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Short communication

Outcome of critically ill patients with influenza virus infection

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ABSTRACT

Background: Influenza is a major cause of morbidity and mortality, with its greatest burden on the elderly and patients with chronic co-morbidities in the intensive care unit (ICU). An accurate prognosis is essential for decision-making during pandemic as well as interpandemic periods.
Methods: A retrospective cohort study was conducted to determine prognostic factors influencing short term outcome of critically ill patients with confirmed influenza virus infection. Baseline characteristics, laboratory and diagnostic findings, ICU interventions and complications were abstracted from medical records using standard definitions and compared between hospital survivors and non-survivors with univariate and multivariate logistic regression analyses.
Results: 111 patients met the inclusion criteria. Acute respiratory distress syndrome (ARDS) complicated ICU course in 25 (23%) of the patients, with mortality rate of 52%. Multivariate logistic regression analysis identified the following predictors of hospital mortality: Acute Physiology and Chronic Health Evaluation (APACHE) III predicted mortality (Odds ratio [OR] 1.49, 95% confidence interval [CI] 1.1–2.1 for 10% increase), ARDS (OR 7.7, 95% CI 2.3–29) and history of immunosuppression (OR 7.19, 95% CI 1.9–28).
Conclusions: APACHE III predicted mortality, the development of ARDS and the history of immunosuppression are independent risk factors for hospital mortality in critically ill patients with confirmed influenza virus infection.

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1. Background

Seasonal influenza is an acute respiratory illness caused by influenza A or B viruses which occurs every year and causes more than 200,000 hospitalizations and 40,000 deaths[1] in the United States each year. Although it is uncertain when the next pandemic influenza will happen, even seasonal influenza poses a major challenge to hospitals. So it is essential to understand and determine the prognosis of patients with seasonal influenza who require respiratory support and ICU admission. The need for mechanical ventilation[2] and severity of illness[3] had previously been identified as poor prognostic factors of influenza. However, specific prognostic features including presence of complications such as acute respiratory distress syndrome (ARDS), bacterial superinfection and the effects of vaccination status have not been systematically studied.

2. Objectives

We conducted an observational cohort study to determine the outcome of patients with laboratory proven influenza who were admitted to the ICUs of two academic medical centers and to identify specific prognostic features associated with mortality and morbidity in this patient population.

Abbreviations: ICU, intensive care unit; ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; OR, Odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ALI, acute lung injury; MV, mechanical ventilation; NIV, non-invasive mechanical ventilation; CPAP, continuous positive airway pressure; CDC, Center for Disease Control; SARS, severe acute respiratory syndrome; ACIP, Advisory Committee on Immunization Practices; SD, standard deviation; IQR, interquartile range.

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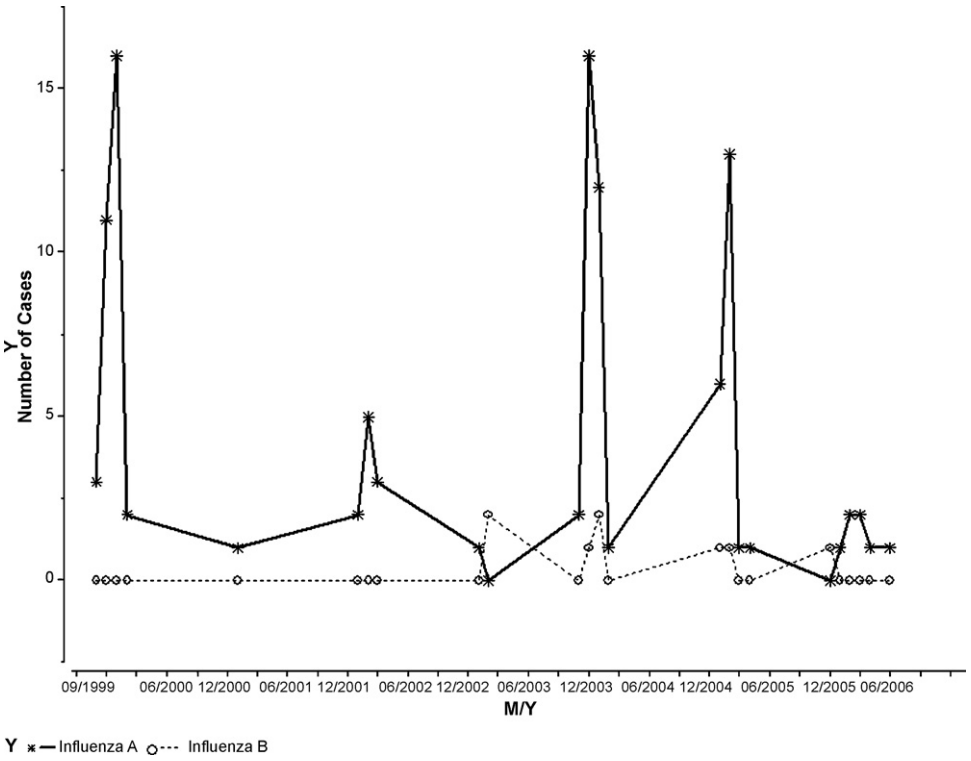

