

# Risk Factors Associated with Invasive Pulmonary Mycosis Among Severe Influenza Patients in Beijing City, China

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**Objective:** Influenza co-infection with fungal infection increases the risk of death. Our study was to estimate risk factors associated with invasive pulmonary mycosis (IPM) among severe influenza patients at a single center in Beijing, China.

**Methods:** A retrospective chart review was carried out of all patients with severe influenza admitted to respiratory the department including the respiratory intensive care unit (RICU) during the 2014 to 2019 influenza seasons in Beijing Chao-yang hospital, China. We compared the differences of characteristics and examination outcomes between IPM patients and non-IPM patients, and explored the predictors of IPM by a multivariate logistic regression.

**Results:** Influenza associated IPM was found in 65 of 131 (49.62%) patients. The average age of IPM patients was  $57.28 \pm 14.56$  years and 70.77% were male. The mortality rate was much higher in the IPM group than the non-IPM group (34.85% versus 18.46%,  $P=0.026$ ). Older age, hyp immunity, liver disease, hypertension, positive serum GM test, steroids using, gasping, gastrointestinal symptoms, high APECHEII, low oxygenation index, other viruses co-infection, bacterial co-infection, low lymphocyte counts, low CD4+ T-cell counts, low CD8+ T-cell counts, low RBC, low hemoglobin, low platelets, high N%, low total protein, high CRP, low albumin, low fibrinogen, high BUN, positive serum GM test, more mechanical ventilation requirement, and more renal replacement requirement were risk factors of influenza IPM co-infection.

**Conclusion:** IPM is a severe complication of influenza hospitalizations. It is associated with increasing mortality, longer hospital stays, and higher hospital charges compared with non-IPM patients. Clinicians caring for patients with severe influenza should consider IPM.

**Keywords:** influenza, invasive pulmonary mycosis, infection, hospitalization, incidence rate

## Introduction

Influenza is an heterogeneous disease which can cause 3–5 million severe cases and 250,000–500,000 deaths every year.<sup>1</sup> Its severity varies widely because of patients, different ages, complications, mortality, onset season, duration, and response to drugs, so the pathogenesis and prognosis of each influenza patient is different.<sup>2</sup>

In our clinical work, we find severe influenza patients are often complicated with bacterial and/or fungal infection, which greatly increases the mortality rate of patients, prolongs the time of hospitalization, and increases the personal and social economic burden.<sup>3,4</sup>

Invasive pulmonary mycosis (IPM) is a well-recognized disease occurring in immunocompromised patients. In recent years, influenza has been confirmed as

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a risk factor for IPM, because influenza can inhibit the immune system of patients, creating an ideal environment for the occurrence of bacterial and fungal infections.<sup>5</sup> Influenza associated IPM increases the difficulty of treatment and the risk of death in patients. Shu et al<sup>6</sup> pointed out the mortality rate of IPM influenza co-infection is about 50–60%, which is 5-times higher than that among patients with influenza infection alone.

From the first article published in 1952 about influenza co-infected with aspergillus to now,<sup>7</sup> almost all research about influenza associated fungal infection focused on aspergillus, and most relevant research reports appeared in the form of case reports and small case series.<sup>8–11</sup> There is no research focus on other types of fungal co-infection and no systemic research to investigate the characteristics of fungus influenza co-infections.

Our study aimed to analyze all important information of severe influenza patients who were admitted to Beijing Chao-yang Hospital during the 2014 to 2019 influenza season, and explore potential risk factors of influenza IPM co-infection.

## Materials and Methods

### Study Population and Groups

#### Cases Selection

All hospitalized patients who were confirmed with severe influenza in the respiratory department including the RICU of Beijing Chao-Yang Hospital during January 2014 to March 2019 were our subjects. We collected the main data from the electronic medical record system for daily work.

#### Group Division

All selected influenza patients were divided into two groups: IPM group and non-IPM group. The patients in the IPM group were infected with proven or probable IPM, and patients in the non-IPM group were without evidence of fungal infection while hospitalized. Cases involving nonspecific viral infections or without confirmatory influenza testing, insufficient patient information, possible invasive pulmonary fungal infection, or fungal colonization were excluded.

