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Original Research Article

A study among patients hospitalized with suspected Influenza a (H1N1) infection at a tertiary care hospital in Ahmedabad city of Gujarat state, India

Kirti Rahul[1], Abhas Shah[2], A Bhagyalaxmi[3], Geeta Kedia[4]
[1]Tutor, Community Medicine Department, PDU Govt Medical College, Rajkot, Gujarat, India
[2] State Technical officer, Scalling up RMNCH+A Project, USAID, Haryana, India
[3]Associate Professor, Community Medicine Department, B J Medical College, Ahmedabad, Gujarat, India
[4]Professor, Community Medicine Department, B J Medical College, Ahmedabad, Gujarat, India

***Corresponding author**
Kirti Rahul
Email: rahulkirti.d@gmail.com

Abstract: In the post-pandemic period, India has experienced outbreaks during the period between August and October 2010; May and July 2011; March and October 2012 and now in January and March 2013. This study summarizes the clinical and epidemiological characteristics of all patients with suspected influenza-like illness that were hospitalized at a tertiary care center in Ahmedabad, Gujarat. From 1st January to 30th April 2013, 254 patients with influenza-like illness were admitted to Civil Hospital and tested for H1N1. Data was collected about demographic and clinico-epidemiological characteristics and details of treatment and final outcomes were noted. 163 tested positive for H1N1 and 91 were negative. Maximum patients were reported from younger age group of 15-45yrs in both the groups. There was relative sparing of the elderly among H1N1 positive patients (p=0.0074). Significantly higher proportion of females among positive patients was reported (p= 0.0016). However, there was no gender difference in the outcome of both positive and negative cases. There was no significant difference in the fatalities between both the groups (p=0.983) as 41 (25.15%) positive and 23(25.27%) negative patients died. Among H1N1 positive patients, there were significantly more deaths among referred patients (p= 0.0002). Study did not find any significant association between co-morbid conditions and poor outcome in both the groups. Study observed higher deaths among referred cases which could be due to delay in approaching health care facilities, lack of involvement of private sector in early diagnosis and management and also delay in referral services.
Keywords: Influenza-like illness; H1N1 positive; H1N1 negative; referred.

INTRODUCTION

A novel influenza A (H1N1) virus resulting from triple re-assortment emerged in Mexico and the USA in 2009 [1]. In late April 2009, WHO declared that the emergence of this virus represented a 'public health emergency of international concern' and on June 2009, raised the phase of pandemic alert to six, indicating the emergence of the new influenza pandemic [2]. The WHO declared the post-pandemic phase on August 10, 2010 [3] but the Health Ministry of the Government of India in a statement noted that a large number of swine flu cases would surface in the post pandemic period and a significant level of virus transmission is expected. In the post-pandemic period, India has experienced outbreaks during the period between August and October 2010; May and July 2011; March and October 2012 and now in January and March 2013 [4].

Globally swine flu has reached the post-pandemic level, India has witnessed a rise in swine flu (H1N1) cases and Gujarat is among the few states in the country where number of Swine Flu cases are significantly rising.[5] According to the Health Ministry, a total of 4,820 cases were reported in the country this year till June 16 with Delhi topping the list with 1,506 cases. Gujarat follows Delhi with 1,029 cases reported during the period. Though Delhi registered the highest number of cases, the deaths were mere 16 with death rate of 1.1% in comparison to Gujarat where 195 deaths due to swine flu were reported with death rate of 19%.[6] The death rate in 2009 came to 15 deaths per month. In 2010, when the virus was at its peak, the death rate rose to 30 per month. In 2013, however, the death rate had touched 48 in the month of March.7 To identify the contributing factors for high mortality, a study was undertaken among patients admitted with suspected influenza-like illness at a tertiary care hospital in Gujarat.

