The Prevalence and the Impacts of Pulmonary Bacterial Coinfections and Secondary Bacterial Pneumonia in Patients with Severe Influenza Pneumonitis

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Research

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Abstract

Background: This study investigated the prevalence and clinical outcomes of pulmonary bacterial coinfections and secondary bacterial pneumonia in patients with severe influenza pneumonitis. The causative pathogens and their clinical impacts were analyzed.

Methods: We retrospectively analyzed the data of adult patients with severe influenza pneumonitis admitted to our medical ICUs from January 2014 to May 2018. Bacterial confection (in first 48 h) and secondary bacterial pneumonia (from 48 h to 1 week) were confirmed by chest radiographs and positive findings in the respiratory specimen obtained from lower airway. The risk factors of pulmonary coinfection were evaluated. The outcomes of patients with or without pulmonary coninfection or secondary bacterial pneumonia were also analyzed.

Results: We identified 117 critically ill patients with laboratory-confirmed influenza pneumonitis admitted to the medical ICUs. *Klebsiella pneumoniae* (31.4%) and *Staphylococcus aureus* (22.8%) were the most commonly identified bacteria in patients with bacterial coinfection. A high proportion of methicillin-resistant *Staphylococcus aureus* was noted. Liver cirrhosis and diabetes mellitus were the independent risk factors for bacterial coinfection. *Acinetobacter baumannii* (28%) and *S. aureus* (25%) were the most often identified bacteria in patients with secondary bacterial pneumonia. Patients with secondary bacterial pneumonia had longer period of mechanical ventilation, longer ICU stay and hospital stay, and higher mortality.

Conclusions: Bacterial coinfection or secondary infection in patients with severe influenza pneumonitis were associated with higher rates of morbidity and mortality in ICU patients. Earlier diagnosis and appropriate therapy, especially in patients with liver cirrhosis and diabetes mellitus, should be cautiously considered.

Introduction

Influenza, including the most common causes of human influenza A subtypes H1N1, H3N2, and influenza B, is an acute viral respiratory infection that causes widespread annual epidemics infecting up to 20% of the population and resulting in significant morbidity and mortality.[1, 2] Most of the affected people have mild illness comprising a sudden onset of fever, sore throat, cough, runny rose, headache, myalgia, and malaise.[2] However, influenza can also cause severe illness or even death, especially in high-risk individuals such as elderly people, those with certain comorbid chronic diseases, and immunocompromised patients.[3, 4] The World Health Organization estimates that global influenza epidemics result in 3–5 million cases of severe illness and 290,000–650,000 deaths annually.[5, 6] Remarkably, from April 12, 2009, to April 10, 2010, there were 60.8 million cases and 12,469 deaths in the United States due to swine-origin influenza A (pandemic 2009 A/H1N1).[7] Influenza epidemics cause morbidity and mortality from direct viral effects, coinfection of bacterial pneumonia, and secondary bacterial complications. Evidence indicating influenza predisposing to bacterial coinfections has been

observed in seasonal influenza epidemics, past pandemics, pathology studies, and animal models.[8–12] Influenza can cause cell damage and death within the host's airway, which leads to an upregulation in the production of toxins. This phenomenon generates an inflammatory response, causing the release of cytokines and chemokines, more commonly referred to as a cytokine storm. This storm is a variable that promotes damage to pulmonary tissue, leaving the pulmonary tissue vulnerable to infection. Moreover, bacterial pathogens in the lower respiratory tract may cause influenza infection.[13] In previous published studies (between 2009 and 2012), the most important bacterial coinfections during an influenza epidemic were *Streptococcus pneumoniae* and *Staphylococcus aureus*.[14, 15] However, empiric antibiotics were not widely available to cover those bacterial pathogens of both coinfection and secondary bacterial pneumonia, and it is believed that it led to higher mortality rates in critical patients. Inappropriate initial antibiotics for pneumonia are usually associated to extended intensive care unit stay and are linked with an increased risk of mortality.[16, 17] Therefore, in the present study, we collected and analyzed the prevalence data of bacterial coinfection (during the first 48 h of hospitalization) and secondary bacterial pneumonia infection (after 48 h to 1 week) of patients with laboratory-confirmed influenza pneumonitis admitted to our medical intensive care units (ICUs). Our aims are to determine the distribution of bacterial coinfections and secondary bacterial infections in patients with severe influenza in the ICUs and to identify the most common bacterial species to provide more appropriate therapy. The impacts of bacterial coinfections and secondary infections in severe influenza patients were also analyzed.

