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Flu-IV score: a predictive tool for assessing the risk of invasive mechanical ventilation in patients with influenza-related pneumonia

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Abstract

Aim: To develop an assessment tool to predict invasive mechanical ventilation (IMV) among influenza-related pneumonia (Flu-p) patients within 14 days of admission. Methods: In total, 1107 Flu-p patients from five teaching hospitals were retrospectively enrolled from January 2012 - December 2019 and used to develop a predictive model. Results: Overall, 10.6% (117/1107) of patients underwent IMV within 14 days of admission. Multivariate regression analyses revealed that the following factors were associated with IMV: early neuraminidase inhibitor use (-2 points), lymphocytes $< 0.8\times109$/L (1 points), multi-lobar infiltrates (1 point), age [?] 65 years old (2 points), systemic corticosteroid use (2 points), PaO2/FiO2 $<$ 300 mmHg (2 points), respiratory rate [?] 30 breaths/min (3 points), and arterial PH $<$ 7.35 (3 points). A total score of six points was used to identify patients at risk of IMV. This model had a sensitivity of 88.79%, a specificity of 87.55%, and exhibited better predictive performance than the ROX index (AUROC = 0.927 vs 0.688, p $<$ 0.001), modified ROX index (AUROC = 0.927 vs 0.747, p $<$ 0.001), and HACOR scale (AUROC = 0.927 vs 0.524, p $<$ 0.001). Conclusions: Flu-IV scores can be used to reliably predict 14-day IMV rates in Flu-p patients.

Flu-IV score: a predictive tool for assessing the risk of invasive mechanical ventilation in patients with influenza-related pneumonia

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Conclusions: Flu-IV scores can be used to reliably predict 14-day IMV rates in Flu-p patients.

- **Key notes**
- We developed an easy-to-use predictive tool (Flu-IV score) for early assessing the risk of IMV in patients with Flu-p.
- The Flu-IV score included eight variables, and a total score of six points was used to identify patients at risk of IMV.
- The model exhibited better predictive performance than the ROX index, modified ROX index , and HACOR scale.

Key words: Influenza; Pneumonia; Invasive mechanical ventilation; Prediction rule

Introduction

Influenza is a common viral respiratory disease that affects between 5% and 10% of the population of the world each year, resulting in 3-5 million severe infections and between 290,000 and 650,000 annual deaths attributable to influenza-related illness [1]. Owing to the significant morbidity and mortality associated with disease, influenza is considered by many researchers to be one of the greatest threats to global public health at present [2].

Influenza-related pneumonia (Flu-p) is a severe form of influenza infection associated with over 50% of influenza-relate hospitalization and mortality [3]. Flu-p can progress from relatively mild disease to more severe cases that can cause ARDS or respiratory failure such that patients must often undergo invasive mechanical ventilation (IMV) within 3-10 days following initial symptom onset [4-5]. The need for IMV is linked to higher rates of patient morbidity and mortality [6], and evaluating a given patient's odds of requiring IMV is thus a valuable prognostic approach. However, the risk factors associated with the need for IMV have not been fully clarified. Certain assessment tools have been established in an effort to gauge the odds of IMV in individuals suffering from acute hypoxemic respiratory failure, including the ROX index (pulse oximetry/FiO_2 to respiratory rate) [7], modified ROX index (PaO_2/FiO_2 to respiratory rate) [8], and HACOR scale (heart rate, respiratory rate, arterial pH, PaO_2/FiO_2 and Glasgow Coma Scale) [9]. These tools, however, are not specific to Flu-p patients, nor have any studies specifically examined their predictive power in individuals suffering from Flu-p, and there is thus a clear need for the development of a reliable tool that can predict the requirement for IMV in Flu-p patients at an early time point prior to the onset of potential respiratory failure.

As such, we performed the present retrospective multicenter study with the goal of developing an accurate and easy-to-use assessment tool capable of predicting the odds of a given Flu-p patient undergoing IMV within 14 days of admission.

Materials and methods

2.1 Patient recruitment

For this study, patients for whom influenza virus nucleic acid testing was performed in the microbiology labs of five tertiary hospitals in China (Supplementary Material 1) from January 1st, 2012 – December 31st, 2019 were screened for eligibility. Those patients with confirmed Flu-p were enrolled in this study. Patients were excluded if they: (i) were not classified as having community-onset pneumonia (hospitalized

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within the last 28 days, with pneumonia onset [?] 48 h after admission [10]), as the inclusion of nosocomial pneumonia cases had the potential to complicate result interpretations; (ii) were < 18 years old; (iii) were immunocompromised, given that this had the potential to adversely impact influenza clinical outcomes [11]; or (iv) had been intubated prior to admission.