## Definitions

### Definition of Influenza

Diagnosis of influenza virus infection was based on a positive result from a probe-based reverse-transcriptase polymerase chain reaction (RT-PCR) test for influenza

from lower respiratory tract specimens or nasopharyngeal swab.<sup>8,9</sup>

### Definition of Severe Influenza

Patients needed to meet one or more of the following clinical features: (1) Persistent fever >3 days, accompanied by severe cough, expectoration of purulent sputum, blood sputum, or chest pain; (2) Fast breathing rate (>30 times/min), dyspnea, and cyanosis of lips; (3) Altered mental status: slow reaction, drowsiness, restlessness, convulsion, etc; (4) Severe vomiting and diarrhea with dehydration; (5) Pneumonia; and (6) Underlying diseases were significantly aggravated, with organ dysfunction or failure. These diagnostic criteria come from the 2018 influenza treatment program of China.

### Definition of IPM

Patients had proven IPM if there was microscopic evidence of dichotomous branching hyphae with a positive culture for fungus spp through an endobronchial biopsy, irrespective of host factors or clinical features.<sup>12,13</sup> Probable IPM requires a host factor, clinical features, and mycological evidence of fungus (positive smear or/and culture of sputum or bronchoalveolar lavage fluid).<sup>14–16</sup>

### Data Collection and Analysis

We collected the main data of selected patients from the electronic medical record system in our hospital, including demographics, underlying diseases, and the use of immunosuppressive agents and steroids longer than 7 days before or after admission and main examinations, data, complications, needs for organ support, lengths of total hospitalization days, and mortality.<sup>13</sup> Our collected examination data included laboratory examinations and radiological examinations. Laboratory examinations included the influenza type, white blood count (WBC), and lymphocyte and CD4+ T lymphocyte counts, fasting blood glucose (FBG), myocardial enzymes, main data of liver function and kidney function, and airway secretions culture during hospitalizations. Radiological examinations mainly included chest CT images. For those with IPM, data on the number of days between the diagnoses of influenza and IPM, the fungus species from lower respiratory tract (LRT) cultures, serum and/or bronchoalveolar lavage fluid (BALF), galactomannan (GM) and 1-3- $\beta$ -D-glucan test (G) levels, and antifungal therapy information were also collected. We first described the overview of this influenza pandemic (from January 2014 to March 2019) and fungus co-infection. Then we compared all collected

data between two groups. At last, we performed a logistic regression analysis to explore the condition's risk factors of IPM in influenza patients.

## Statistical Analysis

All data were analyzed with SPSS 22.0 software. Quantitative data was expressed as  $\bar{x}\pm SD$  and were compared using *t*-tests when distributed normally. Non-normally distributed quantitative data was expressed as medians and quartiles, and we compared the difference by using Wilcoxon rank-sum tests.  $\chi^2$  tests was used to compare the difference of categorical data. In order to identify independent risk factors for influenza co-infected with IPM, we used a multivariate logistic regression to analyze variables with a *P*-value less than 0.2.

## Results

### Characteristics of Patients

In our study, a total of 131 influenza patients in the respiratory department (including RICU) at Beijing Chao-yang Hospital due to respiratory failure from January 2014 to March 2019 met our requirements. The mortality rate was 26.72% (35 cases). The incidence of IPM influenza co-infection was 49.62% (65 cases); two patient were diagnosed by histopathology, 63 patients were diagnosed as probable fungal infection, the mean age of IPM patients was 57.28±14.56 years, 70.77% were male, the mean time from influenza diagnosis to IPM diagnosis was 15.62±8.86 days, and the mortality rate of the IPM group was 35.38% versus 18.18% in the non-IPM group. In IPM cases, cardiovascular diseases (heart disease or hypertension) (47, 71.21%), diabetes mellitus (DM) (16, 24.24%), and chronic pulmonary disease (15, 23.08%) were the top three comorbidities, and 70.77% of patients in the IPM group had immune deficiency (Tables 1 and 2).

