A Hospital-Based Nonconcurrent Cohort Study on Factors Associated with in-Hospital Mortality in Patients with Laboratory Confirmed Influenza

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Abstract

Background and Aim: Influenza is a disease with varied clinical presentation and varied mortality reported in existing literature. The study aimed to determine the factors associated with mortality in patients hospitalized with influenza infection. **Materials and Methods:** This was a 5-year nonconcurrent cohort study done in a tertiary care center in Southern India. Patients with laboratory confirmed influenza infection diagnosed between January 2013 and October 2018 were recruited into the study. **Results:** A total of 130 patients were recruited. Diabetes (45.4%) and chronic obstructive pulmonary disease (COPD) (26.1%) were the most common comorbid illnesses. Thirty-one patients (23.8%) required admission to the intensive care unit (ICU) and 58 patients required ventilation (noninvasive/mechanical ventilation [MV] – 44.6%). Influenza A was the most common isolated strain (46.9%). Univariate analysis demonstrated that a high pneumonia severity index ($P < 0.0001$), CURB 65 > 2 ($P < 0.0001$), MV dependency ($P < 0.0001$), need for ICU stay ($P < 0.0001$), low PF ratio ($P < 0.0001$), COPD ($P = 0.021$), secondary bacterial pneumonia ($P < 0.0001$), acute respiratory distress syndrome ($P = 0.0004$), and acute kidney injury ($P = 0.0006$) were the significant factors associated with in-hospital mortality. Multivariate analysis demonstrated that new onset/worsening renal dysfunction was the only factor significantly associated with in-hospital mortality in patients admitted with influenza. **Conclusions:** Our study showed a mortality of 12.3% ($n = 16$) and new onset/worsening renal dysfunction was the only patient factor associated with mortality. Early recognition of complications and appropriate treatment may reduce mortality in patients admitted with severe influenza. We recommend influenza vaccination for at-risk populations to reduce severity and mortality.

Keywords: Influenza, mortality, multivariate model

Introduction

Influenza is a vaccine preventable viral infection with varied clinical manifestations and complications.[1] Influenza infection can result in severe disease with debilitating complications and mortality.[2] Extremes of age groups and patients with chronic obstructive pulmonary disease (COPD) are at the highest risk of influenza hospitalizations, morbidity, and mortality with various factors influencing susceptibility and severity.[3,4] Worldwide, data on the burden on morbidity and mortality due to influenza have resulted in extended vaccination policies and programs, with incorporation of the vaccine into national immunization schedules.[5] However, in India, we find ourselves combatting a variety of other infectious disease that testing, treatment, and vaccination against influenza are not commonly done.

Laboratory diagnostics availability is restricted to tertiary care centers and vast majority of health-care providers rely on clinical diagnosis and empiric management strategies. The recognition of "at-risk" populations and targeted vaccination remains the most important public health intervention for preventing the burden of the disease and reducing influenza-related deaths.[6,7] This study was carried out to characterize the clinical presentation of patients requiring

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admission for influenza, determine mortality in this cohort and identify factors associated with mortality.

MATERIALS AND METHODS

Design

This was a hospital-based 5-year nonconcurrent cohort study done in Christian Medical College, Vellore, a tertiary care center in Southern India. Adults with laboratory confirmed Influenza diagnosed between January 2013 and October 2018 were consecutively recruited into the study. The institutional ethics committee approved the study. Patients <16 years were excluded from the study. The study population was divided into survivors and non-survivors.

Data collection

Patient data pertaining to demographics, clinical manifestations, symptoms and signs, imaging, risk factors, vaccination information, laboratory reports, treatment, and outcome were collected from hospital records and discharge summaries.

Statistical analysis

Data were entered using Epidata and univariate and multivariate binary logistic regression analysis were performed using SPSS software (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.) to determine factors predicting mortality in patients admitted with influenza. The Student's *t*, Mann–Whitney U, Fischer's exact, and Chi-square tests with continuity correction were used for univariate comparisons whenever appropriate. Variables with $P < 0.05$ in the univariate analyses were entered into multivariate Cox proportional hazards model to determine independent factors associated with in-hospital mortality in patients admitted with laboratory confirmed influenza. In all analyses, a $P < 0.05$ was considered to indicate statistical significance. All probabilities were two-tailed.