Fig. 1. Number of influenza A and B cases during the study period.

3. Study design

This retrospective cohort study included consecutive patients with laboratory proven influenza who were admitted to the ICU from 1999 to 2006 at the Mayo Clinic, Rochester, MN (24 beds, closed medical ICU) and the University of Virginia, Charlottesville, VA (16 beds, closed medical ICU). The study was approved by the Institutional Review Board at both institutions. Laboratory proven influenza virus infection was defined as follows[4]: one or more signs or symptoms of flu-like illness, including abrupt onset of fever, cough, headache, and myalgia accompanied by the laboratory evidence of influenza virus infection. Testing for influenza was performed by a rapid antigen test, polymerase chain reaction, viral culture, or immunohistochemical stain for influenza A and B in respiratory secretions.

Acute Physiology and Chronic Health Evaluation (APACHE III) scores were prospectively collected and probability of death was calculated based on data from the first 24 h of ICU admission.[5] Immunosuppression was defined as therapy with immunosuppressants, chemotherapy, radiation or long term/recent high dose of steroids; or active leukemia, lymphoma or AIDS.[5] Acute lung injury (ALI) and ARDS were defined according to the American–European Consensus Conference.[6] Primary and secondary bacterial infections were defined according to Center for Disease Control (CDC) criteria.[7]

3.1. Statistical analysis

A stepwise multiple logistic regression procedure was performed to evaluate the independent impact of each variable on hospital mortality. Clinically important variables associated with outcome of interest ($P < 0.1$) in univariate analysis were introduced into a forward, stepwise, logistic regression model, taking into consideration clinical plausibility and co-linearity between the variables. JMP 7.0.1 computer software (SAS Institute, Cary, NC) was used for the analysis. P-values <0.05 were considered statistically significant.

4. Results

A total of 111 patients, 54 (48.6%) male, 106 Caucasian (95.4%), with a mean age of 65.3 ± 18.9 were admitted to the medical ICUs of two tertiary care hospitals. While the patients at Mayo Clinic were older (68 vs 56, $P = 0.006$), the severity of illness was similar in both centers (median APACHE III score 69 vs 76, $P = 0.13$). Most patients (97.3%) were admitted to the hospital from November to April. There were 103 influenza A cases (92.7%) and 8 influenza B cases (7.2%). The number of the influenza cases during the observation period is shown in Fig. 1. There was no difference in mortality between influenza A and influenza B (18.5% vs 25%, $P = 0.65$). Sixty-four patients (57.7%) had pre-existing chronic pulmonary disease and 19% were immunosuppressed. Only 35 (31%) patients had received influenza vaccination before hospital admission, although the vast majorities (106, 95%) were eligible for routine vaccination based on age and/or chronic disease criteria.

