ORIGINAL ARTICLE

Clinical Profile and Outcome of H1N1 Influenza Infection at a Tertiary Care Teaching Hospital

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Abstract:

Background: The 2009 flu outbreak in humans, known as "swine influenza" or H1N1 influenza A, refers to influenza A due to a new H1N1 strain called Swine-Origin Influenza Virus A (S-OIV). Global pandemics with high mortality and morbidity occur when a virulent new viral strain emerges. *Aim and Objectives:* To study demography, clinical profile and outcome of H1N1 influenza infection at a tertiary care teaching hospital. *Material and Methods:* This was a prospective observational study conducted at the teaching hospital during six month period. It was a time bound study over a period of six months (from 1st July 2018 to 30th December 2018). All suspects with throat swab/nasal swab positive for influenza H1N1 virus by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) with age more than 15 years were included in the present study. Data were analysed for mean, percentage, standard deviation and Chi square test for quantitative data by using Microsoft Excel spread sheet. *Results:* A total 60 patients were admitted with confirmed diagnosis of H1N1 infection. Out of the 21 (35%) were males and 39 (65%) were females, predominated by female gender (p=0.001). The mean age in male (46.14 ± 20.058) was relatively more compared to female gender (36.33 ± 11.50). The male gender had more co-morbidities and risk factors compared to female patients (p=0.01) and was statistically significant. Out of total 21 male patients 7 patients died because of bilateral pneumonia and Acute Respiratory Distress Syndrome (ARDS) and Multi-Organ Dysfunction (MOD) with case fatality rate of 33.33%. Out of total 39 female patients 5 patients died with case fatality rate of 12.82%. *Conclusion:* The present study highlighted the disease burden associated with H1N1 infection. The advancing age, male gender, associated co-morbidities and delayed presentation were the risk factors for mortality in present cohort study of H1N1 patients. The community awareness, early case detection and timely management can reduce the disease burden at large.

Keywords: Swine influenza, H1N1, Bilateral pneumonia, Acute Respiratory Distress Syndrome**,** Multi-Organ Dysfunction

Introduction:

The 2009 flu outbreak in humans, known as "swine influenza" or H1N1 influenza A, refers to influenza A due to a new H1N1 strain called Swine-Origin Influenza Virus A (S-OIV). The new swine flu virus is actually a genetic mixture of two strains, both found in swine, of unknown origin. S-OIV can be transmitted from human to human and causes the normal symptoms of influenza. Genetic re-assortments in the influenza virus have caused fast and unpredictable changes leading to recurrent epidemics of febrile respiratory disease [1, 2].

Materials and Methods:

To study demography, clinical profile and outcome of H1N1 influenza infection at a tertiary care teaching hospital.

Settings and Design:

This was a prospective observational non interventional study of all the confirmed cases of

swine flu who were admitted in Krishna Hospital and Medical Research Centre, Karad, Maharashtra, India.

Sample size:

It was a time bound study over a period of six months (from 1st July 2018 to 30th December 2018). This study was approved by Institutional Ethics and Protocol Committee. All patients aged more than 15 years, whose throat or nasal swab was positive for H1N1 virus were included in this study. Detailed history was taken and clinical examination was done. History of travel to endemic areas in the previous 2 weeks or contact with a diagnosed or suspected influenza patient was emphasized. Basic laboratory investigations and an arterial blood gas analysis at the time of admission, and chest radiograph were done. Requirement of ventilator support was assessed. Subsequently, patients were followed up till the time of discharge and or final outcome. All the cases of H1N1 were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) of the respiratory specimen including throat/nasopharyngeal/nasal swabs from ambulatory patients and tracheal aspirates of intubated patients. Detailed history, clinical manifestations, and investigations [complete blood count, renal function tests, liver function tests, electrocardiogram (ECG) and chest radiogram, Arterial Blood Gas Analysis (ABGA), sputum for bacterial culture and antibiotic sensitivity, serum electrolytes (Na^+, K^+)] were done. Clinical profile was analyzed with reference to age distribution, gender distribution, duration of stay, risk factors, complications, ventilator support (Non-invasive or Invasive) and outcome. The patients were placed in one of the following categories (Category-A, Category-B and Category-C), according to the guidelines provided by the Ministry of Health & Family Welfare: Seasonal Influenza A (H1N1) [1, 2]. All the confirmed cases of swine flu were isolated and treated with Oseltamivir according to the standard protocol. Broad spectrum antibiotics and mechanical ventilator support were given whenever needed [3-6].