MATERIALS AND METHODS

The study was hospital-based and data was collected retrospectively for all patients hospitalized with suspected influenza-like illness at Civil Hospital, Ahmedabad, which is the largest tertiary care hospital in India. This institution provides Out Patient Department (OPD) facilities where suspected influenza cases are attended to and their clinical samples are tested by a state-of-art institutional laboratory in the Department of Microbiology, which is also the State Reference laboratory for virological testing. The hospital has a dedicated isolation ward for the management of hospitalized cases. Also, most of the seriously ill cases of Influenza from Ahmedabad and neighbouring areas and also from adjoining states are referred to this hospital for intensive care as the hospital provides advanced life-saving support.

From 1st January 2013 to 30th April 2013, a total of 254 patients were admitted to the hospital with influenza-like illness. They were tested for influenza A (H1N1) and included for analysis. The complete data of these patients was obtained from the Medical records and Statistical Department of the hospital. The data collected included demographic variables like age, gender and geographical location; pregnancy; symptoms on admission; associated co-morbid conditions; final outcome of the patients; duration between onset of illness and first contact with a healthcare facility; duration between onset of illness and start of antiviral treatment; time from onset of illness to the final outcome; initial approach to either government or private hospital. The treatment protocol followed at Civil Hospital was also analyzed using variables like result of H1N1 testing; provision of antiviral treatment and its duration; duration of hospitalization. Approval by the institutional review board was not required because this infectious disease fell under the jurisdiction of the Epidemic Disease Control Act (1897), which allows the collection of data on emerging pathogens when it is of public health interest, and was invoked by the state health department in August 2009[8].

Laboratory confirmation

Throat swabs were collected from all the ILI patients Influenza A (H1N1) virus was detected by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) assay using the CDC/WHO testing protocol for influenza A (H1N1)[9] (TaqMan®**;** Life Technologies TM real time PCR CDC protocol).

Definition

Influenza like illness (ILI) is defined as fever (temperature of 100° F (37.8°C) with cough or sore throat in the absence of a known cause other than influenza. A person with ILI with laboratory confirmation for influenza A (H1N1) on a throat swab by real- time reverse transcriptase polymerase chain reaction (RT-PCR) was considered as confirmed case of Influenza A (H1N1).[10]

Data analysis

Data entry and analysis was done in Microsoft Excel 2007. Z-test and Chi-square tests were applied to calculate p-values at 95% confidence interval.

RESULTS

Demographic & Spatial characteristics of patients

From 1st January 2013 to 30th April 2013, a total of 254 patients were admitted to Civil Hospital, Ahmedabad with ILI. 173(68.1%) were referred from other health facilities including private hospitals and rest 91(31.9%) cases directly came to Civil Hospital. Out of all those suspected, 163 were tested positive and 91 were negative giving the case positivity rate 64.1%. 111(44%) were females and 143(56%) were males (M: F Ratio=1.3:1).

The number of individuals suspected as well as confirmed to be H1N1 positive peaked during the months of January to April with maximum number of confirmed cases being reported during March where 89 (54.6% of all confirmed) tested positive for H1N1. Overall, maximum deaths were also seen in March. 22 out of 89 had expired with a case fatality rate of 24.7% during that month.

The median age of the patients was almost identical in both Influenza H1N1 positive and negative patients. Maximum numbers of patients in both the groups were reported from younger age bracket i.e. 15-45yrs (53.37% and 49.45% in H1N1 positive and negative patients respectively), however the difference was not found to be statistically significant (p= 0.55, 95% CI). One noteworthy finding was that significantly less number of patients in the geriatric age group i.e. >60years were reported amongst H1N1 positive patients as compared to negative patients (p= 0.0074).

Male: Female Ratio among positive patients was 1:1 while it was 2:1 among negative patients. Females were significantly more affected with H1N1 as out of 111 female cases tested, 81(73%) were positive for H1N1 whereas out of 143 male patients, only 82(57.35%) were positive (p= 0.0016). Out of 111 suspected female cases, 24 were pregnant and 19 of the tested positive for H1N1. 3(15.8%) were in the first trimester, 6 (31.6%) were in the second trimester, and 10(52.6%) were in the third trimester.

