Title: Risk factors and characteristics of patients with hospital-acquired influenza A: A Matched Case-Control Study

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Risk factors and characteristics of patients with hospital-acquired influenza A: A Matched Case-Control Study

Abstract

**Background:** Nosocomial influenza A brings hospitalized patients additional cost of care and considerable mortality, but predictors for hospital-acquired influenza A at the early stage remained unidentified. We aimed to describe the characteristics of patients vulnerable for hospital-acquired influenza A and identify its risk factors, which would help clinicians control nosocomial infection and ease the burden of treatment.

**Methods:** A case-control study was conducted in hospitalized patients aged $\geq 18$ years in a level A tertiary teaching hospital during the 2018-2019 influenza A season. Information of patients was retrieved from hospital-based medical records system. Hospital-acquired influenza A was defined as cases diagnosed 7 days or more after admission, who had no signs of viral respiratory infection on admission. The controls with no influenza infection were selected by the following criterion. Namely, patients were exposed to the same setting in the same period of time. We identified risk factors using conditional logistic regression and described characteristics of hospital-acquired influenza A through comparing the clinical data between influenza infected patients and controls.

**Results:** Of 412 hospitalized patients with influenza A from all departments of the investigated hospital, 93 (22.6%) cases were classified as hospital-acquired influenza A. Older age (>65 years old) accounted for 34.4%. Hypertension (41.9%), coronary heart disease (21.5%) and cerebrovascular disease (20.4%) were the most common
comorbidities. Before the infection of hospital-acquired influenza A, patients presented more lymphocytopenia (51.6% VS 35.5%, P=0.027), hypoalbuminemia (78.5% VS 57.0%, P=0.002) and pleural effusion (26.9% VS 9.7%, P=0.002) than matched controls. Notably, infected patients had a longer hospital stay [18(12-27.5) days VS 14(11-20) days, P=0.002], and higher mortality (10.8% VS 2.2%, P=0.017 ). Lymphocytopenia (OR: 3.107; 95% CI 1.238-7.796; P =0.016), hypoalbuminemia (OR: 2.241; 95% CI 1.099-4.570; P =0.027) and pleural effusion (OR: 3.094; 95% CI 1.263-7.583; P =0.014) were independently associated with hospital-acquired influenza A.

**Conclusions:** Lymphocytopenia, hypoalbuminemia and pleural effusion were independent risk factors that could help identify patients at high risk of hospital-acquired influenza A, which extended hospital stay and was associated with high mortality.

**Key words:** influenza, human; nosocomial infection; risk factors

**Background**

The mutation rate of influenza A virus is the highest among the three species of influenza virus that has been reported, including A, B and C[1]. Influenza A is a highly contagious viral disease of the respiratory tract and may cause large-scale human-to-human transmission annually in winter and spring. Outbreaks of influenza A virus infection in hospitalized patients have already been reported in different clinical settings such as neonate intensive care unit[2], geriatric[3] or hematological unit[4]. Hospital-acquired influenza A, related to hospitalized patients with underlying
diseases, undoubtedly brings additional treatment burden and health threat.

Nosocomial infection may be associated with poor prognosis. In Germany, a fatal outcome was recorded as high as 9% of nosocomial influenza infection, which was mainly associated with influenza virus A(H1N1) pdm09\(^5\). And in Sweden, hospital-acquired influenza A also had a high mortality of 9.6\%\(^6\). What’s more, hospital-acquired influenza A infection was an independent factor associated with mortality of patients admitted to the intensive care unit (ICU)\(^7\).

Hospitals are semi-closed settings and hospitalized patients are in a state of congregation. Infected patients in incubation period can be asymptomatic as sources of transmission\(^8\) and the longest incubation period is 7 days\(^9\), which make a great challenge for the prevention and control of influenza A among hospitalized patients.

Therefore, early recognition of patients with high risk of hospital-acquired influenza A plays an important role in early measures to limit the possibility of influenza A outbreak among hospitalized patients.

