ORIGINAL ARTICLE

Epidemiology and Outcomes of HIN1 Pneumonia in ICU

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Abstract

Introduction: Pandemic influenza H1N1/09 emerged for the first time in April 2009 and has spread widely across India since then. The number of cases have increased over time with the increasing need for respiratory support, causing significant morbidity and mortality. We evaluated the clinical course and outcomes of patients infected with Influenza A (H1N1) admitted to three multidisciplinary intensive care units (ICU) in Chennai.

Materials and methods: We performed a combined retrospective and prospective observational study of all patients admitted with H1N1 pneumonia at three multidisciplinary ICUs in Chennai from October 1, 2018, to January 31, 2019. Data including demographics, risk factors, and clinical courses were recorded. Outcome data including mortality was tracked up to 28 days.

Results: A total of 167 patients were admitted during the study period of which 154 were included in this analysis. The mean age of presentation was 58.2 ± 15.6 years and 59.1% of them were males. The mean acute physiology and chronic health evaluation (APACHE) IV and sequential organ failure assessment (SOFA) scores were 62.8 ± 23.2 and 5.8 ± 3.9 respectively. Oxygen delivery devices were required in 25.3% for a mean duration of 26.5 ± 5.7 hours. Non-invasive ventilation or high-flow nasal cannula (HFNC) was needed in 33.1% of patients for 59.9 ± 64.5 hours. The proportion of patients requiring mechanical ventilation was 41.6%. Rescue measures in the form of proning, use of inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO) were initiated for refractory hypoxemia in 26.6%, 14.1%, and 6.3% respectively. The mean duration of ventilator support was 8.5 ± 8 days. Tracheostomy was required in 20.3% of patients and 7.8% were ventilator dependent at 28 days. The mean ICU and Hospital length of stay were 8.3 ± 10.3 and 12.2 ± 14.1 days respectively and overall 28-day mortality was 20.1%.

Conclusion: A significant proportion of H1N1 patients admitted to the ICU required high-level respiratory support including non-invasive ventilation (NIV), HFNC, or invasive ventilation. Deployment of rescue therapies was common and the overall mortality rate was similar to those reported from Western countries.

Keywords: H1N1 pandemic influenza, Pandemic, Reverse transcription polymerase chain reaction.

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Introduction

The H1N1 Influenza virus was first reported from Mexico and the United States of America in April 2009 and spread worldwide within a very short period resulting in a global pandemic. A total of 74 countries and territories were involved when WHO declared a pandemic in June 2009.

India reported 45,101 cases and 2,679 deaths by the end of October 2010. In 2015, with a mutant strain of H1N1, almost 10,000 cases and 774 deaths were recorded.[1] However, during 2017 the virus spread rapidly throughout the country which showed wide variations in terms of period (two peaks in a year), place (North-Eastern states reporting cases for the first time), and person (predominantly among children).[2] In Gujarat, mortality was highest in the age group of 15–60 years (67.9%), followed by those >60 years of age (22.9%), and only 25 deaths (5.8%) in children below 5 years of age.[3] The majority who died, had one or more comorbidities predominantly being cardiovascular (35%) followed by diabetes (28%) lung diseases (12%), and renal diseases (9%).[4]

In 2017, the Michigan variant was predominant, which replaced the California subtype seen in 2016. Since then, influenza infections are being reported annually and especially after 2017, there were typical epidemiological characteristics different from the previous years in terms of periodicity where two peaks were noted between January–March and July–September. In 2018, despite a sharp increase in the number of cases, the number of deaths halved but again in 2019, mortality doubled.[3,5]

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The intermittent rains in Tamil Nadu have caused a rise and fall in the morbidity pattern of H1N1 cases every alternate year since 2010.[6] We carried out a combined retrospective and prospective analysis of the medical records, in order to study the clinico-epidemiological characteristics of H1N1 epidemics in hospitalized patients from the city of Chennai, Tamil Nadu.