RESULTS

Demographics

One hundred and thirty adults with laboratory confirmed influenza were identified from the hospital records in the prespecified 5-year period [Table 1]. The mean age was 51.8 (±17.5) years. Among them, 55 patients (42.3%) were men and 75 (57.7%) were women. Eleven patients (8.5%) were health-care workers. Twenty-three patients (17.7%) admitted to being current smokers. Temporal clustering of cases was seen with maximum cases admitted in the months of February ($n = 32$, 24.8%) and October ($n = 18$, 14%) [Figure 1]. Six patients had received pneumococcal vaccination within 5 years and two patients had received annual influenza vaccination.

Risk factors

Relevant comorbid illnesses were noted from the admission records. The most common primary diseases were diabetes mellitus ($n = 59$, 45.4%), COPD ($n = 34$, 26.1%), and ischemic heart disease ($n = 27$, 20.8%) [Table 1]. The other

Table 1: Patient demographics of 130 patients admitted with influenza

Characteristics	Mean value
Female, *n* (%)	75 (57.7)
Age, mean (SD)	51.8 (17.5)
Hospital stay, mean (range)	8.1 (2- 48) days
Pneumonia severity index, mean (SD)	104.8 (43.1)
CURB 65, mean (SD)	1.3 (1.1)
Charlson comorbidity index, mean (SD)	1.9 (2.2)
Risk factors, *n* (%)	
Smoking	23 (17.7)
COPD	34 (26.1)
Diabetes mellitus	59 (45.4)
Pregnancy	7 (5.4)
CCF/IHD/RHD	27 (20.8)
Others	63 (48.5)
Radiological findings - opacity, *n* (%)	
Alveolar	18 (13.8)
Interstitial	55 (42.3)
Mixed	36 (27.7)
Normal	21 (16.2)
ICU admission, *n* (%)	31 (23.8)
Mechanical ventilation, *n* (%)	26 (20.0)
Influenza strain, *n* (%)	
A	
H1N1	61 (46.9)
H3N2	35 (26.9)
Others	19 (14.6)
B	15 (11.5)
Outcome, *n* (%)	
Alive	114 (87.6)
Dead	16 (12.3)

SD: Standard deviation, RHD: Rheumatic heart disease, IHD: Ischemic heart disease, CCF: Congestive cardiac failure, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, CURB 65 - Acronym - Confusion, Uremia, Respiratory Rate and Blood Pressure, Community-acquired pneumonia
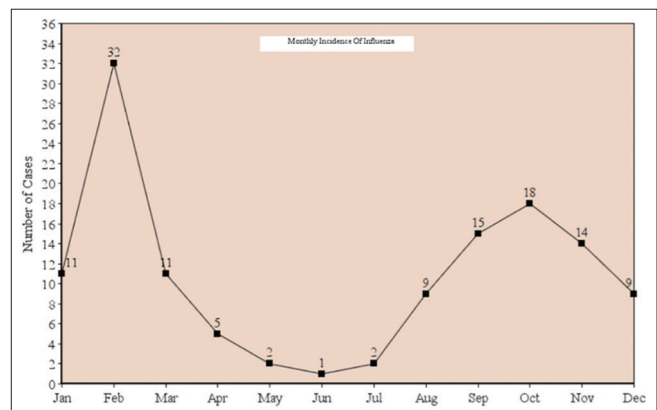

Figure 1: Graph showing the monthly incidence of Influenza cases admitted to the hospital

diagnoses were asthma ($n = 7$, 17.7%), chronic liver disease ($n = 2$, 1.5%), current immunosuppression ($n = 11$, 8.5%), current malignancy ($n = 3$, 2.3%), rheumatic heart disease ($n = 2$, 1.5%), morbid obesity ($n = 9$, 6.9%), chronic neurological disease ($n = 8$,

6.2%), chronic kidney disease (CKD) (*n* = 15, 11.5%), and chronic rheumatologic condition (*n* = 8, 6.1%). Seven women admitted with influenza were pregnant (5.4%).

Clinical manifestations, signs, and scores

The most common patient reported symptoms were cough (*n* = 125, 96.2%), fever (*n* = 114, 87.7%), and breathing difficulty (*n* = 92, 70.8%). 77.7% and 63.8% of the patients had tachycardia and tachypnea at admission, respectively. 13.8% (*n* = 18) patients presented with shock. Respiratory findings commonly encountered included wheeze and crackles. The mean pneumonia severity index (PSI) score was 104.8 ± 43.1. The mean CURB 65 score was 1.3 ± 1.1.