Thirty-nine (35.1%) patients had bacterial isolates causing superimposed infections (*Staphylococcus aureus* 48.7%). ARDS complicated ICU course in 25 (23%) patients. The median (interquartile range [IQR]) duration of mechanical ventilation was 3.0 days (2.0–6.8). The median (IQR) lengths of ICU and hospital stays were 3.0 days (1.3–6.5) and 9.2 days (5.7–15.0), respectively. Overall hospital mortality was 18.9% (Mayo 25% vs Virginia 15.4%, $P = 0.60$).

The comparison of demographics and clinical characteristics and interventions between hospital survivors and non-survivors is presented in Tables 1 and 2. Multivariate logistic regression analysis identified the following predictors of hospital mortality: Acute Physiology and Chronic Health Evaluation (APACHE) III predicted mortality (Odds ratio [OR] 1.49, 95% confidence interval [CI] 1.1–2.1 for 10% increase), ARDS (OR 7.7, 95% CI 2.3–29) and history of immunosuppression (OR 7.19, 95% CI 1.9–28).

Table 1
Baseline characteristics of hospital survivors and non-survivors.

Variable		Survivors ($n=90$)	Non-survivors ($n=21$)	P-value
Age, mean ± SD, years		64.7 ± 19.0	68.0 ± 18.5	0.470
Male gender		40 (44)	14 (66)	0.066
Alcohol, N (%)		13 (14.4)	0	0.124
Smoking, N (%)		41 (45.6)	6 (28.6)	0.100
Influenza type A ($n=103$), N (%)		84 (93.3)	19 (95.0)	0.569
Previous vaccination, N (%)		27 (30)	8 (38)	0.472
Prodromal symptoms, N (%)				
Fever		55 (61)	14 (67)	0.721
Cough		72 (80)	16 (76)	0.698
Dyspnea		77 (85)	16 (76)	0.294
Gastrointestinal		26 (29)	5 (23)	0.620
Myalgia		22 (24)	5 (23)	0.951
Admitting diagnoses, N (%)				
Community acquired pneumonia		42 (47)	12 (57)	0.164
Acute congestive heart failure		8 (9)	1 (5)	0.778
COPD exacerbation		22 (24)	4 (19)	0.546
Other		18 (20)	4 (19)	0.921
APACHE III score mean ±SD ($n=107$)		67 ± 18	82 ± 20	0.001
McCabe class,	0	33 (37.9)	0	
N (%)	1	47 (54.0)	7 (38.9)	<0.001
($n=105$)	2	7 (8.1)	11 (61.1)	
Co-morbidities, N (%)				
COPD		46 (51)	9 (43)	0.495
Coronary artery disease		31 (34)	5 (24)	0.348
Diabetes mellitus		31 (34)	5 (23)	0.302
Hypertension		45 (50)	11 (52)	0.844
Hypothyroidism		19 (21)	3 (14)	0.479
Immunosuppression		10 (11)	11 (52)	<0.001
Transplant		5 (5.6)	2 (9.5)	0.615
Chronic steroid use (%), N (%)		23 (25.6)	8 (38.1)	0.284
PaO_2/FiO_2 ($n=109$), median (IQR)		204 (134.7–290.4)	155 (72–195.3)	0.003
pH ($n=109$), median (IQR)		7.42 (7.29–7.46)	7.37 (7.26–7.43)	0.153

Note: SD = standard deviation; COPD = chronic obstructive pulmonary disease; APACHE III = Acute Physiology and Chronic Health Evaluation III; IQR = interquartile range.

Table 2
Interventions and complications after ICU admission.

Variable	Survivors ($n=90$)	Non-survivors ($n=21$)	P-value
Bacterial superinfection, N (%)	28 (31.1)	11 (52.4)	0.066
Bacteremia, N (%)	6(7)	5(23)	0.017
ARDS, N (%)	13 (14.4)	12 (57.1)	<0.001
Sepsis, N (%)	6 (6.7)	2 (9.5)	0.563
Mechanical ventilation, N (%)	67(74)	20(95)	0.037
Non-invasive ventilation, N (%)	12 (13.3)	1 (4.8)	0.456
Both non-invasive and invasive ventilation, N (%)	8 (8.9)	15 (71.4)	0.039
Duration of mechanical ventilation, days, median (IQR)	3(2–6)	5 (1.7–9.2)	0.227
Hospital length of stay, days, median (IQR)	8.9 (5.7–14)	11 (5.3–26)	0.670

Note: ARDS = acute respiratory distress syndrome; IQR = interquartile range.