Statistical analysis:

Data were analysed for mean, percentage, standard deviation and Chi square test for quantitative data by using Microsoft Excel spread sheet.

Results:

A total of 60 patients with confirmed diagnosis of H1N1 infection over a period of 6 months were admitted. Of them 21 (35%) were males and 39 (65%) were females, predominated by female gender ($\chi 2$: 10.8, DF: 1, 'p'= 0.001015). The female gender was outnumbered in present cohort study of patients with H1N1 with male to female ratio of 0.538 (1:2). The mean age in male patients (46.14, ±20.058) was relatively more compared to that of female (36.33 ±11.50) patients (Table 1).

Table 1: Demographic Distribution of Patients with H1N1 Infections

Gender	Mean ± SD	Total	Percentage
Males (yrs)	**46.14 ± 20.05**	21	35
Females (yrs)	**36.33 ± 11.50**	39	65
Total	**82.47 ± 31.55**	**60**	**100**
χ^2: 10.8; dF:1; p=0.001			

The other laboratory parameters were comparable amongst the gender with no significant statistical significance. (Table 2).

Table 2: Mean and Standard Deviation of Quantitative Data

Variables	Males Mean ± SD	Females Mean ± SD	Total Mean ± SD
Age	46.14 ± 20.058	36.33 ± 11.50	39.76 ± 17.66
Duration of stay	7.95 ± 4.198	8.05 ± 1.52	6.12 ± 4.18
Hb	13.38 ± 2.990	10.76 ± 1.35	11.68 ± 2.72
Leukocytes Count	7795.23 ± 4843.49	7707.69 ± 3559.49	7738.33 ± 4851.07
Platelet Count	1.67 ± 0.586	1.9 ± 0.526	1.82 ± 0.696
Total Bilirubin	0.78 ± 0.304	0.546 ± 0.208	0.628 ± 0.316
Direct Bilirubin	0.24 ± 0.169	0.182 ± 0.1	0.205 ± 0.126
Indirect Bilirubin	0.53 ± 0.226	0.364 ± 0.115	0.423 ± 0.238
Creatinine	1.109 ± 0.399	0.951 ± 0.057	1.006 ± 0.334

None of the above parameters differ significantly when compared between male and female patients. Out of the 21 male patients, 13 (61.90%) and of a total 39 female patients, 6 (15.38%) with H1N1 infection had co-morbidities in the form of IHD, COPD and diabetes mellitus. The male patients with co-morbidities were significantly higher compared to female patients with co-morbidities (p=0.01). (Table 3).

Out of the 12 (20%) patients, who were on Invasive Ventilation (IV) 7(58.33%) patients were males and 5(41.66%) were female patients, and out of total 12 patients on NIV, 5 (41.66%) were males and 7 (58.33%) were female patients. (Table 4).

