Clinical Profile and Mortality Among Novel Influenza A (H1N1) Infected Patients: 2009-2010 Jodhpur, Rajasthan Pandemic


Abstract

Objectives: Influenza causes annual seasonal epidemics around the world. Periodically, a genetically novel strain of influenza circulates worldwide, causing an influenza pandemic. The present study aims to assess the clinical profile, factors determining the response, prognosis of the disease and outcome in H1N1 positive patients during 2009-2010 H1N1 pandemic, so that epidemiology of the disease could be known and high risk groups can be identified.

Methods: Medical records of the H1N1 positive patients, confirmed by RT-PCR method, admitted in ICU/Isolation ward in M.D.M. Hospital, Jodhpur during pandemic of H1N1 influenza (2009-2010) were retrieved and retrospectively studied, the data collected was analysed.

Results: During the study period there were 221 H1N1 positive admissions. The age group most affected was 21-40 years in both males (52%) and females (67%). There were 80 deaths; mortality was high in rural population (64%) and pregnant women particularly in third trimester (80%). Common presenting symptoms were Cough, Fever, Breathlessness, Sore throat, Nasal Discharge, Expectoration and Body aches, other less common symptoms were Headache, Vomiting, Diarrhoea and Fatigue.

Conclusion: Swine flu influenza infection took its heaviest toll in terms of human lives and economy because the young and productive population was mostly affected. Pregnant women and the patients with co-morbid conditions were the susceptible population and thus preventive and therapeutic interventions should be directed to them. Early vaccination of high risk groups and high index of suspicion in the symptomatic patients and chemoprophylaxis accordingly can save many human lives.

Introduction

Influenza, commonly referred to as the flu, is an infectious disease caused by RNA viruses of the family Orthomyxoviridae (the influenza viruses), that affects birds and mammals.1 Swine influenza (also called Mexican flu, pig influenza, swine flu, hog flu and pig flu, stomach flu or 24-hour flu) is an infection by any one of several types of swine influenza virus. Swine influenza virus (SIV) or S-OIV (swine-origin influenza virus) is any strain of the influenza family of viruses that is endemic in pigs.2 As of 2009, the known SIV strains include influenza C and the subtypes of influenza A known as H1N1, H1N2, H3N1, H3N2, and H2N3.3

The most common symptoms of the disease are chills, fever, sore throat, muscle pains, severe headache, coughing, weakness/fatigue and general discomfort. In more serious cases, influenza causes pneumonia, which can be fatal, particularly for the young and the elderly.4 The patients with asthma, neurological disorder, diabetes, immunosuppression, cardiovascular disorder, chronic renal disorder, chronic obstructive pulmonary disease are more susceptible for getting H1N1 infection.5,6

Influenza spreads around the world in seasonal epidemics, resulting in the deaths of between 250,000 and 500,000 people every year,7 up to millions in some pandemic years. Three influenza pandemics occurred in the 20th century and killed tens of millions of people,8 with each of these pandemics being caused by the appearance of a new strain of the virus in humans. In April 2009 a novel flu strain that combined genes from human, pig, and bird flu, initially dubbed “swine flu” and also known as H1N1 “influenza A/H1N1, emerged in Mexico, the United States, and several other nations.9,10 The World Health Organization officially declared the outbreak to be a pandemic on June 11, 2009, the WHO's declaration of a pandemic level 6 was an indication of spread, not severity, the strain actually having a lower mortality rate than common flu outbreaks.11

M. D. M. Hospital, Jodhpur was made a tertiary care centre for sick swine flu patients for whole of western Rajasthan and all ILI Category C patients (except children) were referred and admitted here. A separate ICU with all equipment including ventilators and isolation ward with all facilities was made in MDM to combat swine flu infection. A standard protocol was made for management of these patients. Sample collection was done with expertise according to recommended guidelines and was sent to DMRC laboratory for testing of H1N1 by RT-PCR method. Daily progress of patients in terms of clinical and laboratory parameters was monitored and documented.
Table 1: Characteristics and outcome of patients