Patients And Methods

Patients

We retrospectively evaluated the data of patients (aged > 20 years) with laboratory-confirmed influenza infection admitted to the medical ICUs between January 2014 and May 2018 in the Chiayi Chang-Gung Memorial Hospital, a 1369-bed primary care and referral regional teaching hospital that included two adult medical ICUs, in southern Taiwan. The inclusion criteria were (1) patients with confirmed influenza pneumonitis accompanied by complications of multiorgan failure (altered function in two or more organ systems during an acute illness), unstable blood pressure (systolic blood pressure < 90 mmHg or mean arterial pressure < 60 mmHg), or acute respiratory failure requiring mechanical ventilation and ICU admission and (2) all these patients should have received antiviral treatment with either oseltamivir or peramivir. These patients were categorized into (1) cases with bacterial coinfection among severe cases of influenza requiring medical ICU admission, (2) severe cases of influenza requiring medical ICU admission without bacterial coinfection, (3) cases of secondary bacterial infection among severe cases of influenza requiring medical ICU admission, and (4) severe cases of influenza requiring medical ICU admission without secondary bacterial infection. We also collected the detailed clinical and physiological data using Acute Physiology and Chronic Health Evaluation (APACHE) II score. Patients were excluded from the study if they were aged < 20 years or had mild flu-like symptoms and treated as outpatients or in general wards.

Diagnosis of influenza infection

Influenza virus A or B infection was confirmed by a positive finding in the respiratory specimen (nasopharyngeal swab and/or pharyngeal swab) using the rapid influenza diagnostic test (Formosa One Sure Flu A/B Rapid Test Kit) or reverse transcriptase–polymerase chain reaction (QiAamp Viral RNA Mini Kit; TAIGEN Bioscience Corporation, Taiwan).

Diagnosis of pulmonary bacterial coinfection

Bacterial coinfection was confirmed by a positive finding on chest radiograph (infiltration and/or consolidation change) along with a positive culture in the respiratory specimen (obtained from sputum, endotracheal aspiration, bronchial washing, or bronchoscopic bronchoalveolar lavage samples) in the first 48 h of hospitalization.

Diagnosis of secondary bacterial pneumonia

Secondary bacterial infection was confirmed using clinical symptoms (for example, fever, cough, increased sputum production, and tachypnea) and a positive finding on chest radiograph (infiltration and/or consolidation change) along with a positive culture in the respiratory specimen (obtained from sputum, endotracheal aspiration, bronchial washing, or bronchoscopic bronchoalveolar lavage samples) between 48 h to 1 week after hospital admission.

Data collection and definitions

A standardized form was designed for clinical data collection. The data were primarily retrieved from the hospital's electronic medical records and were supplemented by a secondary manual search. The following data were collected: age, gender, body mass index, associated medical conditions, APACHE II score during first 24 h admitted to the ICU, results of laboratory tests, results of bacterial specimens from sputum, endotracheal aspiration, bronchial washing, or bronchoalveolar lavage, in-hospital complications, days of invasive mechanical ventilation, days of ICU stay, days of hospital stay, and overall mortality.

Statistical analysis

The clinical characteristics, underlying medical diseases, and laboratory findings as well as complications of survivors and non-survivors were compared using the chi-square test for categorical variables and the independent sample t-test for numerical variables. Differences were considered to be statistically significant at $p < 0.05$. Significant variables in the univariate analyses were entered into a multivariate logistic regression model to identify independent predictors. Data were entered and analyzed using the Statistical Package for the Social Sciences statistical software (version 26.0; SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics and outcomes

A total of 117 critically ill patients, including 70 men and 47 women, with a median age of 67 years with laboratory-confirmed influenza virus infection admitted to the medical ICUs from January 2014 to May 2018 were evaluated in this study. Influenza A virus was detected in 98 (84%) patients, of whom 29 had H1N1, 25 had H3N2, and 44 had un-typable influenza A. Influenza B virus was detected in 19 (16%) patients. All of them received antiviral therapy (either oseltamivir or peramivir) during the first 48 h of admission to the hospital. Of the 117 patients, 25 died, indicating an overall ICU mortality rate of 21.3%. The median duration of mechanical ventilation, ICU stay, and hospital stay were 11.8, 13.1, and 23.8 days, respectively. The most commonly associated underlying disease was hypertension, followed by diabetes mellitus, chronic obstructive pulmonary disease (COPD) and liver cirrhosis. Table 1 summarizes the clinical characteristics and outcomes of the included patients.

