

Original Research Article

Critical insights in India: factors linked to ICU admission and mortality in influenza cases

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ABSTRACT

Background: Influenza remains a major public health concern globally, causing significant morbidity and mortality. Severe influenza infections are often complicated by pulmonary co-infections and may require intensive care, but data on risk factors contributing to worse outcomes in Indian settings are limited. The objective of the study was to identify risk factors associated with severe influenza outcomes and to assess the prevalence of pulmonary co-infections among hospitalized influenza patients.

Methods: A retrospective cross-sectional study design was opted. Three-years data from 625 laboratory-confirmed influenza patients was analysed. Regression models were used to identify predictors of ICU admission and mortality.

Results: Most patients aged above 18 years and there was higher male population. Influenza A/H1N1 was the most common subtype (66.88%). 39.1% patients required ICU admission and 33.4% had mortality. Influenza A/H1N1 infection, age >18 years, female gender, obesity (BMI >30 kg/m²), respiratory failure, viral pneumonia, renal insufficiency, stroke, diabetes mellitus, and presence of dyspnea or fever were associated with increased odds of ICU admission. Independent risk factors for mortality included Influenza A/H1N1 infection, age >65 years, obesity, hypertension, hepatic disease, respiratory failure, bacterial co-infections, and prior use of immunosuppressants or antibiotics after admission. Pulmonary co-infections were identified in 29.92% (viral) and 24.96% (bacterial) of cases, with *Klebsiella pneumoniae* and RSV being the predominant pathogens.

Conclusions: Severe influenza outcomes were significantly associated with specific host factors, viral subtypes, and secondary infections. Targeted prevention strategies, early intervention, and improved vaccination coverage, especially among high-risk groups, may reduce the burden of severe influenza-related illness and mortality in India.

Keywords: Respiratory tract infections, Epidemiologic factors, Secondary infections, Causality, Retrospective study

INTRODUCTION

Influenza poses a significant global health threat, causing seasonal epidemics and occasional pandemics. It primarily affects respiratory system, also may cause severe pulmonary co-infections or respiratory distress, worsening the severity of the illness, resulting in increased morbidity, hospitalizations or intensive care requirement and mortality.¹⁻⁸ The global burden of

seasonal influenza is 3-5 million cases causing about 2,90,000 to 6,50,000 respiratory deaths annually and the last four influenza pandemics caused nearly 60 million deaths. The highest burden of annual influenza-associated deaths was seen in sub-Saharan Africa, the western Pacific, and southeast Asia.⁹ In low- and middle-income countries like India, about 36% deaths are caused due to seasonal influenza associated respiratory illnesses. The global burden of disease study reported about 8.2 million

severe lower respiratory tract infections (LRTIs) attributable to influenza in 2017 and 145,000 deaths.¹⁰ A recent study at Karnataka revealed 25.58% prevalence and 22.72% mortality associated with influenza.¹¹ Despite widespread efforts to control its spread through vaccination and antiviral treatments, influenza remains a major public health concern, particularly among vulnerable populations such as the elderly, young children, and individuals with underlying health conditions.¹²

Understanding the factors contributing to the severity of influenza infection is crucial for improving patient outcomes and guiding public health interventions in India, where healthcare resources may be limited in certain regions.^{13,14} However, there is limited data in India about the risk factors associated with severe influenza infections resulting in more ICU admissions and deaths.¹¹ Knowing which, helps in controlling the spread of the infection and associated worse outcomes. It is also essential to assess the co-infections of influenza to improve the broader clinical management strategy. Therefore, this study aims to understand the interplay between host factors, viral characteristics, and secondary infections, with the influenza outcomes.

Objectives

The objectives of the study were to identify the risk factors contributing to severity of influenza; to study the rates of pulmonary co-infections among influenza patients and by identifying these factors, the study hopes to inform better-targeted treatment strategies and improve preventive measures for high-risk populations in India.