Materials and Methods

This was a combined retrospective and prospective observational study in which the demographic characteristics, treatment, and outcomes for critically ill patients with laboratory-confirmed H1N1 infection admitted in three different ICUs of Apollo Hospitals, Chennai during the period from September 2018 to January 2019 were collected.

All adult patients (defined as 16 years or more in age) with H1N1 were diagnosed by reverse transcriptase polymerase chain reaction (RT-PCR) of respiratory samples and requiring ICU admission were identified by screening laboratory records. As this was a notifiable disease to the local authority, during our study, the notification registry of our hospital was also reviewed, and ensured that all notified cases were captured.

All patients who got admitted to the ICU fulfilled the standard admission criteria. All patient management decisions were made by the physician providing care in the ICU. The following information was recorded: Demographics, comorbidities, time from onset of illness to diagnosis and ICU admission, and the time to first antiviral dose administration. Relevant history including presence of sick contacts and travel history, previous history of specific H1N1 immunization, and baseline vitals on admission in ICU including Glasgow Coma Scale (GCS), temperature, heart rate, mean arterial pressure, and respiratory rate were recorded.

Acute physiology and chronic health evaluation (APACHE) IV and sequential organ failure assessment (SOFA) score were used within 24 hours of ICU admission for illness severity. Comorbidities were recorded and scored according to the Charlson Comorbidity Index (CCI). For all admitted patients with suspicion or confirmed H1N1 infection, standard infection control measures were practiced which included strict hand hygiene, isolation of patients, and usage of personal protective equipment (PPE).

Treatment details include antiviral drugs (Oseltamivir), supportive measures for respiratory failure either through O_2 delivery devices, non-invasive ventilation (NIV), intubation, and mechanical ventilation in severe cases (rescue therapies in refractory cases as required), the proportion of patients who had the presence of shock on admission or during the stay, the need for renal replacement therapy (RRT), development of secondary infections and follow up cultures were also recorded.

In all the enrolled patients follow-up was done up to 28 days. Outcome variables included duration of mechanical ventilation, ICU and hospital length of stay, and ICU and hospital mortality at 28 days of onset of illness.

Statistical Analysis

Continuous variables were expressed by mean ± standard deviation (SD) and discrete variables as counts (percentage). For the epidemiological/clinical characteristics of the patients, differences among groups were assessed using the Chi-square test and Fisher's exact test for categorical variables and the Student's *t*-test or Mann-Whitney *U* test for continuous variables. A *p*-value of 0.05 or less was considered statistically significant.

Results

A total of 167 patients were admitted of whom 13 lost follow-up at 28 days from admission due to various reasons. The baseline characteristics of the patients in the study are represented in Table 1.

Table 1: Baseline characteristics of all patients

Variables	*N = 154*
Age (years)	58.2 ± 15.6
Male : Female (%)	59 : 41
History of travel, *n* (%)	49 (31.8%)
History of exposure to sick contacts, *n* (%)	34 (22.1%)
Charlson Comorbidity Index	4.7 ± 3.0
APACHE IV score	62.8 ± 23.2
SOFA (at ICU admission)	5.8 ± 4.0
Clinical frailty scale	3.9 ± 1.9
Days from symptoms onset to ICU admission	4.0 ± 2.1
Days from symptoms onset to first antiviral dose	4.6 ± 2.2

Baseline Characteristics

The average age of patients was 58.2 ± 15.6 years with 44% of them being greater than 60 years of age. Of all the patients 59% were males. The proportion of patients who reported exposure to sick contacts was 22.1 and 31.9% had a recent travel history. The mean APACHE IV and SOFA scores were 62.8 ± 23.2 and 5.8 ± 3.9 respectively. The mean Charlson CCI was 4.7 ± 3 and the mean clinical frailty score was 3.9 ± 1.9 respectively. About 31 patients (20.1%) were obese with body mass index (BMI) >30. Among our study patients, 8 were diagnosed previously or in the current admission to have COPD, 3 were pregnant, 2 had solid organ malignancy and 1 patient was a post-renal transplant recipient on immunosuppressive therapy.