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td></td>
<td>63 (29%)</td>
<td>158 (71%)</td>
</tr>
<tr>
<td>Residence</td>
<td>Rural (%)</td>
<td>Urban (%)</td>
</tr>
<tr>
<td>Rural (%)</td>
<td>26</td>
<td>84</td>
</tr>
<tr>
<td>Urban (%)</td>
<td>37</td>
<td>74</td>
</tr>
<tr>
<td>Outcome</td>
<td>Death</td>
<td>Discharge</td>
</tr>
<tr>
<td>Death</td>
<td>14 (54)</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Discharge</td>
<td>9 (24)</td>
<td>28 (76)</td>
</tr>
<tr>
<td>Death</td>
<td>28 (76)</td>
<td>37 (44)</td>
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<tr>
<td>Discharge</td>
<td>37 (44)</td>
<td>47 (56)</td>
</tr>
<tr>
<td>Death</td>
<td>47 (56)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Discharge</td>
<td>20 (27)</td>
<td>54 (73)</td>
</tr>
<tr>
<td>Age Group (Yrs.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>21-40</td>
<td>8 (31)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>41-60</td>
<td>5 (19)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Day of Presentation after onset of symptoms (Days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>9 (35)</td>
<td>14 (38)</td>
</tr>
<tr>
<td>6-10</td>
<td>4 (15)</td>
<td>10 (38)</td>
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<tr>
<td>&gt; 10</td>
<td>1 (4)</td>
<td>0 (0)</td>
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</table>

Material and Method

This retrospective clinical hospital based study was conducted in department of medicine at Dr. S. N. Medical College, Jodhpur. Medical records of all H1N1 positive patients, confirmed by RT-PCR, admitted to the isolation ward and ICU of M.D.M. hospital, Dr. S. N. Medical College, Jodhpur, Rajasthan, India, during 2009-2010 pandemic were retrieved from the Medical Information and Records Department of the hospital. The data was collected by filling preformed proforma from the medical records of the patients. The data was analysed by using computer software SPSS, epi-info. Data extracted from the case records included personal and epidemiological data, laboratory reports, and outcome. Data were expressed as mean standard deviation (SD), and frequency was expressed as a percentage. Computation of $P$ values was done by $t$ test and chi-squared analysis. $P < 0.05$ was considered statistically significant.

Results

This retrospective study was based on collection of data from 221 H1N1 positive patients, admitted in ICU /Isolation ward in MDM Hospital Jodhpur during pandemic 2009-2010. They were confirmed as positive cases of H1N1 influenza by RT-PCR method.

Out of total 221 patients 63 (29%) were males and 158 (71%) were females. 141(64%) of these patients were discharged and 80(36%) succumbed to death. Total numbers of male deaths were 23(29%) while numbers of female deaths were 57(71%). The age group most affected was 21-40 years in both males (52%) and females (67%). Rural populations were at higher risk for death (64%). The characteristics of patients and their outcome are shown in Table 1.

Presenting Symptoms

Cough (97%) was the most common symptom followed by fever (90%). Breathlessness which was present in 176 (80%) patients was considerably associated with high mortality. The symptoms with which patients presented are shown in Figure 1.

Co-Morbid Conditions

It was found that the most common associated illnesses were respiratory diseases (69%) i.e. Pulmonary tuberculosis, COPD, Asthma etc, followed by renal diseases (8%), while in urban males it was cardiovascular system(41%) followed by respiratory system(32%) disease, hypertension, renal failure and central nervous system diseases. Cardiovascular co-morbid conditions were significantly associated with mortalities (p value < 0.006). These are shown in Figure 2.

Clinical and Investigation Findings

Tachypnoea and low arterial oxygen saturation were significant risk factors for the mortality. 49 (78%) out of 63 admitted male patients with H1N1 disease presented with bilateral middle lobe and lower lobe opacity in chest X-ray PA view. 138 (87%) out of 158 admitted female patients with H1N1 disease presented with bilateral middle lobe and lower lobe opacity in chest X-ray PA view. Bilateral lower lobe and middle lobe involvement (79%) was most common X-ray chest finding among expired patients. Normal total leucocyte count, increased transaminase levels and hepatomegaly was significantly associated with H1N1 infection but not so with mortality. The clinical and investigation findings and their correlation with outcome of patients is shown in Table 2.

