

A Comparison of Demographic, Epidemiological and Clinical Characteristics of Hospital Influenza-related Viral Pneumonia Patients

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Research article

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Abstract

Background

The comparison of the demographic, epidemiological, and clinical characteristics of hospital human influenza (influenza A (H1N1) pdm09, H3N2, and B) -related and hospitalized avian-origin influenza A (H7N9)-related viral pneumonia patients has not been reported.

Methods

A retrospective study was conducted in hospitalized influenza-related viral pneumonia patients.

Results

The average age of hospitalized human influenza A -related viral pneumonia patients was lower than B pneumonia patients ($p < 0.05$), human influenza A -related patients in the 35–49-year-old group were more than those with B pneumonia patients ($p < 0.05$), and relatively less in the ≥ 65 -year-old group than B pneumonia patients ($p = 0.079$). The proportion of patients who have at least one comorbid condition to human influenza A pneumonia was lower than B and H7N9 pneumonia ($p < 0.05$). The proportion of invasive mechanical ventilation (IMV), lymphocytopenia, elevated lactate dehydrogenase, and d-dimer to hospitalized human influenza A-related viral pneumonia patients was higher than B pneumonia patients ($p < 0.05$), but lower than H7N9 pneumonia patients ($p < 0.05$).

Conclusions

Hospital influenza B-related viral pneumonia mainly affects the elderly and people with underlying diseases, while human influenza A pneumonia mainly affects the young adults; however, the mortality was similar. The proportion of severe cases to hospital human influenza A-related viral pneumonia patients was higher than those of B pneumonia patients but lower than H7N9 pneumonia patients. Pulmonary consolidation and positive bacterial culture (sputum) were independently associated with IMV, while shock, white blood cell count $> 10,000/\text{mm}^3$, and positive bacterial culture (blood or sputum) were independently associated with death to three types hospitalized influenza-related viral pneumonia patients.

Background

Influenza causes considerable morbidity during each annual influenza season. In April 2009, the influenza A (H1N1) pdm09 (pH1N1) virus emerged in Mexico and the USA and spread globally [1]. Since the first report of pneumonia that was caused by the pH1N1 virus in Mexico [2], severe cases have been documented worldwide. Influenza B virus has been classically considered less pathogenic than influenza A virus in adults and mostly responsible for mild respiratory infections, while severe illness and poor prognosis have been associated with bacterial coinfection [3, 4]. On March 30, 2013, three individuals with severe pneumonia were found to be infected with a novel avian-origin influenza A (H7N9) virus that

had not been detected in humans and animals previously. As of May 9, 2013, 131 laboratory-confirmed cases were reported, including 32 deaths [5], and the majority of these patients were reported in China.

2017–2018 influenza season was dominated by pH1N1 and B viruses along with co-circulation of H3N2 virus, this season provided a unique opportunity to directly compare the demographic, epidemiological, and clinical characteristics of hospitalized human influenza A (pH1N1 and H3N2)-related viral pneumonia patients to the hospital influenza B-related viral pneumonia patients. Also, we compared the demographic, epidemiological, and clinical characteristics of these hospitalized human influenza (pH1N1, H3N2, and B)-related viral pneumonia patients to the hospital H7N9-related viral pneumonia patients in 2017, and aimed to discover the factors independently associated with invasive mechanical ventilation (IMV) or death among these three types hospitalized influenza-related viral pneumonia patients.

Methods

Study Design and Study Population

A retrospective study was conducted from November 1, 2017 to March 31, 2018 at the First Affiliated Hospital, College of Medicine, Zhejiang University, China. All patients, > 14 years of age and with hospital stay > 24 h with confirmed human influenza A or B-related viral pneumonia were included in this study. In addition to above factors, those with confirmed H7N9-related viral pneumonia from January 1, 2017 to May 3, 2017 were also included. This study was approved by the Ethical Board of the hospital.

This retrospective study evaluated the reverse transcriptase-polymerase chain reaction (RT-PCR) tests and computed tomography results daily in hospitalized patients with confirmed human influenza A- or B-related viral pneumonia or H7N9-related viral pneumonia. These cases were assessed by an Infectious Disease doctor and nasopharyngeal swabs (NPS) or sputum specimens were collected within the first 24 h of hospitalization and processed immediately. All radiological evaluations were performed by two radiologists who were blinded to the clinical information.