Although clinical and epidemic features of nosocomial infection have been documented for many years in different studies\(^{10, 11}\), few studies focusing on risk factors of hospital-acquired influenza A are in place. Compared with the published literatures\(^{7, 12}\), we defined each matched control case more strictly, who must hospitalize in the same department and in the same period of time without infection instead of community-acquired influenza. This monocentric retrospective matched case-control study was designed to analyze influenza A virus infection medical records from a level A tertiary teaching hospital in Xi’an China during the 2018-2019
influenza A season, aiming to identify risk factors for hospital-acquired influenza A and vulnerable individuals at early stage.

**Methods**

**Design and study population**

This was a monocentric retrospective matched case-control study. Patients hospitalized more than 24 hours with laboratory-confirmed influenza A infection were selected from wards of different departments of a level A tertiary teaching hospital in Xi’an China from December 1st, 2018 to April 1st, 2019. Those less than 18 years old were excluded in this study. Formatted case report forms(CRFs) were used to collect clinical informations of hospital-acquired influenza A patients. Furthermore, one control case was matched to each patient case and collected through the same CRFs.

**Case definitions**

According to the definition of the "Diagnostic and treatment protocol for influenza(2018 version)[8]" released by National Health and Family Planning Commission of the People’s Republic of China, the main manifestations of influenza-like illness (ILI) were fever, headache, myalgia, and general malaise, chills; most patients had systemic symptoms such as muscle and joint aches, fatigue, and loss of appetite, with sore throat, dry cough, nasal congestion, runny nose, and retrosternal discomfort. Those who met the above ILI criteria were considered to be suspected influenza A cases. Confirmed diagnosis of influenza A was made by ILI manifestation combined with assessment of real-time reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs. Considering the maximum
incubation period of influenza was up to 7 days\(^9\), hospital-acquired influenza A was defined as cases diagnosed 7 or more days after admission, who had no signs of viral respiratory infection on admission. In addition, pneumonia and chronic obstructive pulmonary disease patients were screened for influenza A virus upon admission. Because the influenza virus mainly spreads through aerosols, droplet or contact \(^{13}\), and age might be a confounding factor of influenza infection\(^{14}\), we matched every hospital-acquired influenza A patient with one control case. The control group should also be exposed to the same setting in the same period of time, in other words, controls must have been hospitalized for 7 days or more in a ward of same department at the date of the matched patients’ diagnosis of influenza A. Age difference was within 5 years. In addition, patients in the control group showed no ILI manifestation during hospitalization, namely, with no necessity of RT-PCR test, and were considered no infection of influenza A.

**Data collection**

A case report form (CRF) was designed for data collection, including demographics (age, sex), date of hospital admission, date of diagnosis of influenza A virus infection, length of hospital stay, laboratory findings, comorbidities, inpatient department, ICU admission; corticoids, initial radiographic findings and outcomes.

According to previous reports\(^{7, 9}\), the median incubation period of the virus was 2 days (range, 1 to 7). To reflect pre-infection characteristics and avoid the influences of influenza infection, we collected data of every nosocomial infection case at the time of 7 days before the influenza A diagnosis. After that, the same date was
determined for collecting data of each matched control.

**Statistical analysis**

Categorical variables were presented as counts (percentages). Continuous variables were presented as mean and standard deviation (SD) when data followed a normal distribution, or as median and interquartile range (25th to 75th percentile) when distribution departed from normality. The characteristics between patients with hospital-acquired influenza A and matched controls were compared. The t-test or Mann-Whitney U test was used for comparing continuous variables. The chi-squared (\( \chi^2 \)) test was used to compare categorical variables. Statistical significance was set at \( P < 0.05 \). All variables with \( P \) values < 0.15 in the univariate analysis were included in conditional logistic regression to identify the independent risk factors of hospital-acquired influenza A after 7 days hospital admission. Analysis was performed using statistical software SPSS (version 20.0).