METHODS

A retrospective cross-sectional study was conducted at 2 tertiary care hospitals after obtaining ethics waiver from the internal institutional review board. (RP/PP/10-2024) Data was collected from all laboratory confirmed influenza patients, who were admitted to the wards and ICUs of the hospitals from 1st August 2021 to 1st August 2024. Cases were identified from the database of the medical records department; following purposive sampling technique. The study excluded patients admitted for the same indication on more than one occasions and those who left against medical advice. All the relevant clinical details of patients were collected from their case sheets and entered into Microsoft Excel spreadsheet.

Comprehensive data was gathered on patient demographics, co-morbidities, use of immunosuppressive medications prior to hospitalization, clinical signs and symptoms at presentation, ICU treatment requirements, development of bacterial, fungal, or viral co-infections within the hospital stay, use of neuraminidase inhibitors (oseltamivir), and the final mortality outcome. BMI was categorised as underweight (<18 kg/m²), normal weight

(18 to 25 kg/m²), overweight (25 to 30 kg/m²) and obese (>30 kg/m²).

Statistical analysis

Statistical analyses were performed using STATA, Version 14.0. Descriptive statistics were summarized for all the study variables based on the data distribution. A Uni-variate logistic regression analysis was performed to identify risk factors for ICU admission and in-hospital mortality in patients admitted. Sequentially, a multivariate logistic regression was used to identify independent risk factors. A p-value of 0.05 was considered for statistical significance.

RESULTS

We analyzed data of 625 influenza patients. Majority of patients were in the age group of 18 and 65 (71.04%), with male predominance. (57.28%) Only five females presented were pregnant. Smoking and alcohol consumption were rare, with 95.36% of patients not smoking or drinking. BMI distribution revealed 43.68% and 13.76% patients as overweight & obese respectively, with 33.28% having normal BMI.

The most prevalent subtypes of influenza among the studied population were Influenza A/H1N1 (66.88%), followed by Influenza A/H3N2 (25.92%) & Influenza B (7.2%). Co-morbidities were remarkable in most patients. About 60.2% presented with pulmonary diseases like respiratory failure (32.96%), viral pneumonia (12.96%), asthma (8.64%), COPD (4%), covid-19 infection or OSAS (<1% each) and 34.4% patients presented with cardio-vascular diseases like hypertension (30.56%), heart failure (2.1%) & MI (1.8%). Other co-morbidities reported include DM (26.4%), renal insufficiency (9.6%), hepatic disease (5.4%), sepsis or MODS (8%), stroke (1.9%), RA (1.1%) and CNS tumor, encephalopathy and hernia in less than 1% influenza patients.

Clinically, fever (80.32%) and dyspnea (48.16%) were the commonest reported symptoms, with 39.2% of patients presenting both. Respiratory illness prognosed and oxygen support was required in 49.92%, non-invasive and invasive ventilation were required in 23.84% and 21.28% patients respectively. During the entire hospital stay, about 29.92% patients had viral co-infections and 24.96% had bacterial co-infections & only 1.1% had fungal infections. The pulmonary coinfections showed a higher distribution of respiratory viral (30.4%) and bacterial (28.16%) pathogens, with fungal infections being less common. (1.44%) Among the bacterial co-infections, *Klebsiella pneumoniae* is the most prevalent (61.54%), followed by *Escherichia coli* (17.95%), and *Pseudomonas* spp (8.33%). Other bacteria, such as *Enterobacter cloacae* and *Acinetobacter baumannii*, are less frequent but still notable. Fungal co-infections are dominated by *Candida albicans* (57.14%) and viral

infections by respiratory syncytial virus (RSV) (77.01%) (Table 1).

Table 1: Distribution of organisms causing pulmonary co-infections in influenza patients.

