglobin; ALB: Albumin; BUN: Blood urea nitrogen; PH: Hydrogen ion index; pO<sub>2</sub>/FiO<sub>2</sub>: Arterial pressure of oxygen/fraction of inspiration oxygen; ICU: Intensive care unit; IDSA/ATS: Infectious Diseases Society of America/American Thoracic Society; BTS: British Thoracic Society; DNA: deoxyribonucleic acid.

## Declarations

**Consent for publication** Not applicable

**Ethics approval and consent to participate** The study was carried out according to Declaration of Helsinki and obtained the approval of the local Ethics Committee (Beijing Jishuitan Hospital). Protocol number 201911-15. Given the retrospective nature of the study, the Ethics Committee determined that an informed consent was not necessary.

**Data availability** All data generated or analysed during this study are included in this published article [and its supplementary information materials].

**Competing interests** The authors declare that they have no conflict of interest.

**Funding** This study is funded by Beijing JST research (ZR-201921).

**Author contributions** Study concept and design: LC, XdH. Acquisition of data: LC, XdH, YIL, CxZ, XqX. Statistical analysis of data: LC. Drafting of the manuscript: LC. Critical revision of the manuscript for important intellectual content: XdH, XqX. All authors agree with the article submission. All authors read and approved the final manuscript.

**Acknowledgements** The authors would like to express their gratitude to EditSprings (<https://www.editsprings.com/>) for the expert linguistic services provided.

