ORIGINAL RESEARCH

Enhancing Prognostic Assessment for Influenza-Associated Pneumonia: An Examination of Contributing Risk Factors

Yi Lin, MSc; Yuping Li, MSc; Xiang Lian, BS; Zhenping Qian, BS; Weijie Wang, MSc; Pingguang Zhu, BS

ABSTRACT

Objective • This study aims to analyze the prognostic risk factors influencing patient outcomes in cases of influenza-associated pneumonia.

Methods • We comprehensively analysed clinical data from patients admitted to the First Affiliated Hospital of Wenzhou Medical University between December 2017 and April 2019. Patients with confirmed influenza-associated pneumonia, determined through nucleic acid detection in throat swabs or sputum samples, were included in the study. The collected data were meticulously analyzed to identify significant prognostic risk factors.

Results • A total of 151 patients diagnosed with influenza-associated pneumonia were included in the final analysis, yielding a fatality rate of 19.87% (30/151). The application of multivariate regression analysis revealed that several independent risk factors significantly affected the prognosis of patients afflicted with influenza-associated pneumonia. These included lymphocyte count (L), oxygenation index (O), albumin (A), and urinary (U) levels. Receiver operating characteristic (ROC) curve analysis further elucidated the prognostic value of these factors. Specifically, the Composite Index LOAU (Lymphocyte, Oxygenation index, Albumin, Urinary) demonstrated a robust area under the curve (AUC) of 0.909 (95% CI: 0.851-0.950), surpassing the performance of established scoring systems, such as the pneumonia severity index (PSI) (AUC = 0.746), Apache II (AUC = 0.732), and CURB-65 (AUC = 0.662). These differences were statistically significant ($P < .05$).

Conclusions • The prognosis of influenza-associated pneumonia can be effectively predicted by assessing peripheral blood parameters, including lymphocyte count, albumin level, urinary markers, and the oxygenation index upon admission. Notably, the Composite Index LOAU, as a comprehensive amalgamation of these factors, holds promising potential to enhance prognostic precision and management outcomes in cases of influenza-associated pneumonia. (*Altern Ther Health Med.* 2023;29(8):370-375).

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INTRODUCTION

Influenza-associated pneumonia, characterized by pneumonia resulting from either the influenza virus alone or its co-infection with other pathogens (such as viruses, bacteria, fungi, etc.), is the prevalent complication and primary contributor to mortality in cases of influenza virus infection.[1] The accurate assessment and prediction of the severity and prognostic outlook for individuals afflicted by influenza-associated pneumonia serve as foundational elements underpinning diverse diagnostic and therapeutic strategies.[2]

Several scoring systems are presently available to aid clinicians in evaluating the mortality risk and severity of community-acquired pneumonia patients. CURB-65 and PSI (pneumonia severity index) have demonstrated validity as effective measures for predicting 30-day mortality in individuals affected by community-acquired pneumonia.[3] The APACHE II (Acute Physiology and Chronic Health Evaluation II) scoring system also finds predominant utility in prognosticating outcomes among acute and critically ill patients.[1-4]

However, there is a lack of clinical scores or indicators exists for the comprehensive assessment of the severity in patients with influenza-associated pneumonia. Therefore, this study aims to investigate and compare clinical indicators that can offer enhanced accuracy in appraising the condition and prognosticating outcomes among individuals affected by influenza-associated pneumonia.

METHODS

Study Design

The study follows a retrospective design, analyzing clinical data from patients admitted to the First Affiliated Hospital of Wenzhou Medical University between December 2017 and April 2019. It employs multivariate regression analysis to explore the relationship between identified clinical indicators and the prognosis of influenza-associated pneumonia.

Inclusion and Exclusion Criteria

Adult patients admitted to the First Affiliated Hospital of Wenzhou Medical University between December 2017 and April 2019 and diagnosed with influenza were included in the retrospective analysis if they met the following criteria: (1) Age ≥ 18 years; (2) Presented with acute respiratory symptoms such as fever, cough, and sore throat; (3) Tested positive for influenza virus nucleic acid (via RT-PCR) in throat swabs or sputum samples before admission or within 48 hours after admission; (4) Chest X-ray or chest CT revealing pulmonary ground-glass opacity, consolidation, or multifocal exudative lesions.