Treatment Given

These patients were treated with Oseltamivir, Zamanavir if needed, Oxygen and Ventilatory therapy according to need,
intravenous antibiotics and fluids, low dose steroids and symptomatic therapy according to WHO guidelines.

**Mortality and Cause of Death**

The most common cause of death was Bilateral Pneumonia with ARDS with hypoxic respiratory failure followed by septicaemia and multi organ dysfunction syndrome (Postmortem autopsy could not be done). The causes of death in the patients are shown in Figure 3. Prior to expiry all the patients were given ventilator support for variable duration and it was found that most of the patients who died developed type 1 hypoxic respiratory failure. Few of them also developed type 2 (Hypercarbic) respiratory failures.

**Pregnancy and H1N1**

In our study it was found that out of total 158 admitted females 37 (23%) were pregnant. Of these 4 (11%) were in first trimester, 18 (49%) were in second trimester and 15 (40%) were in third trimester. Maximum deaths were observed in the third trimester. Foetal outcome was very poor only one child could be saved but his mother expired.

Pregnant females were at higher risk for infection, H1N1 infection predominantly affected the latter half of pregnancy (89%). Pregnancy was associated with increased mortality in females particularly in third trimester (80%). The outcome of pregnant patients is shown in Table 3.

**Discussion**

The present study was aimed to assess the clinical profile, factors determining the response, prognosis of the disease and outcome in H1N1 positive patients so that epidemiology of the disease could be known and high risk groups can be identified. The study was done on 221 H1N1 positive patients who were admitted in Mathura Das Mathur hospital, Jodhpur during pandemic 2009-2010.

In our study we found that total number of male patients admitted was 63 (29%), out of which 26 (41%) were Rural and 37 (59%) were Urban. Overall mortality among males was 37%. Among rural males 14 (54%) succumbed to death while 12 (40%) survived. Among urban males 9 (24%) succumbed to death while 28 (76%) survived. This was statistically significant with a p value of < 0.017 i.e. rural males were at significantly higher risk for death. In both Rural and Urban males the most affected age group was 21-40. In rural males 65% and in urban males 48% were among this age group. Maximum number of deaths was also in this group (57% in rural males and 44% in urban males). Our study is supported by the study of A Puvanalingam et al,16 who also found the similar result that H1N1 infection predominantly affected the younger age group.
The study also showed that total number of female patients admitted was 158 (71%), out of which 84 (53%) were rural and 74 (47%) were urban. Overall mortality among females was 36%. Among rural females 37 (44%) succumbed to death while 47 (56%) survived. Among urban females 20 (27%) succumbed to death while 54 (73%) survived. This was statistically significant with a p value < 0.026 i.e. rural females were significantly at a higher risk for death. In both rural and urban females the most affected age group was 21-40. In rural females 49 (58%) were in this age group while in urban females 37 (50%) were in this age group. Maximum number of deaths was also in this age group (68% in rural females and 65% in urban females).

This was also supported by various studies. Rogelio Perez-Padella et al in their study in Mexico concluded that more than half of the patients were between 13 and 47 years of age. Anand Kumar et al in their study of critical illness concluded that among the 168 patients with confirmed or probable 2009 influenza A(H1N1), the mean (SD) age was 32.3 (± 21.4) years. Seema Jain et al in their study of 272 hospitalised patients in U.S found that the median age of patients who died was 26 years. D.B. Kadam et al in their study of H1N1 positive patients in Pune concluded that the mean age of the survivor’s population was 31.4 years, while that of succumbed patients was 36.23 years.