General Medical Management

The mean time from symptoms onset to hospital admission was 4 ± 2.1 days and for initiation of treatment was 4.6 ± 2.2 days. None of the patients were immunized with influenza vaccine and all patients received Oseltamivir and empirical antibiotic therapy. Most frequent regimens were beta-lactams in combination with Macrolides in 59 (38.3%), beta-lactams with Tetracyclines in 48 (31.1%), and carbapenems in 31 (20.1%) of the patients.

Respiratory Support

In our study, 25.3% (*n* = 39) required only oxygen delivery devices at presentation for a mean duration of 26.5 ± 5.7 hours. The respiratory status of eight patients deteriorated requiring NIV/HFNC for mild to moderate hypoxemia and 4 patients subsequently required intubation and initiation of mechanical ventilation support (Fig. 1). Among the 4 intubated patients, 3 survived and one patient succumbed to septic shock and multiorgan dysfunction syndrome (MODS). The mean APACHE IV and SOFA in this subgroup were 49.5 ± 15.5 and 3.3 ± 2.3 respectively. The ICU and hospital length of stay was 2.9 ± 2.2 and 9.6 ± 18.7 days respectively.

Non-invasive ventilation or high flow nasal cannula (HFNC) was required in 33.1% (*n* = 51) at presentation for a mean duration of 59.9 ± 64.5 hours. Of the 51 patients treated with NIV, 11 of them were subsequently intubated due to worsening clinical status while forty of the remaining patients were continued on NIV support and all forty survived. The mean APACHE IV and SOFA in this subgroup are 52.2 ± 18.4 and 4.4 ± 2.2 respectively. The mean ICU and hospital length of stay in this subset of patients is 7.4 ± 7.7 and 11.3 ± 8.7 days respectively.