Exclusion criteria comprised: (1) Outpatient cases; (2) Absence of flu-associated pneumonia diagnosis before admission or within 48 hours of admission; (3) Patients with incomplete clinical data.

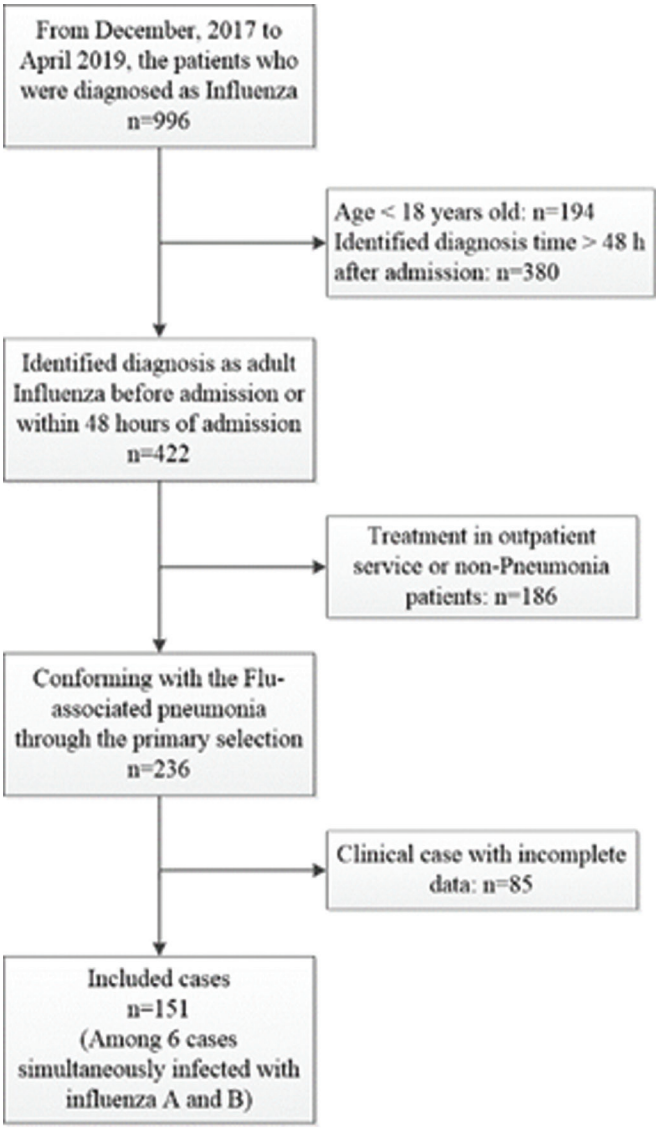
Data Collection and Prognostic Stratification

The study gathered important patient information, underlying medical conditions, vital signs, clinical symptoms, most critical laboratory test results within 48 hours of admission, imaging characteristics, and treatment outcomes for individuals meeting the admission criteria. CURB-65, PSI, and APACHE II scores were computed for each patient. The patient cohort was categorized into two groups based on their prognosis: survivors and deceased individuals. The deceased group encompassed patients who either succumbed or experienced deterioration within 30 days of hospitalization, with death confirmation obtained through telephone follow-up. The comparative analysis assessed differences in clinical indicators between the surviving and deceased groups.

Statistical Analysis

The data were processed using SPSS 22.0 software (IBM, Armonk, NY, USA). For normally distributed measurement data, mean ± standard deviation ($\bar{x} \pm s$) was employed, and a two-independent samples *t* test or t's test was applied to compare the two groups. Non-normally distributed measurement data were presented as median (quartiles) M (QL, QU), and comparison was conducted using a nonparametric rank-sum test (Mann-Whitney test). Count data were expressed as composition ratios, and a chi-square test using the Fisher or exact method was utilized for group comparisons. Logistic regression analysis was employed to identify independent risk factors impacting patient outcomes. Receiver Operating Characteristic (ROC) curve analysis was performed, assessing the predictive capabilities of each score through the determination of the Area Under the Curve (AUC).