### Comparisons of Two Groups

#### General Information

The incidence of IPM influenza co-infection in our study was 49.62%. Among all these IPM patients, the number with candida co-infection was 55 (84.62%), aspergillus co-infection was 23 (35.38%), sporozoan co-infection was four (6.15%), and many patients suffered two or more kinds of fungus.

There were more patients with immunodeficiency on admission in the IPM group than non-IPM group (70.77% versus 51.52%, *P*=0.024). Immunodeficiency in our study

**Table 1** Demographics of Patients Diagnosed with Severe Influenza (N=131)

	Non-IPM (n=66)	IPM (n=65)	P-value
Age, years	52.97±14.34	57.28±14.56	0.09
Gender			0.295
Male, n	41	46	
Female, n	25	19	
Underlying lung disease, n	12	15	0.546
Chronic heart disease, n	8	12	0.350
Hypertension, n	27	35	0.188
Digestive disorders, n	1	1	0.991
Diabetes, n	11	16	0.3
Liver disease, n	1	4	0.166
Tumor, n	0	4	0.044
Cerebrovascular disease, n	1	2	0.568
Connective tissue disease, n	2	3	0.507
Hyperthyreosis, n	0	1	0.319
Pregnancy, n	0	2	0.157
Connective tissue disorders, n	2	3	0.661
Transplantation, n	3	3	0.985
Renal failure, n	0	4	0.044
Benign hematopathy, n	1	2	0.568
HIV, n	0	1	0.319
BMI (≥28), n	15	9	0.189
Steroid use, n	17	26	0.083
Hypoimmunity, n	34	46	0.024

mainly referred to age >65 years, immunosuppressant use, steroid use, connective tissue disease, diabetes, renal failure, liver disease, COPD, HIV, malignant tumor, and organ transplantations. When we compared age, immunosuppressant use, steroid use, connective tissue disease, diabetes, renal failure, liver disease, COPD, HIV, malignant tumor, and organ transplantations as independent variables, other variables have no statistical difference except tumor and renal failure between two groups. In addition, the differences in gender, heart disease, obesity, chronic heart failure, digestive diseases, hypertension, cerebrovascular disease, hyperthyreosis, pregnancy, and benign hematopathy between two groups were not statistically significant. There were nine patients in the IPM group and 15 patients in the non-IPM group when body mass index (BMI) was bigger than 28 was selected as the cut-off point (the difference of BMI is also not statistically significant, *P*=0.189).

**Table 2** Symptoms, Admission Assessment, Pathogens, and Outcomes of Patients

	Non-IPM (66)	IPM (65)	P-value
Fever, n	62	62	0.713
Breathlessness, n	46	55	0.042
Cough, n	63	60	0.546
Sputum, n	62	60	0.712
Hemoptysis, n	3	1	0.317
Debilitation, n	2	2	0.988
Chest pain, n	1	0	0.319
Gastrointestinal symptom, n	3	7	0.18
Headache, n	4	3	0.713
Pharyngeal abnormalities, n	2	1	0.568
Nasal discomfort, n	2	1	0.568
Other viruses co-infection, n	18	30	0.033
Mycoplasma co-infection, n	5	1	0.091
Highest heart rate, times/min	102.91±19.72	103.32±16.16	0.896
Respiratory frequency, times/min	27.73±7.67	29.43±8.58	0.233
Urine volume during the first 24 hours of admission, mL	1,765.50±841.35	1,700.74±887.10	0.699
APECHEII score	8.85±6.34	11.94±6.50	0.007
SOFA score	4.59±3.56	4.82±2.49	0.677
SIRS score	3.83±1.83	4.29±1.55	0.124
Blood PH	7.41±0.073	7.41±0.085	0.952
Arterial pO <sub>2</sub> on admission	76.45±23.03	72.70±22.82	0.352
Arterial pCO <sub>2</sub> on admission	37.91±9.90	37.75±12.00	0.933
Oxygenation index	192.10±14.70	166.11±97.72	0.165
Chest radiograph score	3.41±0.91	3.57±0.83	0.295
Interval between onset and antiviral treatment, days	8.38±8.36	9.29±7.09	0.501
Treatment time before admission, days	11.62±11.09	11.40±8.07	0.896
Length of hospitalization, days	17.36±12.56	26.79±26.73	0.011
Mortality, n	12	23	0.026