Out of the total 21 male patients, 7 patients died because of bilateral pneumonia and Acute Respiratory Distress Syndrome (ARDS) and multi-organ dysfunction (MOD), with a case fatality rate of 33.3%. Out of the total 39 female patients, 5 patients died due to same cause with a case fatality rate of 12.8%. All deaths in present cohort study were associated with bilateral pneumonia with ARDS which could be associated with either bacterial or viral aetiology other than

Table 3: Co-morbidities Associated in Patients with H1N1 Infection

Co-morbidities	Female (n=39)	Males (n=21)
Ischemic Heart Disease	1	4
Chronic Obstructive Pulmonary Disease	3	4
Diabetes Mellitus	2	5
p=0.01	6 (15.38%)	13 (61.90%)

Table 4: Mode of Ventilation Used for Patients with H1N1 Infection

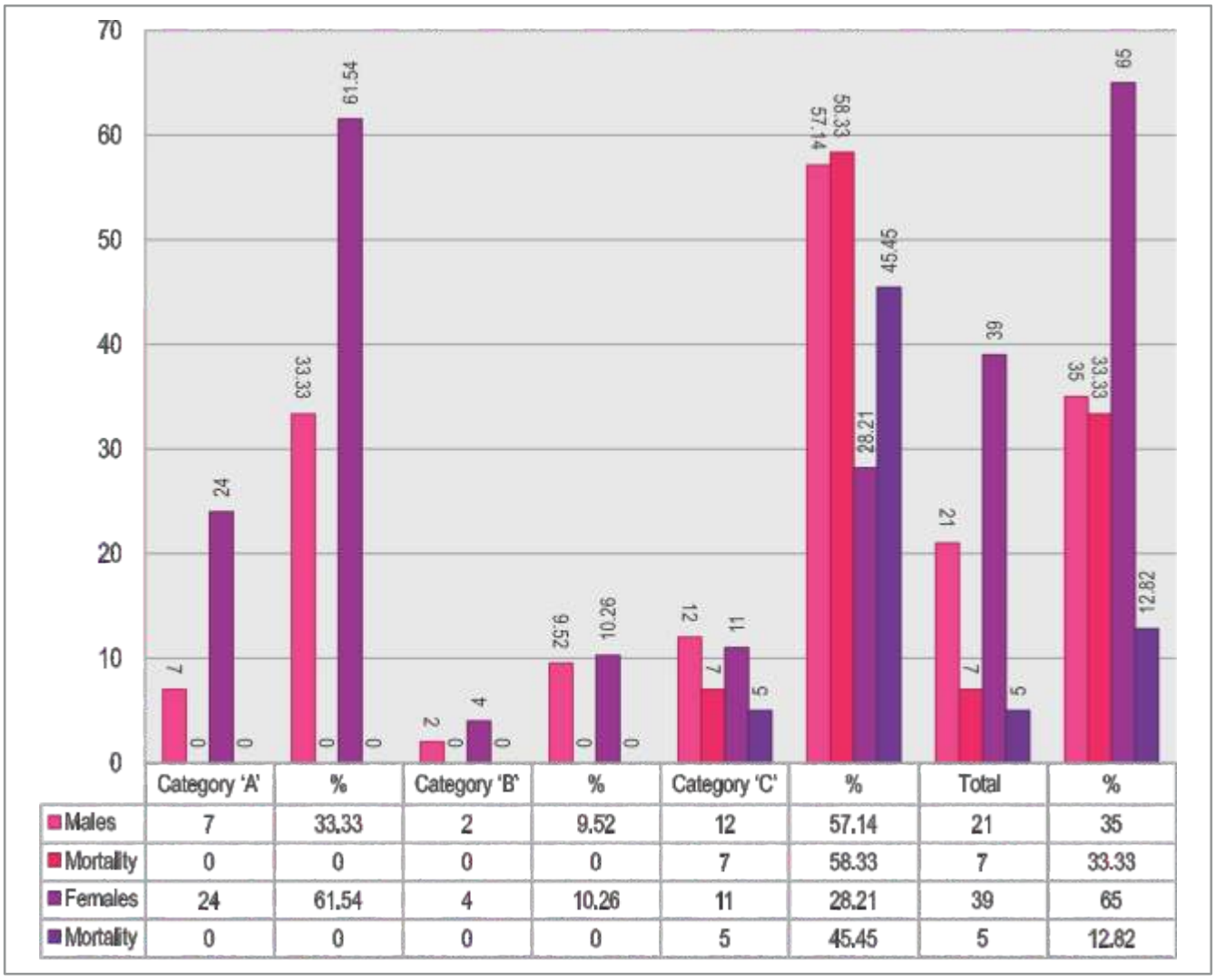
Type of ventilation	Male (n=21) (%)	Female (n=39) (%)	Total (n=60)	Percentage
Invasive ventilation	7 (33.33)	5 (12.82)	12	20
Non invasive ventilation	5 (23.81)	7 (17.95)	12	20
Total (n=60)	12 (57.14)	12 (30.76)	24	40

