Predictors of mortality in hospitalized patients with influenza: a five-year experience from a tertiary care centre in Pakistan

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Abstract

Influenza outbreaks are associated with significant morbidity. Our aim was to determine the factors associated with increased mortality in hospitalized patients admitted with diagnosis of influenza, at a tertiary care center in Pakistan. This study included all adult patients with an influenza infection, confirmed by real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) at Aga Khan University Hospital Pakistan. In our study, 112 patients with laboratory-confirmed influenza virus infection were admitted at our hospital from the 1st of January 2013 to the 31st of December 2018. Eighty-nine patients (79.46%) were managed in ward or special care units and 23 patients (20.5%) received treatment in intensive care unit (ICU). The overall mortality in our study was 15/112 (13.4%) with the mortality rate of ICU patients being 47.8% while the mortality rate of patients treated in special care units and wards was only 4.5%. The mean age of patients with influenza infection was 58.1 years (±16.6). Influenza virus type A was found in 87 patients (77.6%), while influenza type B was present in only 25 (22.4%) patients. Out of the 15 non-survivors, 14 had influenza A. Only 17 patients (15.2%) were found to have positive culture of respiratory specimen, out of which 3 were non-survivors and 14 were survivors. Our analysis identified septic shock (odds ratio 45.24; 95%, confidence interval 6.20-330; p<0.001), renal failure (odds ratio 10.88; 95%, confidence interval 1.61-73.52; p=0.01) and ICU stay (odds ratio 17.22; 95%, confidence interval 2.68-110.5; p=0.003) as independent risk factors associated with in-hospital mortality.

Introduction

Influenza, commonly known as flu is an infection caused by influenza virus which is an RNA virus belonging to *Orthomyxoviridae* family [1]. Most of the epidemic of influenza is usually caused by two types of viruses, influenza A and influenza B. Influenza A is further subcategorized into subtypes *e.g.*, influenza A (H1N1) viruses, influenza A (H3N2) viruses based on characteristics of two surface antigens, hemagglutinin (HA) and neuraminidase (NA) [2]. The spectrum of disease from influenza virus ranges from mild flu like illness to acute respiratory distress syndrome (ARDS). Annual epidemics caused by influenza virus are not only a major burden to health care resources, but also associated with high mortality rates [3]. Globally, 3-5 million cases of influenza are reported per annum and the estimated global mortality rate is between 291,243-645,832 per year [4]. During 2017-2018 influenza season the overall influenza related mortality in Europe was estimated to be 25.4 (95% CI 25.0-25.8) per 100,000 population [5].

The burden of disease in Asia is much higher than Europe. Eleven thousand seven hundred thirty-four (11,734) laboratory-confirmed influenza cases were reported in 19 Asian countries between 2010-2017 [6]. In 2015, about more than 30,000 cases and 1731 deaths were reported in India alone [7]. In a laboratory-based influenza surveillance study conducted between 2007 and 2017 a total of 3475 influenza cases were detected in Pakistan. In 2017, influenza related death from Pakistan was reported to be 2.0 per 100,000 [8,9]. Despite the annual epidemics of influenza in Pakistan there have been very few studies done on the disease from our country. To be better prepared to handle influenza epidemics and to decrease the mortality rates associated with the disease, it is of paramount importance to know the predictors of mortality of influenza. Respiratory failure is the major cause of mortality in patient with influenza infection [10]. A study from India,

during influenza outbreak of 2015 showed that the requirement of intubation was the only significant predictor of mortality related to the disease [11]. In a meta-analysis, which included 600,000 patients, risk factors for influenza associated mortality were age, atrial fibrillation and pneumonia [12].

To our knowledge, there is no published five-years study from Pakistan on predictors of influenza related mortality. The purpose of this study is to identify factors associated with mortality in hospitalized influenza over a period of five years at tertiary care hospital in Pakistan.