Compared with the non-IPM group, the patients in the IPM group were in more serious conditions (Acute Physiology, Age, Chronic Health Evaluation II, APECHE II score was 11.94±6.50 points versus 8.85±6.34,  $P=0.007$ ). The mean length of total hospital stay was 26.79±26.73 days in the IPM group versus 17.36±12.56 days in the non-IPM group ( $P=0.011$ ). Fever (62, 95.4%), cough (60, 92.3%), sputum production (62, 95.4%), and breathlessness (55, 84.6%) were the major presenting symptoms. IPM patients needed more time to recover than non-IPM patients. Twenty-three IPM patients died and 12 non-IPM patients died. The mortality rate in the IPM group was much higher than the non-IPM group (34.85% versus 18.46%,  $P=0.026$ ) (Tables 1 and 2).

### Examinations Outcomes

Lymphocyte count in the IPM group was lower than the non-IPM group [(0.82±0.59)\*10<sup>9</sup>/L versus (1.09±0.74)\*10<sup>9</sup>/L,  $P=0.023$ ], especially CD4+ T cells ( $P<0.001$ ) and CD8+ T cells ( $P=0.003$ ). So was RBC [(3.94±1.00)\*10<sup>9</sup>/L

versus (4.28±0.69)\*10<sup>9</sup>/L,  $P=0.023$ ], hemoglobin (120.11±25.35 versus 133.41±40.87,  $P=0.027$ ), platelets (155.14±78.29\*10<sup>9</sup>/L vs 191.39±109.60\*10<sup>9</sup>/L,  $P=0.031$ ), N% (80.79±11.96 versus 73.77±19.56,  $P=0.015$ ), and albumin (30.53±4.359 versus 32.89±5.134,  $P=0.005$ ). There was no statistically significant difference in WBC, absolute neutrophil counts, C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), d-dimer levels, clotting time, fibrinogen, creatine kinase (CK), creatine kinase-myocardial isoenzyme (CK-MB), creatinine, blood urea nitrogenemia (BUN), indirect bilirubin, direct bilirubin, total protein, influenza type, and FBG of the first day after admission between two groups. The patients co-infected with bacterial and other kinds of viruses were more likely to suffer IPM ( $P<0.05$ ). The consolidation was seen more often than ground-glass attenuation in the CT imaging of IPM patients, but there was no statistically significant difference ( $P=0.537$ ). The incidence of pleural effusion was similar between the two groups (Table 3).