The study design was approved by the Ethics Committee of Beijing Jishuitan Hospital (No.201911-15). Given the retrospective nature of the study, the Ethics Committee determined that an informed consent was not necessary.

2.2 Study definitions

Patients with Flu-p were defined as individuals for whom polymerase chain reaction (PCR) analyses of respiratory specimens (including sputum, nasal/nasopharyngeal swabs, bronchial aspirates, and bronchoalveolar lavage fluid) were positive for influenza viral RNA, and for whom respiratory symptoms and chest radiographic findings were consistent with newly emergent chest infiltrates. The decisions to initiate IMV were taken by the attending physicians, based on the presence of any of the following intubation criteria: respiratory or cardiac arrest, respiratory pauses with loss of alertness or gasping for air, severely impaired consciousness, major agitation inadequately controlled by sedation, signs of exhaustion, massive aspiration, inability to manage respiratory secretions appropriately, and hemodynamic instability without response to fluids and vasoactive agents. Additionally, patients were also intubated in case of subsequent worsening of gas exchange or respiratory distress despite supportive measures [12]. Early neuraminidase inhibitor (NAI) therapy was defined as the administration of NAI agents within two days of symptom onset [132]. Systemic corticosteroid treatment was defined by the administration of one or more systemic corticosteroid doses before invasive ventilation and after admission. Community-acquired co-infecting respiratory pathogens were defined as pathogens detected via standard microbiological techniques (Supplementary Material 2) within 48 h following admission [14].

2.3 Data Collection

Data extracted from patient medical records with a standard case report form included demographic details, patient comorbidities (see Supplementary Material 3), patient symptoms, vital signs, laboratory results, radiographic findings before invasive ventilation at the day of admission (if there were multiple results, the worst value was extracted), community-acquired co-infecting respiratory pathogens, patient management, and outcome data (including NAI use, antibiotic use, systemic corticosteroid administration, IMV, and 14-day mortality). Outcomes for those hospitalized for < 14 days were established through follow-up via telephone.

2.4 Statistical analysis

In total, 1107 Flu-p patients were identified and enrolled in this study. These patients were then randomly assigned to derivation and validation cohorts (80% and 20% of patients, respectively), which were respectively used to develop and validate our prognostic model.

In addition, these 1107 patients were separated into two groups based upon whether or not they underwent IMV within 14 days following admission. Baseline characteristics were then compared between these two patient groups, and all variables which yielded a $P < 0.1$ in these initial univariate analyses were incorporated into a multivariate stepwise logistic regression model to identify risk factors associated with 14-day IMV rates. To ensure model simplicity, each risk factor was assigned an integer score value associated with its corresponding regression coefficient (β) value. Model cutoff scores were then defined using receiver operating characteristic (ROC) curves based upon Youden's index. Kaplan-Meier analyses were conducted to compare rates of IV between patients above and below this cutoff score (high-risk and low-risk, respectively). The area under the ROC curve (AUROC) was used to gauge the prognostic performance of this model based upon overall sensitivity and specificity values.

A Kolmogorov–Smirnov test was used to assess result normality, with normally and non-normally distributed variables being presented as means ± standard deviation and medians, respectively. Continuous variables

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were evaluated with Mann-Whitney *U* tests or Student's t-tests, whereas categorical variables were assessed with Fisher's exact test or chi-squared tests. A two-tailed $P < 0.05$ was indicative of significance. SPSS 22.0 or MedCalc 19.0 were used for all statistical testing.

Results3.1 Patient screening

A total of 3405 hospitalized patients who were found to be positive for influenza viral RNA during the study period were screened for eligibility, of whom 1107 with laboratory-confirmed Flu-p were enrolled in this study. Flu-p was associated with influenza A virus and influenza B virus infections in 683 and 424 of these patients, respectively (Figure 1).

3.2 Patient characteristics

Enrolled patients exhibited a median age of 61.0 years, and were 54.5% (603/1107) male. The most prevalent comorbidities in these patients included cardiovascular disease (22.7%, 251/1107), diabetes mellitus (13.4%, 148/1107), and cerebrovascular disease (10.3%, 114/1107). Upon admission, 42.4% (462/1089) of patients presented with lymphocytes $< 0.8\times10^9$/L, 49.1% (515/1048) presented with $PaO_2/FiO_2 < 300$ mmHg, 11.7% (129/1107) presented with confusion, and 14.4% (159/1107) presented with a respiratory rate [?] 30 breaths/min (Table 1).