Organism causing pulmonary co-infection	Frequency	Percentage
Pulmonary bacterial co-infection (n=176)		
<i>Klebsiella pneumonia</i>	96	61.54
<i>Escherichia coli</i>	28	17.95
<i>Pseudomonas spp</i>	13	8.33
<i>Enterobacter cloacae</i>	5	3.21
<i>S. aureus</i>	4	2.56
<i>Acinetobacter baumannii</i>	4	2.56
<i>Streptococcus mitis</i>	3	1.92
<i>Acinetobacter lwoffii</i>	3	1.92
<i>H.influenzae</i>	2	1.28
<i>Methicillin resistant Staphylococcus cohnii</i>	2	1.28
<i>Stenotrophomonas spp</i>	2	1.28
<i>S. heamolyticus</i>	2	1.28
<i>S. pneumoniae</i>	1	0.64
<i>Enterococcus faecium</i>	1	0.64
<i>Citrobacter freundii</i>	1	0.64
<i>Klebsiella oxytoca</i>	1	0.64
<i>Proteus mirabilis</i>	1	0.64
<i>Morganella morganii</i>	1	0.64
<i>Klebsiella aerogenes</i>	1	0.64
<i>Moraxella Catarrhalis</i>	1	0.64
<i>Serratia marcescens</i>	1	0.64
<i>Sphingomonas paucimobilis</i>	1	0.64
<i>MTB</i>	1	0.64
Unknown bacterial pathogen	1	0.64
Pulmonary fungal infection (n=9)		
<i>Candida albicans</i>	4	57.14
<i>Aspergillus niger</i>	2	28.57
<i>Aspergillus fumigatus</i>	1	14.28
<i>Zygomycetes</i>	1	14.28
<i>Aspergillus species</i>	1	14.29
Pulmonary viral infection (n=190)		
RSV	145	77.01
Corona virus	17	9.09
HPIV	7	3.74
CMV	6	3.21
HSV	4	2.14
Human Rhinovirus	4	2.14
Adenovirus	4	2.14
hMPV	3	1.6

MTB- Mycobacterium tuberculosis, RSV- Respiratory Syncytial Virus, HPIV- Human Para-influenza virus, CMV- Cytomegalovirus, HSV- Herpes simplex virus, hMPV- Human metapneumovirus

The analysis of treatment related data revealed that highest proportion of patients (90%) were on oseltamivir, 36.6% patients were on antibiotics with broad spectrum

antibiotics (25.4%). Only 10.4% patients were given immunosuppressants and systemic steroids were given to 40.5% patients of our cohort. Totally, 39.1% influenza patients had severe illness and required ICU care. Patients in ICU had 5.58 higher odds of mortality than those in wards (95% CI: 3.86, 8.05) and mortality was seen in 33.4% admitted influenza patients.

Uni-variate logistic regression analysis of ICU admission with demographic and clinical variables revealed that Influenza A/H1N1, age above 18 years, female gender, alcohol intake, BMI>30, RF, viral pneumonia, renal insufficiency, stroke, DM, presence of clinical symptoms of fever or dyspnea or both, first AB use by the time of hospital admission, use of oseltamivir and viral co-infections were found to be associated with ICU admission among the influenza patients. Influenza A/H1N1& RF were associated with increased odds of severe outcomes which dramatically increased in the adjusted model. Additionally, older age (>65 years) was significantly associated with poor outcomes. The presence of dyspnea and both together were also strongly linked to adverse outcomes. Other factors such as smoking, alcohol consumption, and co-infections (specifically viral) showed varying degrees of association, with alcohol consumption showing an increased risk in the adjusted model. Factors like pregnancy, BMI, and certain co-morbidities (such as asthma and viral pneumonia) either show no significant effect or only weak associations (Table 2). Factors like fungal or bacterial coinfections, use of immune-suppressants, systemic steroids, CNS tumors, CVDs like HTN, MI, HF and hepatic disease, OSAS, COPD, had no association with ICU admission among the influenza patients.