**Table 3** Laboratory Examinations and Radiological Findings Between the Two Groups

	Non-IPM (n=66)	IPM (n=65)	P-value
WBC, *10 <sup>9</sup> /L	7.73±5.07	7.37±3.86	0.643
Neutrophils, *10 <sup>9</sup> /L	7.85±10.72	6.13±3.68	0.224
N%	73.77±19.56	80.79±11.96	0.015
Lymphocyte, *10 <sup>9</sup> /L	1.09±0.74	0.82±0.59	0.023
L%	17.01±11.68	13.30±8.53	0.04
RBC, *10 <sup>12</sup> /L	4.28±0.69	3.94±1.00	0.023
Hemoglobin, g/mL	133.41±40.87	120.11±25.36	0.027
Platelets, *10 <sup>9</sup> /L	191.39±109.60	155.14±78.29	0.031
CRP, mg/L	9.70±7.54	12.58±12.43	0.111
ESR, mm/h	23.69±18.85	26.23±20.48	0.462
PCT, ng/mL	9.3±31.40	8.09±32.73	0.83
BUN, mmol/L	6.95±4.78	8.33±5.68	0.133
Creatinine, μmol/L	90.59±76.81	105.31±109.67	0.375
Fasting blood glucose on admission, mmol/L	8.57±5.40	7.93±3.51	0.42
ALT, U/L	46.59±52.53	52.03±57.14	0.572
AST, U/L	100.61±231.90	95.05±136.55	0.868
Albumin, g/L	32.89±5.13	30.53±4.36	0.005
Total protein, g/L	60.48±8.36	57.94±9.83	0.112
Direct Bilirubin, umol/L	10.29±17.60	7.44±6.87	0.224
Indirect bilirubin, umol/L	6.67±3.39	9.14±22.97	0.39
CK, U/L	284.77±625.90	350.78±511.13	0.51
CK-MB, ng/mL	1.95±4.009	1.98±3.306	0.964
LDH, U/L	575.53±527.71	608.72±406.60	0.688
D-dimer, mg/L	7.01±10.34	17.04±87.72	0.358
TT, S	19.67±5.16	19.55±2.79	0.87
APTT, S	32.39±10.63	32.16±9.37	0.896
PT, S	13.24±4.35	13.85±9.30	0.631
Fibrinogen, mg/L	424.24±190.70	385.96±141.97	0.195
CD4+ T cell, cell/μL	398.92±271.75	238.54±149.27	0
CD8+ T cell, cell/μL	217.11±165.50	147.45±85.91	0.003
CD4+ T cell /CD8+ T cell	2.24±1.30	1.86±1.07	0.073
Pleural effusion, n	33	39	0.25

(Continued)

**Table 3** (Continued).

	Non-IPM (n=66)	IPM (n=65)	P-value
Imaging			0.537
Ground-glass attenuation, n	33	26	
Consolidation, n	33	39	
G test, n	14	15	0.87
GM test, n	13	21	0.123
Complicated arrhythmia, n	8	7	0.808
Bacterial co-infection, n	15	30	0.007
Steroid use after admission, n	25	18	0.153
Antibiotic combination, n	50	53	0.637
Influenza virus type			0.545
Influenza A, n	56	59	
Influenza B, n	6	3	
Influenza A±B, n	3	4	

### Organ Support Comparison

The need of extracorporeal membrane oxygenation (ECMO) support in two groups did not differ significantly ( $P=0.517$ ). More patients in the IPM group needed mechanical ventilation (including IPPV and non-invasive ventilation) (71.21% versus 55.38%,  $P=0.035$ ) and renal replacement therapies (19.70% versus 6.15%,  $P=0.018$ ) compared with the non-IPM group, but there was no difference in use of non-invasive ventilation and invasive positive pressure ventilation (IPPV) ( $P=0.731$ ), and the application time of mechanical ventilation and renal replacement therapies was not significantly different either (Table 4).

**Table 4** Organ Support Needs and Complications Between the Two Groups

	Non-IPM (n=66)	IPM (n=65)	P-value
ECMO, n	10	13	0.517
ECMO days	16.7±13.23	20.85±14.72	0.492
Mechanical ventilation, n	36	47	0.035
Non-invasive ventilation, n	8	9	0.731
IPPV, n	28	38	
Mechanical ventilation days	24.97±13.29	28.21±16.38	0.336
Renal replacement therapy, n	4	13	0.018
Renal replacement therapy days	20.75±9.74	23.54±11.68	0.673

### Risk Factors for Influenza Co-Infection with IPM (Table 5)

We performed a multivariate logistic-regression analysis to investigate risk factors of IPM in influenza patients. In our study we found that older age, hypimmunity, liver disease, hypertension, positive serum GM test, steroids using, gasping, gastrointestinal symptoms, high APECHEII, low oxygenation index, other viruses co-infection, bacterial co-infection, low lymphocyte counts, low CD4+ T cell counts, low CD8+ T cell counts, low RBC, low hemoglobin, low platelets, high N%, low total protein, high CRP, low albumin, low fibrinogen, high BUN, positive serum GM test, more mechanical ventilation requirement, and more renal replacement requirement were independent risk factors of influenza virus infection combined with IPM, as shown in Table 5.