H1N1 infection. Associated co morbid conditions also play an important role in increasing overall morbidity and mortality amongst H1N1 infected patients (Fig. 1).

The mean age for female patients were 45 years (±16.87) and male patients were 59.14 years (±14.05). The mean age was relatively more than female patients in the present study. The percent mortality was significantly higher in male patients compared to that in female patients (p=0.005). (Table 5). The different categories of H1N1 patients and their relation to mortality are shown in Fig. 1. Chest radiogram of patients with H1N1 is shown in Fig. 2.

Table 5: Mortality, Mean, Standard Deviation and Co-morbidities Profile of Patients with H1N1 Infection

Sex	Total Mortality	Percentage Mortality	Chi-square Value
Male (n=21)	7	33.33	χ^2=3.6 dF:1
Female (n=39)	5	12.82	
Overall mortality rate	12	20	
Parameters	**Female Patients with Mortality**	**Male Patients with Mortality**	
Variables	**Mean ± SD**	**Mean ± SD**	
Age (Years)	45.00 ± 16.87	59.14 ± 14.05	
Duration of stay (Days)	4.80 ± 4.44	6.57 ± 4.35	
Hb%	10.86 ± 1.79	11.30 ± 3.92	
Leukocytes Count	13260 ± 4996	10600 ± 7333	
Platelet Count (Lakh)	1.23 ± 0.22	1.29 ± 0.60	
Total Bilirubin	0.96 ± 0.37	0.81 ± 0.40	
Serum Creatinine	1.36 ± 0.27	1.39 ± 0.59	



	Category 'A'	%	Category 'B'	%	Category 'C'	%	Total	%
Males	7	33.33	2	9.52	12	57.14	21	35
Mortality	0	0	0	0	7	58.33	7	33.33
Females	24	61.54	4	10.26	11	28.21	39	65
Mortality	0	0	0	0	5	45.45	5	12.82