**Results**

**Epidemic characteristics**

In the 2018-2019 influenza A season, a total of 1336 hospitalized patients who had influenza-like illness were included in the analysis (Figure 1). 412 (30.8%) patients were diagnosed influenza A through RT-PCR during their stay in the hospital. Diagnosis on January accounted for 67.5% and had the highest positive rate. Suspected influenza A patients from Nephropathy and Geriatric had higher positive diagnosis rate than the total hospital level (61.4% VS 30.8%, \( \chi^2 = 28.43, P < 0.001 \); 45.6% VS 30.8%, \( \chi^2 = 9.63, P = 0.002 \)). Patients of all ages in the hospital had the
potential of influenza A infection.

93 cases were confirmed with hospital-acquired influenza A in total departments of hospital. Males accounted for 53.8%. Cases were mainly concentrated in January 2019 (82.8%). Among all inpatient departments, Geriatrics (16.1%), Neurology (16.1%) and Hematology (14.0%), and Cardiac Surgery (14.0%) were mostly affected. 23.7% had a history of ICU admission during this hospitalization. Older age (>65 years old) accounted for 34.4%.

**Clinical characteristics of patients with hospital-acquired influenza A**

The median age was 58 years. Approximately 60.2% of patients had underlying diseases. Hypertension (41.9%), coronary heart disease (21.5%) and cerebrovascular disease (20.4%) were the most common comorbidities. 26.9% of patients were diagnosed pneumonia on admission. Before hospital-acquired influenza A being confirmed, remarkable lymphocytopenia was presented (51.6% VS 35.5%, P=0.027) compared to matched controls exposed to the same setting in the same period of time. Meanwhile, lymphocyte count was overtly lower [1070(630-1660) /mm³ VS 1300(880-1820) /mm³, P=0.045]. Anemia accounted for 55.9%. Hypoalbuminemia and pleural effusion were also frequently presented in infected patients (78.5% VS 57.0%, P=0.002; 26.9% VS 9.7%, P=0.002). Corticoids was used on 50.5% patients before diagnosis. Notably, patients with hospital-acquired influenza A had a longer hospital stay [18(12-27.5) days VS 14(11-20) days, P=0.002] and higher mortality (10.8% VS 2.2%, P=0.017) (**Table 3**).

A total of 10/93 (10.8%) patients with nosocomial infection died. Median age of
fatal cases was 90.5 years old (range, from 39 to 94). 6 cases with poor basic physical conditions were from Geriatrics, aged from 90 to 94 years old. 2 cases were from Neurology, aged 89 and 68 years old respectively, with cerebrovascular disease and its sequelae, namely bedridden, combined with protracted and intractable pneumonia on admission. 1 case was from Cardiac Surgery, 39 years old, who had rheumatic heart disease with atrial fibrillation, as well as severe myocardial injury after mitral valve replacement. 1 case was from Hematology, 56 years old, immunosuppressed with diffuse large B-cell lymphoma.

Risk factors of nosocomial infection

Univariate analysis showed that lymphocytopenia, hypoalbuminemia and pleural effusion might be associated with hospital acquired influenza A. All the three risk factors and anaemia (P value = 0.142 < 0.15) were included in the conditional logistic regression analysis. Finally, lymphocytopenia (OR: 3.107; 95% CI 1.238-7.796; P =0.016), hypoalbuminemia (OR: 2.241; 95% CI 1.099-4.570; P =0.027) and pleural effusion (OR: 3.094; 95% CI 1.263-7.583; P =0.014) were found as independent risk factors of hospital-acquired influenza A (Table 4).

Discussion

To the best of our knowledge, this is the first retrospective matched case-control study of risk factors for hospital-acquired influenza A including all the different departments of a hospital in a single complete influenza A season. We are the first to demonstrate that lymphocytopenia, hypoalbuminemia, pleural effusion are independent risk factors for hospital-acquired influenza A. Furthermore, hospital-
acquired influenza A may increase the length of hospital stay and mortality of hospitalized patients.