Since Civil Hospital, Ahmedabad is a large tertiary level healthcare center which not only caters to the whole of Gujarat but also to the neighbouring states, it was found that 45% and 55% of the patients

diagnosed as H1N1 positive and negative respectively reported from outside of Ahmedabad district. A total of 21 patients (8.27%) came from the state of Rajasthan, situated north-east of Gujarat. More than 60% of the patients in both the groups were referred to Civil Hospital from other healthcare facilities. (TABLE 1)

Table 1: Demographic characteristics of H1N1 positive and negative patients and median duration

Characteristics	H1N1 positive (%) (n=163)	H1N1 negative (%) (n=91)	p value*
Age (years)			
Median age-years(range)	41 (1month-80years)	42 (6month-85years)	-
<14	9 (5.52)	4 (4.4)	>0.05
15-45	87 (53.38)	45 (49.45)	>0.05
46-60	55 (33.74)	24 (26.37)	>0.05
>60	12 (7.36)	18 (19.78)	**<0.05**
Gender			
Male	82 (50.31)	61 (67.03)	**<0.05**
Female	81 (49.69)	30 (32.97)	
Geographical location of residence			
Ahmedabad District	74 (45.4)	50 (54.94)	>0.05
Outside Ahmedabad District	89 (54.6)	41 (45.06)	
Final Outcome			
Survived	122 (74.85)	68 (74.73)	>0.05
Died	41 (25.15)	23 (25.27)	
Pregnancy status (n=111)			
Pregnant	19 (23.46)	5 (16.67)	>0.05
Non-Pregnant	62 (76.54)	25 (83.33)	
Health facility first visited			
Civil Hospital (New cases)	51 (31.29)	30 (32.97)	>0.05
Other Hospitals (Referred cases)	112 (68.71)	61 (67.03)	
Co-morbid illness			
Present	73 (44.78)	35 (38.46)	>0.05
Absent	90 (55.22)	56 (61.54)	
Anti viral Treatment			
Oseltamivir given	163 (100)	87 (95.6)	-
Median duration of Antiviral treatment	7 days (1-16 days)	2 days (1-12 days)	-
Median duration from onset of symptoms to first contact with a healthcare facility	3 days (1-20 days)	3 days (1-20 days)	-
Median duration from onset of symptoms to start of Antiviral Treatment	5 days (1-31 days)	4 days (1-44 days)	-
Median duration from onset of symptoms to death	10 days (2-37 days)	11 days (2-44 days)	-
Median duration of Hospitalization	8 days (1-26 days)	3 days (1-15 days)	-

***p-value <0.05 is considered significant at 95% confidence interval**

Clinical characteristics & outcome of the patients

173 (68.1%) patients went to some other medical facility before being referred to Civil Hospital. 85% of them took consultation from a private healthcare provider. Majority (79%) were not tested for Influenza A (H1N1) in the first medical facility and Oseltamivir was given to only 13% of the cases at the first facility they visited. Oseltamivir was given to all 163 patients who tested positive for H1N1 at Civil Hospital Ahmedabad and 96% of negative patients also received this drug. Among H1N1 positive patients, breathlessness was the most common symptom (75%) followed by fever and productive cough whereas among negative patients fever followed by productive cough was the commonest presentation. Only 35% of them complained of breathlessness. Only 14(8.6%) of the H1N1 positive patients received Oseltamivir within 48 hours of the onset of symptoms; 44(27%) received it within 72 hours; 92(57%) received it after 5 days of onset. 73(44.8%) and 35(38.5%) of H1N1 positive and negative patients respectively had any underlying co-morbid conditions. (TABLE 2)