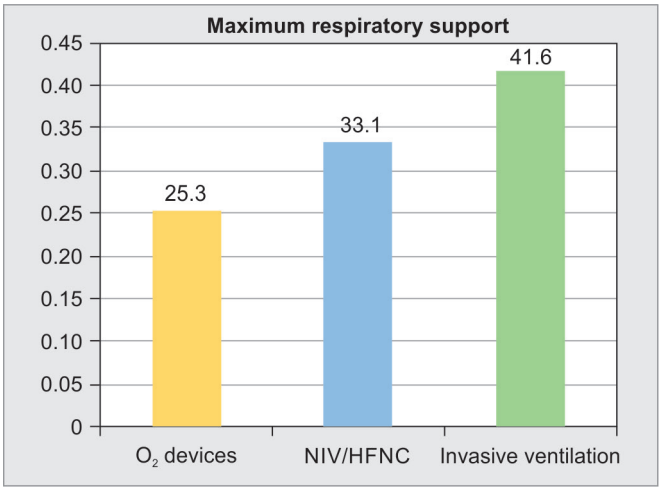

Fig. 1: Proportion of patients in each category of respiratory support

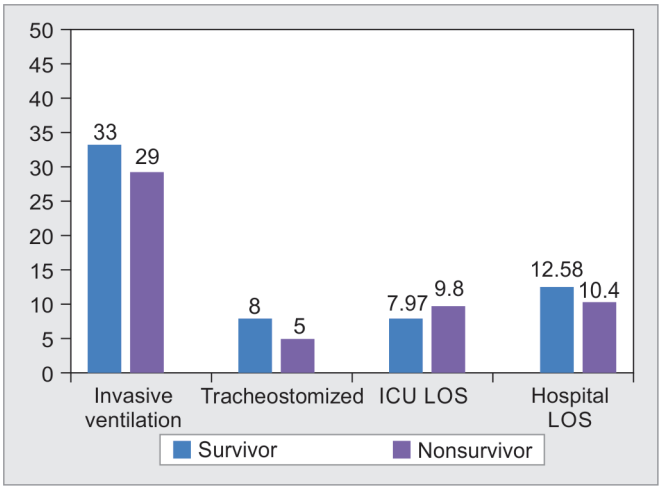

Fig. 3: Intensive care unit parameters

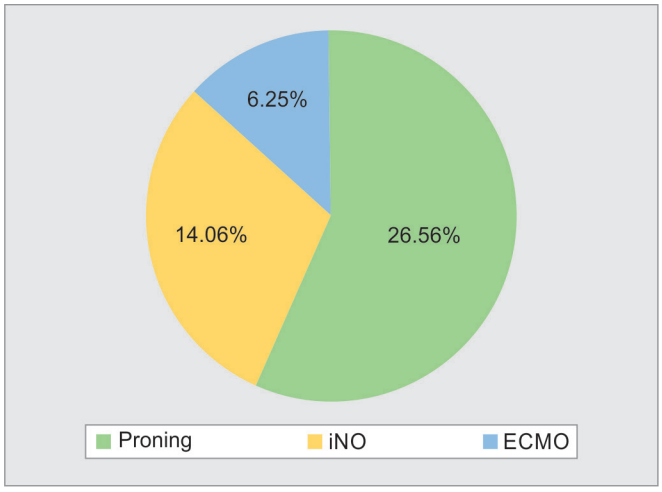

Fig. 2: Rescue measures

Mechanical ventilation was required in 41.6% (n = 64) at presentation for a mean duration of 8.5 ± 8 days. The mean APACHE IV and SOFA in this subgroup are 79 ± 21.2 and 8.5 ± 4 respectively. Of these patients, 75% were ventilated using volume-assisted mode. The highest plateau and driving pressures are 24.35 ± 6.33 cm H_2O and 15.51 ± 4.57 cm H_2O respectively.

Rescue measures for refractory hypoxemia in the form of proning inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO) were initiated in 26.6% (n = 17), 14.1% (n = 9), and 6.3% (n = 4) respectively among the ventilated patients (Fig. 2). Inhaled nitric oxide was used in a total of 9 patients of whom 2 survived. A total of 21 patients required prone ventilation, out of which 4 had contraindications for proning and hence were initiated on ECMO. Among the 17 patients prone, only 2 survived (Survival 11.8%). The remaining 15 patients did not respond to proning and were offered ECMO therapy. However, ECMO could be initiated in a total of four patients only due to lack of family consent, financial constraints, and/or reasons of futility.

Tracheostomy was performed in 20.3% (n = 13) ventilated patients after a mean duration of 9.46 ± 2.1 days and 7.8% were ventilator dependent at 28 days of follow-up. Eight (61.5%) of the tracheostomised patients were still alive at 28 days. The mean ICU and Hospital length of stay was 8.3 ± 10.3 and 12.2 ± 14.1 days respectively (Fig. 3).

Organ Dysfunction

Acute kidney injury (AKI) was present on admission in 17 patients. Overall, 49 (29.3%) patients had AKI at some stage of their illness. About 25 patients with AKI required RRT, and 11 patients among them survived. All survivors were no longer requiring RRT at the time of discharge from the hospital. Circulatory dysfunction requiring vasopressors was noted in 47 (30.5%) patients during their course of illness and 28 (59.5%) of the patients died.

Secondary Infections

Hospital-acquired infections (HAI) complicated the ICU course in 22 patients of whom 16 developed ventilator-associated pneumonia (VAP), 4 developing bloodstream infections, and 2 developed urinary tract infections.