Methodology

We conducted a retrospective cross-sectional study from January 13-December 18, at Aga Khan University Hospital in Pakistan which is a 750 bedded JCIA accredited tertiary care hospital. We included patients aged 18 and above, of both sexes, who had symptoms of influenza like illness (temperature of 37.8°C or higher along with cough or sore throat) confirmed by Real-time Reverse-Transcriptase Polymerase Chain-reaction (RT-PCR). Nasal swabs were taken under aseptic precautions of all patients admitted with influenza like illness.

Clinical data was collected from review of patient's daily records. Radiological and laboratory data were obtained from electronic records. Data was collected regarding baseline demographics, symptoms at time of admission, oseltamivir prescription, antibiotics, any positive cultures (blood, sputum, and urine), hospital and Intensive Care Unit (ICU) length of stay. All the interventions undertaken like invasive and non-invasive ventilation, renal replacement therapy, use of vasopressors, and cases of septic shock were recorded. Data was also obtained for the oxygen requirements, development of ARDS and use of steroids. Data regarding development of complications and clinical outcome at discharge was also collected. Ethical review committee of Aga Khan Hospital had approved the study.

Statistical analysis

A descriptive analysis was done for demographic and clinical features. The results were presented as mean ± SD for quantitative variables and numbers (percentage) for qualitative variables. Differences in proportions, between survivors and non-survivors, were assessed by using the Chi-square test or Fisher exact test where appropriate. To assess univariate associations between the outcomes and potential predictors, odds ratios (ORs) and their 95% confidence intervals (CIs) were computed by logistic regression analysis. All p-values were two sided and considered as statistically significant if <0.05. All significant factors on univariate analysis were considered for inclusion in the multivariable logistic model.

All analyses were conducted by using the SPSS software, release 16.0.

Results

In our study, 112 patients with laboratory confirmed influenza virus infection were admitted at our hospital from 1st January 2013 to 31st December 2018. Eighty-nine patients (79.46%) were man-

aged in ward or special care units and 23 patients (20.5%) received treatment in ICU. Although the overall mortality in our study was 13.4%, the mortality rate of patients admitted in ICU with influenza was 47.8%. The mean age of patients with influenza infection was 58.1 years (±16.6). The majority of patients (42% of the total number) were between 60 and 75 years of age but the 40-60 years age group was found to have the highest mortality rate (23.33%). Even though 62.5% (70/112) of all patients were female, male patients had higher mortality (19.02%v/s 10%). Fourteen patients were pregnant and all but one of them survived.

A total of 72 out of 112 patients (64.2%) had at least one co morbid illness. Hypertension (n=54, 48.2%) and Diabetes (n=51, 45.5 %) were two most common comorbid conditions in our study population. Other co-morbid observed were, chronic lung diseases (n=32, 28.6%), heart disease (n=18, 16.1%) and renal impairment (n=12, 10.71%), while neurological diseases were present in only 4 patients (3.5%) (Figure 1). Among all co-morbid conditions, heart diseases were the only one which were more prevalent in non-survivors (4/15, 26.7%) compared to survivors (14/89, 14.4%; the results though were not statistically significant). The time between onset of symptoms and hospital admission ranged from 1-25 days, with a median of 5 days. It was 5.1±2.7 days in survivors and 7±5.2 days in non-survivors. Fever (93%) and cough (90%) were the most common symptoms, followed by shortness of breath (61%). The clinical presentations were equally distributed among survivors and non-survivors. Only 20 patients (17.9%) received invasive mechanical ventilation, out of which 10 died. Forty patients received non-invasive ventilation.

Influenza virus type A was found to be the most common strain of influenza in this setting. Eighty-seven patients (77.6%) were positive for influenza type A, while influenza type B was present in only 25 (22.4%) patients. Out of the 15 non-survivors, 14 had influenza A.