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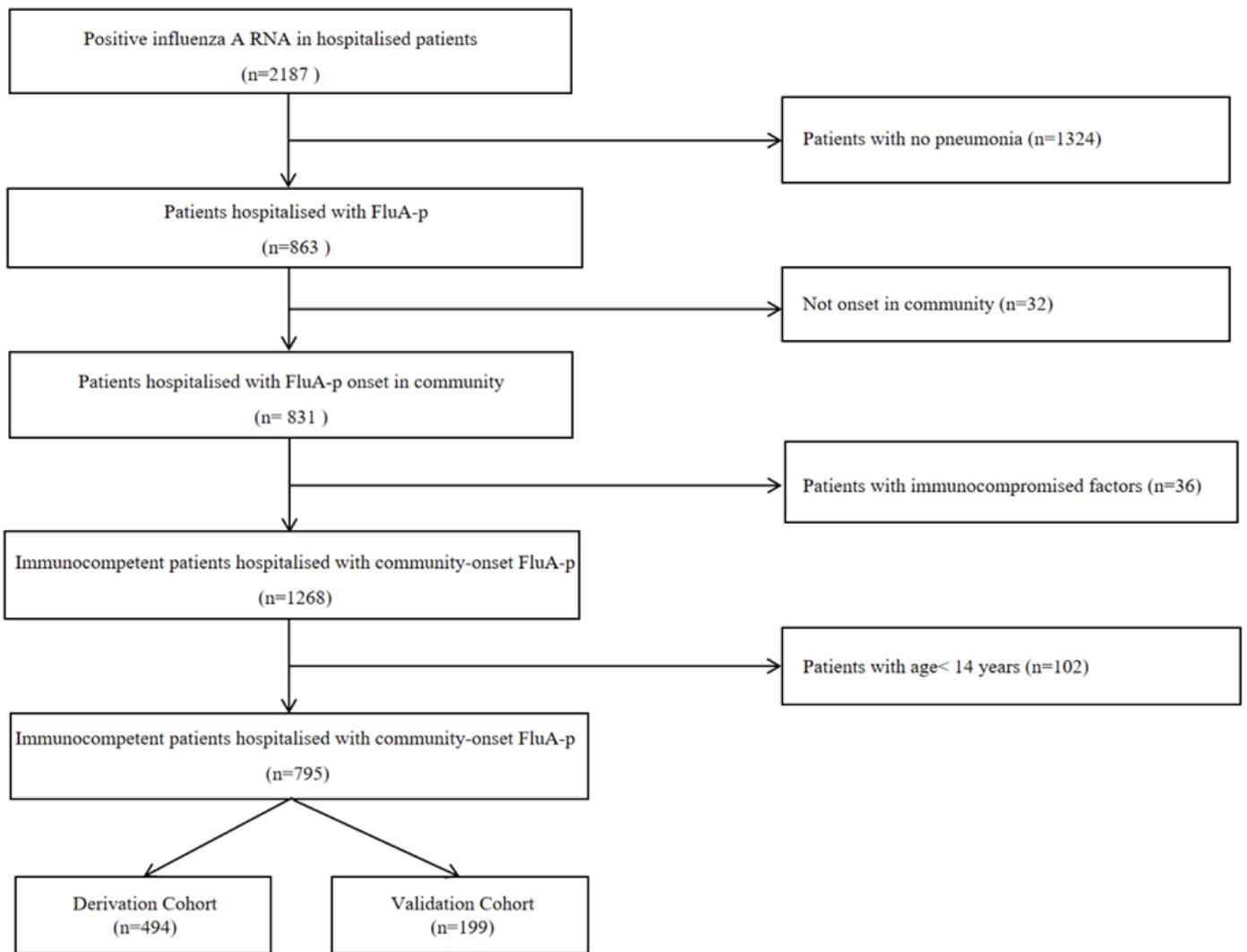
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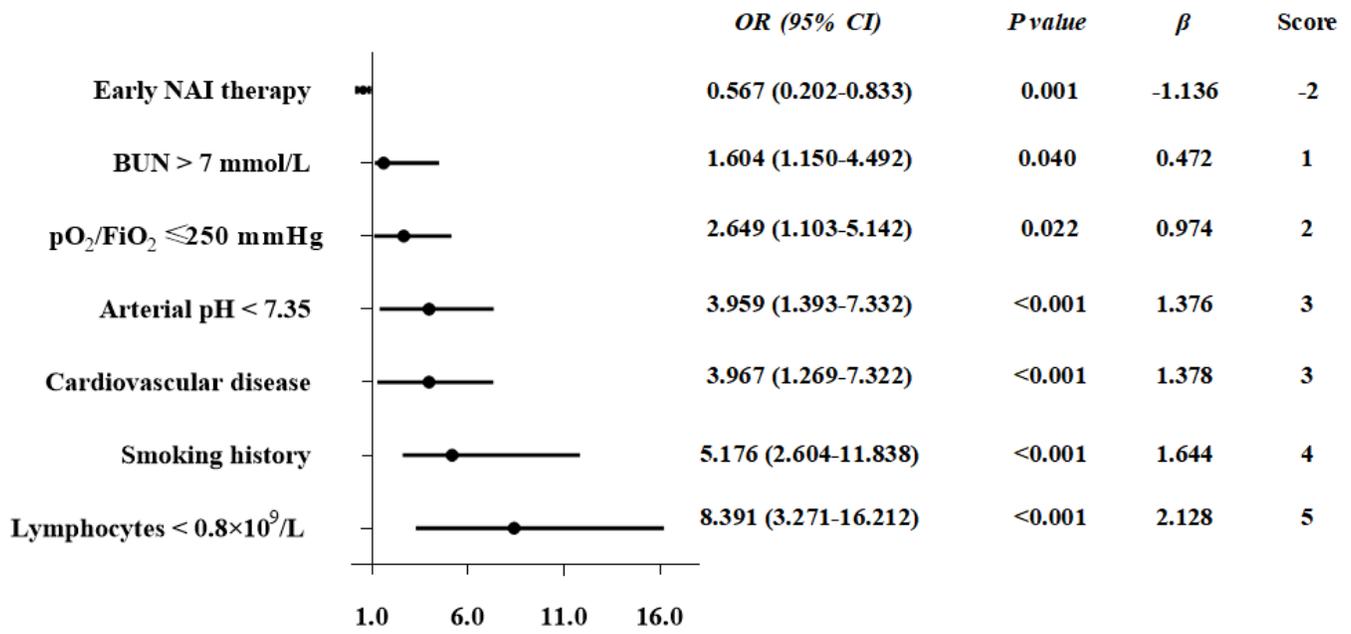
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## Figures