Table 1
Characteristics of patients with severe influenza pneumonitis admitted to medical ICUs

	N = 117
Age (years)	67.5 ± 16.6
Gender	
Male	70 (60%)
Female	47 (40%)
Body mass index (BMI)	24.1 ± 4.7
Type of influenza	
A/H1N1	29 (25%)
A/H3N2	25 (21%)
A/un-typable	44 (38%)
B	19 (16%)
Co-morbidities	
Hypertension	68 (58%)
Diabetes mellitus	43 (37%)
Chronic obstructive pulmonary disease	22 (19%)
Liver cirrhosis	10 (9%)
Chronic kidney disease	9 (8%)
End-stage renal disease	6 (5%)
Asthma	6 (5%)
APACHE II score	17 ± 6.6
Pulmonary bacterial Coinfection	32 (27%)
Secondary bacterial pneumonia	22 (19%)
Dyas of mechanical ventilation	11.8 ± 8.7
Days of ICU stay	13.1 ± 9.96
Days of hospital stay	23.8 ± 19.8
lCU mortality	25 (21.3%)
28-day in-hospital mortality	18 (15.4%)

Bacterial coinfection and secondary bacterial pneumonia

Bacterial coinfection, defined as a positive culture in the aforementioned respiratory specimen and a positive finding on CXR (infiltration and/or consolidation) during the first 48 h of hospital admission, was detected in 32 (27.4%) patients with 35 positive pathogens (Table 2). *Klebsiella pneumoniae* (31.4%) was the most often identified bacterium, followed by *Staphylococcus aureus* (22.8%), *Streptococcus pneumoniae* (11.4%), and *Pseudomonas aeruginosa* (11.4%). Methicillin-resistant *Staphylococcus aureus* (MRSA, n = 6, 17.1%) was more prevalent than methicillin-susceptible *S. aureus* (n = 2, 5.7%).

Table 2. Bacteria identified in coinfection and secondary bacterial pneumonia in patients with severe influenza pneumonitis

Pulmonary bacterial coinfection	Number	Secondary bacterial infection	Number
Klebsiella pneumoniae	11	*Acinetobacter baumannii*	4
Methicillin-resistant *Staphylococcus aureus* (MRSA)	6	*Acinetobacter baumannii*–multidrug-resistant strain	3
Methicillin-susceptible *Staphylococcus aureus (MSSA)*	2	Methicillin-resistant *Staphylococcus aureus* (MRSA)	4
Streptococcus pneumoniae	4	Methicillin-susceptible *Staphylococcus aureus* (MSSA)	2
Pseudomonas aeruginosa	4	*Klebsiella pneumoniae*	2
Escherichia coli	3	*Klebsiella pneumoniae* with positive Modified Hodge test	2
Stenotrophomonas maltophilia	2	*Pseudomonas aeruginosa*–Carbapenem-resistant strain	2
Serratia marcescens	1	*Pseudomonas aeruginosa*	1
Acinetobacter baumannii – Carbapenem-resistant strain	1	*Escherichia coli*	2
Klebsiella oxytoca–multidrug-resistant strain	1	*Stenotrophomonas maltophilia*	2

Secondary bacterial pneumonia was detected in 24 (21%) specimens (Table 2). *Acinetobacter baumannii* (28%) was the most commonly identified bacterium, followed by *S. aureus* (25%), *K. pneumoniae* (17%), and *P. aeruginosa* (13%). *S. pneumoniae* was not identified after 48 h of hospital admission. Meanwhile, more drug-resistant specimens were detected among patients with secondary infections (MRSA 17%, multidrug-resistant *Acinetobacter baumannii* strain [MDRAB] 13%, modified Hodge test-positive *K. pneumoniae* [MHT-KP] 8%, and carbapenem-resistant *Pseudomonas aeruginosa* [CRPA] strain 8%).