Data Collection and Definitions

Clinical data were acquired from electronic medical records. The following variables were recorded: demographics, comorbid conditions, current smoking status, alcohol abuse, pregnancy, body mass index (BMI), clinical feature, laboratory data, radiographic finding, complication, treatment, and clinical outcome. The definitions of obesity, current smoking status, alcohol abuse, confirmed human influenza A or B, confirmed H7N9, lymphocytopenia, thrombocytopenia, influenza-related viral pneumonia, rhabdomyolysis, acute kidney injury, immunosuppression, early antiviral therapy, exposure to live poultry and severe cases were provided in the Supplementary Appendix.

Statistical Analysis

Categorical variables were compared by the chi-square or Fisher's exact test. Continuous variables were compared by the t-test or the Mann–Whitney test. The multivariate logistic regression analysis of factors

potentially associated with IMV or in-hospital mortality included the variables that were significant in the univariate analysis and clinically important variables. Statistical significance was established at p-value < 0.05. All statistical analyses were performed using SPSS v.18. (SPSS Inc., Chicago, IL, USA).

Results

Demographic and Epidemiological Characteristics

From November 1, 2017 to March 31, 2018, a total of 4,297 cases of laboratory-confirmed human influenza A and B viral infection were reported in our hospital. Of these, 2335 cases were human influenza A (about 85% were pH1N1 and 15% were H3N2), 1880 cases were influenza B, and 82 cases were infected with both viruses. Finally, 138 cases of hospitalized human influenza A-related viral pneumonia and 59 cases of hospitalized influenza B-related viral pneumonia were included in this study. From January 1, 2017 to May 3, 2017, a total of 18 cases of hospitalized H7N9 -related viral pneumonia were also included in the current study. The median age of hospitalized human influenza A-related viral pneumonia patients was lower than those with B pneumonia (57 years (interquartile range (IQR), 45.8–66.3) vs. 62 years (IQR, 53–74); $p = 0.034$). In the 35–49-year-old age group, the proportion of hospitalized human influenza A-related viral pneumonia patients was 23.9%, which was higher than B pneumonia patients (10.2%; $p = 0.027$). In the ≥ 65 -year-old group, the proportion of hospitalized human influenza A-related viral pneumonia patients was 32.6%, which was relatively lower than B pneumonia patients (45.8%; $p = 0.079$; Table 1). The proportion of comorbid conditions in hospitalized human influenza A-related viral pneumonia patients was 58%, which was lower than the B pneumonia patients and hospitalized H7N9 pneumonia patients (78% vs. 77.8%; $p = 0.013$). In the hospitalized patients with influenza B-related viral pneumonia, the proportion of patients with the concomitant hematological disease was 16.9%, relatively higher than those with human influenza A pneumonia and H7N9 pneumonia (8.7% vs. 0%; $p = 0.085$). One hospitalized pregnant patient had human influenza A-related viral pneumonia, and none of the patients presented influenza B-related viral pneumonia and H7N9-related viral pneumonia in pregnancy. The proportion of obesity to the three types of hospitalized influenza-related viral pneumonia patients was similar. Interestingly, 66.7% of hospitalized H7N9-related viral pneumonia patients were exposed to live poultry.

Clinical Characteristics and Diagnostic Findings

The most common symptoms of the three types of hospital influenza-related viral pneumonia patients were fever, cough, sputum production, shortness of breath, and fatigue. Compared to hospitalized influenza B-related viral pneumonia patients, the proportion of low-grade fever to human influenza A pneumonia patients was low (10.6% vs. 20.4%; $p = 0.046$; Table 2).

At the time of admission, the median value of hemoglobin in hospitalized human influenza A-related viral pneumonia patients was 124 g/dL (IQR: 104–139), higher than B pneumonia patients 117 g/dL (IQR, 95–130) ($p = 0.018$). The proportion of lymphocytopenia in hospitalized human influenza A-related viral pneumonia patients was 83.3%, higher than B pneumonia patients (69.5%; $p = 0.028$). The proportion of