Only 17 patients (15.2%) were found to have positive culture of respiratory specimen, out of which 3 were non-survivors and 14 were survivors. *Staphylococcus aureus* was the most common isolated organism (37% of overall culture positive organism), followed by *Aspergillus* spp. (29% of overall culture positive organism). Among non-survivors, two patients had sputum culture positive for *Acinetobacter* and 1 had positive sputum culture for *H. influenzae*. All patients received oseltamivir and the mean duration between the onset of symptoms and the initiation of therapy was
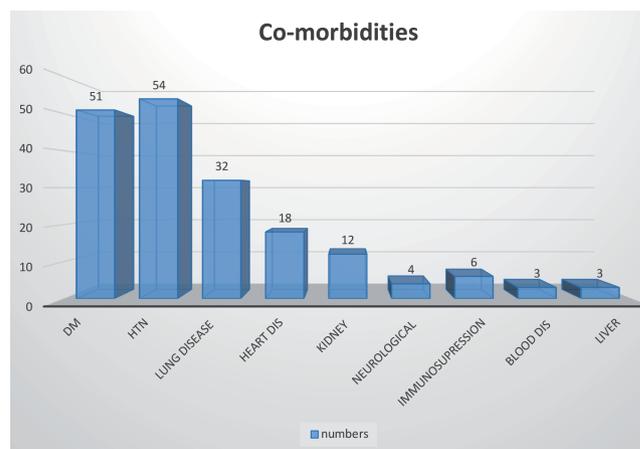

Figure 1. Influenza and comorbid illnesses.

5.3±3.3 days. Delay in the initiation of oseltamivir was associated with increased complications.

The most common influenza related complications that were observed in our study was secondary bacterial pneumonia (65%) followed by acute renal failure (30%). Among survivors, renal failure was present in 24/89 (26.96%) patients and among non-survivors, it was present in 10/15 (66.66%) patients. ARDS was reported in 16/112 (14 %) of the patients, out of which 9 were non-survivors. Seventeen patients (15%, of total influenza patients) were diagnosed with septic shock and it was found to be more prevalent in non-survivors. Eleven out of fifteen (73.33%) non-survivors were found to have septic shock, while amongst survivors, only 6/89 (6.74%) had the complication. Cardiac complications, as a group were present in 27 patients (24.1%) among which 16 patients had acute coronary syndrome; among these patients 12 were survivors and 4 were non-survivors. Eleven patients developed arrhythmias during their hospital stay and only one of them was a non-survivor. Steroids were given to 61 patients (54.5%), out of which, 10 of them were non-survivors (66.66%). The average length of a hospital stay for a non-survivor was 12.23±7.8 days, while that of survivor was 6.53±6.1 days. The length of ICU stay was also longer for non-survivors as compared to survivors (10.23±6.6 days *vs* 7.73±5.8 days).

Univariate and multivariate logistic regression was used to identify predictors of mortality in influenza (Table 1). The length of hospital stays (p=0.01), prolonged duration between the onset of illness and hospital admission (p=0.03), the length of ICU stays (p<0.001), invasive ventilation (p<0.001), ARDS (p=0.001), respiratory failure (p=0.008), septic shock (p<0.001) and acute renal failure (p<0.001) were considered to be significant in the univariate analysis. The multivariate analysis identified septic shock (odds ratio 45.24; 95%. confidence interval 6.20-330; p<0.001), renal failure (odds ratio 10.88; 95%. confidence interval 1.61-73.52; p=0.01) and ICU stay (odds ratio 17.22; 95%. confidence interval 2.68-110.5; p=0.003) as independent risk factors associated with in-hospital mortality (Table 2).