Outcomes

The 28-day mortality in our study was 20.1% and the mean time to death after ICU admission was 9 ± 8.7 days. The mortality rate among patients aged less than 50 years was 25.8% and in those above 50 years was 74.1%. Among the non-survivors, 29 patients required mechanical ventilation which accounted for about 45.3% mortality in the ventilated group. Non-survivors had a statistically significant higher baseline Charlson Comorbidity Index, APACHE, and SOFA score compared to those who survived (p-value 0.001). The P/F ratio at admission in non-survivors was significantly very low than in those who survived (p-value 0.001). There was also a higher rate of septic shock in the non-survivors compared to survivors (15.4% vs 87%, p = 0.003) (Table 2).

Discussion

The Centers for Disease Control and Prevention (CDC) reported two patients getting infected with influenza A (H1N1) virus in the United States in 2009. Since then there have been several studies across the world describing the clinical and epidemiological characteristics of H1N1 in critically ill patients. While the illness was self-limited in most affected patients and was in the younger age group (30–40 years), there were many who had rapid progression to severe acute respiratory distress syndrome (ARDS). Mexico city

Table 2: Comparison of baseline characteristics for hospital survivors and non-survivors in patients with H1N1 influenza pneumonia

	Survivors (N = 123)	*Non-survivors (N = 31)*	*p-value*
Age, mean (SD)	58 ± 15.8	58.8 ± 14.9	0.751
Charlson Comorbidity index (CCI), mean (SD)	4.4 ± 2.9	5.9 ± 3.3	0.014
APACHE IV, mean (SD)	57.3 ± 20.4	84.3 ± 20	0.001
SOFA, mean (SD)	4.6 ± 3.0	10.6 ± 3.5	0.001
Clinical frailty scale (CFS), mean (SD)	3.9 ± 1.8	4.2 ± 2	0.414
Days from symptoms onset to ICU admission, mean (SD)	4.4 ± 2.2	5.2 ± 2.1	0.154
Tidal volume (mL), mean (SD)	366.6 ± 45.3	356.6 ± 34.5	0.318
Driving pressure, mean (SD)	14.6 ± 4.5	16.6 ± 4.4	0.126
P/F ratio, mean (SD)	126.1 ± 61	94.1 ± 54	0.001
Septic shock, *n* (%)	19 (15.4%)	27 (87%)	0.003
AKI, *n* (%)	11 (8.9%)	14 (45.1%)	0.451
Tracheostomized, *n* (%)	8	5	0.676
ICU LOS, mean (SD)	7.9 ± 10.6	9.8 ± 9.0	0.378
Hospital LOS, mean (SD)	12.6 ± 15	10.4 ± 9.1	0.451

hospitals reported the highest mortality as they were unprepared for this epidemic.[7]

Data from India has been sparse. In a study by Dhawale et al. in 2015, the mean age of presentation was <50 years, whereas in our study, it was more than 50 years. The differences could possibly be due to the exclusion of the pediatric age group in our study.[8,9] Linderman et al. found that the H1N1 virus mutated in later years which might explain the high susceptibility seen in middle-aged adults during 2013–2014.[10] In the post-pandemic years, the afflicted patients were noted to be older with a higher prevalence of pulmonary and cardiac disease. They were also sicker on initial presentation and had higher mortality (41%).[11]

Outcomes in our study population are different from other studies likely because of higher baseline comorbidities. In contrast, several studies from Mexico showed that most of the patients were previously healthy with no major comorbidities.[12–14]Although a systematic review and meta-analysis by Mertz et al. concluded that the level of evidence is low for "any risk factor", their results showed that elderly people, obesity (BMI >30), presence of chronic health conditions, including immunosuppression, and pregnant females in late stages of pregnancy or postpartum period were risk factors for poor outcomes which were similarly observed in our study.[15]

Patients were admitted at an average of 4 ± 2.1 days after the onset of symptoms which was similar to the findings from other studies where sicker patients generally began to deteriorate from 4 to 6 days after the onset of symptoms.[16] A total of 55 (35.7%) patients were transferred to our center from other hospitals of which eleven of them were already intubated and ventilated prior to admission.