### Discussion

After the 2009 H1N1 influenza pandemic outbreak, there were more and more studies describing influenza co-infection. However, almost all reports focused on bacteria and aspergillus co-infection and there was no study to report other kinds of fungus co-infection.<sup>10,11,17-22</sup> Our study may be the first to systematically and comprehensively summarize the clinical characteristics of influenza co-infected with IPM. Based on the sample size of cases and complete data,

**Table 5** Binary Logistic-Regression Analysis for Risk Factors and Predictors of Prognosis for IPM in Patients with Influenza

	Wald	P-value	Odds Ratio	95% Confidence Interval	
				Inferior	Superior
Age	119.141	<0.001	1.039	1.032	1.047
Hyp immunity	7.651	0.006	0.766	0.634	0.925
Liver disease	51.767	<0.001	4.225	2.853	6.256
Hypertension	22.505	<0.001	0.687	0.588	0.802
Steroids using	19.943	<0.001	0.68	0.574	0.806
Gasping	25.154	<0.001	0.607	0.5	0.738
Gastrointestinal symptoms	89.437	<0.001	0.275	0.211	0.36
APECHE II	88.015	<0.001	1.078	1.061	1.095
Oxygenation index	221.44	<0.001	1.009	1.008	1.011
N%	61.657	<0.001	1.029	1.021	1.036
Lymphocyte counts	94.636	<0.001	2.458	2.051	2.946
L%	6.177	0.013	1.016	1.003	1.029
RBC	14.007	<0.001	1.293	1.13	1.479
Hemoglobin	104.978	<0.001	0.981	0.978	0.985
Platelets	12.083	0.001	1.002	1.001	1.003
CRP	68.31	<0.001	1.05	1.038	1.062
Blood urea nitrogen	251.046	<0.001	0.846	0.829	0.864
Albumin	141.887	<0.001	0.879	0.86	0.898
Total protein	37.787	<0.001	1.042	1.028	1.055
Fibrinogen	12.96	<0.001	1.001	1	1.001
CD4+ T cell counts	54.81	<0.001	0.997	0.996	0.998
CD8+ T cell counts	88.208	<0.001	0.994	0.993	0.995
CD4+ T cell counts /CD8+ T cell counts	30.601	<0.001	0.741	0.666	0.824
GM test	26.96	<0.001	0.648	0.551	0.764
Bacterial co-infection	232.467	<0.001	0.224	0.184	0.271
Other viruses co-infection	53.362	<0.001	0.553	0.471	0.648
Mechanical ventilation	16.348	<0.001	0.619	0.491	0.781
Renal replacement therapy	60.681	<0.001	0.333	0.253	0.439

we think our study is very valuable for clinical diagnosis and medication guidance.

The incidence of IPM influenza co-infection in our study was about 49.62%; therefore, we speculate the incidence of IPM influenza co-infection in critically ill patients in northern China is also about 50%. Among all these IPM patients, we found three kinds of fungus: candida was the most common (84.62%), aspergillus was the second (35.38%), the third was sporozoan (6.15%). Compared with non-IPM patients, IPM patients needed longer hospital stay, more substantial consumption of health care resources, and had higher in-hospital mortality.

In our study, we found the most common presenting clinical features of IPM were fever, dyspnea, and cough, which is in agreement with prior studies,<sup>9,21,23–25</sup> but these symptoms also happened in non-IPM patients, so we think they have no diagnostic value. In radiological images, we mainly compared the difference of

consolidation and ground-glass opacities by HRCT, consolidation was seen more often than ground-glass opacities in the CT imaging of IPM patients, but there was no statistical difference in the two groups as a result. The CT images of invasive pulmonary aspergillosis and candidiasis were similar. Consolidation is the most common feature of the two diseases, randomly distributed consolidation is more likely in candidiasis, while centrilobular nodules and consolidation suggest invasive pulmonary aspergillosis. Previous studies have pointed out that CT halo sign and vacuole are not helpful in distinguishing different fungal diseases,<sup>26</sup> so we didn't assess these two features.