**Figure 1**

Patient screening algorithm for FluA-p



**Figure 2**

Multivariate analysis associated with mortality of FluA-p patients

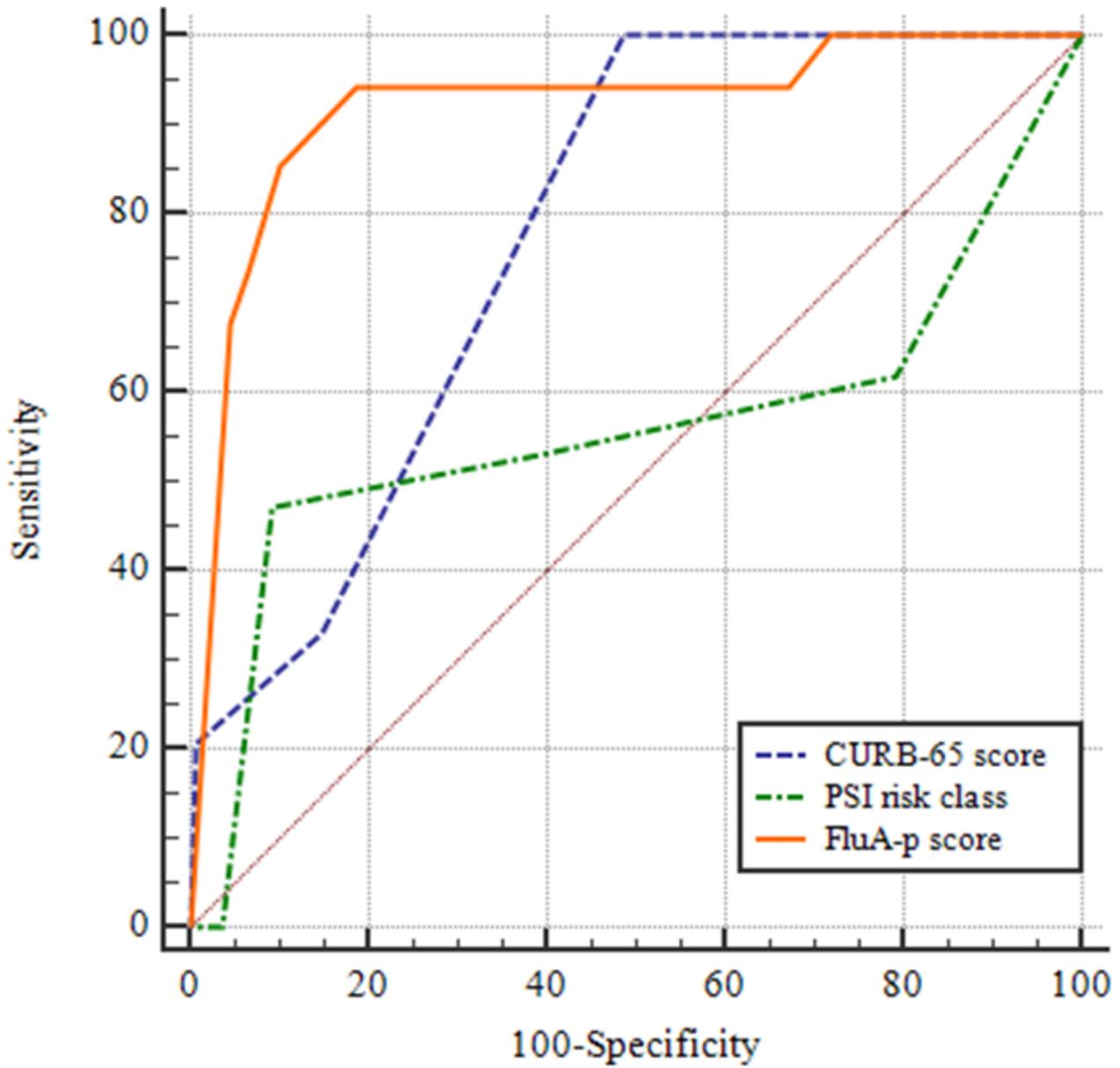


Figure 3

ROCs for mortality prediction of three severity scores in FluA-p patients