Impacts of pulmonary bacterial coinfection and secondary bacterial infection

Compared with patients without coinfection, those diagnosed with severe influenza coinfected along with bacterial pneumonia had a significantly higher severity (higher APACHE II scores) and longer ICU stay. Although not significantly different, patients with bacterial coinfection were of older age and had low body mass index (BMI). There was no significant difference in the duration of mechanical ventilation, hospital stay and mortality between patients with or without bacterial coinfections (Table 3). In addition, although there were no significant differences in age and BMI, severe influenza patients with secondary bacterial pneumonia had significantly higher APACHE II score, longer ICU stay and hospital stay. Numerically longer mechanical ventilation use and higher mortality (21.4 vs. 9.6 days and 31.8% vs. 18.9%, respectively) were also found in patients with secondary bacterial infection, although the difference did not reach to a statistical significance (Table 4).

Table 3
Comparison between severe influenza pneumonitis with or without pulmonary bacterial coinfection.

	With coinfection	Without coinfection	P value
Patient number	32 (27%)	85 (73%)	
Age (years)	70.7 ± 15.7	66.3 ± 16.9	0.198
BMI	22.9 ± 4.2	24.5 ± 4.8	0.12
Secondary bacterial infection	6 (19%)	16 (19%)	0.993
Influenza A	27 (84%)	71 (84%)	0.912
Co-morbidity			
Hypertension	22 (69%)	46 (54%)	0.153
Chronic obstructive pulmonary disease	6 (19%)	16 (19%)	0.993
Asthma	1 (3%)	5 (6%)	0.574
Liver cirrhosis	6 (19%)	4 (5%)	0.015
Diabetes mellitus	17 (53%)	26 (31%)	0.024
Chronic kidney disease	2 (6%)	7 (8%)	0.719
End-stage renal disease	3 (4%)	3 (1%)	0.201
APACHE II score	20.5 ± 7	15.7 ± 6	< 0.005
Days of mechanical ventilation	12.8	11.5	0.72
Days of ICU stay	16.8 ± 13.6	11.7 ± 7.8	0.014
Days of hospital stay	25.8 ± 19.7	23 ± 19.9	0.504
ICU Mortality	7 (21.8%)	18 (21.1%)	0.935

Table 4
Comparison between severe influenza pneumonitis with or without secondary bacterial infection.

	With Secondary bacterial infection	Without Secondary bacterial infection	P value
Patient number	22 (19%)	95 (71%)	
Age (years)	65.7 ± 17.3	67.9 ± 16.6	0.586
BMI	23.3 ± 4	24.2 ± 4.8	0.391
Coinfection	6 (27%)	26 (27%)	0.993
Influenza A	17 (77%)	81 (85%)	0.36
Co-morbidity			
Hypertension	15 (68%)	53 (56%)	0.288
Chronic obstructive pulmonary disease	5 (23%)	17 (18%)	0.601
Asthma	2 (10%)	4 (4%)	0.35
Liver cirrhosis	3 (14%)	7 (8%)	0.343
Diabetes mellitus	12 (55%)	31 (33%)	0.055
Chronic kidney disease	1 (5%)	8 (8%)	0.539
End-stage renal disease	1 (5%)	5 (5%)	0.891
APACHE II	19.6 ± 5	16.4 ± 6.8	0.043
Days of mechanical ventilation	21.4	9.6	0.055
Days of ICU stay	17.5 ± 13.2	12.1 ± 8.8	0.02
Days of Hospital stay	32.1 ± 25.4	21.8 ± 17.9	0.03
ICU Mortality	7 (31.8%)	18 (18.9%)	0.184

Risk factors for bacterial coinfection or secondary bacterial pneumonia

Table 5 shows the patients' underlying medical diseases and their relationship with bacterial coinfection and secondary bacterial pneumonia. Results of multivariate analysis demonstrated that liver cirrhosis (odds ratio [OR]: 4.673; 95% confidence interval [CI]: 1.224–17.848; $p < 0.05$) and diabetes mellitus (OR: 2.572; 95% CI: 1.117–5.919; $p < 0.05$) were independent predictors of bacterial pneumonia coinfection in

patients with critically ill influenza. Otherwise, there were no obvious independent predictors, including in patients with bacterial pneumonia coinfection, to predict secondary bacterial pneumonia.