elevated aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and d-dimer (DD) in hospitalized human influenza A-related viral pneumonia patients was higher than that of B pneumonia patients (46.7% vs. 25.9%, $p = 0.007$; 67.9% vs. 51%, $p = 0.033$; 76.5% vs. 62.5%, $p = 0.049$). The proportion of pulmonary ground-glass opacities in hospitalized human influenza A-related viral pneumonia patients was 35.5%, higher than B pneumonia patients 20.3% ($p = 0.035$). The median value of white blood cell counts in hospitalized H7N9-related viral pneumonia patients was $4400/\text{mm}^3$ (IQR: 3475–5625), lower than human influenza A pneumonia patients and B pneumonia patients ($7000/\text{mm}^3$ (IQR: 4300–9550) vs. $6900/\text{mm}^3$ (IQR: 4300–12600); $p = 0.008$). The median value of lymphocyte count in hospitalized H7N9-related viral pneumonia patients was $425/\text{mm}^3$ (IQR: 375 – 625), lower than human influenza A and B pneumonia patients ($745/\text{mm}^3$ (IQR: 448–1208) vs. $1020/\text{mm}^3$ (IQR: 550–1690); $p = .001$). The proportion of lymphocytopenia in hospitalized H7N9-related viral pneumonia patients was 100.0%, higher than human influenza A and B pneumonia patients (83.3% vs. 69.5%; $p = 0.006$). The proportion of elevated AST, creatine kinase (CK), DD, and LDH in hospitalized H7N9-related viral pneumonia patients was higher than human influenza A and B pneumonia patients (77.8% vs. 46.7% vs. 25.9%, $p < 0.001$; 76.5% vs. 17.9% vs. 9.8%, $p < 0.001$; 94.4% vs. 76.5% vs. 62.5%, $p = 0.016$; 100% vs. 67.9% vs. 51%, $p = 0.001$). The proportion of positive culture (blood or sputum) on presentation or during hospitalization in the hospitalized H7N9-related viral pneumonia patients (bacterial and fungal) was 61.1% and 33.3%, respectively, higher than the human influenza A and B pneumonia patients (21.1% vs. 21.3%; $p = 0.002$) (15.8% vs. 6.4%; $p = 0.028$). The proportion of pulmonary ground-glass opacities and pulmonary consolidation in hospitalized H7N9-related viral pneumonia patients was 55.6% and 100.0% respectively, higher than the human influenza A and B pneumonia patients (35.5% vs. 20.3%; $p = 0.012$), (63.8% vs. 49.2%; $p < 0.001$).

Complications, Treatment, and Clinical Outcomes

In the current study, the proportion of intensive care unit (ICU) admission in hospitalized human influenza A-related viral pneumonia patients was 19.6%, which higher than 6.8% of B pneumonia patients ($p = 0.024$). The proportion of IMV in hospitalized human influenza A-related viral pneumonia patients was 16.7%, which also higher than that in B pneumonia patients 3.4% ($p = 0.01$) (Table 3). The proportion of IMV and extracorporeal membrane oxygenation (ECMO) treatment in hospitalized H7N9-related viral pneumonia patients was 38.9% and 11.1%, respectively, which was higher than that in human influenza A and B pneumonia patients (16.7% vs. 3.4%; $p = 0.001$), (1.4% vs. 0%; $p = 0.048$). The median value of hospital expense of hospitalized H7N9-related viral pneumonia patients was 66095.6 Yuan (IQR, 42450.6–129574.2), which was higher than that of human influenza A and B pneumonia patients (IQR, 25642.3 Yuan (13184.5–53805.7) vs. 18316.8 Yuan (IQR, 11111.1–35750.5); $p < 0.001$). There was no difference in death to three types of hospitalized influenza-related viral pneumonia patients.

In the treatment, the rate of antifungal drug use for H7N9 was 72.2% and that for glucocorticoid in hospitalized H7N9-related viral pneumonia patients was 100%, which was higher than human influenza A and B pneumonia patients (30.4% vs. 37.3%; $p = 0.002$), (55.8% vs. 40.7%; $p < 0.001$). All the hospitalized

human influenza A-related viral pneumonia patients and hospitalized influenza B-related viral pneumonia patients were treated with aseltamivir or peramivir or both, and all the hospitalized H7N9-related viral pneumonia patients were treated with a combination of aseltamivir with peramivir. However, the time from onset of illness to administration of antiviral therapy in hospitalized H7N9-related viral pneumonia patients was 4 days (IQR, 3–8.3), which was relatively shorter than that of human influenza A and B pneumonia patients (7 days (IQR, 5–10.8) vs. 6 days (range, 3–14); $p = 0.089$). The time of administration of antiviral therapy to virus-negative time of hospitalized H7N9-related viral pneumonia patients was 5.5 days (IQR, 2.8–10), shorter than human influenza A and B pneumonia patients (10 days (IQR, 6–14.5) vs. 11 days (IQR, 6–17.75); $p = 0.007$).