Even though there is strong evidence that the antivirals are beneficial and the effect is larger when treatment was commenced within 48 hours of the onset of illness, the study done by McGeer et al. in Canada reported mortality reduction even beyond 48 hours of the onset of illness.[17] We could not derive the exact time of initiation of oseltamivir from the onset of illness in our study as several patients were transferred to us from different centers. Thus, we cannot comment on whether it has any relation with the duration or severity of the illness.[17,18]

The mean APACHE IV and SOFA scores in our study were significantly higher in non-survivors reflecting the multiorgan involvement in sicker patients. This was similar to the findings from Kumar et al.[18] Some authors have also previously used SOFA score for triage during pandemic periods due to its simple calculation and our results support this.[19]

We observed AKI in 38.5% of our patients which is more than the incidence of AKI of 7.1% in a study done by Kumar et al. Renal replacement therapy was required in 16.2% of our total patient population and in 11 out of the 31 patients who did not survive.[18] A smaller case series of six patients from Mexico with acute renal failure also revealed a high case fatality rate.[14] AKI in this population is likely multifactorial, resulting from inflammatory injury, shock, hypoxemia of acute lung injury, renal vasoconstriction, and rhabdomyolysis.[20]

There are varied results of the use of NIV in acute respiratory failure, and the etiology of hypoxemia may be contributing to its success. Non-invasive ventilation failure and mortality rates are usually significantly higher when used outside level I recommendations. In the severe acute respiratory syndrome (SARS) outbreak (2003), non-invasive ventilation was used successfully for managing patients even with severe hypoxemia.[21] Similarly, in the study by Chawla et al., out of 36 patients who required positive pressure ventilation, 17 were successfully managed only with NIV.[22] Ferrer et al.[23] compared NIV to conventional oxygen delivery in patients with severe hypoxemic respiratory failure and found that NIV decreased the rates of intubation especially in the subgroup of patients with pneumonia, but not in those with ARDS, in whom the intubation rates were higher. A meta-analysis concluded that NIV does not decrease the intubation rates, so there is no strong evidence to support its use in ARDS.[24] In our study, we observed that early initiation of noninvasive ventilation (NIV) was helpful in preventing progression to respiratory failure and thereby reducing the intubation rates.[3]

Acute, severe respiratory failure requiring invasive ventilation was a cardinal feature of severe H1N1 infection in 41.6% of our patients. Other studies demonstrated higher utilization of invasive mechanical ventilation. Domínguez-Cherit et al.[7] reported in 82.7% of patients and in the study by Kumar et al.[18] used in 81% of patients with respiratory failure. This might be due to the higher use of NIV and the cost implications of invasive mechanical ventilation may have been the reason for lower rates in our study.

Rescue measures in the form of prone ventilation inhaled nitric oxide and ECMO was deployed in patients with refractory hypoxemia. Kumar et al.,[18] reported the use of proning (3%), iNO (13.7%), and ECMO (4.2%) in 137 patients who were mechanically ventilated. The median duration of patients requiring mechanical ventilation was 12 days and overall mortality at 90 days was 17.3%. These results were very similar to the findings of our study.

The inferences derived from our study have a few limitations. The data was collected from tertiary centers in South India which might not reflect the outcomes from other parts of the country. False negative tests also might not estimate the true burden of 2009 H1N1 influenza in our patients. Nonetheless, with these caveats, knowledge of the rate of ICU admission and occupancy due to the 2009 H1N1 influenza can inform the planning, assessment, and management of critical care needs in our setup.

Conclusion

H1N1 pneumonia ARDS is associated with high mortality, especially in the elderly. Higher APACHE, SOFA scores, lower P/F ratio at admission, and development of septic shock during the hospital stay influenced mortality in our study. Prompt initiation of oral Oseltamivir in resource-poor settings preferably within 48 hours of symptoms onset may be a reasonable option. Optimal NIV usage in mild to moderate H1N1 ARDS with appropriate infection control precautions appears to be a safe strategy to optimize outcomes.

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