In China, according to the online information of archived by National Health Commission, the number of influenza cases from January to April 2019 was 1.575 million, a big leap if compared with only 0.768 million in the whole year of 2018. The influenza epidemic was significantly more severe than before. Influenza weekly released by Chinese National Influenza Center showed that in the first, fifth, and ninth week of 2019, influenza A virus was still the main pathogen, accounting for 99.5%, 98.4%, and 90.6% of influenza cases in the northern provinces. Based on this background, we reviewed the occurrence of seasonal influenza A in an large academic hospital at Xi’an China.

Our study has several strengths. Firstly, hospital-acquired influenza A was defined as a patient being confirmed infection from the seventh day of hospitalization with no previous suspicion. Secondly, we matched one control case for each hospital-acquired influenza A patient from the same hospitalized department with age difference within 5 years. Controls must have been hospitalized for 7 days or more when the matched patients were diagnosed nosocomial infection. With strict definition and control matching, this comparative analysis was more accurate and the conclusions were more convincing. Finally, hospital-acquired influenza A cases were selected from all the different departments of the hospital in a single influenza A season, indicating that nosocomial infection was caused by identical or similar influenza A virus strains, which ensured the comparability and homogeneity of clinical data.
Among all influenza cases detected in hospitalized patients, approximately 23% were classified into the group of hospital-acquired influenza A in our study. Part of the reason for this large proportion may be the big leap of influenza cases nationwide in China in early 2019 compared with previous years. In a tertiary care hospital of France, during the 2016-2017 influenza A season, 25% of hospitalized infection cases were considered hospital-acquired infection\textsuperscript{[12]}. A German university hospital reported 24% hospital-acquired infection cases in the season 2012-2013 and 20% in the season 2013-2014\textsuperscript{[5]}. Lower rate was also observed. In the UK, during the 2009 H1N1 pandemic, 2% of hospitalized cases were considered hospital-acquired infections\textsuperscript{[18]}. In an epidemiological study based on data of six seasons from 2010-2011 to 2015-2016 in Spain, among hospitalized patients with confirmed severe influenza, 5.6% were classified as nosocomial influenza\textsuperscript{[19]}. The discrepancy is acceptable due to variations in study designs and differences between region and virus strains. Currently, there is no consensus for declaring an influenza outbreak in hospital. According to published researches, nosocomial influenza outbreak is defined by an increase in cases of nosocomial influenza in a short time and limited space\textsuperscript{[20, 21]}.

Nephropathy and Geriatric had a higher diagnosis rate of suspected influenza A than the average level of the hospital. Most patients in Nephropathy Department have chronic kidney diseases, leading to a multitude of immune system defects\textsuperscript{[22]}. Among them, decreased chemotaxis and phagocytosis of monocyte/macrophage, B-cell lymphopenia, depressed CD4\textsuperscript{+} and CD8\textsuperscript{+} T-cells have been documented\textsuperscript{[23]}. Therefore, they were more vulnerable to serious morbidity and mortality associated with
influenza infection[24]. Corticoids were common drugs used in Nephropathy, but recent research showed that it might enhance replication of respiratory viruses[25]. Age > 65 years was deemed as a high risk factor of infection[26]. Thus, suspected patients from the Department of Geriatric with poor basic physical condition might be more likely to have positive diagnosis. In annual seasonal influenza A epidemics, these two clinical departments required more attention to disease prevention and diagnosis.