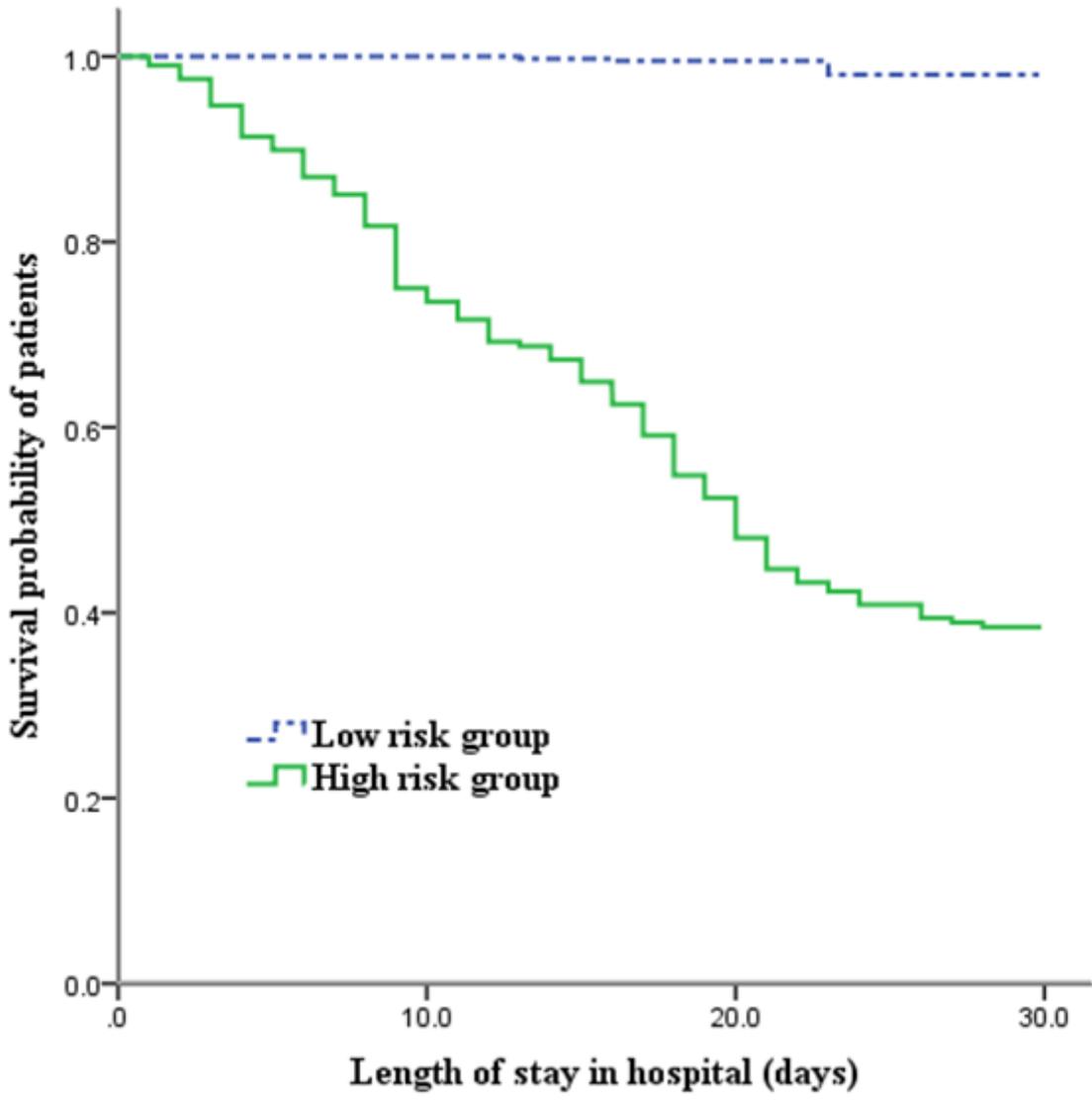


Figure 4

Fig 3 Survival of FluA-p patients by different levels of FluA-p scores. For 30-day mortality: FluA-p score < 7: Low risk; FluA-p score  $\geq$  7: High risk

## Supplementary Files

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