The study revealed that fever was the most common presentation among rural males (96%) followed by cough (84%) while in urban males cough was the most common symptom (100%) followed by fever (82%). Breathlessness was a symptom that was significantly associated with high mortality in both rural and urban males (p value < 0.003). It also showed that cough was the most common presentation among rural females (98%) and also in urban females (99%) followed by fever (95% among rural females and 86% among urban females). Breathlessness was a symptom that was significantly associated with high mortality in both rural and urban females (p value < 0.032). This view was also supported by various studies. K. N Bhatt et al in their study showed that fever (98.70%) and cough (94.15%) were most common presenting symptoms. Rashmi Ranjan Das et al in their study showed that fever was the most common symptom, followed by cough and rhinorrhoea. D.B. Kadam et al in their study of H1N1 positive patients in Pune concluded that fever was the most common symptom (95%) followed by cough (88%) and breathlessness (77%). Breathlessness was a symptom that was significantly associated with deaths.

The study concluded that 43% of rural males and 51% of urban males presented within five days of onset of symptoms while 57% of rural males and 49% of urban males presented after five days. Late presentation was significantly associated with high mortality in rural males (p value < 0.014) but not so in urban males (p value < 0.772). It was also found that 46% of rural females and 40% of urban females presented within five days of onset of symptoms while 54% of rural females and 60% of urban females presented after five days. Late presentation was significantly associated with high mortality in rural females (p value < 0.034) but not so in urban females (p value < 0.313). One possible explanation could be negligence of initial symptoms leading to delayed presentation and institution of antiviral therapy. Poor health and referral system at peripheral level added to the problem. This view was supported by Rogelio Perez-Padella et al in their study in Mexico who concluded that one contributing factor for death in the patients may have been delayed admission and delayed initiation of oseltamivir. K. N. Bhatt et al and D.B. Kadam et al in their study concluded that higher mortality was associated with delayed presentation and late institution of oseltamivir.

The study revealed that most common co-morbid condition associated with rural males was diseases of the respiratory system (69%) followed by renal system (8%) while in urban males it was cardiovascular system (41%) followed by respiratory system (32%). Cardiovascular co-morbid conditions were significantly associated with mortalities (p value < 0.006). It also showed that most common co-morbid condition associated with rural females and urban females was diseases of the respiratory system (35% and 47% respectively) followed by cardio vascular system (8% and 16% respectively). No co-morbid condition was significantly associated with mortality. Seema Jain et al in their study of 272 hospitalised patients in U.S found that thirteen patients who died (68%) had an underlying medical condition, including neurologic disease (21%), asthma or COPD (16%). D. B. Kadam et al in their study of H1N1 positive patients in Pune found that co-morbidities were present in 46% of the study population of which 31% had a single while 15% had more than one co-morbidities.

Our study concluded that 12% of rural males and 46% of urban males had normal respiratory rate at presentation while 88% rural males and 54% urban males were tachypnoeic (respiratory rate > 20/min). Tachypnoea as a whole was a significant risk factor for mortality (p value < 0.001). It also showed that 22% of rural females and 40% of urban females had normal respiratory rate at presentation while 78% rural females and 60% urban females were tachypnoeic. Tachypnoea as a whole was a significant risk factor for mortality (p value < 0.001). This view is supported by D.B. Kadam et al in their study of H1N1 positive patients in Pune who concluded that tachypnoea was significantly associated with death in H1N1 positive patients.

The study concluded that 4% of rural males and 8% of urban males were in shock (systolic BP < 90 mm of Hg) at presentation and all of them succumbed to death. It also showed that 2% of rural females and 3% of urban females were in shock at presentation and all of them succumbed to death. So shock was invariably associated with a fatal outcome.

The study concluded that 54% of total rural males and 73% of urban males had normal arterial oxygen saturation at presentation. All the rural male patients with low saturation (< 90%) succumbed to death while 6% of urban males with low saturation survived. Thus low saturation was significantly associated with high mortality. It also showed that 48% of total rural females and 76% of urban females had normal arterial oxygen saturation at presentation. 81% of rural female patients with low saturation (< 90%) succumbed to death while 72% of urban females with low saturation died. Thus low saturation was significantly associated with high mortality. This view was supported by Anand Kumar et al in their study who found that low saturation was associated with ICU admissions and increased mortality.