Fig. 1: Category Wise Distribution of H1N1 Patients with Mortality

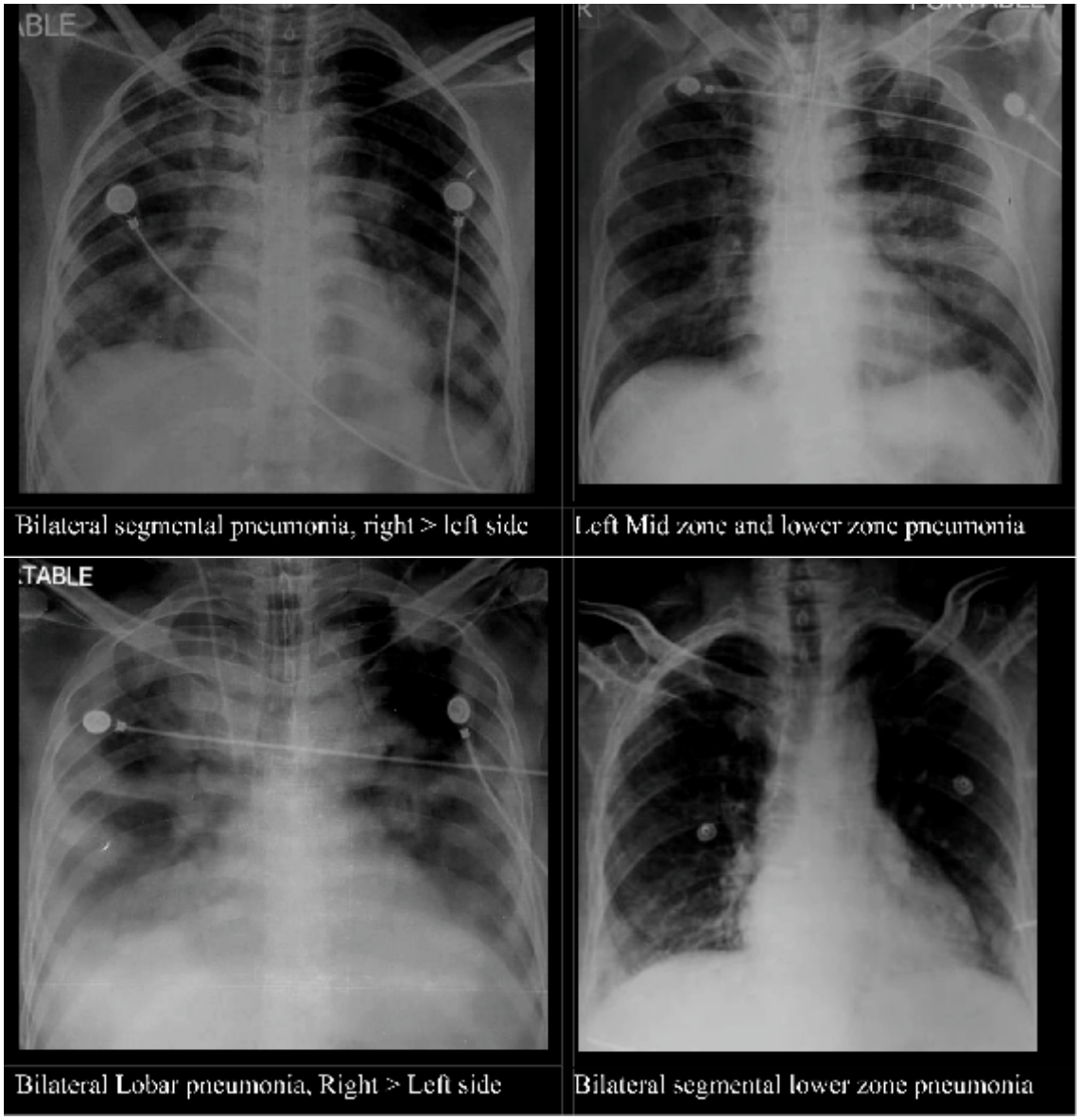


Fig. 2: Chest Radiogram of Patients with H1N1

Discussion:

Pandemic H1N1 (pH1N1/2009) virus was detected in the first quarter of 2009 in the west coastal region of North America and spread very rapidly to other countries. World Health Organization (WHO) formally declared the pandemic in 2009. The first positive case of P-09-H1N1 in India was reported in 2009 at Hyderabad airport with a history of travelling to the affected area. Swine flu is a viral fever caused by mutated strain influenza 'A' virus subtype H1N1, which infects humans and is a combination derived from a re-assortment of six gene segments from the triple re-assortant swine origin virus and two gene segments from the Eurasian influenza 'A' (H1N1)

