Original Research Article

Clinical aspects and outcome of patients with swine flu among survivors and non-survivors

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ABSTRACT

Background: Swine flu is an infective disease caused by any one of the several types of Influenza viruses. The world saw its first pandemic of swine flu this century in the year 2009 when the WHO raised a world-wide pandemic alert to level 6 on June 11, 2009. In India, first few cases (index cases) of swine flu were reported from Pune, Maharashtra. The most recent outbreak of this dreaded infection was reported during late winter of 2015.

Methods: The present study was retrospective study. In order to collect the data, we reviewed medical charts of patients who were hospitalized in our hospital during the study period. Diagnosis of swine flu was confirmed after sending the blood-samples to Government approved laboratories in Pune and Mumbai. Real time, Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) method was employed for serological diagnosis. Forty-five confirmed cases of swine flu were included in this retrospective study. The primary objective of this study was to highlight the differences in the clinical profile as well as outcome between the patients who survived the attack of swine flu and those who did not.

Results: Forty-five of these patients tested positive for H1N1 amounting to a positivity rate of 52.94%. Cough (93.3%) was the most common symptom followed by fever (88.8%) and breathlessness (82.2%). Patients who did not survive were more likely to have associated co-morbid conditions like Hypertension, Diabetes, cardio-vascular disease, pre-existing lung disease and pregnancy though this was not statistically significant (p=0.189). Acute Respiratory Distress Syndrome (ARDS), Multi-Organ Dysfunction (MOD) and secondary bacterial infections were among the most common conditions that lead to death.

Conclusions: Early detection of swine flu through meticulous screening in the community with a high index of suspicion followed by prompt and adequate treatment can go a long way in preventing another pandemic. Creating awareness among the lay people about personal as well as public hygiene is also vital to prevent the spread of this viral illness.

Keywords: ARDS, Cough, Fever, MOD, Swine flu

INTRODUCTION

In the year 1953, Wilson Smith and colleagues isolated Influenza- a virus which belongs to the family of Orthomyxovirus. Since 1918 the world has seen three pandemics of this dreaded infection resulting in loss of thousands of lives.1,2 After receiving reports of sustained transmission of Influenza-A virus in two continents, the World Health Organization (WHO) issued a phase-6 pandemic alert on 11th of June, 2009.3 Originating in La Gloria region of Mexico in April, 2009, Influenza-A caused at least eighteen thousand and three hundred deaths spread across seventy-four countries.4 During the period between the year 2009 and 2015, India registered...
The new Influenza-A (H1N1) virus is known to have sustained human-to-human transmission. Characteristics of this new virus are:

- It was formed from triple-Reassortment of swine virus lineages.
- Continent of origin (North America, not Asia).
- Season for outbreak was different than usual influenza season (spring, not late fall).
- Cohort group at risk for infection (Children and young adults, not infants or elderly).

Infection with influenza-a virus affects predominantly young population and usually leads to Acute Respiratory Distress Syndrome (ARDS) requiring intensive care in the ICUs. Secondary or super-added bacterial infection causing pneumonia is quite common (20-30%) in young patients of swine flu. Pregnancy and associated metabolic conditions are known to increase the severity of the disease and influence outcome.

The increased incidence of severe illness and high rate of transmissibility exerts a massive burden on the ICUs and hospital resources. In spite of India being the second most populous nation in the world, safety measures against highly infectious and transmissible disease like swine flu are notoriously inadequate. Even though creation of public awareness and employment of immunization has helped to some extent, the threat of another major outbreak of swine flu continues to be high in India. During the current year (2017) cases of swine flu have been reported from Mumbai, Pune region of Maharashtra and also the states of Karnataka and Gujarat. So far 915 confirmed cases of swine flu have been detected as of on 6 April 2017. Amongst them Eighty-Five patients died.

This retrospective study was conducted to describe our experience of managing serologically confirmed cases of swine flu in our hospital during the period between 1st January, 2015 and 30th of April, 2015. Our main objective is to highlight difference in the clinical presentation and outcome between the survivors and non-survivors of swine flu. The present study describes clinical features of forty-five confirmed cases of swine flu.