Laboratory parameters

The mean total white blood cell count was 9047.7 ± 5006.2 cells/µL. The mean PaO2 noted was 61.1 ± 12.2 mmHg, with a mean PF ratio of 284.5 ± 82.8. Influenza A was the most commonly isolated strain (61 patients, 46.9%).

Radiological findings

Common radiological findings included interstitial infiltrates (*n* = 55, 42.3%) followed by mixed pattern (*n* = 36, 27.7%). Alveolar infiltrates were noted in 18 patients (13.8%) and 21 patients (16.2%) had normal chest radiographs at admission. 80.8% (105) patients had bilateral infiltrates.

Treatment and initial therapy at admission

Thirty-one patients (23.8%) required intensive care unit (ICU) admission. The mean duration of ICU stay was 8.4 days (range 1–29). Twenty-six patients (20%) required mechanical ventilation (MV) and 32 patients (24.6%) required noninvasive ventilation. Seventy-eight patients (60%) received oseltamivir at admission. 53.8%, 92.3%, and 9.2% patients received a beta lactam beta lactamase inhibitor, azithromycin, and a carbapenem at admission, respectively.

Complications

The in-hospital mortality noted in this study was 12.3% (*n* = 16). Secondary bacterial pneumonia was diagnosed in 54 patients (41.5%), which included 26 patients (20%) with microbiologically proven and 28 patients (21.5%) with clinically/radiologically diagnosed pneumonia (no microbiological evidence). *Acinetobacter sp.* was the most common isolate in the sputum/endotracheal aspirate of patients with proven secondary bacterial pneumonia (eight patients, 30.8%). Other isolates included nonfermenting Gram-negative bacilli (19.2%), *Klebsiella* sp. (15.4%), and *Pseudomonas sp.* (11.5%). Acute respiratory distress syndrome (ARDS) was the second-most common complication noted in 45 patients (34.6%). Acute kidney injury (AKI)/acute worsening of CKD was noted 41 patients (31.5%). Less common complications encountered were myocarditis (2.3%), congestive cardiac failure (4.6%), acute coronary syndrome (3.1%), encephalitis (3.1%), and nosocomial bacteremia (6.1%) [Table 2].

Table 2: Complications

Complication	Frequency
Secondary bacterial pneumonia, *n* (%)	
Proven	26 (20.0)
Suspected	28 (21.5)
Total	54 (41.5)
Myocarditis, *n* (%)	3 (21.5)
CCF, n (%)	6 (4.6)
Acute coronary syndrome, *n* (%)	4 (3.1)
ARDS, *n* (%)	45 (34.6)
Encephalitis, *n* (%)	4 (3.1)
Nosocomial bacteremia, *n* (%)	8 (6.1)
Acute kidney injury/acute worsening of CKD, *n* (%)	41 (31.5)
Organisms isolated in secondary pneumonia (*n*=26), *n* (%)	
Acinetobacter	8 (30.8)
NFGNB	5 (19.2)
Klebsiella	4 (15.4)
Pseudomonas	3 (11.5)
Others	6 (23.1)

SD: Standard deviation, CKD: Chronic kidney disease, ARDS: Acute respiratory distress syndrome, CCF: Congestive cardiac failure, NFGNB: Nonfermenting Gram-negative bacilli

Factors associated with mortality

The results of the univariate analysis showed that patients in the nonsurvival group had higher mean PSI score (*P* ≤ 0.0001) and higher mean CURB 65 score (*P* ≤ 0.0001). Nonsurvivors were also noted to have higher frequency of MV (*P* ≤ 0.0001) and need for ICU stay (*P* ≤ 0.0001). The mean PaO2 and PF ratio were significantly lower in the patients who died (*P* < 0.0001, *P* < 0.0001). Hyperlactatemia was also associated with mortality (*P* = 0.01). Premorbid diagnosis of asthma was the only comorbid illness that was associated with mortality on univariate analysis. Nonsurvivors had higher incidence of secondary bacterial pneumonia, both total and proven (*P* < 0.0001, *P* < 0.0001), higher incidence of AKI/acute worsening CKD (*P* = 0.0006), and higher incidence of ARDS (*P* = 0.0006). Eleven factors that were statistically significant in the univariate model as described above and two factors from expert recommendation were included in the multivariate logistic regression analysis. The factors from expert recommendation included pregnancy and premorbid diagnosis of COPD. The multivariate model showed that AKI/acute worsening CKD was the only factor significantly associated with in-hospital mortality (*P* = 0.026). The other factors which showed statistical significance on the univariate model failed to be statistically significant on the univariate analysis [Table 3].