Factors associated with IMV due to Three Types Hospitalized Influenza-related Viral Pneumonia Patients

In the univariate analysis, the three types hospitalized influenza-related viral pneumonia patients with IMV had significantly higher neutrophil percentage, C-reactive protein, AST, DD, blood urea nitrogen, pro-B-type natriuretic peptides, and partial pressure arterial oxygen/fraction of inspired oxygen ($\text{PaO}_2:\text{FiO}_2$) levels than the three types hospitalized influenza-related viral pneumonia patients without IMV. Furthermore, the proportion of patients with shortness of breaths, lymphocytopenia, elevated procalcitonin, AST, CK, DD, and LDH, positive bacterial culture (sputum) on presentation or during hospitalization, positive bacterial culture (blood or sputum) on presentation or during hospitalization, CURB-65 score ≥ 2 , bilateral pneumonia, and pulmonary consolidation in the three types of hospitalized influenza-related viral pneumonia patients with IMV was significantly higher than those without IMV, while the lymphocyte count in the three types of pneumonia patients with IMV was lower than those without IMV (Table S1 in the Supplementary Material). In the multivariate analysis, pulmonary consolidation (odds ratio (OR): 13.67; 95% confidence interval (CI): 1.54–121.12; $p = 0.019$) and positive bacterial culture (sputum) at the time of presentation or during hospitalization (OR: 7.71; 95% CI: 2.48–24.03; $p < 0.001$) were independently associated with IMV in the three types hospitalized influenza-related viral pneumonia patients (Table S3 in the Supplementary Material).

Factors Associated with Death due to the three Types Hospitalized Influenza-related Viral Pneumonia Patients

In the univariate analysis, the three types of hospitalized influenza-related viral pneumonia patients who die in the hospital had significantly higher neutrophil percentage, hemoglobin, blood platelet counts, C-reactive protein, DD, blood urea nitrogen, pro-B-type natriuretic peptides, and $\text{PaO}_2:\text{FiO}_2$ levels than the survivors. Also, the proportion of elevated white blood cell count and procalcitonin, positive bacterial culture (sputum) on presentation or during hospitalization, CURB-65 score ≥ 2 , IMV, shock to the three types hospitalized influenza-related viral pneumonia patients who die in the hospital was significantly higher than that of the survivors (Table S2 in the Supplementary Material). In the multivariate analysis, shock (OR: 13.16; 95% CI: 2.06–84.07; $p = 0.006$), white blood cell count $> 10,000/\text{mm}^3$ (OR: 7.22; 95% CI: 1.47–35.58; $p = 0.015$) and positive bacterial culture (blood or sputum) on presentation or during

hospitalization (OR: 6.27; 95% CI: 1.36–28.85; $p = 0.018$) were independently associated with death in the three types hospitalized influenza-related viral pneumonia patients (Table 4).

Discussion

This was the first study that compared the demographic, epidemiological, and clinical characteristics of hospitalized human influenza-related viral pneumonia patients with H7N9 pneumonia patients. The study revealed that the hospitalized human influenza A-related viral pneumonia patients were younger than those with B pneumonia, and the infection was primarily detected in young adults. On the other hand, the influenza B-related viral pneumonia was common in the elderly, usually with comorbid conditions. Hospitalized human influenza A-related viral pneumonia patients was severer than B pneumonia patients, but milder than H7N9 pneumonia patients.