METHODS

This is a retrospective study included the confirmed cases of Influenza-A viral infection that were treated in our Hospital, during the period starting on 1st January, 2015 and ending on 30th April, 2015. All of these cases were confirmed by Reverse Transcriptase, Polymerase Chain Reaction (RT-PCR) of the respiratory specimens. Detailed history, clinical manifestations and investigations (Complete blood count, renal function test, creatine kinase, lactate dehydrogenase, electrocardiogram, chest radiograph and arterial blood gas) were recorded. Sequential Organ Failure Assessment (SOFA) and Acute Physiology And Chronic Health Evaluation Score (APACHE 2) were calculated on admission. Clinical profile was analyzed with reference to age, sex and time distribution, severity of symptoms, risk factors, complications and ultimate outcome.

All of these patients were isolated and treated with Oseltamivir. Broad spectrum antibiotics and ventilator support (non-invasive/invasive) were given when required.

Microbiological studies

Nasopharyngeal swab specimens and tracheal/bronchial aspirate samples were taken after tracheal intubation. After collecting, labeling and placing in appropriate transport medium, the samples were dispatched to a Government recognized centre for viral detection in Pune and Mumbai – maintaining the cold chain throughout. Results were received within 3-5 days. Samples for fungal cultures and bacterial culture by Bactec method were also obtained for analysis in our laboratory when required.

Statistical analysis

Data analysis was conducted using software for statistics. Descriptive statistics were obtained for all the study variables. All the categorical variables were compared using Chi Square and Fishers exact test and continuous variables using students t-test. Data were expressed in terms of mean, SD and percentage. For all the statistical analysis, P<0.05 was considered as statistically significant.

RESULTS

During the late winter months of Jan-April, 2015, we noticed a sudden and significant increase in the number of visits to the out-patient department and in-door admissions with flu-like symptoms, acute onset breathlessness and pneumonia. Out of a total number of hundred and forty patients who visited our Emergency Room during this period with symptoms of respiratory disease, eighty-five had pneumonia and flu-like symptoms. All of them were tested for H1N1 infection after admission – forty-five of them tested positive for Influenza-A or swine flu.

These patients were aged between 15 and 80 years. The mean age was 43.5 years for the patients who survived swine flu while the mean age of those who did not survive was 36.5 years. Of the forty-five patients who
tested positive, 58% (n=26) were male and 42% (n=19) were female (p=0.751) (Figure 1).

Figure 1: Sex-wise distribution of cases.

More than half of these patients, i.e. 77.7% (n=35) were between 15 and 50 years of age. Out of the forty-five patients, 71.1% (n=32) survived while the remaining 28.8% (n=13) died. Among the thirty-two survivors, 59.3% (n=19) were male and 40.62% (n=13) were female. Among the thirteen non-survivors 53.8% (n=7) were male and 46.1% (n=6) were female.

This sex distribution ratio was however not statistically significant (p=0.751). Twenty-three patients had pre-existing medical conditions. Twelve of them had arterial hypertension, nine had type II diabetes mellitus, one had undergone CABG, two had undergone PTCA, four had COPD, two had tested positive for HIV and two female patients were pregnant.

Of the 32 patients who survived 43.7% (n=14) had premorbid conditions and of the 13 patients who died 69.23% (n=9) had premorbid conditions. However, this finding was not significant statistically (p=0.189).

The time between onset of symptoms and admission to the hospital was 1-8 days (median of 4.81). Maximum number of admissions took place in the month of March while mortality rate was highest in February. Almost all patients had fever (88.9%) with a body temperature of more than 38 degree Celsius, cough (93.3%) and dyspnea or respiratory distress (82.2%), rhinorrhea (60%), myalgia (24%), hypotension (24%), headache (20%) and diarrhea (11%). The mean APACHE 2 (Acute Physiology and Chronic Health Evaluation 2) score done on admission was 5.71 for survivors and 10.61 for non-survivors was significant (p<0.0001).