Figure 1. Screening flow chart for included cases



Note: This figure illustrates the stepwise process of case selection, highlighting the criteria and numbers at each stage that led to the inclusion of cases in the study.

RESULTS

Epidemiological Characteristics and Disease Profile of Influenza Cases

A total of 996 cases of influenza were diagnosed, with 151 cases meeting the inclusion criteria following screening, as depicted in Figure 1. The mean age was 64.44 ± 14.68 years, and 92 cases (60.9%) were male. Within 30 days, the mortality rate stood at 19.9%. The average length of hospital stay was 14.39 days. In terms of influenza classification, 119 cases (78.8%) were infected with influenza A, 26 cases (17.2%) with influenza B, and 6 cases (4.0%) with both influenza A and B.

Underlying Diseases

Prevalent underlying diseases included respiratory conditions in 44 cases (29.1%), encompassing chronic

Table 1. Analysis of Risk Factors Affecting The Prognosis of Patients With Influenza-Associated Pneumonia (Count Data)

Index	Survival Group (n = 121)	Deceased Group (n = 30)	χ^2	*P* value
Male	71 (58.7%)	21 (70.0%)	1.295	.255
Infection With Influenza A	95 (78.5%)	24 (80.0%)	0.052	.974
Infection With Influenza B	21 (17.4%)	5 (16.7%)		
Infection With Influenza A and B	5 (4.1%)	1 (3.3%)		
Underlying Diseases				
Respiratory diseases	38 (31.4%)	6 (20.0%)	1.514	.218
Blood system disease	7 (5.8%)	2 (6.7%)	0.000	1.000
Angiocardiopathy	22 (18.2%)	7 (23.3%)	0.411	.521
Cerebrovascular Diseases	5 (4.1%)	6 (20.0%)	6.766	.009
Liver Disease	11 (9.1%)	2 (6.7%)	0.014	.952
Renal Disease	10 (8.3%)	4 (13.3%)	0.255	.613
Diabetes	24 (19.8%)	5 (16.7%)	0.155	.693
Clinical Symptom				
Fever	103 (85.1%)	27 (90.0%)	0.157	.692
Cough	113 (93.4%)	28 (93.3%)	0.000	1.000
Bloody Phlegm	17 (14.0%)	6 (20.0)	0.279	.597
Chest Pain	3 (2.5%)	0 (0.0%)		1.000
Breathing Difficulties	85 (70.2%)	26 (86.7%)	3.328	.068
Pleural Effussion	32 (26.4%)	16 (53.3%)	8.015	.005
Mixed Infections	43 (35.5%)	20 (66.7%)	9.581	.002

Note: The table presents the distribution of various risk factors among the survival group (n = 121) and the deceased group (n = 30) of patients with influenza-associated pneumonia. The χ^2 test was used to assess the significance of differences between the two groups. Results are displayed for categorical variables; *P* values less than .05 were considered statistically significant.

Table 2. Analysis of Risk Factors Affecting the Prognosis of Patients With Influenza-Associated Pneumonia (Measurement Data)