Nosocomial viral infections are less likely to be reported than nosocomial bacterial infections, for reasons including historical attention to bacterial infection[27], difficulties in diagnose and limited numbers of antiviral drugs[11]. Droplet precautions with single room isolation, as an important infection control procedure, are necessarily required for all suspected or confirmed cases, which however consumes a lot of medical resources. In addition, patients in the incubation period up to 7 days are the source of transmission and difficult to be found immediately, bringing a great challenge for the prevention and control of nosocomial influenza. In our study, the mortality rate of hospital-acquired influenza A was 10.8%, which approximated the rate of 9% reported in Germany[5], indicating that nosocomial infection was associated with high death rate and prolonged hospital stay compared with control group. For these reasons, the prevalence and incidence of nosocomial influenza should receive much more attention.

According to our results, January had the highest incidence of influenza A. Geriatric and Neurology had most hospitalized patients of hospital-acquired influenza
A, followed by Hematology and Cardiac Surgery. During influenza season, patients who underwent cardiac surgery were more likely to develop ARDS\textsuperscript{[28]}. In this study, patients from Cardiac Surgery all had underwent surgery before infection. And whether cardiac surgery increases the risk of influenza infection remains an interesting question in need of further investigation.

Lymphopenia is common in influenza A infection\textsuperscript{[29]} and associated with poor outcomes\textsuperscript{[30]}. Influenza viral replication is initially controlled by innate immunity and subsequent adaptive immune responses (T cells and antibody-producing B cells), achieving viral clearance and host recovery\textsuperscript{[31]}. This may explain the frequent outbreaks of influenza in Hematology for many years\textsuperscript{[4, 32, 33]}.

Hypoalbuminemia is the result of the combined effect of inflammation and inadequate protein and caloric intake in patients with chronic disease such as chronic renal failure\textsuperscript{[34]}. Hypoalbuminemia is frequently observed in hospitalized patients, so early detection of vulnerable individuals is nonnegligible for implement infection-control efforts. We do not suggest albumin supplementation to patients with hypoalbuminemia only for influenza prevention, but measures like droplet precautions with single room isolation may be mandatory.

Pleural effusion seems to be hypoalbuminemia’s radiographic findings. In this study, all patients with pleural effusion had hypoalbuminemia, but pleural effusion could also be caused by pleural infections. Actually 34.2% hypoalbuminemia patients had pleural effusion, thus, pleural effusion was an independent risk factor apart from hypoalbuminemia. So a full risk assessment may only be achieved after a combination
of radiography with laboratory tests for hospital-acquired influenza A.

Some limitations in our study should be noted. Due to the nature of retrospective matched case-control study, the vaccination history of the two cohorts was not fully available, which was an important confounder factor for influenza infection. The adoption of a relatively stringent definition of hospital-acquired infection will lose parts of cases which may understate the true risk of acquiring influenza A in the hospital. Finally, the clinical data from patients hospitalized for more than 7 days due to severe primary diseases might exaggerate the impact of nosocomial infection, thus the clinical characteristics of hospital-acquired influenza A might be overstated.

**Conclusions**

This study shows that hospital-acquired influenza A extends hospital stay and is associated with high mortality, which ought to be paid more attention to. Influenza precautions need to be taken to protect hospitalized patients who present lymphocytopenia, hypoalbuminemia or pleural effusion, on account of their high possibility to be infected hospital-acquired influenza A.

**Abbreviations**

ICU: Intensive care unit; CRFs: Case report forms; RT-PCR: Real-time reverse transcriptase polymerase chain reaction; ILI: Influenza-like illness; SD: Standard deviation; IQR: Interquartile range; COPD: Chronic obstructive pulmonary disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; TBIL: Total bilirubin; DBIL: Direct Bilirubin; BUN: Blood urea nitrogen; CRE: Creatinine;

**Author contributions**

LQS, KY and NZ conceived and designed the study. NZ and CCG were responsible
for data collection. KY analyzed data and wrote the original draft. HYQ and AHW helped perform analysis with constructive discussions. LQS supervised the implement and revised the manuscript. All authors reviewed and approved the manuscript.

**Funding**

This study was supported by the National Natural Science Foundation of China (Grant No. 81570072).