### Table 1: Comparison of variables between survivors and non-survivors.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients who survived (N=32)</th>
<th>Patients who died (N=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-yrs (Mean±SD)</td>
<td>43.56±12.974</td>
<td>36.54±15.29</td>
<td>0.125</td>
</tr>
<tr>
<td>Male sex</td>
<td>19 (59.4)</td>
<td>7 (53.8)</td>
<td>0.751</td>
</tr>
<tr>
<td>Intubation required no.</td>
<td>11 (34.4)</td>
<td>13 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Co existing condition</td>
<td>14 (43.8)</td>
<td>9 (69.2)</td>
<td>0.189</td>
</tr>
<tr>
<td>LDH (Mean±SD)</td>
<td>520.43±226.29</td>
<td>1228.31±521.66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatine Kinase (Mean±SD)</td>
<td>396.34±304.99</td>
<td>899.92±468.66</td>
<td>0.0001</td>
</tr>
<tr>
<td>WBC count (Mean±SD)</td>
<td>6396.875±304.854</td>
<td>13476.92±695.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PaO2-mm Hg (Mean±SD)</td>
<td>79.1±20</td>
<td>62.15±25.638</td>
<td>0.0005</td>
</tr>
<tr>
<td>PaCO2-mm Hg (Mean±SD)</td>
<td>34.6±4.96</td>
<td>40.9±14.85</td>
<td>0.03</td>
</tr>
<tr>
<td>Ph (Mean±SD)</td>
<td>7.41±0.052</td>
<td>7.4123±0.181</td>
<td>0.95</td>
</tr>
<tr>
<td>Pao2 : Fio2 (Mean±SD)</td>
<td>227.59±146.669</td>
<td>87.32±51.84</td>
<td>0.0017</td>
</tr>
<tr>
<td>APACHE (Mean±SD)</td>
<td>5.719±2.773</td>
<td>10.61±7.054</td>
<td>0.0016</td>
</tr>
<tr>
<td>SOFA (Mean±SD)</td>
<td>5.906±1.146</td>
<td>9.92±2.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Opacity</td>
<td>2 (6.3)</td>
<td>7 (53.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Inotrope no.</td>
<td>4 (12.5)</td>
<td>12 (92.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of hospital stay (Mean±SD)</td>
<td>7.84±5.30</td>
<td>8.54±4.89</td>
<td>0.677</td>
</tr>
<tr>
<td>Non Invasive ventilator (Bipap)</td>
<td>11 (34.37)</td>
<td>1 (7.69)</td>
<td>0.067</td>
</tr>
<tr>
<td>Invasive Mechanical ventilator</td>
<td>0</td>
<td>12 (92.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Length of ventilation (Mean±SD)</td>
<td>6.72±3.22</td>
<td>8.18±3.89</td>
<td>0.298</td>
</tr>
</tbody>
</table>

The mean SOFA (Sequential Organ Failure Assessment) score was 5.90 for survivors and 9.92 for non-survivors which was significant (p<0.0001). This indicated that severity of the symptoms at the time of initial presentation was significantly more among the patients who died than those who survived (Table 1).

### Laboratory results

At the time of admission leukocyte count ranged between 3200-16000 with a mean of 6396 (SD ±304) in survivors, and 13476 (SD+6958) in non-survivors and was found to be significant (p <0.0001), lactate dehydrogenase was
raised with a mean of 520 (SD±226) in survivors, and 1228 (SD±521) in non-survivors was significant (p<0.0001). Eleven patients had LDH >1000. Creatine Kinase showed a mean of 396 (SD±304) in survivors, and 899 (SD ±468) in non- survivors, which was also statistically significant (p <0.0001). Six patients had creatine kinase levels >1000. Results of other routine laboratory tests were normal.

Blood cultures and endotracheal cultures were sent on admission and as indicated later. Central line, pus and stool cultures were also obtained where appropriate. Two patients had positive blood cultures, eleven had positive ETT cultures, fourteen had positive sputum cultures. Acinetobacter and Group A Streptococcus aerogenes were found in seven patients each respectively, three patients grew Coagulase negative staphylococci. One patient each had Citrobacter, Pneumococcus, Escherichia coli, Methicillin Resistant Staphylococcus Aureus and Klebsiella pneumonia infection respectively. Antibiotics were used where necessary as per the culture reports. Pneumonia on chest radiograph was present in 78.12% (n=25) of survivors and 100% (n=13) of non-survivors. On chest radiograph more than ¼ quadrant opacity was found in 2/32 (6.25%) of survivors and 7/13 (53.84%) of non-survivors. This finding was significant (p <0.001). Findings on chest radiograph were consistent with acute respiratory distress syndrome in all patients requiring mechanical ventilation.

Twenty-one patients who did not require ventilation support were treated and discharged to home for isolation. The average stay of whole cohort was 7.84 days (SD±5.30) in survivors and 8.54 days (SD±4.89) in non-survivors which was statistically insignificant (p = 0.677). Of the total forty-five patients 53.33% (n=24) patients required ventilation. Most of them, 44.44% (n =20) were on Non- Invasive ventilation (NIV) initially, of which eight needed invasive mechanical ventilation (IMV) eventually. Four patients had come intubated on admission. Of the thirteen non- survivors 92.30% (n =12) needed invasive mechanical ventilation and none of them survived. Mortality of patients receiving only NIV was 5% (1/20) and mortality in patients receiving NIV followed by invasive mechanical ventilation was 40% (8/20).