Table 5
Multivariate analysis of independent risk factors associated with pulmonary bacterial coinfection in patients with severe influenza pneumonitis.

	Odds Ratio	95% Confidence Interval
Liver cirrhosis	4.673	1.224–17.848
Diabetes mellitus	2.572	1.117–5.919
Hypertension	1.865	0.789–4.411
Chronic obstructive pulmonary disease	0.995	0.351–2.819
Asthma	0.516	0.058–4.597
Chronic kidney disease	0.743	0.146–3.780
End stage renal disease	2.828	0.540-14.803
Age	1.017	0.991–1.044
BMI	0.928	0.844–1.020

Discussion

The results of our study showed that pulmonary bacterial coinfection occurred in 27% (32 /117) of patients with severe influenza pneumonitis. Those with bacterial coinfection had higher severity and longer ICU stay. Diabetes mellitus and liver cirrhosis were the independent risk factors for bacterial coinfection in patients with severe influenza pneumonitis. We also demonstrated that 19% (22/117) of patients with severe influenza pneumonitis had secondary bacterial pneumonia during the course of hospitalization. Those with secondary bacterial pneumonia had higher severity and longer ICU and hospital stay.

Unlike previous studies that reported that *S. pneumoniae* was the most frequent cause of bacterial coinfection,[18–20] the most common coinfection pathogens identified in our study were *K. pneumoniae* (31.4%), followed by *S. aureus* (22.8%), *S. pneumoniae* (11.4%), and *P. aeruginosa* (11.4%). This result was similar to a previous report from Taiwan.[21] The higher percentage of *K. pneumoniae* coinfection could be related to the higher rates of chronic diseases such as diabetes mellitus, COPD or liver cirrhosis in our patients. A previous study reported significant increases in the incidence of MRSA infections in the past decade, particularly community-associated MRSA (CA-MRSA).[22] In the pandemic of coronavirus disease 2019 (COVID-19), MRSA was also the most common and important bacteria in coinfection.[23] In

our study, 22.8% of the identified isolates were *S. aureus* among patients with coinfection, and 75% of these isolates were MRSA. This finding of coinfection pathogens supports the Infectious Disease Society of America recommendations for broad-spectrum antibiotic coverage for influenza-related pneumonia, particularly to cover CA-MRSA in patients with influenza-related pneumonia.[24]

In case of secondary bacterial pneumonia, *A. baumannii* (28%) was the most often identified bacterium, followed by *S. aureus* (25%) and *K. pneumoniae* (17%). *S. pneumoniae* was not detected among secondary infection. Meanwhile, 66.7% of the *S. aureus* isolated were MRSA. Other drug-resistant specimens were also detected in patients with secondary infection (MDRAB 13%, MHT-positive *K. pneumoniae* 8%, and CRPA strain 8%). Those drug-resistant organisms should be covered by empiric antibiotic therapy if nosocomial pneumonia was suspected in these patients.

The risk factors including clinical symptoms, medical disease history, laboratory tests, and complications possibly contributed to poor patient outcomes after influenza virus infection remain to be elucidated. Understanding the risk of bacterial coinfection and secondary bacterial pneumonia and the distribution of variable pathogens in patients with influenza in the ICU can help physicians choose the appropriate antibiotics to minimize patient morbidity and mortality as well as prevent the individual and societal risks of using unnecessary antibiotics. Consistent with previous studies,[25–28] our study found that liver cirrhosis (OR: 4.673; 95% CI: 1.224–17.848) and diabetes mellitus (OR: 2.572; 95% CI: 1.117–5.919) were independent predictors of pulmonary bacterial coinfection in patients with severe influenza pneumonitis. Previous studies have described that cellular immune response was decreased, whereas antibody production was intact, in patients with advanced liver cirrhosis, and IFN-γ response was relatively poor[29]. In addition, influenza virus itself can cause hepatitis, and influenza-induced toxic metabolites and proinflammatory cytokines such as TNF-α, IL-1, and IL-6 might contribute to hepatic damage[30, 31]. On the other hand, neutrophil chemotaxis and adherence to intracellular bactericidal activity, opsonization, vascular endothelium, phagocytosis, and cell-mediated immunity are all deteriorated in diabetic patients with hyperglycemia.[32, 33] Therefore, patients with liver cirrhosis and diabetes mellitus can have an immunosuppression status due to viral and bacterial infections, resulting in adverse complications and increasing the overall mortality. Therefore, influenza vaccine should be recommended to cirrhotic and diabetic patients.