Index	Survival Group (n = 121)	Deceased Group (n = 30)	*t*/*t*′	*P* value
Age	63.70±14.63	67.40±14.79	-1.237	.218
Hospital Day	14.18±13.11	15.23±15.43	-0.379	.705
Temperature	37.74±0.91	37.75±1.21	-0.073	.942
Breathing Rate	21.75±5.99	25.70±9.04	-2.272	.029
Heart Rate	95.43±20.12	97.37±18.88	-0.478	.634
Mean Arterial Blood Pressure	91.47±15.45	92.69±13.58	-0.397	.692
Leucocyte Count	8.88±7.55	9.90±6.15	-0.688	.493
Hemoglobin	121.65±21.45	110.60±27.44	2.056	.047
Hematocrit	0.37±0.06	0.33±0.08	2.530	.012
Platelet Count	175.42±79.55	141.40±76.23	2.114	.036
Neutrophil Count	7.10±5.71	8.92±5.71	-1.559	.121
Lymphocyte Count	0.88±0.57	0.41±0.22	7.170	<.001
Monocyte Count	0.60±1.24	0.29±0.23	1.358	.176
Oxygenation Index	258.11±111.48	155.10±85.98	4.720	<.001
Alanine Aminotransferase	46.40±45.72	267.60±809.925	-1.495	.146
Total Bilirubin	8.33±7.57	13.27±10.36	-2.452	.019
Albumin	30.35±4.13	26.83±3.16	4.363	<.001
Blood Glucose	9.10±3.91	11.54±5.32	-2.357	.024
Use Nitrogen	7.40±4.96	13.06±7.90	-3.748	.001
Serum Creatinine	83.30±60.58	145.40±171.71	-2.045	.049
Blood Sodium	135.93±4.64	136.00±4.86	-0.078	.938
Blood Potassium	3.69±0.53	3.63±0.58	0.545	.587
Creatine Kinase	289.50±738.01	2935.13±10450.42	-1.386	.176
Procalcitonin	2.84±10.58	8.13±20.41	-1.376	.178
Curb-65 Scores	1.36±1.03	1.97±0.93	-3.114	.003
PSI Scores	87.28±34.53	116.90±29.55	-4.320	<.001
APACHE II Scores	10.43±5.90	15.00±5.78	-3.815	<.001

Note: This table presents a comprehensive examination of various clinical parameters regarding patient prognosis for influenza-associated pneumonia. Statistical comparisons between the survival group (n = 121) and the death group (n =3 0) were conducted using *t* tests. Significance is indicated by *P* values, with $P < .05$ considered statistically significant.

obstructive pulmonary disease, bronchiectasis, asthma, old tuberculosis, lung cancer, pulmonary aspergillosis, and interstitial lung disease. Nine cases (6%) involved hematologic malignancies such as leukemia and lymphoma. Cardiovascular diseases were present in 29 cases (19.2%), primarily coronary atherosclerotic heart disease, cardiac insufficiency, and arrhythmia.

Cerebrovascular diseases were observed in 11 cases (7.3%), mainly linked to sequelae of cerebral hemorrhage, cerebral infarction, and Alzheimer's disease. The liver disease affected 13 cases (8.6%), predominantly hepatitis B, hepatitis C, liver cirrhosis, and liver cancer. Kidney diseases were found in 14 cases (9.3%), including chronic nephritis, chronic renal insufficiency, nephrotic syndrome, and post-renal transplantation cases. Additionally, 29 cases (19.2%) were associated with type 2 diabetes mellitus.

Microbiological Profiling of Isolates in Respiratory Specimens

Routine sputum and/or bronchoscopic alveolar lavage cultures revealed the presence of specific pathogens, with diagnoses including 34 cases of *Acinetobacter baumannii*, 8 cases of Pseudomonas aeruginosa and *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, *Burkholderia*, *Corynebacterium striatum*, *Escherichia coli* (1 case), *Enterobacter cloacae* (1 case), *Actinomyces*, *Streptococcus pneumoniae* (23 cases), *Candida albicans* (6 cases), and *Rhizobium* (1 case).

Univariate Analysis

Patient Characteristics and Clinical Parameters. In the univariate analysis assessing the baseline characteristics of patients with influenza-related pneumonia, notable trends emerged. The proportion of patients with combined cerebrovascular disease, pleural effusion, and concurrent bacterial or fungal infections was significantly higher in the deceased group compared to the survival group ($P < .05$), as illustrated in Table 1.

Vital Signs, Laboratory Indices, and Scoring Systems. Further examination in the univariate analysis encompassed vital signs, the worst values of laboratory indices within 48 hours of admission, and the scores derived from CURB-65, PSI, and APACHE II. Among patients in the deceased group, elevated respiratory rate, neutrophil count/lymphocyte count ratio, total bilirubin, blood glucose, urea nitrogen, and blood creatinine were observed compared to the surviving group, with statistically significant distinctions ($P < .05$). Conversely, parameters including red blood cell pressure, hemoglobin, lymphocyte count, platelet count, oxygenation index, and albumin exhibited lower values in the deceased group ($P < .05$). Moreover, CURB-65, PSI, and APACHE II scores were significantly higher in the deceased group compared to the survival group ($P < .05$), as detailed in Table 2.