Table 2: Symptoms on admission and details of underlying co-morbid conditions

Symptoms	H1N1 Positive (n=163) (%)	H1N1 Negative (n=91) (%)
High Fever	97 (59.5)	56 (61.53)
Rhinorrhea	30 (18.4)	15 (16.48)
Productive Cough	97 (59.5)	51 (56.04)
Dry Cough	66 (40.49)	40 (43.95)
Sore throat	41 (25.15)	10 (10.98)
Breathlessness	128 (78.52)	32 (35.16)
Headache	23 (14.11)	6 (6.5)
Altered consciousness	10 (6.1)	5 (5.4)
Co-morbid illness		
Diabetes	26 (15.9)	16 (17.58)
CVD	53 (32.5)	21 (23.1)
Lung Disease (TB, COPD)	21 (12.88)	15 (16.48)
Renal Disease	22 (13.49)	6 (6.5)
Liver Disease	14 (8.5)	4 (4.3)
Cancer	7 (4.2)	4 (4.3)
Neurological Disease	12 (7.3)	9 (9.8)
HIV	1 (0.6)	2 (2.15)
Malaria	3 (1.8)	2 (2.15)
Others (Hypo & Hyperthyroidism)	14 (8.5)	4 (4.3)

There was no significant difference in the fatalities between H1N1 positive and negative patients as out of 163 cases who tested positive from H1N1, 41(25.15%) died and among 91 negative cases, 23(25.27%) died (p= 0.983). Among H1N1 positive cases, less the 2% of the deaths were reported from patients aged <14 yrs and >60yrs. Deaths among patients aged 15 years to 45 years was higher in H1N1 positive patients (26/87, 29.9%) as compared to negative patients (9/45, 20%) but the difference was not significant (p= 0.1977). On the contrary, deaths among patients aged 60 years or above was greater in negative patients (8/18, 44.44%) than positive patients (2/12, 16.67%). This difference was also not found to be significant. (TABLE 3)

Table 3: Age-group wise outcome among H1N1 positive and negative patients

Age group (years)	H1N1 positive			H1N1 negative		
	Survived (%)	Died (%)	Total (%)	Survived (%)	Died (%)	Total (%)
<14	8 (88.89)	1 (11.11)	9 (100)	4(100)	0 (0)	4 (100)
15-45	61(71.12)	26(29.88)	87 (100)	36(80)	9(20)	45(100)
46-60	43(79.19)	12(21.81)	55 (100)	18(75)	6(25)	24(100)
>60	10(83.33)	2(16.67)	12 (100)	10(55.55)	8(44.45)	18(100)
Total	122(74.85)	41(25.15)	163 (100)	68(74.73)	23(25.27)	91(100)

Out of 173 patients who were referred from other facilities to Civil Hospital, 51 (29.5%) died which included 36 H1N1 positive cases. Among H1N1 positive patients, there were more deaths in those who were referred (36/112, 32.14%) than in those who directly came to Civil Hospital (5/51, 9.81%) and the difference was significant (p= 0.0002). Although females were found to be affected more with H1N1, there was no gender difference in the outcome in case of both H1N1 positive and negative patients. 9 females out of the 24 who were pregnant succumbed of which 6 tested positive for H1N1 and 3 were found to be negative. There was no significant difference in the outcome between pregnant and non-pregnant women in both the groups. The prevalence of co-morbid conditions among patients who expired in both the groups was less than 50%. The study did not find any significant association between presence of co- morbid conditions and outcome in both H1N1 positive and negative patients. (TABLE 4)