Discussion

This study reported on a series of hospitalized patients with laboratory confirmed influenza infection, from January 2012-December 2018, at a tertiary care hospital. The overall mortality rate in our study was found to be 13.4%, which is comparable to similar studies done globally and also from other countries in region [12]. The ICU stay, along with the presence of septic shock and acute renal failure, were found to be strong predictors of mortality in our hospitalised patients with influenza. In this study, 20.5% of the influenza patients received treatment in the ICU which is found to be higher than the number reported in the literature [13,14]. As our hospital's ICU only admits patients requiring invasive mechanical ventilation and level 3 care, the mortality rates are therefore indicative of severity of the disease, leading to ARDS and the need of mechanical ventilation. The ICU mortality rate in this study was found to be 47.8% which is higher than other ICU mortality rates observed worldwide [14-17]. Our ICU patients were older with average age of 66, with diabetes and hypertension in 2/3rd of them, which might be contributing, to high mortality. This indicates that, severe form of influenza is associated with high mortality, compared to milder form of the disease. Septic shock in our study was found to be a very strong predictor of mortality in influenza patients, being present in 11 out of 15 patients (73.33%)

who did not survive compared to only 6% of survivors. Difficult management of septic shock, in the presence of worsening hypoxemia and ARDS seems to be the likely reason behind these results [18]. This association between septic shock and influenza, though was not directly compared in previous studies done globally but reported in literature [19,20,22].

In our study 10/15 that is 66.66% of non-survivors had renal failure. This appeared to be another strong predictor of influenza mortality, as is also shown, in most of the studies done globally [22-24]. The mortality rate was higher in middle-aged group, in spite of the lower incidence in current study. This is consistent with results of the previous studies, which also showed higher mortality among middle aged group [25,26]. We need further large-scale investigations to identify the true relationship between age group and influenza mortality In our study, females had lower mortality rates compared to males, even though the majority of the influenza patients were females. Although previous literature regarding influenza related complications showed higher mortality in male patients as compared to female, it would be inappropriate to assume association of male gender with increased risk of mortality due to non-availability of sufficient epidemiological data [27,28]. Time from onset of symptoms to hospital admission was found to be associated with increased risk of mortality in our study. Delay in seeking medical care with severe influenza, hence resulting in late initiation of antiviral therapy are associated with poor outcomes [29,30]. This is also signifying a lack of primary and secondary care facilities in our country, where patients are instead brought to tertiary care facilities, with more severe and advance stage of disease. In present study, only 17 patients had positive sputum culture for secondary bacterial or fungal infection. This could be attributed to early initiation of empirical antibiotics at our institute. *Staphylococcus Aureus*, as expected, was the commonest organism isolated, which is in line with all previous reports [31,32]. Similarly, fungal infections were also found to be the second highest reported infection, in our study. Influenzas infection is a risk factor for invasive pulmonary aspergillosis even in immunocompetent patients and can lead to invasive disease [33,34]. The pathogen *Aspergillus fumigatus* was isolated in 5 out of 17 culture positive patients. All patents with *Aspergillus* isolated in respiratory secretion had underlying obstructive airway diseases. This finding can therefore be due to colonization of respiratory tract by the organism, as all patients improved without any antifungal therapy. The high incidence of co-infections might be result of some immune defect in these patients, making them more susceptible to acquire these infections.

Our study has few limitations. It is a single centre study done at a tertiary care university hospital. The number of cases is therefore limited, and they are also more severe in intensity as compared to cases in district hospitals. The findings observed from this university hospital study might not be generalizable to other hospitals. The lack of disease severity scoring system like APACHE or SOFA makes it difficult to truly ascertain the risk of mortality in these patients. Being a retrospective study, we might have some inadequate data. Our sample size was small, and the results observed might change if the study is done with a larger sample size.

Despite the above limitations, our study has shown novel findings about mortality prediction in hospitalized influenza patients during five-years period. The mortality of influenza in our institute was 13% but it reached a significantly high percentage of 47.2% in severe influenza patient requiring mechanical ventilation and ICU admissions.

Table 1. Predictors of mortality in influenza.