swine virus lineage. Antigenic variation, antigenic-drift and antigenic shift of Hemagglutinin (HA) and Neuraminidase (NA) proteins enables the virus to escape the host immune response. Antigenic drifts in the HA subtype are associated with seasonal epidemics. Antigenic shifts in HA subtype are associated with pandemics. Swine-flu is a viral fever caused by a new mutated strain Influenza 'A' virus subtype H1N1, which infects humans [7-11]. In the present study, a total 60 patients were admitted with confirmed diagnosis of H1N1 infection. Out of them 35% were males and 65% were females, predominated by female gender. In the present cohort study, maximum cases were found in the month of August, September and October (2/3rd cases). The case fatality rate was 33.33% in male patients and 12.82% in females, due to bilateral pneumonia with H1N1 infection and ARDS. The advancing age, associated co-morbidities and delayed presentation could be the reason for relatively high mortality amongst male patients. The mean age of patient with mortality was 45 ±16.87 years for female patients and 59.14 ±14.05 years for male patients. Amaravathi *et al.* (2015) in their study reported 88 (17.12%) to be positive for H1N1 with the mean age of 31.15 years affecting both genders equally with epidemic peaked in the month of January. These differences as compared to the present study could be due to environmental factors. In the present study 12 (57.14%) male patients and 11(28.21%) female patients were in category 'C' which is comparable with Amaravathi *et al.* were majority of patients in category 'C' (59.09%). Similar to the present study, Amaravathi *et al*. quoted hypertension, diabetes, existing lung diseases; cardiovascular diseases, smoking habit, alcohol consumption and pregnancy as the major risk factors. In the present cohort study of H1N1 patients, 33.33% mortality was among males and 12.82% among female population with an overall mortality rate of 20%. Amaravathi *et al.* reported an overall mortality of 14.77% (*n* = 13) with Multiple Organ Dysfunction Syndrome (MODS) and ARDS were the most common causes of death. These findings were comparable with the present study [12]. As per the data from the Ministry of Health and Family Welfare, in the post-pandemic period (since 2010), India has reported more than 62,000 laboratory confirmed H1N1 (pdm09) cases with nearly 5000 deaths (8.064%). The cases had a major peak in rainy season and a minor peak in winter-spring season. Based on the number of reported deaths due to H1N1, the Case-Fatality Ratio (CFR) of 5.8% among the laboratory confirmed cases during January-March 2015 (ranged between 3.6 and 23.3 %). These findings were comparable with the present study in which, the overall mortality rate was 20%. During the 2009 pandemic, India reported 27,236 laboratory confirmed cases of pandemic influenza A (H1N1) with 981 (3.6%) deaths. The World Health Organization announced that the pandemic virus will continue as seasonal influenza virus. Therefore, sporadic H1N1 cases as well as localized outbreaks of varying magnitude are expected in the post-2009 pandemic period [13]. The influenza virus belongs to the genus Orthomyxovirus, which consists of influenza A, B, and C viruses. Global pandemics with high mortality and morbidity occur due to a virulent new viral strain, against which the population has no immunity. The influenza 'A' virus was responsible for three global pandemics. Swine

Influenza is common among pigs caused by type 'A' influenza (subtypes H1N1, H1N2, H2N1, H3N1, H3N2 and H2N3). The novel H1N1 strain is responsible for global pandemic of swine origin influenza. The pandemic influenza 'A' H1N1 2009 virus (A/2009/H1N1) has caused the first pandemic influenza. Tests used to detect influenza virus infections in humans can include Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), virus isolation. The Centers for Disease Control and Prevention (CDC) has developed a Real Time RT-PCR (rRT-PCR) assay to detect seasonal influenza. Swine influenza viruses also can cause moderate to severe illness in humans and affect persons of all age groups. People in close contact with swine are at high risk of acquiring infection. In the present study overall mortality rate was 20% (12/60) which was slightly more compared to data in 2015, in which, in India in (2015) 10,000 cases of swine influenza were reported with 774 (7.74%) deaths, which could be because of present study is hospital based (catering critically ill patients) and not community based [14]. Shrikhande *et al* (2012) reported a total of 67 (27.01%) samples from 247 patients who were pandemic influenza A/H1N1 positive. Overall, 22.38% of the patients came in contact with proven cases of pandemic H1N1. These findings were comparable with the present study with an overall mortality rate of 20% [7]. Siddharth *et al.* (2012) observed that the most common presentation (42.30%) of Influenza 'A' H1N1 cases was fever and cold-like features. A total 108 of the tested patients were found to be positive for the disease H1N1. Maximum cases were detected in the month of December, and the patients less than 40 years of age accounted for 81.4% (44 cases) of the cases. Influenza 'A' H1N1 resulted in death of 54.9% (28) of the admitted cases, of which 46% (12) deaths occurred within 48 h of admission [15]. Compared to present cohort study of patients with H1N1 the mortality in the study by Siddharth *et al.* was high. Naik *et al.* (2012) quoted 142 (30.47%) who were found to be positive for H1N1with M:F ratio of 1.3:1 with mean age of 20–40 years (47.18%), with occurrence of cases in the month of August 2010 (49.14%). Naik *et al.* stated that the outcome of disease was poor in females, which was not comparable with present study, in which mortality was more in male population. The duration of illness before hospitalization was longer and stay in the hospital was shorter in the cases who succumbed. These findings were similar to the present study [16]. Mukherjee *et al.* (2010) reported 382 (12.86%) were positive for influenza A, 284 (74.35%) were subtyped as pandemic H1N1 (pH1N1) with a peak in July and August (rainy season) in Eastern India, similar to the present study. The four deaths were attributed to pH1N1 infection in 2010, had underlying serious medical complications with highest Infection rate and were in age group of >55 years [17]. Similarly advancing age, co morbidities were the risk factors for high mortality in the present cohort study of H1N1 patients. We compared the present study findings with various studies from different parts of India (Table 6).