Another conclusion derived was that 38% of rural males and 35% of urban males had high pCO2 (> 40) at presentation. It was also found that 58% of rural females and 30% of urban females had high pCO2 at presentation. There was no statistical significant difference between rural and urban and male and female mortalities associated with high pCO2.

The study also revealed that 35% of rural males and 30% of urban males had acidosis (pH < 7.35) at the time of presentation. All the rural males with acidosis succumbed to death while 37% of urban males with acidosis died. Acidosis was significantly...
was found in 11% of urban females. This view was supported in their study of H1N1 infection. This was supported by Rogelio Perez-Padella et al in their study in Mexico who found that one of the most consistent laboratory characteristics in H1N1 infection was a TLC within normal limits. There was no significant association between TLC and death in both males and females.

In our study, it was also found that 76% of rural males and 58% of urban males had B/L middle lobe and lower lobe involvement in the X-ray chest P-A view while 24% of rural males and 3% of urban males had B/L lower lobe involvement. 36% of urban males had U/L consolidation and another 3% had consolidation with pleural effusion. It was also found that 61% of rural females and 37% of urban females had B/L middle lobe and lower lobe involvement in the X-ray while 25% of rural females and 52% of urban females had B/L lower lobe involvement. Normal X-ray was found in 11% of urban females. This view was supported by K. N. Bhatt et al in their study who found that involvement of both lungs is more common than single lung involvement (Figure 4).

It was found that 73% of rural males and 54% of urban males had normal TLC at presentation. It was also found that 69% of rural females and 70% of urban females had normal TLC at presentation. Thus normal TLC was significantly associated with H1N1 infection. This was supported by Rogelio Perez-Padella et al in their study in Mexico who found that one of the most consistent laboratory characteristics in H1N1 infection was a TLC within normal limits. There was no significant association between TLC and death in both males and females.

In our study, it was found that 58% of rural males and 33% of urban males had normal neutrophil distribution. Increased neutrophil percentage was associated with more mortality in rural males (31%) but not in urban males (13%). It was also found that 52% of rural females and 62% of urban males had normal neutrophil distribution. Increased neutrophil percentage was not associated with more mortality in rural females (23%) and urban females (15%).

The study concluded that 66% of rural males and 30% of urban males had increased lymphocyte counts. It was also seen that 60% of rural females and 43% of urban females had increased lymphocyte counts. There was no significant association between lymphocyte percentage and mortality in both males and females.

The study revealed that 46% of rural males and 65% of urban males had increased blood urea at presentation. Increased blood urea was associated with more deaths in rural males but was not statistically significant (p value 0.225). It also showed that 33% of rural females and 27% of urban females had increased blood urea at presentation. Increased blood urea was statistically associated with more deaths in both rural females (p value 0.088) and urban females (p value < 0.001).

In our study, it was found that 27% of rural males and 32% of urban males had increased S. Creatinine at presentation. Increased S. Creatinine was associated with more deaths in rural males but was not statistically significant (p value 0.275). It also showed that 14% of rural females and 11% of urban females had increased S. Creatinine at presentation. Increased S. Creatinine was statically associated with more deaths in both rural females (p value < 0.001) and urban females (p value < 0.001).

The study revealed that 92% of rural males and 97% of urban males had increased SGOT at presentation. It was also found that 70% of rural females and 63% of urban females had increased SGOT at presentation. Increased SGOT was associated with H1N1 infection but there was no significant association with mortality.

In our study, it was seen that 92% of rural males and 97% of urban males had increased SGPT at presentation. It also showed that 54% of rural females and 51% of urban females had increased SGPT at presentation. Increased SGPT was associated with H1N1 infection but there was no significant association with mortality. The above facts were supported by Anand Kumar et al in their study that although non pulmonary acute organ dysfunction was common, mortality was more with severe hypoxaemia multisystem organ failure and requirement for prolonged mechanical ventilation.