The univariate logistic regression analysis revealed that Influenza A/H1N1, age above 18 years, pregnancy, smoking and alcohol consumption, underweight or obesity, co-morbidities like asthma, RF, viral pneumonia, HTN, hepatic disease, renal insufficiency, stroke, symptoms of fever & dyspnea or both, use of antibiotics after admission, systemic steroids by the time of admission and bacterial or viral co-infections as risk factors of mortality among influenza patients. Influenza A/H1N1 showed strong association with increased odds of severe outcomes in both unadjusted and adjusted. Smoking was also a significant risk factor, with higher odds in both models. Patients with respiratory failure were at significantly higher risk. Clinical symptoms such as dyspnea or both fever & dyspnea showed a strong association with reduced odds in the adjusted model. After adjusting the confounding factors, the multi-variate analysis disclosed Influenza A/H1N1, age>65 years, obesity, co-morbidities like HTN, hepatic disease, RF, clinical symptoms of fever, dyspnea or both; bacterial co-infections, use of immunosuppressants before & antibiotic use after admission as the independent risk factors (Table 3).

Table 2: Odds ratios for patient characteristics, co-morbidities, clinical symptoms, and co-infections in influenza-related outcomes: A. ICU admission.

Patient characteristic	UOR	95% CI	P value	AOR	95% CI	P value
Type of influenza						
Influenza A/H1	2.29	1.35,3.86	0.002*	41.73	8.04,216.55	0.000*
Age category (years)						
Less than 18	Reference					
18 to 65	9.34	3.68,23.67	0.000*	2.27	0.29,17.94	0.436
More than 65	10	3.74,26.74	0.000*	9.51	1.10,81.82	0.04*
Gender						
Male	Reference					
Female	1.71	1.23,2.38	0.001*	1.65	0.63,4.35	0.309
Pregnancy						
Yes	0.76	0.64,0.91	0.003*	1.19	0.58,2.48	0.63
No	Reference					
Smoking						
Yes	3.13	1.43,6.86	0.004*	0.3	0.02,4.04	0.365
No	Reference					
Alcohol						
Yes	2.31	1.08,4.91	0.031*	14.94	1.89,187.85	0.036*
No	Reference					
BMI						
Normal	Reference					
Obesity	0.35	0.19,0.63	0.000*	3.15	0.65,15.24	0.154
Co-morbidities						
Pulmonary disease (any)						
Respiratory Failure	151.49	75.01,305.97	0.000*	3976.83	749.61,21097.89	0.000*
Viral pneumonia	1.18	1.01,1.38	0.033*	0.81	0.46,1.43	0.469
Renal insufficiency	5.02	2.76,9.12	0.000*	4.61	0.87,24.51	0.073
Neurological disease (any)						
Stroke	8.09	1.76,37.28	0.007*	3.51	0.08,149.61	0.512
Diabetes mellitus	1.87	1.31,2.66	0.001*	1.59	0.48,5.21	0.444
Clinical symptoms						
Fever	0.61	0.41,0.91	0.014*	1.76	0.34,9.19	0.5
Dyspnea	7.66	5.30,11.06	0.000*	53.58	6.01,478.37	0.000*
Both	3.54	2.52,4.97	0.000*	0.01	0.0007,0.15	0.001*
Use of oseltamivir on admission						
Yes	10.56	3.78,29.49	0.000*	0.11	0.03,0.29	0.000*
No	Reference					
First antibiotic administration						
Before admission	Reference					
At the time of admission	0.47	0.33,0.65	0.000*	0.08	0.03,2.75	0.000*
Pulmonary viral co-infections						
Yes	1.82	1.29,2.58	0.001*	1.49	0.53,4.23	0.444
No	Reference					

*Statistically significant at $p < 0.05$. UOR: Unadjusted Odds Ratio, representing the crude association between risk factors and MM without controlling for confounding variables; AOR: Adjusted Odds Ratio, representing the association after accounting for potential confounders.

Table 3: Odds ratios for patient characteristics, co-morbidities, clinical symptoms, and co-infections in influenza-related severe outcomes: B. mortality.