Table 4: Comparison of final outcome of H1N1 positive and negative cases

Characteristic	Survived (%)	Died (%)	p value*
Disease status			
H1N1 positive (n=163)	122 (74.85)	41 (25.15)	>0.05
H1N1 negative (n=91)	68 (74.73)	23 (25.27)	
Referral Status			
H1N1 positive (n=163)			
Referred (n=112)	76 (67.86)	36 (32.14)	**<0.05**
New (n=51)	46 (90.19)	5 (9.81)	
H1N1 negative (n=91)			
Referred (n=61)	46 (75.41)	15 (24.59)	>0.05
New (n=30)	22 (73.33)	8 (26.67)	
Gender wise distribution			
H1N1 positive (n=163)			
Male (n=82)	62 (75.6)	20 (24.4)	>0.05
Female (n=81)	60 (74.07)	21 (25.93)	
H1N1 negative (n=91)			
Male (n=61)	48 (78.69)	13 (21.31)	>0.05
Female (n=30)	20 (66.67)	10 (33.33)	
Pregnancy status			
H1N1 positive (n=81)			
Pregnant (n=19)	13 (68.42)	6 (31.58)	>0.05
Non Pregnant (n=62)	47(75.8)	24.2)	
H1N1 negative (n=30)			
Pregnant (n=5)	2 (40)	3(60)	>0.05
Non Pregnant (n=25)	18 (72)	7(28)	
Geographical location			
H1N1 positive (n=163)			
Ahmedabad (n=74)	60 (81.08)	14 (18.92)	>0.05
Outside Ahmedabad (n=89)	62 (69.66)	30.34)	
H1N1 negative (n=91)			
Ahmedabad (n=50)	37 (74)	13 (26)	>0.05
Outside Ahmedabad (n=41)	31 (75.61)	10 (24.39)	
Underlying co-morbid conditions			
H1N1 positive (n=163)			
Present (n=73)	54 (73.97)	19 (26.03)	>0.05
Absent (n=90)	68 (75.55)	24.45)	
H1N1 negative (n=91)			
Present (n=35)	23 (65.71)	12 (34.29)	>0.05
Absent (n=56)	45 (80.35)	11 (19.65)	

***p-value <0.05 is considered significant at 95% confidence interval**

DISCUSSION

The current outbreak of swine flu in India is in keeping with the scenario sketched out by the World Health Organization (WHO) when it declared the H1N1 pandemic over in 2010. WHO had at the time warned that in the post-pandemic years, localized outbreaks were expected as the virus "would take on the behavior of seasonal influenza virus and continue to circulate for some years to come". While the latest outbreak is less worrisome than its predecessor in 2009-10, the government and international organizations say the H1N1 virus is now endemic to India. This means the virus is widespread in India and could potentially combine with existing endemic strains and form newer, more lethal strains. Experts say the epidemiology of the virus is much the same as that of viruses like HIV/AIDS, cholera and Chikungunya. All these diseases started as waves in different countries, assumed pandemic proportions and went on to become endemic diseases in different countries [4]. Patients testing negative for H1N1 were most probably suffering from seasonal influenza or other viral or bacterial infections of the lower respiratory tract.

The present study found 64.17% of the cases positive for H1N1. A study conducted by Chilean Task Force for study of Pandemic Influenza a (H1N1) reported the total positivity of H1N1 to be 62.79% [11]. Studies from Panama and Portugal reported positivity as 17.1% and 30.8% respectively [12, 13] Studies conducted in the state of Gujarat [14] and other parts of India [15, 16] during the 2009 Influenza A (H1N1) pandemic reported positivity rate between 9.56% to 35.45% among hospitalized patients.

As Influenza a (H1N1) spreads via aerosols, the disease is expected to rise with fall in temperature during winter months. India is even more vulnerable because of its climate. While in most countries the H1N1 virus makes an appearance during the winter season, in India it surfaces twice a year – during the monsoon and winter seasons [15, 16] During the 2009 H1N1 pandemic, Gujarat observed a sharp rise in the number of H1N1 cases during the winter months of December to February [15]. In this study, the unusual finding was that the suspected as well as confirmed cases started rising in January and maximum cases as well as deaths were reported in the month of March. This phenomenon could be due to the chances of the virus changing its character and evolving, though the role of prolonged winter this year cannot be ruled out.

Studies from different countries have consistently reported higher rates of H1N1 infection among younger persons [13-15], [18-21] A study in Australia by Chang *et al.;* [21] reported that patients with H1N1 influenza were significantly younger than those presenting with seasonal influenza. However, this study did not find any significant difference in the number of young people who were positive for H1N1 than those who tested negative. This study observed relative sparing of the elderly among H1N1 patients. Attack rates were lower in senior citizens than in younger persons, possibly due to past immunological experiences with related H1N1 viruses [22].The present study noted significantly higher proportion of females among H1N1 positive patients as compared to negative patients. The Male: Female Ratio among H1N1 cases as reported by Tulloch *et al.* [12] and Mishra *et al.;*[23] were 1:2.2 and 1:1.4 respectively. 44.8% of H1N1 positive patients had associated co-morbid illness. Chudasama *et al.;* [14] reported 33.2% prevalence of underlying medical conditions among H1N1 positive patients. Prevalence as high as 70% was reported from the United States [18].