The study concluded that 19% of rural males and 16% of urban males had hyponatraemia while 4% of rural males and 19% of urban males had hypernatraemia. All the patients with deranged sodium levels expired among rural males while 38% of urban males who had deranged sodium levels succumbed to death. It was also found that 19% of rural females and 32% of urban females had hyponatraemia while 6% of rural females and 3% of urban females had hypernatraemia. 86% of the patients with deranged sodium levels expired among rural females while 31% of urban females who had deranged sodium levels succumbed to death.

The study revealed that 24% of rural males and 11% of urban males had hypokalaemia while 15% of rural males and 13% of urban males had hyperkalaemia. All the patients with deranged potassium levels expired among rural males while 89% of urban males who had deranged potassium levels succumbed to death. Hence deranged potassium levels was significantly associated with deaths (p value < 0.001). It also showed that 26% of rural

Fig. 4 : X-ray chest PA view
and urban females had hypokalaemia while 26% of rural females and 33% of urban females had hyperkalaemia. 52% of patients with deranged potassium levels expired among rural females while 27% of urban females who had deranged potassium levels succumbed to death. Hence deranged potassium levels were not significantly associated with deaths in females.

In our study it was found that out of total 158 admitted females 37 (23%) were pregnant of these 11% were in first trimester, 49% were in second trimester and 40% were in third trimester. Thus H1N1 infection predominantly affected the latter half of pregnancy. Maximum deaths were observed in the third trimester. This was supported by A Puvanalingam et al21 in their study who found that there was an increased risk of H1N1 influenza infection during the third trimester of pregnancy. Out of 37 pregnant females 31(84%) were rural and 6(16%) were urban. Out of 31 rural females 20(65%) expired and 11(35%) survived. All 6 urban females expired. Thus pregnancy was a factor associated with increased mortality in females (mortality rate 70%) as against non-pregnant females (mortality rate 26%). This was also seen by Seema Jain et al18 and D.B. Kadam et al19 in their study of H1N1 positive patients who concluded that pregnancy was a risk factor associated with increased mortality.

In our study it was concluded that most common cause of death among males was B/L Pneumonia with ARDS with hypoxic respiratory failure (75%). Another 13% died of septicemia and multi organ dysfunction syndrome. 12% (4% each) expired due to pneumothorax, acute left ventricular failure and HIV infection. It was also found that most common cause of death among females was B/L Pneumonia with ARDS with respiratory failure (72%). Another 16% died of septicemia and multi organ dysfunction syndrome. Other causes responsible for death were rheumatic heart disease (4%), renal failure (4%), acute left ventricular failure (2%) and diabetic ketoacidosis (2%). Prior to expiry all the patients were given ventilator support for variable duration and it was found that most of the patients who died developed type 1 hypoxic respiratory failure. Few of them also developed type 2 (Hypercarbic) respiratory failure. This fact was supported by various studies. Louie J. K. et al22 in their study of H1N1 Influenza in California found that the most common causes of death were viral pneumonia and acute respiratory distress syndrome. D.B. Kadam et al20 in their study of H1N1 positive patients in Pune concluded that patients who developed pneumonia and respiratory failure succumbed to death in more number. A Puvanalingam et al21 in their case study of the clinical profile of H1N1 swine flu influenza found that most common cause of death in patients was due to pneumonia and respiratory failure.

**Conclusion**

Our study demonstrates that swine flu influenza infection took its heaviest toll in terms of human lives and economy because the young and productive population was mostly affected. Pregnant women and the patients with co-morbid conditions were the susceptible population and thus preventive and therapeutic interventions should be directed to them. Primary prevention in form of vaccination and spread of herd immunity will help in combating this infection. Secondary prevention in form of early diagnosis and treatment, identifying alarming signs and symptoms such as severe breathlessness, tachypnoea, shock, bilateral infiltrates on X-ray and decreased saturation and prompt referral to a centre well equipped with ICU facilities can save lots of valuable human lives.

**References**