These 117 critically ill patients with laboratory-confirmed influenza pneumonitis and were admitted to the medical ICU in the present study, had the 28-day mortality and in-hospital mortality rates being 15.4% and 21.3%, respectively. This result was similar to that of a previous study involving 444 adult hospitalized patients with influenza in the United States.[34] A mortality rate of 20.6% had also been reported in a prospective multicenter observational cohort study of 2,059 patients admitted to ICUs for influenza infection.[35]

Previous studies have mentioned that community-acquired bacterial coinfection can predict severity and mortality in patients admitted with influenza-associated pneumonia.[36] Our study demonstrated that compared with patients without coinfection, those diagnosed with bacterial coinfection with had a

significantly higher severity (higher APACHE II score) and longer ICU stay, but there was no significant difference in the duration of mechanical ventilation, length of hospital stay or mortality rate. The rate of mortality was similar to a previous report,[37] which may be related to the increasing recognition of influenza, so that the intensivist could provide more optimal care in the ICU.

A higher mortality was reported in patients with nosocomial infections among those hospitalized with severe influenza A.[38] Our research found the ICU stay and hospital stay were significantly longer in this patient group. Longer period of mechanical ventilation and higher mortality (21.4 vs. 9.6 days, P = 0.055 and 31.8% vs. 18.9%, P = 0.183, respectively) were also found in patients with secondary bacterial infection, although the difference had no statistical significance. This study provides data to clinicians to recognize that secondary bacterial infection is a contributor for increased morbidity and mortality in patients with severe influenza pneumonitis. The statistical insignificance could be related to the small case numbers in this study.

This study has some potential limitations. First, given the retrospective nature of the study, we did not collect information on previous influenza or pneumococcal vaccination. The impact of previous influenza vaccination could not be evaluated in this study. Second, due to the small case number, the statistical power might not be sufficient to assess the risk factors for mortality within this subpopulation. Third, the study population consisted of adult patients; therefore, the results cannot be generalized to pediatric patients. The strengths of this study include a detailed description of medical disease information at presentation and the entire bacterial specimen data of critically ill patients with influenza. We have also emphasized the key factors associated with bacterial coinfection and secondary bacterial infection in critically ill influenza patients and provided data to physicians to select the appropriate empiric antibiotics to minimize patient morbidity and mortality.

Conclusions

Bacterial coinfection and secondary infection were important complications in patients with severe influenza in the ICU, with *K. pneumoniae* being the most common coinfection pathogen and *A. baumannii* being the most commonly identified pathogen in secondary infection. A high prevalence of MRSA in patients with coinfection and secondary infection was also noted. Liver cirrhosis and diabetes mellitus were independent risk factors for bacterial coinfection. Moreover, bacterial secondary infection appeared to be associated with higher rates of morbidity and mortality in ICU patients. Prevention and treatment of bacterial coinfection and secondary infection should be an integral component of a pandemic plan, particularly for patients with severe influenza infection requiring ICU care.

Abbreviations

ICU: intensive care unit.

BMI: Body mass index.

APACHE II score: Acute Physiology and Chronic Health Evaluation II score.

COPD: chronic obstructive pulmonary disease.

MRSA: Methicillin-resistant *Staphylococcus aureus*.

MSSA: Methicillin-susceptible *Staphylococcus aureus*.

MDRAB: multidrug-resistant *Acinetobacter baumannii.*

MHT-KP: modified Hodge test-positive *Klebsiella pneumoniae*.

CRPA: carbapenem-resistant *Pseudomonas aeruginosa*.

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Chang-Gung Medical Foundation. (IRB No.: 202001202B0). Informed consent was waived by the IRB.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

WCL, MCH, YHT and MJH have made substantial contributions to the conception and design of the work. CCC, CML, SWL, CKL, YCL, YHF, SYH, TMY have made substantial contributions to the acquisition, analysis, and interpretation of data. WCL and MCH have drafted the work. MJH have substantively reviewed and revised the work.

All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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