During the 2009 pandemic, obese patients showed high morbidity and mortality rate [6]. Another study demonstrated that obese mice infected with influenza virus have diminished cell cytotoxicity, delayed pro-inflammatory cytokine expression, and higher mortality than lean mice controls [7]. In the current study, the proportion of obesity in the three types of hospitalized influenza-related viral pneumonia patients was similar. However, further studies on the mechanism underlying obesity and severe influenza are essential. Pregnancy was also identified as a risk factor for complications, such as pneumonia or death from pH1N1 virus infection [8]. However, other studies have reported that the influenza pH1N1 virus was not associated with poor outcomes in hospitalized pregnant women as compared to non-pregnant women at reproductive age in terms of early diagnosis and antiviral therapy [9]. In this study, the number of pregnant women was small, we can not obtain meaningful results; also, the proportion of patients who have at least one comorbid condition in those with human influenza A-related viral pneumonia was lower than those with B pneumonia. Moreover, the average age of hospitalized human influenza A-related viral pneumonia patients was lower than that of B pneumonia patients, and the proportion of the hospitalized human influenza A-related viral pneumonia patients in the 35–49 age group was more than that of the B pneumonia patients, and the proportion in the ≥ 65 years age group was relatively less than that of the B pneumonia patients. Some studies have reported that influenza B mainly affects the elderly and people with underlying diseases [10, 11]; however, pH1N1 mainly affects young adults, similar to our research. Early-life exposure to an antigenically related virus, i.e., the A (H1N1) strain that circulated after the 1918 pandemic and prior to the 1957 A (H2N2) pandemic might mitigate the severity for the pH1N1 strain in older individuals; this phenomenon explained the survival of elderly in the pandemic.

In the aspect of clinical characteristics and diagnostic findings, the proportion of low-grade fever patients in hospital influenza B-related viral pneumonia was higher than the human influenza A pneumonia patients, it may related with weak pathogenicity of influenza B and quick immune response of the host. The early identification of influenza B might facilitate an effective restriction and clearance of influenza B viral infections [12]. In another study, CK was designated as a biomarker of severity in pH1N1 infection; the elevation of CK was associated with complications, increased length of ICU stay, and healthcare resources [13]. Another study included 155 hospitalized adult patients with pH1N1; LDH was an

independent risk factor of hospital death as assessed by multivariate logistic regression analysis [14]. The elevation of DD may be caused by the embolism of the small pulmonary vessels, then the pulmonary ventilation and blood flow ratio became abnormal, and the blood oxygen saturation declined. Finally, the rate of mortality was elevated; however, this hypothesis needs further substantiation. A lymphocyte count of < 300 lymphocytes/ μL was observed in a subgroup of patients with poor outcome in a study encompassing 239 inpatients with confirmed influenza virus infection [15]. Thus, we can conclude that the proportion of elevated CK, LDH, DD, and lymphocytopenia was positively relative to the severity of influenza. In this study, the elevated LDH, DD, and lymphocytopenia in hospitalized human influenza A-related viral pneumonia patients was higher than that in B pneumonia patients, and the elevated CK, LDH, DD, and lymphocytopenia in hospitalized H7N9-related viral pneumonia patients was higher than that in human influenza A and B pneumonia patients. The proportion of ICU admission and invasive mechanical ventilation in hospitalized human influenza A-related viral pneumonia patients was higher than that in B pneumonia patients. The proportion of IMV and ECMO treatment and the median value of hospitalization expense in hospitalized H7N9-related viral pneumonia patients were higher than that in human influenza A and B pneumonia patients. However, the mortality did not differ in the three types of hospitalized influenza-related viral pneumonia patients. Taken together, it can be concluded that the proportion of severe cases in hospitalized human influenza A-related viral pneumonia patients was higher than that of B pneumonia patients and lower than that of H7N9 pneumonia patients, albeit with similar mortality. A study consisting of 57 cases of H7N9 patients and 14 cases of pH1N1 patients demonstrated that the proportion of acute respiratory distress syndrome to H7N9 was much higher than that of pH1N1 [16], which was also observed in the current study. Furthermore, the proportion of ICU admission and IMV to pH1N1 was 2-fold higher than that of B, and no difference was detected in the mortality as reported by a study including 2791 cases of adult patients [17]. Another study reported that the mortality of adults influenza B patients was similar to that of pH1N1 patients [18]. Although all the influenza viruses infect the respiratory epithelium from the nasal passages to bronchioles, pH1N1 tends to infect pneumocytes and interalveolar macrophages, causing extensive areas of inflammation in the alveoli, which could partially explain the increased severity [19–22]. Hospitalized influenza B-related viral pneumonia mainly affects the elderly and those with underlying diseases, rendering them as severe cases, such that the mortality of B pneumonia patients was elevated and similar to human influenza A pneumonia patients.