In total, 33.5% (371/1107) patients were found to be co-infected with other community-acquired pathogens, including *Klebsiella pneumoniae* (32.6%, 121/371), *Streptococcus pneumoniae* (29.9%, 111/371), and *Staphylococcus aureu* s (19.79%, 73/371) (Supplementary Material 4).

Of these patients, 33.5% (391/1107) underwent NAI treatment within 48 h following symptom onset, while 12.7% (141/1107) were administered systemic corticosteroids before IMV following admission. Non-invasive mechanical ventilation (NIMV) and IMV were respectively conducted within 14 days of admission for 11.6% (128/1107) and 10.6% (117/1107) of patients. The all-cause 14-day mortality rate for these patients was 3.2% (35/1107) (Table 1).

The baseline clinical characteristics and outcomes between patients in the derivation and validation cohorts were similar (Supplementary Material 5).

3.3 Risk factors associated with 14-day IMV rates in Flu-p patients

Next, univariate analyses were conducted which identified age [?] 65 years old, influenza A virus infection, the presence of solid malignant tumors, a respiratory rate [?] 30 breaths/min, a leukocyte count $> 10\text{x}10^9$/L, ALB < 35 g/L, arterial PH < 7.35, $PaO_2/FiO_2 < 300$ mmHg, early NAI therapy, and systemic corticosteroids use before IMV to be associated with 14-day IMV rates in Flu-p patients (Table 1).

In a subsequent multivariate logistic regression model, factors that were identified as independent predictors of a higher risk of requiring IMV in Flu-p patients (Figure 2) included: early NAI use (*OR*0.041, *95% CI* 0.005-0.171, $p = 0.004$; -2 points), lymphocytes $< 0.8\text{x}10^9$/L (*OR* 6.081,*95% CI* 2.414-15.318, $p < 0.001$; 1 point), multilobar infiltrates (*OR* 4.515, *95% CI* 1.182-17.249,$p = 0.028$; 1 point), age [?] 65 years old (*OR* 10.941,*95% CI* 3.917-30.561, $p < 0.001$; 2 points), systemic corticosteroid administration (*OR* 10.787, *95% CI*3.124-37.245, $p < 0.001$; 2 points), $PaO_2/FiO_2 < 300$ mmHg (*OR* 14.015, *95% CI* 4.829-40.673, $p < 0.001$; 2 points), respiratory rate [?] 30 breaths/min (*OR* 57.766,*95% CI* 19.365-172.316, $p < 0.001$; 3 points), and arterial PH < 7.35 (*OR* 64.887, *95% CI*7.476-132.174, $p < 0.001$; 3 points).

3.4 Assessment of the predictive performance of Flu-IV scores

The AUROC value for the Flu-IV score model developed based upon the above multivariate analysis was 0.927 in our overall patient cohort (*95% CI* 0.906 - 0.944), and was higher than that of the ROX index (AUROC = 0.688, *95% CI* 0.654 - 0.721, $p < 0.001$), modified ROX index (AUROC = 0.747, *95% CI* 0.715 - 0.778, $p < 0.001$), or HACOR scale (AUROC = 0.524,*95% CI* 0.488 - 0.560, $p < 0.001$) (Supplementary Material 6 and Figure 3). Similar findings were also independently made in both our derivation cohort

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(Supplementary Material 7 and Supplementary Figure 1) and validation cohort (Supplementary Material 8 and Supplementary Figure 2).

Table 2 compiles the mortality rates, sensitivity, and specificity values associated with our Flu-IV score model in the overall patient cohort. Patients were stratified into high- and low-risk cohorts based upon whether they had Flu-IV scores that were above or below the optimal cutoff score of 6 points. Subsequent Kaplan-Meier curves confirmed that high-risk patients were significantly more likely to require IMV relative to low-risk patients (49.5% vs 1.8%, log-rank test, $p< 0.001$) (Figure 4).

Discussion

This was a multicenter retrospective study designed to develop a novel model capable of predicting the odds of IMV within 14 days of admission for Flu-p patients. Our resultant Flu-IV risk score model was more accurate and exhibited better predictive performance relative to the ROX, modified ROX, and HACOR scales when evaluating these patients.