DISCUSSION

Adults admitted with influenza have high mortality and morbidity. However, this depends on the severity of the illness and the number of organ systems involved. Mortality reported in existing literature is highly nonuniform as the disease has varied presentation ranging from mild clinical

Table 3: Mortality of influenza infection in hospitalized adults

Characteristics	Outcome		P
	Dead (16)	Alive (114)	
Age, mean (SD)	57.9 (16.5)	50.9 (17.6)	0.136
Pneumonia severity index, mean (SD)	160.2 (31.9)	96.9 (38.6)	<0.0001
CURB 65, mean (SD)	2.9 (1.0)	1.1 (0.9)	<0.0001
Charlson comorbidity index, mean (SD)	2.6 (2.9)	1.8 (2.1)	0.362
Clinical course			
Duration of hospital stay, mean (SD)	8.3 (6.1)	8.1 (6.8)	0.9111
Mechanical ventilation, *n* (%)	14 (87.5)	12 (10.5)	<0.0001
Duration of mechanical ventilation, mean (SD)	7.8 (6.0)	10.1 (8.2)	0.426
ICU stay, *n* (%)	13 (81.2)	18 (15.7)	<0.0001
Duration of ICU stay, mean (SD)	7.9 (6.2)	8.3 (0.7)	0.729
Laboratory parameters at admission, mean (SD)			
PaO_2	46.1 (5.9)	64.2 (10.8)	<0.0001
Creatinine	1.2 (0.5)	1.3 (1.1)	0.660
PF ratio	172.3 (58.4)	307.6 (66.7)	<0.0001
Lactate	3.5 (2.4)	1.7 (1.1)	0.01
Co-morbid illnesses, *n* (%)			
Smoking	5 (3.8)	18 (13.8)	0.125
Asthma	0	7 (5.4)	0.586
COPD	8 (6.2)	26 (20.0)	0.021
Diabetes mellitus	5 (3.8)	54 (41.5)	0.236
Pregnancy	1 (0.8)	6 (4.6)	0.868
Chronic liver disease	0	2 (1.5)	0.843
Immunosuppression	1 (0.8)	10 (7.7)	0.739
Current malignancy	1 (0.8)	2 (1.5)	0.221
CCF/IHD/RHD	1 (0.8)	26 (20.0)	0.241
Severe obesity	2 (1.5)	7 (5.4)	0.332
Chronic neurological disease	1 (0.8)	7 (5.4)	0.986
CKD	2 (1.5)	13 (10.0)	0.864
Chronic rheumatological disease	2 (1.5)	6 (4.6)	0.436
Complications, *n* (%)			
Secondary bacterial pneumonia			
Total	14 (87.5)	40 (35.1)	<0.0001
Proven	10 (62.5)	16 (14.0)	<0.0001
Suspected	4 (25.0)	24 (21.1)	0.717
Myocarditis	1 (6.2)	2 (1.7)	0.223
CCF	2 (12.5)	4 (3.5)	0.085
Acute coronary syndrome	1 (6.2)	3 (2.6)	0.409
ARDS	14 (87.5)	31 (27.2)	0.0004
Encephalitis	0	4 (3.5)	0.847
Nosocomial bacteremia	2 (12.5)	6 (5.2)	0.239
Acute kidney injury/worsening CKD	12 (75.0)	29 (25.4)	0.0006
Strain of influenza			
A			
H1N1	10	51	0.192
H3N2	2	33	0.194
Others	2	17	0.800
B	2	13	0.897

SD: Standard deviation, CKD: Chronic kidney disease, ARDS: Acute respiratory distress syndrome, RHD: Rheumatic heart disease, IHD: Ischemic heart disease, CCF: Congestive cardiac failure, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, PF: PaO_2/FiO_2, CURB: Community-acquired pneumonia

illness to severe disease requiring intensive care and MV. Pawelka *et al*. reported 5.6% in-hospital mortality and 9.4% 90-day mortality in a prospective study done on patients with laboratory confirmed influenza.[8] A considerably higher rate (38% in-hospital mortality) was reported by Sun *et al*. in patients with severe influenza with ARDS.[2] In our study,

16 patients (12.3%) died during the index admission for influenza. However, it is important to note that this was a nonuniform cohort with disease severity varying from mild to very severe disease. Forty-five patients (34.6%) had ARDS recognized at admission or during the index hospitalization. Mortality in this subset of patients with ARDS was 31.1%. Thirty-one patients (23.8%) required ICU admission and 26 patients (20%) required MV.