Multifactorial Regression Analysis

The logistic regression analysis employing the LR method identified significant risk factors, as presented in Table 3. Independent prognostic risk factors for patients with influenza-associated pneumonia encompassed lymphocyte count (L), oxygenation index (O), albumin (A), and urea nitrogen (U). ROC curves were individually constructed for these independent risk factors, with corresponding optimal cut-off values analyzed (Table 4, Figure 2). Notably, patients with

Table 3. Logistic Regression Analysis of Independent Risk Factors Affecting the Prognosis of Patients with Influenza-Associated Pneumonia

Index	Regression Coefficient	*P* Value	OR Value	The 95% Confidence Interval	
				Lower Limit	Upper Limit
Lymphocyte Count (L)	-3.469	.003	0.031	0.003	0.296
Oxygenation Index (O)	-0.009	.005	0.991	0.985	0.997
Albumin (A)	-0.199	.013	0.820	0.700	0.960
Urea Nitrogen (U)	0.101	.010	1.106	1.024	1.195
Constant	6.943	.005	1035.977		

Note: This table presents the logistic regression analysis results aimed at identifying independent risk factors influencing the prognosis of patients with influenza-associated pneumonia. A *P*-value less than 0.05 indicates statistical significance. The odds ratio (OR) reflects the increase or decrease in the odds of the outcome associated with a one-unit change in the predictor, along with its 95% confidence interval (CI).

Table 4. Jordans for Each Indicator ROC Curve

Index	Auc	Cutoff Value	Sensitivity	Specificity	Youden Index
Lymphocyte Count (L)	0.810	0.705	0.579	0.933	0.512
Oxygenation Index (O)	0.776	146.38	0.851	0.633	0.485
Albumin (A)	0.761	29.85	0.562	0.900	0.462
Urea Nitrogen (U)	0.759	10.15	0.600	0.835	0.435

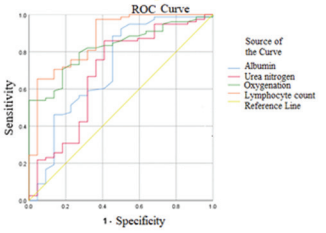
Abbreviations: AUC - Area Under the Curve; Youden Index is calculated as Sensitivity+Specificity - 1.

Table 5. Comparison of AUC Values for Each Score

Scoring System	AUC	SE	The 95% Confidence Interval		*P* value
			Lower Limit	Upper Limit	
LOAU	0.909	0.0253	0.851	0.950	Reference Value
PSI	0.746	0.0481	0.668	0.813	.0018
APACHE II	0.732	0.0496	0.653	0.800	.0006
CURB-65	0.662	0.0501	0.580	0.737	<.0001

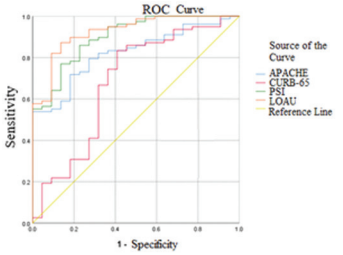
Abbreviations: AUC: Area Under the Curve; LOAU: Composite Index (Lymphocyte, Oxygenation index, Albumin, Urea nitrogen); PSI: Pneumonia Severity Index; APACHE II: Acute Physiology and Chronic Health Evaluation II; CURB-65: Confusion, Urea, Respiratory rate, Blood pressure, Age 65 or older.

Figure 2. ROC Curves for Lymphocyte Count, Oxygenation Index, Albumin, and Urea Nitrogen to Predict the Prognosis of Influenza-Associated Pneumonia



Note: The ROC curves displayed in this figure represent the predictive performance of lymphocyte count, oxygenation index, albumin, and urea nitrogen as indicators for assessing the prognosis of influenza-associated pneumonia. The area under the curve (AUC) values provide insights into the accuracy and effectiveness of each parameter in predicting patient outcomes.