**Availability of data and materials**

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The identities of patients were anonymized and individual patient informed consent was not obtained given the non-interventional and retrospective nature of the study. The analysis of the database was approved by the Research Ethics Committee of Xijing hospital, Xi’an China.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Acknowledgements**

Not applicable.

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Figure 1. Flow chart of patients included in the analysis

Hospitalized patients with influenza-like illness and tested by influenza A nucleic acid RT-PCR N=1336

RT-PCR positive patients N=412
Epidemic characteristics: Diagnosis time, Department, Positive rate, Age, Sex

Excluded patients N=319
Diagnosis ≤ 6 days, Age < 18 years

Hospital-acquired influenza A N=93
Diagnosis ≥ 7 days

Matched controls N=93
Same hospitalized department, stay ≥ 7 days at the time of the matched patients’ diagnosis
Table 1. Epidemic characteristics of influenza A diagnosed among hospitalized patients

| Variables               | Positive No. | Negative No. | Positive diagnosis rate of suspected influenza A (%) |
|-------------------------|--------------|--------------|---------------------------------------------------|
| Total patients          | 412          | 924          | 30.8                                              |
| Nephropathy             | 43           | 27           | 61.4                                              |
| Geriatric               | 47           | 56           | 45.6                                              |
| Neurology               | 46           | 78           | 37.1                                              |
| Hematology              | 28           | 58           | 32.6                                              |
| Cardiac Surgery         | 35           | 79           | 30.7                                              |
| Cardiology              | 36           | 82           | 30.5                                              |
| Gastroenterology        | 33           | 91           | 26.6                                              |
| Rest Department         | 158          | 478          | 24.8                                              |
| Sex                     |              |              |                                                   |
| Male                    | 232          | 532          | 30.4                                              |
| Female                  | 180          | 392          | 31.5                                              |
| Influenza A season      |              |              |                                                   |
| December 2018           | 5            | 9            | 35.7                                              |
| January 2019            | 278          | 395          | 41.3                                              |
| February 2019           | 83           | 225          | 26.9                                              |
| March 2019              | 29           | 206          | 12.3                                              |
| April 2019              | 17           | 89           | 16.0                                              |
| Age, years              |              |              |                                                   |
| > 65                    | 111          | 225          | 33.0                                              |
| > 18~65                 | 271          | 630          | 30.1                                              |
| > 12~18                 | 9            | 25           | 26.5                                              |
| > 6~12                  | 4            | 8            | 33.3                                              |
| ≥6                      | 17           | 36           | 32.1                                              |
Table 2. Epidemic characteristics of 93 patients with hospital acquired influenza A

| Variables                | Hospital-acquired influenza A No. | Percentage(%) |
|--------------------------|-----------------------------------|---------------|
| Total patients           | 93                                | 100           |
| Department               |                                   |               |
| Geriatric                | 15                                | 16.1          |
| Neurology                | 15                                | 16.1          |
| Hematology               | 13                                | 14.0          |
| Cardiac surgery          | 12                                | 13.0          |
| Nephropathy              | 6                                 | 6.5           |
| Gastroenterology         | 6                                 | 6.5           |
| Respiratory              | 5                                 | 5.4           |
| Rest                     | 21                                | 22.6          |
| ICU admission            | 22                                | 23.7          |
| Diagnosed time           |                                   |               |
| December 2018            | 0                                 | 0.0           |
| January 2019             | 77                                | 82.8          |
| February 2019            | 13                                | 14.0          |
| March 2019               | 3                                 | 3.2           |
| April 2019               | 0                                 | 0.0           |
| Sex                      |                                   |               |
| Male                     | 50                                | 53.8          |
| Female                   | 43                                | 46.2          |
| Age > 65 years           | 32                                | 34.4%         |