5. Discussion

This two center retrospective cohort study confirmed significant mortality and morbidity of critically ill patients with laboratory proven seasonal influenza.[8] Poor prognostic features included the development of ARDS, history of immunosuppression and higher severity of illness. Although most of the patients were eligible for vaccination, we observed strikingly low vaccination rate. Our study also confirmed the high frequency of *S. aureus* superinfection in patients with influenza similar to the previous report.[9]

Similar to previous studies of hospitalized patients' severity of illness was associated with increased hospital mortality rate in our cohort.[10] Importantly, our findings suggest that death during interpandemic periods is commonly associated with ARDS, which is similar to the pandemic findings.[11] An important risk factor for both the development of ARDS and mortality was immunosuppression.[12] The mechanisms of the development of ARDS associated with influenza are still undetermined and may include direct cytotoxicity and apoptosis of alveolar epithelial cells, as well as modification of the host inflammatory response with or without concurrent or secondary bacterial infection.[13] Recently, angiotensin converting enzyme receptors have been identified as the key targets for alveolar cell cytotoxicity secondary to severe acute respiratory syndrome (SARS).[14]

During interpandemic periods, patients with influenza pneumonia are more likely to have underlying cardiopulmonary disease, with mortality reported from 6% to 29%.[15] More than half (58%) of patients in our cohort had a history of chronic lung disease.[16]

A pooled cohort study published after the meta-analyses demonstrated a small but significant reduction in mortality in vaccinated elderly individuals (1.0% vs 1.6% in unvaccinated individuals[17]). In our study, only 35 (31.5%) patients admitted to the

ICU with laboratory confirmed influenza were vaccinated, although the vast majority (95%) who were not vaccinated were eligible based on either age (68.5%) or chronic co-morbidity criteria (82.9%) according to Advisory Committee on Immunization Practices (ACIP) criteria.[18] Although the degree of protection in elderly patients is less than that afforded to healthy younger adults,[19] our findings potentially indirectly support the benefit from influenza vaccination for vulnerable patient population with only 35% vaccination rate.[20–22]

Antiviral therapy is an important strategy for the control of influenza disease while the efficacy of these agents is limited by timing of administration. Good results were obtained when the antiviral treatment was started within 48 h after inoculation[23] and only a few studies showed good results when the antiviral treatment was started after 48 h.[24] Patients with acute respiratory failure secondary to influenza often do not enter the ICU until 2–4 days after the onset of symptoms, when the viral load in respiratory secretions is already high, which make it difficult to evaluate the efficacy of antiviral therapy in our study.

Since only a minority of patients admitted to ICU who meet clinical definition of influenza actually do get laboratory testing, our study likely grossly underestimated the incidence of influenza virus infection and skewed the results towards sicker patients with high complication rates. Consequently, the prognostic features may not be generalizable. Information on the dominant circulating subtype and strain was not collected in the study period which makes it difficult to evaluate the effectiveness of vaccination.

In conclusion, critical illness associated with laboratory proven influenza in the interpandemic period mimics pandemics findings with high prevalence of ARDS complication and poor prognosis associated with ARDS. Better understanding of the mechanisms of development of this devastating complication is needed for the development of effective prevention and therapeutic strategies. Low vaccination rate in a cohort of predominantly elderly patients with high frequency of underlying chronic lung disease and immunosuppression indirectly supports large scale quality improvement efforts aimed at mandatory vaccination of vulnerable populations.

Conflict of interest

None.

Acknowledgments

M.Y. and R.W. performed data collection and management; G.L., M.K. and E.F. analyzed results and drafted the manuscript; W.C.H, S.G.P., B.A., J.D.T. and O.G. designed the research and revised the manuscript.

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