Figure 3. ROC Curves of the Combined Index LOAU with PSI, APACHE II, and CURB-65 Scores for Predicting the Prognosis of Influenza-Associated Pneumonia



Note: This figure presents the ROC curves comparing the combined index LOAU (Lymphocyte, Oxygenation Index, Albumin, and Urea Nitrogen) with the PSI, APACHE II, and CURB-65 scores. The curves illustrate the performance of these scoring systems in predicting the prognosis of influenza-associated pneumonia, with the area under the curve (AUC) values serving as indicators of their respective predictive abilities.

influenza-associated pneumonia exhibited increased mortality rates when presenting with lymphocyte counts < 0.705×10^9/L, oxygenation indices < 146.38 mmHg, albumin levels < 29.85 g/L, and urea nitrogen levels > 10.15 U/L upon admission.

Comparative Analysis of Scoring Systems

The ROC curves illustrating the performance of the Composite Index LOAU [lymphocyte count (L), oxygenation index (O), albumin (A), and urea nitrogen (U)] in conjunction with PSI, APACHE II, and CURB-65 scores to predict patient mortality are depicted in Figure 2. The area under the ROC curve, accompanied by its corresponding 95% confidence interval, for the Composite Index LOAU, was 0.909 (0.851-0.950), while for PSI, APACHE II, and CURB-65 scores, they were 0.746 (0.668-0.813), 0.732 (0.653-0.800), and 0.662 (0.580-0.737), respectively.

Comparative analysis utilizing the *Z* test unveiled the superior predictive ability of the Composite Index LOAU over PSI, APACHE II, and CURB-65 scoring systems in predicting mortality among patients with influenza-associated pneumonia. All disparities were statistically significant ($P < .05$), as elucidated in Table 5.

DISCUSSION

Influenza-related pneumonia emerges as a pulmonary infectious ailment precipitated by the infiltration of the influenza virus into the lower respiratory tract. Early presentation of influenza symptoms is often accompanied by a notable mortality rate.[5] A comprehensive study involving 444 adult influenza patients within US hospital settings reported a mortality rate of 20.9%.[6] Furthermore, Francisco et al.[7] documented a mortality rate of 20.6% among 2059 patients admitted to the ICU due to influenza infection. The observed case fatality rate of 19.9%, consistent with the abovementioned study, remains notably elevated. Thus, there exists substantial importance in promptly and precisely assessing disease severity, prediction, and proactive intervention strategies to mitigate the case fatality rate associated with influenza-related pneumonia.

Other studies suggest that factors such as age, concurrent comorbidities, and obesity influence the prognosis of H1N1 influenza A-associated pneumonia. While the APACHE II and PSI scores predominantly gauge disease severity,[8-9] their predictive utility for disease prognosis remains contentious. Consequently, the need for more dependable serological markers to predict disease outcomes remains paramount.

The univariate analysis unveiled several important risk factors for influenza-associated pneumonia in this study. These included the presence of cerebrovascular disease, pleural effusion, concurrent bacterial or fungal infection, elevated respiratory rate, heightened total bilirubin levels, increased blood glucose levels, escalated urea nitrogen levels, elevated creatinine levels, diminished hemoglobin levels, reduced erythrocyte pressure, decreased platelet count, lowered lymphocyte count, diminished partial pressure of oxygen, reduced oxygenation index, decreased albumin levels, augmented CRUB-65 score, elevated PIS score, and increased APACHE II score.

A multifactorial regression analysis of the unilaterally screened risk factors further identified lymphocyte count, oxygenation index, albumin, and urea nitrogen as independent determinants significantly influencing the prognosis of patients afflicted by influenza-associated pneumonia. Notably, the findings of this analysis align with previously conducted national and international studies, wherein diminished lymphocyte count, elevated urea nitrogen levels, and reduced oxygenation index consistently emerged as significant prognostic indicators.[5,10-12]

As observed in this study, the identification of low albumin as an independent prognostic risk factor for influenza-associated pneumonia appears distinct and noteworthy. This observation could be attributed to the correlation between reduced albumin levels and malnutrition among patients, rendering them more susceptible to severe complications that influence their overall prognosis.