ICU, intensive care unit
Table 3. Characteristics of patients before being confirmed hospital-acquired influenza A and matched controls in the same time

| Variables                        | Hospital-acquired influenza A | Matched controls          | P value |
|----------------------------------|-------------------------------|---------------------------|---------|
| Age, years, median (IQR)         | 58 (41.50-69.0)               | 59 (43.50-68.50)          | 0.971   |
| Sex                              |                               |                           |         |
| Male                             | 50 (53.8)                     | 49 (52.7)                 | 0.883   |
| History of smoking               |                               |                           |         |
|                                 | 24 (25.8)                     | 20 (21.5)                 | 0.490   |
| Underlying disease               |                               |                           |         |
| Hypertension                     | 39 (41.9)                     | 34 (36.6)                 | 0.453   |
| Diabetes                         | 16 (17.2)                     | 14 (15.1)                 | 0.690   |
| COPD                             | 6 (6.5)                       | 7 (7.5)                   | 0.774   |
| Coronary heart disease           | 20 (21.5)                     | 22 (23.7)                 | 0.726   |
| Chronic renal failure            | 3 (3.2)                       | 1 (1.1)                   | 0.621   |
| Malignancya                      | 6 (6.5)                       | 8 (8.6)                   | 0.578   |
| Immunosuppressionb               | 15 (16.1)                     | 16 (17.2)                 | 0.844   |
| Haematologic disease             | 13 (14.0)                     | 14 (15.0)                 | 1.000   |
| Cerebrovascular disease          | 19 (20.4)                     | 15 (16.1)                 | 0.448   |
| Autoimmune disease               | 14 (15.1)                     | 10 (10.8)                 | 0.382   |
| Pregnancy                        | 1 (1.1)                       | 1 (1.1)                   | 1.000   |
| Pneumonia on admission           | 25 (26.9)                     | 19 (20.4)                 | 0.301   |
| Laboratory findings              |                               |                           |         |
| Leukocyte count, /mm3, median (IQR) | 7000 (4700-9350)            | 6300 (4650-9700)          | 0.691   |
| Leukocytopenia                   | 16 (17.2)                     | 10 (10.8)                 | 0.205   |
| Neutrophilic granulocyte count, /mm3, median (IQR) | 4650 (2780-6970) | 3950 (2240-6410) | 0.415   |
| Neutrophilopenia                 | 16 (17.2)                     | 11 (11.8)                 | 0.298   |
| Lymphocyte count, /mm3, median (IQR) | 1070 (630-1660)            | 1300 (880-1820)           | 0.045   |
| Lymphocytopenia                  | 48 (51.6)                     | 33 (35.5)                 | 0.027   |
| Haemoglobin, g/L, median (IQR)   | 108 (87.5-133.5)              | 119 (97-139.5)            | 0.068   |
| Anaemia                          | 52 (55.9)                     | 42 (45.2)                 | 0.142   |
| Platelet count, /mm3, median (IQR) | 1800000 (111500-256500)      | 1800000 (141000-250000)   | 0.351   |
| Thrombocytopenia                 | 25 (26.9)                     | 17 (18.3)                 | 0.161   |
| ALT, IU/L, median (IQR)          | 22 (14.5-35.5)                | 24 (16-37.5)              | 0.446   |
| ALT > 50 IU/L                    | 15 (16.1)                     | 11 (11.8)                 | 0.398   |
| AST, IU/L, median (IQR)          | 22 (17-36.5)                  | 22 (17.5-35)              | 0.601   |
| Test            | Value 1 (Mean) | Value 2 (Mean) | p-value |
|-----------------|---------------|---------------|---------|
| AST > 40 IU/L   | 18 (19.4)     | 16 (17.2)     | 0.704   |
| ALB, g/L, median (IQR) | 35.6 (31.55-39.15) | 38.5 (34.75-42.20) | 0.001   |
| Hypoalbuminemia b | 73 (78.5)   | 53 (57.0)     | 0.002   |
| TBIL, µmol/L, median (IQR) | 12.4 (8.2-19.5) | 13.7 (8.75-17.05) | 0.691   |
| TBIL > 20.5µmol/L | 18 (19.4)   | 17 (18.3)     | 0.851   |
| DBIL, umol/L, median (IQR) | 5.1 (3.2-8.55) | 5.3 (3.1-7.75) | 0.932   |
| DBIL > 6.8µmol/L | 32 (34.4)    | 31 (33.3)     | 0.877   |
| BUN, mmol/L, median (IQR) | 5.62 (4.25-7.57) | 5.68 (4.71-7.76) | 0.622   |
| BUN > 8 mmol/L | 21 (22.6)     | 22 (23.7)     | 0.862   |
| CRE, µmol /L, median (IQR) | 61 (50.5-81.5) | 60 (48.5-76.0) | 0.489   |
| CRE > 97µmol /L | 13 (14.0)     | 14 (15.1)     | 0.835   |
| K*, mmol/L, mean (SD) | 4.12 (0.62) | 4.03 (0.49) | 0.254   |
| K* < 3.5 mmol/L | 14 (15.1)     | 12 (12.9)     | 0.672   |
| Na*, mmol/L, mean (SD) | 139.91 (4.81) | 140.02 (4.44) | 0.873   |
| Na* < 137 mmol/L | 25 (26.9)     | 19 (20.4)     | 0.301   |
| Ca*, mmol/L, mean (SD) | 2.14 (0.19) | 2.17 (0.17) | 0.157   |
| Ca* < 2.11 mmol/L | 37 (39.8)    | 30 (32.3)     | 0.285   |