In recent years, the incidence rate of IPM has increased year by year with the aging of the social population, the wide application of hormones, immunosuppressants, cytotoxic drugs, chemoradiotherapy, and the variety of broad-spectrum antibiotics. Candida and Aspergillus are

the two most common pathogens. Pulmonary candidiasis usually infects critically ill patients with hypimmunity, especially those with indwelling catheters, using broad-spectrum antibiotics and diabetes.<sup>26,27</sup> Aspergillus infection accounted for 60% of IPM, especially in patients with acute leukemia and accepting hematopoietic stem cell transplantation,<sup>27,28</sup> and long-term using of steroids and solid organ transplantation also increase the risk of invasive pulmonary aspergillosis.<sup>26,29</sup> Previous studies have confirmed that bacterial co-infection is the first cause of death in influenza patients,<sup>7,16</sup> so the application of powerful broad-spectrum antibiotics is common in severe influenza patients, maybe this is the reason for high incidence of candida infection in our study.

As we know, immunocompromised hosts were more likely to get fungal infection. In our study, we found IPM co-infection with influenza not only happened in immunocompromised hosts but also happened in immune-competent hosts, consistent with previous reports.<sup>9,21</sup> When we compared age, steroid use, liver disease, diabetes, connective tissue disease, underlying lung disease, transplantation, and HIV as a single variable, there was no statistical difference between IPM and non-IPM, the reason for this result may be that the sample size is too small. Therefore, when we evaluate the patient's condition and make a treatment plan, it must comprehensively analyze patients' various characteristics.

So far, the pathogenesis about IPM influenza co-infection is not very clear. Based on the research of many experts, we speculate the possible pathogenesis may be related to the following factors: first, the damage of respiratory mucosa, normal ciliary clearance, and interruption of interleukin secretion caused by influenza virus infection may lead to fungal invasion;<sup>30,31</sup> second, severe influenza may cause the imbalance of T cell differentiation and cell-mediated immune injury, leading to reduce the patient's immune response,<sup>9,21,32</sup> third, the using of corticosteroids and broad-spectrum antibiotics can also cause immune damage and dysbacteriosis;<sup>30</sup> four, inhibition of neuraminidase in host neutrophils by neuraminidase inhibitors such as oseltamivir may increase the chance of fungal infection;<sup>33</sup> five, using of IPPV and ECMO for respiratory support significantly increased the risk of fungus involvement.<sup>34</sup> In our study, the difference of ECMO using, corticosteroids using, and multiple antibiotics using in two groups was not statistically significant, but the level of CD4+ T cells in the IPM group was much lower than the non-IPM group. This result suggests the imbalance of

T cell differentiation and cell-mediated immune injury play an important role in the pathogenesis process of IPM.

Through multivariate logistic regression analysis, we found the influenza patients with older age, hypimmunity, liver disease, hypertension, positive serum GM test, steroids using, gasping, gastrointestinal symptoms, high APECHEII, low oxygenation index, other viruses co-infection, bacterial co-infection, low lymphocyte counts, low CD4+ T cell counts, low CD8+ T cell counts, low RBC, low hemoglobin, low platelets, high N%, low total protein, high CRP, low albumin, low fibrinogen, high BUN, positive serum GM test, more mechanical ventilation requirement and more renal replacement requirement have a high risk of IPM co-infection. Evaluating clinical features and examination outcomes of patients as soon as possible after admission is very critical for medication. Early diagnosis and precise treatment can greatly reduce the mortality of influenza patients.

## Conclusion

Influenza associated IPM is a common and severe complication of influenza patients in the RICU and may lead to a poor outcome even in immune competent individuals. Evaluating the risk factors of influenza associated IPM infection as soon as possible, early diagnosis with multiple biomarker diagnostic strategies and early application of antifungal drugs are critical to improve prognosis. Clinicians caring for patients with severe influenza should consider IPM.

## Ethics and Consent

This study was conducted according to the Declaration of Helsinki, reviewed and approved by the Ethics Committee of Beijing Chao-Yang Hospital. Written informed consent was obtained from selected patients themselves or their close legal relatives.

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## Disclosure

The authors report no conflicts of interest in this work.

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