We found that 10.6% of the patients in the present study necessitated IMV within 14 days of admission, in line with prior reports regarding severe influenza patient outcomes [15-16]. The 14-day mortality of patients that did require IMV was significantly greater than that of patients that did not. As 92.1% of Flu-p patients that undergo IMV do so within 14 days of admission, predicting 14-day IMV rates is critical to appropriate patient management.

We identified multiple variables that are known to be associated with more severe influenza and that were also associated with a higher risk of IMV in Flu-p patients [17], including age > 65 years, a lymphocyte count < $0.8x10^9$/L, and systemic corticosteroid use. Cellular immunity is a key mediator of antiviral responses [18], and advanced age is associated with a decline in overall patient immune status [19]. Severe influenza is also often characterized by lymphocytopenia in 50-100% of cases [20-21], although the mechanistic basis for this finding remains poorly understood. There is some evidence that CD4+ and CD8+ T cells may undergo higher rates of apoptotic death in individuals with severe disease owing to higher circulating levels of soluble Fas ligand and caspase-1 [22], thereby contributing to an overall decline in lymphocyte counts. Such virus-induced lymphocytopenia can delay viral clearance. Alternatively, these lymphocytes may be recruited to the respiratory tract and other organs, resulting in their apparent depletion from circulation [23]. Lymphocyte accumulation within the lungs can drive more severe localized inflammation and tissue damage. Systemic corticosteroid use can suppress overall immune functionality and increase the odds of developing severe nosocomial pneumonia necessitating IMV [24-25].

Severe Flu-p is characterized by impaired pulmonary function and diffuse alveolar damage [26], with tachypnea and decreased PaO_2/FiO_2 serving as direct manifestations of such pulmonary damage. Pneumonia patients also often exhibit metabolic acidosis that is linked to hyper-inflammation and impaired tissue perfusion [27], thereby exacerbating pulmonary damage. Impaired pulmonary function and the retention of carbon dioxide in the lungs can further drive respiratory acidosis, leading to higher rates of NIMV failure and an increased risk of requiring IMV [28]. Inhibiting viral replication at early time points can reduce virus-induced inflammation and tissue damage, thereby decreasing overall influenza-related mortality rates [29]. This has been proven by abundant clinical studies [30-31]. Our data also suggest that early NAI treatment was associated with a lower risk of Flu-p patient intubation.

The ROX, modified ROX, and HACOR scales have been designed to predict the odds of IIMV failure in patients suffering from hypoxemia. Just 49% of patients in the present study cohort exhibited hypoxemia upon admission. Importantly, these scoring systems were not designed for the analysis of Flu-p patients. While some of the variables included in our Flu-IV model were the same as those included in the ROX, modified ROX, and HACOR scales, these tools were not able to reliably predict IMV rates among Flu-p patients. We found that our Flu-IV tool was able to predict IMV rates significantly more reliably than these three scales as determined based upon AUROC values. A Flu-IV cutoff score of 6 was able to effectively stratify Flu-p patients into low- and high-risk categories. Considering its good negative prediction value, the Flu-IV score could be used particularly as a rule-out approach to early discharge patient with a low score.

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Importantly, our Flu-IV scoring model is simple, allowing clinicians to predict the odds of a given patient requiring IMV within 14 days of admission based upon eight parameters that can be readily measured even in small or primary hospitals. This model can be used to evaluate patients at an early time point prior to the onset of respiratory failure, and as such, we believe it represents a valuable tool for the management of Flu-p patients in a variety of clinical settings.

4.1 Strength and limitation

There are certain limitations to this analysis. For one, as this study was retrospective in design, it is susceptible to selection bias. Nucleic acid tests, for example, we conducted based upon the subjective judgment of the attending physicians such that only patients with more severe disease may have undergone such testing, rather than all potentially eligible patients. Furthermore, it was possible that a very few patients required IMV were not intubated owing to noncompliance. As this study was retrospective, we were also unable to retrieve and evaluate patient vaccination data or other missing information, potentially constraining the accuracy of our findings. Patients were also not routinely evaluated for other respiratory viruses, and we are thus unable to exclude the possibility that certain patients may have been co-infected with multiple viruses.

ConclusionIn summary, we developed a reliable and straightforward predictive tool capable of gauging the odds of a given hospitalized Flu-p patient requiring IMV. This tool will help clinicians better evaluate the risks of early intubation for any given patient such that they can make optimal clinical judgments. However, it should be evaluated in more large-sample and prospective studies.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Authors' contributions

Study concept and design: LC, XdH. Acquisition of data: LC, XdH, YlL, 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.

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