Mortality in patients requiring Invasive mechanical ventilation was significantly higher (p<0.0001). NIV was applied to patients who came with severe respiratory distress (RR>35), had Pao2/Fio2 ratio <200 or Spo2<90% on pulse oximeter and patients requiring >10 litres of oxygen with use of accessory muscles of respiration. Though Invasive ventilation with lung protective strategy is recommended in such patients, compelling reasons for our NIV use were, 1) our large experience with NIV 2) NIV is associated with low risk of infection and complications 3) resource and cost constraints. Invasive mechanical ventilation was applied to patients if they had persistent hypoxaemia (pao2<60 mmHg on Arterial Blood Gas analysis), respiratory acidosis (pH<7.1 on ABG), hemodynamic instability (Non-invasive arterial blood pressure of, 80mmHg systolic on high Inotropic support), who could not clear secretions or who worsened on NIV. Severe hypoxaemia was the predominant feature in all patients with a mean Pao2 of 79.1 and 62.15 in survivors and non-survivors and was found to be significant (p<0.0005). Mean pH was 7.41 (SD±0.05) in survivors and 7.4123 (SD 0.181) in non-survivors group (p=0.95, not significant). Pao2/Fio2 ratio with a mean of 227.59 (SD±146.44) in survivors and 87.32 (SD±51.84) in non-survivors and was significant (p <0.0017). Apache 2 scoring with a mean of 5.719 (SD±2.77) in survivors and 10.61 (SD±51.84) in non survivors was significant (p <0.0016). SOFA scoring was a mean of 5.90 (SD±1.14) in survivors and 9.92 (SD±2.36) in non-survivors was significant (p <0.0001). Hypotension requiring Inotrope support was seen in 12.5% (n=4) survivors and in 92.30% (n=12) of non-survivors was statistically significant (p <0.001). Severe respiratory insufficiency with refractory hypoxia and severe septic shock with multi organ failure were the commonest causes of death in 84.61% (n=11) of non-survivors.

**Treatment**

None of the patients had received oral Oseltamivir before admission in the hospital. It was given at the time of admission in a dose of 75 mg twice a day or 150 mg twice a day for duration of 5-10 days.15,16

The higher dose was given considering poor absorption from GIT in critically ill patients.17 Four of our patients received Oseltamivir twenty-four hours after admission. Apart from Oseltamivir, these patients were treated with antibiotics like ceftriaxone, azithromycin, levofloxacin, piperclillin-tazobactum and meropenem – depending on their clinical course. None of our patients was vaccinated earlier for swine flu.

At anytime during the clinical course, steroids were not used. Routine use of steroids may not be ideal for influenza virus infection and may be significantly associated with mortality.18

**DISCUSSION**

Most common symptoms in patients who came for admission was fever (88.8%), productive cough (93.3%) and breathlessness (82.2%).17,19-21 This finding is similar to the study described by Jagannath Rao et al Puvalingam et al, and Dawood et al.19-21

In present study, symptoms were found to be more severe at the time of presentation in patients who ultimately died. Present study points out a certain shift in the age distribution of influenza-A (H1N1) viral illness. We observed that much younger patients are affected by more severe form of this illness (p >0.05).5,9,10 This could be
because of antigenic exposure in previous influenza infections and resultant immunity in older age group as postulated in other studies.\(^1\,\!\!^1\) The mean age was 43.5 years among those who survived swine flu while the same was 36.5 years among those who died (p>0.05), comparable to that found in studies by Ramkrishna K et al and Padilla RP et al.\(^1\,\!\!^1\,\!\!^7\)

Even though we did not notice any significant gender difference in the affliction (p>0.05), there was a slight male preponderance (1.3:1) similar to the study by Chudasama et al and Rogello Padilla P et al.\(^1\,\!\!^1\,\!\!^2\,\!\!^2\) Most of these patients, 48.88% (n=22) were healthy prior to the illness while 51.1% (n=23) of them had certain pre-morbid conditions such as hypertension, diabetes, cardiac disease and pregnancy, which was higher in group of patients who died though statistically not significant (p>0.05) in present study.\(^1\,\!\!^1\,\!\!^4\,\!\!^2\,\!\!^0\)

Thirteen of these patients (28.8%) died ultimately- mostly from Acute Respiratory Distress Syndrome and multi-organ dysfunction (MOD). The findings on chest roentgenograms and subsequent complications in present study were similar to those observed in other Indian studies.\(^2\,\!\!^2\) The non-survivors had severe ARDS with seven patients having more than ¾ quadrant white opacification on chest radiographs as compared to two patients who survived (p<0.05).