The World Health Organization Guidelines recommended that prompt empirical antiviral treatment should be initiated when influenza is suspected, even before laboratory results are known [23]. Improved clinical outcomes have been described among adults treated with antiviral drugs after hospitalization or up to 5 days from illness onset [24–26]. Early antiviral therapy within 2 days of illness accelerated viral shedding and reduced the mortality in patients with H7N9 viral infection [27]. Moreover, compared to early antiviral therapy, H7N9 patients with delayed antiviral therapy became severe cases [28]. Interestingly, in a study comprising of 82 cases of H7N9 virus infection, the time of onset of illness to administration of antiviral therapy was 6 days (IQR: 4–8), longer than that in the current study 4 days (IQR: 3–8.3), and the administration of antiviral therapy to virus-negative time of the study was 7 days (IQR: 5–9), also longer than 5.5 days (IQR: 2.8–10) in the current study; the mortality was 34.1% [29]. Gao et al. [30] reported that

the rate of glucocorticoid use of the H7N9 cases was 62.2%, lower than our study 100% and the mortality was 27%. The mortality of hospitalized H7N9-related viral pneumonia patients was much higher than that of human influenza A and B pneumonia. However, in the current study, the mortality of hospitalized H7N9-related viral pneumonia patients was lower than before and similar to human influenza A and B pneumonia. This phenomenon might be explicated by the initial antiviral time relatively early than before and the rate of glucocorticoid use for H7N9 was high. All our patients received oseltamivir with peramivir that also may reduce the mortality, although these findings need to be substantiated further. In the current study, the proportion of early antiviral therapy in the three types of hospitalized influenza-related viral pneumonia patients was similar.

Nevertheless, the present study has several limitations. First, influenza testing was ordered at the physicians' discretion, and therefore, not all individuals with influenza were tested, or testing could be biased towards severe cases. However, this bias would not affect our main findings because influenza testing was ordered independently of the knowledge of the virus type or subtype. Second, we only included the hospitalized influenza-related viral pneumonia patients and excluded the outpatient cases and hospitalized patients without influenza-related viral pneumonia, such that it cannot reflect the whole disease spectrum. Finally, because the RT-PCR was not accurate absolutely, the real influenza-positive patients may be diagnosed as negative.

Conclusion

In summary, hospitalized influenza B-related viral pneumonia mainly affects the elderly and individuals with underlying diseases, while human influenza A pneumonia mainly affects the young adults; however, the mortality was comparative. The proportion of severe cases to hospital human influenza A-related viral pneumonia patients was higher than B pneumonia patients but lower than H7N9 pneumonia patients. Pulmonary consolidation and positive bacterial culture(sputum) at the time of presentation or during hospitalization were independently associated with IMV due to three types of hospital influenza-related viral pneumonia patients. On the other hand, shock, white blood cell count $> 10,000/\text{mm}^3$, and positive bacterial culture (blood or sputum) at the time of presentation or during hospitalization were associated with death in such patients.

Abbreviations

IMV: invasive mechanical ventilation; pH1N1: influenza A (H1N1) pdm09; H7N9: avian-origin influenza A(H7N9); RT-PCR: reverse transcriptase-polymerase chain reaction; NPS: nasopharyngeal swabs; BMI: body mass index; IQR: interquartile range; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; DD: d-dimer ; CK: creatine kinase; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation; PaO₂:FiO₂: partial pressure arterial oxygen/fraction of inspired oxygen; OR: odds ratio; CI: confidence interval; SCr: serum creatinine

Declarations

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Availability of data and materials

All data generated or analysed during this study are either included in this published article and its supplementary information files or are available from the corresponding author on reasonable request.

Authors' contributions

Study concept and design: Bin Fu and Lingling Tang. Acquisition of data: Bin Fu, Zhengjie Wu, Lingtong Huang, Zhaohui Chai, and Peidong Zheng. Analysis and interpretation of data: Bin Fu, Zhengjie Wu, and Lingling Tang. Drafting of the manuscript: All authors. Critical revision of the manuscript for intellectual content: All authors. All authors agree with the submission.

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Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The local ethics committee (The First Affiliated Hospital, College of Medicine, Zhejiang University) approved this study.

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Tables

Due to technical limitations, Tables 1-4 are provided in the Supplementary Files section.

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