This study improved the prediction of outcomes for patients with influenza-associated pneumonia by creating ROC curves. The ROC curves encompassed the Composite Index LOAU [comprising lymphocyte count (L), oxygenation index (O), albumin (A), and urea nitrogen (U)], along with the PSI, APACHE II, and CURB-65 scoring systems. The outcomes yielded an area under the ROC curve values with 95% confidence intervals: 0.909 (0.851-0.950), 0.746 (0.668-0.813), 0.732 (0.653-0.800), and 0.662 (0.580-0.737), respectively.

A comparative analysis was further performed, indicating that the Composite Index LOAU demonstrated superior predictive prowess when contrasted with the PSI, APACHE II, and CURB-65 scoring systems for forecasting mortality among patients with influenza-associated pneumonia. Importantly, all observed disparities were statistically significant. This finding strongly suggests that the Composite Index LOAU significantly enhances the prognostic accuracy in evaluating individuals with influenza-associated pneumonia.

Importantly, 63 patients in this study underwent routine tests to identify pathogenic organisms in their sputum or through bronchoscopic alveolar lavage. Among them, mixed infections were detected, mainly involving Borrelia burgdorferi. It's worth noting that the risk of getting infected while in the hospital is higher for these patients. Previous research has shown that when severe influenza patients catch infections in the hospital, their chances of morbidity and mortality can increase significantly, sometimes reaching 50% to 60%.[13-14]

Some researchers within the domestic sphere have studied the identification of autonomous risk factors associated with nosocomial infection in severe influenza patients. These factors include advanced age, lymphopenia, ICU admission, mechanical ventilation, sepsis, and anemia.[15] Consequently, the timely implementation of preventive measures among individuals with a heightened susceptibility to nosocomial infection holds the potential for mitigating the case fatality rate.

Furthermore, it is noteworthy that the cohort included 23 patients afflicted by invasive pulmonary aspergillosis (IPA), culminating in an alarmingly elevated case fatality rate of 39.1%. The occurrence of IPA, while relatively uncommon, has been documented in influenza patients. Back in 1952, international researchers documented cases of influenza patients concurrently afflicted by IPA.[16] Subsequently, at least six cases have been reported each decade, with a substantial surge in case reports involving H1N1 influenza patients coupled with IPA, particularly following the 2009 H1N1 pandemic.[17]

A study involving 432 influenza patients within the intensive care units of the Netherlands and Belgium yielded a significant finding, 19% of patients displayed IPA, and within this subset, a staggering 51% died of the condition. Notably, this study also underscored the autonomous role of influenza as a risk factor for IPA occurrence, a relationship associated with higher case fatality rates.[18] The findings of our study showed parallel outcomes observed in foreign studies, revealing a shared pattern characterized by elevated incidence and increased mortality.

Study Limitations

This study has certain limitations. It is important to acknowledge that this study was conducted solely within a single center, with the exclusion of outpatient influenza cases as well as inpatients from pediatric, obstetrics, and gynecology departments. Such selectivity in sample inclusion may introduce inherent bias, and it's noteworthy that the patient cohort size remains restricted. Consequently, the statistical analysis may inherently hold some degree of bias.

CONCLUSION

In conclusion, this study highlights the predictive value of peripheral blood lymphocyte count, albumin, urinary analysis, and oxygenation index at admission in forecasting the prognosis of influenza-associated pneumonia. Incorporating these factors into the Composite Index LOAU demonstrates its potential to enhance prognostic accuracy and refine patient outcomes in influenza-associated pneumonia management. These findings underscore the importance of a multifaceted approach in prognostic assessment, potentially paving the way for more targeted interventions and improved patient care.

DATA AVAILABILITY

The data used to support this study are available from the corresponding author upon request.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

FUNDING

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