Radiographic findings
- Pleural effusion i: 25 (26.9) 9 (9.7) 0.002
- Corticoids j: 47 (50.5) 40 (43.0) 0.304
- Corticoids, days, median (IQR): 6 (3-7) 6 (3-8.5) 0.464
- Length of hospital stay, days, median (IQR): 18 (12-27.5) 14 (11-20) 0.002
- Mortality i: 10 (10.8) 2 (2.2) 0.017

Data expressed as frequencies and percentages in parenthesis unless otherwise stated; IQR: interquartile range (25th to 75th percentile); SD: standard deviation

COPD, chronic obstructive pulmonary disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; DBIL, direct Bilirubin; BUN, blood urea nitrogen; CRE, creatinine; K*, plasma potassium; Na*, plasma sodium; Ca*, serum calcium;

a Malignancy: cancer or haematological malignancies;
b Immunosuppression: chemotherapy or radiotherapy within 1 month before illness onset, using immunosuppressive therapy as a daily dose of ≥ 20mg prednisolone (or its equivalent) for more than 15 continuous days before onset of the illness, and hematopoietic stem cells or solid organ transplant < 10 years.
c Leukocytopenia: leukocyte count < 3500/mm3
d Neutrophilopenia: neutrophilic granulocyte count < 1800/mm3
e Lymphocytopenia: lymphocyte count < 1100/mm3
f Anaemia: haemoglobin < 120g/L for men and < 110g/L for women
g Thrombocytopenia: platelet count < 125 /mm3
h Hypoalbuminemia: ALB < 40 g/L
i Pleural effusion: on single or both sides found by radiographic
j Corticoids: intravenous drip or atomizing inhalation
Table 4. Independent risk factors for hospital-acquired influenza A

| Variables         | OR   | P value | 95%CI     |
|-------------------|------|---------|-----------|
| Lymphocytopenia   | 3.107| 0.016   | 1.238-7.796 |
| Hypoalbuminemia   | 2.241| 0.027   | 1.099-4.570 |
| Pleural effusion  | 3.094| 0.014   | 1.263-7.583 |

Lymphocytopenia: lymphocyte count < 1100/mm3; Hypoalbuminemia: albumin < 40 g/L; Pleural effusion: on single or both sides found by radiographic;