Pao2/Fio2 ratio was severely deranged in non-survivors requiring invasive mechanical ventilation compared to survivors (p<0.05) in present study, as also stated in study by Chawla R et al and Chacko J.\(^2\,\!\!^2\,\!\!^5\) ARDS and hypoxaemia could be because of severe lung inflammation or lung damage directly by the influenza virus.\(^1\,\!\!^1\,\!\!^1\,\!\!^4\) Patients requiring invasive ventilation at the time of admission or later during the course showed a significantly higher mortality (p<0.05) than those who were managed with non-invasive ventilation (NIV) or no ventilation at all.\(^1\,\!\!^7\,\!\!^2\,\!\!^6\)

Laboratory findings like serum lactate dehydrogenase, creatine kinase and white blood cell counts were significantly (p<0.05) deranged in non-survivors when compared to survivors.\(^3\,\!\!^1\) Leukocytosis found in present study could be attributed to secondary infections. Creatine kinase could be raised possibly due to myositis.\(^1\) Similarly circulatory failure requiring Inotropic support was more commonly observed in non-survivors than survivors (p<0.05). The SOFA and APACHE 2 scores at the time of admission were significantly (p<0.05) higher in non-survivors than survivors.\(^1\,\!\!^7\,\!\!^2\,\!\!^5\,\!\!^2\,\!\!^7\) Present study revealed an overall mortality rate of 28.8% (n=13) which is comparable to the studies of Jagannath SR et al (25%), Chudasama RK et al (25%) and Gabriela and Andrea et al (33.5%).\(^8\,\!\!^1\,\!\!^9\,\!\!^2\,\!\!^2\)

Risk factors for severe form of H1N1 influenza-resulting in death are not known. Based on the findings of present study, we postulate that severe clinical features on presentation as denoted by, ARDS as shown by Pao2/Fio2 <200 and ¾ opacities on chest radiographs requiring Invasive ventilation, Hypotension requiring Inotropic support, severe Hypoxaemia requiring Invasive ventilation, severely deranged laboratory parameters like LDH, Creatine Kinase, WBC counts, and high scores (SOFA and APACHE 2) can be poor prognostic markers in patients with swine flu.

All showed statistically significant values (p<0.05) in Non-Survivors when compared to survivors. Similarly delay in visiting the hospital and initiation of therapy with Oseltamivir might have contributed to the most severe form of swine flu leading to death.\(^1\) It is well documented that oral oseltamivir suppresses the viral-load when given early in the course of the disease.\(^2\,\!\!^8\)

A large number of the patients in present study had secondary bacterial infections that were difficult to treat in spite of aggressive usage of antibiotics. This might have probably leaded to death in thirteen of our patients. Culture-based evidence of secondary bacterial or fungal infections usually complicates the critical illness caused by H1N1 virus and it is associated with worse outcomes in spite of almost ubiquitous use of antibiotics.\(^1\,\!\!^1\,\!\!^2\)

Survivors, on the other hand, had milder course of disease and lower values of the above parameters when compared with non-survivors, and, also lower rates of secondary infections.

Ours being a retrospective study, has one drawback - it has a selection bias as positive patients admitted only in our hospital were studied for a short period and the size of the cohort (number of patients) is relatively small. The laboratory investigations and other tests were carried as per the clinical requirement and not according to the standardized protocol.

**CONCLUSION**

The H1N1 (swine flu) influenza is a dreaded viral infection with potentially catastrophic results, though eminently treatable. It is all the more tragic because it was observed in present study to affect younger patients who are otherwise healthy prior to the illness. In young to middle-aged, swine flu can cause pneumonia and severe respiratory distress syndrome leading to death. Higher scoring systems on presentation predict higher mortality. Half of the patients had co-existing medical condition. Older patients had less severe form of illness. Timely initiation of Antiviral therapy can be beneficial.

Early detection of swine flu through meticulous screening in the community with a high index of suspicion followed by prompt and adequate treatment can go a long way in preventing another pandemic. Creating awareness among the lay people about personal as well as public hygiene is also vital to prevent the spread of this viral illness.
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