	Survivors (n=97)	Died (n=15)	p
Age (years)	57.9±17.6	59.5±17.6	0.72
Gende			0.17
Male	34 (35.1)	8 (53.3)	
Female	63 (64.9)	7 (46.7)	
Body mass index	27.3±9.0	25.0±2.9	0.35
Duration, illness-admission	5.1±2.7	7.0±5.2	0.03*
Length of ICU stay	7.7±5.8	10.2±6.6	0.33*
Length of stay	6.5±6.1	12.2±7.8	0.01*
Comorbidities			
Diabetes mellitus	45 (46.4)	6 (40)	0.64
Hypertension	46 (47.4)	8 (53.3)	0.67
Asthma	12 (12.4)	2 (13.3)	0.91
Chronic lung disease	15 (15.5)	3 (20)	0.65
Heart disease	14 (14.4)	4 (26.7)	0.23
Kidney disease	11 (11.3)	1 (6.7)	0.58
Liver disease	3 (3.1)	0	0.49
Neurology disease	4 (4.1)	0	0.42
Immunosuppression	6 (6.2)	0	0.32
Blood disease	1 (1.0)	2 (13.3)	0.04
Pregnancy	13 (13.4)	1 (6.7)	0.68
Symptoms			
Fever	90 (92.8)	14 (93.3)	0.93
Cough	87 (89.7)	14 (93.3)	0.99
Sputum	38 (39.2)	5 (33.3)	0.66
Myalgia	14 (14.4)	3 (20.0)	0.69
Headache	2 (2.1)	0	0.99
Diarrhoea	7 (7.2)	3 (20)	0.13
Nausea and vomiting	8 (8.2)	1 (6.7)	0.99
Confusion	1 (1.0)	1 (6.7)	0.25
Dyspnoea	58 (59.8)	10 (66.7)	0.61
Hypotension	5 (5.2)	2 (13.3)	0.23
Muscle weakness	6 (6.2)	0	0.99
General weakness	8 (8.2)	0	0.59
Upper respiratory tract infection symptoms	29 (29.9)	4 (26.7)	0.99
Arrhythmia	7 (7.2)	6 (40.0)	0.002
Influenza type			
A	73 (75.3)	14 (93.3)	0.18
B	24 (24.7)	1 (6.7)	
ICU stay	12 (12.4)	11 (73.3)	<0.001
Ventilation	10 (10.3)	10 (66.7)	<0.001
Procalcitonin	4.7±13.5	12.6±13.5	0.04*
Treatment			
Steroid	51 (52.6)	10 (66.7)	0.30
TA/sputum positive	14 (17.7)	3 (27.3)	0.42
Bacterial pneumonia	56 (57.7)	11 (73.3)	0.25
Exacerbation of underlying disease	14 (14.4)	1 (6.7)	0.68
Respiratory failure	19 (19.6)	8 (53.3)	0.008
Acute respiratory distress syndrome	9 (9.3)	7 (46.7)	0.001
Pneumothorax	3 (3.1)	0	0.99
Pulmonary disease	13 (13.4)	1 (6.7)	0.68
Acute coronary syndrome	11 (11.3)	5 (33.3)	0.03
Arrhythmias	7 (7.2)	1 (6.7)	0.99
Sepsis/septic shock	6 (6.2)	11 (73.3)	<0.001
Acute kidney injury	23 (24)	11 (73.3)	<0.001
Cerebrovascular accident	2 (2.1)	0	0.99
Seizure	1 (1.0)	0	0.99

Table 2. Factors predicting poor outcome.

	Odd ratio (95% CI)	p
Sepsis/septic shock		
No	1.0	
Yes	45.24 (6.20-330)	<0.001
Acute kidney injury		
No	1.0	
Yes	10.88 (1.61-73.52)	0.01
ICU stay		
No	1.0	
Yes	17.22 (2.68-110.54)	0.003

Conclusions

Our study has showed that development of concomitant septic shock and renal failure increases the odds of mortality in influenza patients. This finding might help clinicians in more vigilant care of these patients with earlier ICU transfers and probable use of invasive hemodynamic monitoring devices in management of these patients.

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