Patient characteristic	Unadj. OR	95% CI	P value	Adj OR	95% CI	P value
Type of influenza						
Influenza A/H1	2.29	1.35,3.86	0.002*	7.85	2.86,21.57	0.000*
Age category						
Less than 18	Reference					
18 to 65 years	9.34	3.68,23.67	0.000*	1.25	0.36,4.33	0.725
More than 65 years	10	3.74,26.74	0.000*	0.56	0.12,2.55	0.033*
Gender						
Male	Reference					
Female	1.71	1.23,2.38	0.001*	0.99	0.52,1.89	0.979
Pregnancy						
Yes	0.76	0.64,0.91	0.003*	0.75	0.48,1.18	0.213
No	Reference					
Smoking						
Yes	3.13	1.43,6.86	0.004*	7.64	1.07,54.39	0.042*
No	Reference					
Alcohol						
Yes	2.31	1.08,4.91	0.031*	2.34	0.37,14.62	0.029*
No	Reference					
BMI						
Normal	Reference					
Obesity	0.35	0.19,0.63	0.000*	5.88	2.02,17.13	0.001*
Co-morbidities						
Pulmonary disease (any)						
Respiratory Failure	151.49	75.01,305.97	0.000*	9.76	4.43,21.5	0.000*
Viral pneumonia	1.18	1.01,1.38	0.033*	0.96	0.66,1.39	0.84
Cardio-vascular disease (any)						
Hypertension	0.63	0.43,0.92	0.018*	0.35	0.14,0.85	0.020*
Renal insufficiency	5.02	2.76,9.12	0.000*	1.82	0.62,5.35	0.278
Neurological disease (any)						
Stroke	8.09	1.76,37.28	0.007*	17.06	0.56,518.26	0.103
Hepatic disease	2.51	1.23,5.14	0.012*	5.82	1.58,21.41	0.008*
Diabetes mellitus	1.87	1.31,2.66	0.001*	0.76	0.34,1.69	0.496
Clinical symptoms						
Fever	0.61	0.41,0.91	0.014*	0.22	0.09,0.58	0.002*
Dyspnea	7.66	5.30,11.06	0.000*	4.78	1.32,17.38	0.017*
Both	3.54	2.52,4.97	0.000*	1.19	0.27,5.23	0.000*
Use of oseltamivir						
Yes	0.32	0.19,0.55	0.000*	0.11	0.04,0.29	0.000*
No	Reference					
First antibiotic admission						
Before admission	Reference					
After admission	0.47	0.33,0.65	0.000*	0.19	0.09,0.41	0.000*
Use of systemic steroids	0.41	0.28,0.59	0.000*	0.35	0.18,0.67	0.002*
Pulmonary viral co-infections						
Yes	1.82	1.29,2.58	0.001*	1.86	0.88,3.94	0.104
No	Reference					
Pulmonary bacterial co-infections						
Yes	0.43	0.27,0.69	0.000*	0.06	0.03,0.15	0.000*
No	Reference					

*Statistically significant at $p < 0.05$; UOR: Unadjusted Odds Ratio, representing the crude association between risk factors and MM without controlling for confounding variables; AOR: Adjusted Odds Ratio, representing the association after accounting for potential confounders.

DISCUSSION

Our study demonstrated high rates of influenza infection among adults above 65 years and noted more severe cases in female patients, that aligned with studies from other regions.¹⁵⁻²⁰ We found obesity as a significant risk factor of ICU mortality as it impairs immune function and respiratory mechanics. Additionally, it is often associated with other co-morbidities like diabetes mellitus, hypertension and heart diseases that aligned with previous studies.^{21,22}

Several observational studies suggest that infection with Influenza A have increased rates of chronic pulmonary conditions & co-morbidities leading to higher hospitalizations & mortality.²³ The dominant subtypes of influenza viruses were H1N1 and H3N2, similar to other studies, that showed higher rates of poor clinical outcomes.^{3,5,17,23-26}

Presence of co-morbidities, especially respiratory & cardio-vascular diseases increased the risk of ICU admissions and mortality.^{3,16,21-23,27} Literature suggests pregnancy as the significant predictor of ICU admissions and associated mortality among severe influenza infections.²² However, our study reported only 5 pregnant women. Fever and dyspnea were the common self-reported symptoms in our study whereas study in Norway reported cough and fever.²⁰