Temporal clustering of cases was seen with maximum cases admitted in the months of February (*n* = 32, 24.8%) and October (*n* = 18, 14%). This was consistent with seasonal Influenza noted in our setting [Figure 1].[9,10] Risk factors associated with increased morbidity and mortality following infection with Influenza reported in existing literature include age >65,[11] women who are pregnant or postpartum (within 2 weeks of delivery),[12] long-term care facility inmates,[11] extreme obesity (body mass index > 40),[4] obstructive airway disease,[13] chronic medical conditions, and immunosuppression.[14] The most common primary diseases noted in our study were diabetes mellitus (*n* = 59, 45.4%), COPD (*n*= -34, 26.1%), and ischemic heart disease (*n* = 27, 20.8%). Although diabetes mellitus has not been described as a typical risk factor for influenza pneumonia, it is been the most commonly quoted comorbid illness in literature.[15] It is important to note that, in patients with diabetes and severe influenza, the clinical course is likely to be stormy with increased risk of secondary bacterial pneumonia and other complications. However, this study did not show a positive correlation between mortality and presence of diabetes as a risk factor.

Secondary bacterial pneumonia is a common complication encountered in patients with Influenza. There is an apparent period of improvement followed by worsening fever, respiratory symptoms and new onset infiltrates on chest radiography. In this study, secondary bacterial pneumonia was diagnosed in 54 patients (41.5%), which included 26 patients (20%) with microbiologically proven and 28 patients (21.5%) with clinically/radiologically diagnosed pneumonia (no microbiological evidence). *Streptococcus pneumoniae* and *Staphylococcus aureus* are the two most common etiological agents isolated in patients with secondary infection complicating Influenza.[16,17] *Acinetobacter sp.* was the most common isolate in the sputum/endotracheal aspirate of our patients with proven secondary bacterial pneumonia (eight patients, 30.8%). All patients with *Acinetobacter* pneumonia were intubated and mechanically ventilated. Hence, it might be more accurate to consider these patients to have a ventilator-associated pneumonia, considering *Acinetobacter* as a typical organism acquired nosocomially in Indian ICU settings.

The factors associated with mortality in the univariate analysis in this study, namely higher disease severity scores, ARDS, need for ICU stay and MV, hyperlactatemia, premorbid diagnosis of asthma, secondary bacterial pneumonia, and new

onset or worsening renal dysfunction are in concordance with factors mentioned in previously published literature.[3,5,6,8,14] The presence of all of the above-mentioned factors signify increased severity of the disease, which correlates with poorer outcome. However, multivariate analysis failed to show positive correlation with mortality for all factors but one (new onset or worsening renal dysfunction). While, renal dysfunction in isolation is not a typical complication of influenza, it signifies the presence of severe disease. The renal dysfunction can easily be explained with prerenal injury due to shock (septic/cardiogenic) or as a consequence of other complications such as secondary bacterial pneumonia resulting in sepsis and multiple organ dysfunction syndrome. The small sample size and the retrospective nature of the study might be the most likely reasons for other factors identified on univariate analysis not showing positive correlation with mortality in the Cox regression model.

CONCLUSION AND RECOMMENDATIONS

This study clearly depicts the morbidity caused by influenza infection in patients requiring hospitalization. Our study showed a mortality of 12.3% (*n* = 16) and new onset/worsening renal dysfunction was the only patient factor associated with mortality. With advances in vaccination technology and introduction of multivalent vaccines made available, the burden caused by the disease can be reduced significantly. The protective efficacy of influenza vaccination has been estimated to be 41% (51% between ages of 18 and 64 years and 37% for ≥65 years).[18] Although the protective efficacy is moderate, it greatly benefits at risk populations who are prone to severe illness and increased mortality. Target vaccination of at risk populations requires change in health policy and vaccination strategies. Early recognition of complications may reduce mortality in patients admitted with severe influenza. We recommend influenza vaccination for at-risk populations keeping the pattern of regional seasonality in mind.

Conflicts of interest
There are no conflicts of interest.

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