The fatality rate among Influenza A (H1N1) patients in our study was 25.15% which was much higher than 0.9% noted by Biswas *et al.* [17]. However the rate was almost identical in negative patients. Chang *et al.* (2010) [22] did not find any difference in the outcome of Influenza A (H1N1) and seasonal influenza patients. However, Mishra *et al.;* [23] reported higher CFR for pandemic H1N1 in comparison to seasonal-A. Since there is no significant difference in the outcome between both the groups, this suggests that unpredictable changes in the viral antigens causing it to acquire higher pathogenecity may not be the reason for high deaths. The reason for more deaths could be due to the fact that this study was limited to only hospitalized patients. Considering that hospitalization and subsequent H1N1 testing would be skewed towards more severely ill, the case-fatality is likely to be an overestimate of what it is among all infected persons or ill persons. Other reason could be delay in seeking the treatment as median duration between onset of symptoms and initiation of antiviral treatment was 5 days (range 1-31 days). This duration was reported to be much lower (1.5-3 days) by studies outside India [18, 19]. Oseltamivir is most effective when started in the first 48 hours of illness. Treatment should be started empirically based on clinical judgment as early as possible even before definitive diagnostic test results become available, i.e., treatment should not wait for laboratory confirmation of influenza.[24] Delay in approach to health care facility activates the cytokine storm leading to respiratory failure and consequent high mortality as was observed in the study since majority of the positive patients presented with breathlessness.

11.66% of the total suspected cases were pregnant. Lower prevalence was reported by Chudasama *et al.;* [14] and Jain *et al.;* [18] (5.5% and 7% respectively). Unlike studies which opine that pregnant women are at increased risk for complications and mortality from H1N1 virus infection, [25, 26] this

study could not find any significant difference in outcomes between pregnant and non-pregnant women among H1N1 positive females. 63.42% of all the deaths among positive patients were observed in the younger age group age (15-45 yrs). Chudasama *et al.;* [14] reported 53.5% of all deaths among positive patients in the same age group. Mishra *et al*. [23] reported 75% of the deaths in the age group of less than 30 years. Less than 50% of patients who died due to H1N1 had underlying medical condition. This is in contrast to study reporting co-morbid conditions among deaths as 80%. [20]

Deaths among H1N1 positive cases were significantly higher in referred cases compared to patients who directly visited Civil Hospital. 88% of expired H1N1 positive patients were referred patients, showing that transportation of such individuals from one center to another and thereby delaying the diagnosis and treatment was associated with poor outcome. Many people from rural areas and small towns initially consult a private consultant or hospital where they are prescribed expensive antibiotics and invasive procedures. Routine testing and antiviral for pandemic influenza is costly and demanding and is rarely available at private clinics. There is widespread panic among them regarding Influenza A (H1N1) and they refer the patients to government hospitals when their condition worsens and H1N1 is strongly suspected. While private hospitals have cath-labs for advanced heart procedures, they don't have single bed or isolation ward equipped with ventilator and portable X-ray machine for H1N1 patients. Eight of the state's 26 districts don't have a single bed in an isolation ward in private hospitals for swine flu patients [27]**.**

CONCLUSION

Our data show that there was no difference in demographic characteristics between the two groups except for the relatively higher incidence among females and sparing of elderly by Influenza a (H1N1). The clinical course, severity and outcomes were similar in both the groups. This suggests that the number of admissions to the hospital reflected the higher burden of disease in the community rather than a greater virulence of the H1N1 virus. Study also observed significantly higher deaths among referred cases which could be due to delay in approaching health care facilities, lack of involvement of private sector in early diagnosis and management and also delay in referral services.

Limitations

This study was basically conducted as a retrospective study in a tertiary care institute. Hence the milder forms of the infection as well as the index case which occurred in the community may have been missed out. Hence this analysis may not reflect the actual distribution of the cases at the population level. Further community based studies are required to analyze the actual impact of H1N1 infection in the community.

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