Pulmonary co-infections with pathogens like bacteria, viruses or fungi were most commonly seen in patients admitted to the ICU. Influenza infection increases the risk of susceptibility to other infections.²⁸ An observational study conducted at China reported 14.4% of secondary bacterial pneumonia cases while our study reported 28.16% cases.³⁰ A study from U.S reported 22.5% bacterial co-infection & 4.5% viral co-infections.²⁹

The most common organisms causing co-infections were RSV, *Klebsiella pneumoniae*, *E coli*, corona virus & *Pseudomonas spp.* in our study. While studies conducted in Netherlands & other parts on India reported predominance of pulmonary bacterial co-infection with *Streptococcus pneumonia*, *Staphylococcus aureus* & *Acinetobacter baumannii*.^{3,25,29}

The ICU admission rate in our study cohort was 39.1%, while that in Brazil, Mexico & USA were 3.3%, 1.8%, 14-19% respectively.¹⁶ The mortality rate of our study was 33.4% while that of Brazil, Mexico, USA, Spain, Costa Rica & Netherlands were 4.6%, 6.9%, <4.7%, 4.8%, 12% & 9% respectively.¹⁶ 66.2% was our ICU mortality; which differed from a Tunisian study that reported ICU mortality of 31.7% and Netherlands study with 38%.^{3,15} A study conducted in Vellore, India reported 23.8% ICU admissions & 20% required MV, which are almost similar to our results.³⁰ Independent risk factors of ICU admission in our study were Influenza A/H1N1, age above 18 years, female gender, alcohol intake, BMI>30,

RF, viral pneumonia, renal insufficiency, stroke, DM, presence of clinical symptoms of fever or dyspnea or both, first AB use by the time of hospital admission, use of oseltamivir and viral co-infections. While factors in a study at Netherlands were Influenza A, dyspnea, a history of MI & OSAS/CSAS.³

We found Influenza A/H1N1, age>65 years, obesity, co-morbidities like HTN, hepatic disease, RF, clinical symptoms of fever, dyspnea or both; bacterial co-infections, use of immunosuppressants before & antibiotic use after admission as the independent risk factors of mortality. Studies from Japan and Saudi Arabia identified female sex, immunocompromised states pneumonia severity index & ischemic heart disease as the risk factors of mortality.²⁵ Age >65 years was found to be the most common predictor of ICU admissions & mortality in hospitalized influenza patients.^{3,15-17} Bacterial co-infections were found to be associated with mortality in Saudi Arabia.²⁴ Viral co-infections were found to be significant predictors of mortality among hospitalized influenza patients.²⁹ Also, an increasing trend for ICU mortality was observed for the systemic use of steroids and non-steroid immunosuppressive drugs before hospitalization in other studies.³ Early treatment with oseltamivir (within two days of symptom onset), before or after hospital admission is found to reduce mortality rates among influenza patients.^{19,31}

Our study found a considerably higher rates of poor clinical outcomes associated with influenza infection and could identify the potential risk factors. Vaccination is the most effective way to prevent influenza and severe influenza-related outcomes.³²⁻³⁴ However, in India, the vaccination coverage is only 2% due to lack of resources and awareness.³⁵ Several capacity building trainings and massive campaigns on the use of influenza vaccines, especially in older adults helps reduce its burden in the country.

Despite of the several strengths our study displays, such as multi-centric design, large sample size and detailed clinical data inclusion, there are certain limitations. The study did not include data on outpatient cases due to difficulties in follow-up, and was unable to assess vaccination status, viral load, or strain characterization because this information was not available in the medical records.

Future researchers may plan for large, prospective, multi-centric studies to expand the evidence on disease severity that would influence a significant policy change to prevent influenza-associated outbreaks & poor outcomes.

CONCLUSION

We identified several risk factors of influenza patients prognosed to severe infection, leading to higher ICU admission rates and mortality. There is a need to

strengthen policies to improve immunization coverage to prevent or reduce the effect of influenza severity.

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