Table 6: Comparison of Various Studies with the Present Study

Author	Population	Highlights of study
Rewar *et al.* (2015) [14]	In India (2015), 10,000 cases of swine influenza were reported with 774 deaths.	High mortality is because of limited treatment options, high risk for secondary infection and frequent need for intensive care of individuals with H1N1 pneumonia
Shrikhande *et al.* (2012) [7]	(n=67) pH1N1 transmission activity has increased since May 2010	22.38% of the patients came in contact with proven cases of pandemic H1N1
Siddharth *et al.* (2012) [15]	(n=108) Maximum cases were detected in the month of December with age less than 40 years	Influenza A H1N1 resulted in death of 28(54.9%) of the admitted cases, of which 46% deaths occurred within 48 h of admission.
Dandagi *et al.* (2011) [18]	In India, total 23.3% patient were positive for H1N1	About 4% of people who have tested positive for swine flu have died.
Mukherjee *et al.* (2010) [17]	The novel pH1N1 virus infection had peak in July and August. Total 25.65% were subtyped as pandemic H1N1 (n=382)	The four deaths were attributed to pH1N1 infection in 2010, had underlying serious medical complications with Infection rate was highest in age group of >55 years of age group.
Naik *et al.* (2012) [16]	n=142 (30.47%) with M:F ratio of 1.3:1 with age >20 – 40 years were common and occurrence of cases were more frequent in August (49.14%)	The outcome of disease was poor in females compared to males. The duration of illness before hospitalization was longer and stay in the hospital was shorter in the cases who succumbed.
Murhekar *et al.* (2016) [13]	Bi-modal peaks (July-August) and winter-spring season with Case-Fatality Ratio (CFR) of 5.8 % (3.6 and 23.3 %)	India has reported more than 62,000 laboratory confirmed influenza A (H1N1) pdm09 cases with nearly 5000 deaths.
Present study	(n=60) Maximum cases were in month of August September and October	The advancing age, male gender, associated co-morbidities, requirement of invasive ventilation and delayed presentation were the risk factors for mortality in present cohort of H1N1 patients. Mortality was more in male gender (33.33%).

Conclusion:

The present study highlighted the burden and significant mortality associated with H1N1 infection. The advancing age, male gender, associated co-morbidities, requirement of invasive ventilation and delayed presentation were the risk factors for mortality in present cohort study of H1N1 patients. The health education, preventive measures, early case detection, strengthening primary health care and referral system and timely intensive care can significantly reduce the disease transmission and overall disease burden associated H1N1.

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