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"CLINICAL PROFILE AND OUTCOME OF INFLUENZA A (H1N1) PATIENT IN TERTIARY CARE CENTRE: A PROSPECTIVE OBSERVATIONAL STUDY"

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ABSTRACT

Epidemic of Influenza A (H1N1) in 2009 caused significant morbidity and mortality throughout the world. A re-emergence of hemagglutinin type 1 and neuraminidase type 1 (H1N1) influenza cases had been noted in India and number of positive cases increased in the year 2015 and 2017. It was a challenging for the health authorities and health centers to deal with the epidemic. The objectives of the present study was to study clinical profile of H1N1 positive patients and its outcome in tertiary care rural hospital. **Materials and Methods**:This study is a prospective observational study conducted at a tertiary care rural hospital with approval from institutional Ethics Committee for Academic Research projects. The data of 77 influenza A (H1N1) positive patients either diagnosed at our hospital or pre-diagnosed patients referred to our hospital since June 2017 to December 2018 were evaluated in the study. **Results**: A total of 77 confirmed cases of H1N1 influenza were detected during the study period of which 36 required Intensive Care Unit admission. Most patients were between 41 and 60 years. The predominant presenting symptoms were fever (94.81%), cough (81.82%), breathlessness (76.62%), and the most common auscultatory finding was bilateral crepitations (70.12%). Around 33.78% of cases presented with diffuse bilateral lung infiltrates on X-ray. 70 of 77 patients (90.90%) survived the disease. **Conclusions**: Early recognition of the disease, and prompt initiation of treatment seem to be the only way to reduce H1N1 disease progression and associated mortality.

KEYWORDS: Hemagglutinin type 1 and neuraminidase type 1 subtype, India, influenza A virus, Intensive Care Units, reverse transcriptase polymerase chain reaction.

INTRODUCTION

Influenza, commonly known as the "flu" is an acute infection of respiratory tract that caused by influenza viruses. Influenza can lead to varying degree of respiratory infections ranging from mild flu to severe and life-threatening pneumonia, bronchitis, ARDS (acute respiratory distress syndrome) and even death. Swine (flu) influenza (H1N1) is a novel influenza A virus which comprises of a re-assortment of 4 different genetic elements, namely, swine, human, avian, and Eurasian, which combines into a single influenza virus. Three influenza viruses occur in humans: A, B, and C. In 20th century three pandemic caused by three different novel virus strain in 1918, 1957,1968.[1] In late March-April 2009, an outbreak of influenza A virus infection was detected in Mexico, with subsequent cases observed in many other countries.[2][3] On 11th June 2009, the World Health Organisation (WHO) declared a global pandemic of novel influenza A (H1N1) was underway by raising the worldwide pandemic alert level to Phase 6.[4] However, 2017 was an unusual year, with the virus spreading rapidly in various parts of the country, and

showing epidemiological characteristics different from previous years.[5] This epidemic was notoriously seen to affect the younger population in the age group of 15-40 years thereby affecting the workhouse of the country. There are very limited number of studies on influenza virus related disease in India. This analysis is our experience from a tertiary care hospital admitting H1N1 positive cases. We aimed to study the clinical and radiological profile of H1N1 patients at the time of initial presentation, during hospital stay and its influence on mode of treatment and outcome. This was a prospective observational study of reported cases admitted from June 2017 to December 2018.

MATERIAL AND METHODS

Study was done in Department of General Medicine, Government Medical College, Miraj (Maharashtra), India. Profile of cases from both PVPGHS Sangli and GMCH Miraj was studied. Obtained data was categorized as per Government of India, Ministry of Health and Family Welfare guidelines into Category (A, B and C) hospitalized in the months of June 2017 to

December2018 in both hospitals. Relevant history, clinical manifestations at presentation, investigations (complete blood count, renal function test, liver function test, chest X‑ray, and arterial blood gas analysis), and outcome of all the cases were recorded. Treatment details including antiviral drugs, requirement for ventilation, and use of other supportive measures were also recorded.

STATISTICAL ANALYSIS
Data analysis was done by using IBM SPSS software. Chi square test was used for comparative analysis. Following other statistical methods have been employed in the present study:

1) Independent samples 't' test – unpaired.

TABLE NO -1 (AGE WISE DISTRIBUTION).

Age in years	No of patients	Percentage of patients
18-40	25	32.47
41-60	36	46.75
> 60	16	20.78
Total	77	100

The predominant symptom at presentation were fever (94.81%), cough (81.82%), breathlessness (76.62%), and sore throat (58.44%).

TABLE NO -2 (SIGNS/SYMPTOMS).

Symptoms	No of patients	Percentage of patients
Fever	73	94.81
Cough	63	81.82
Breathlessness	59	76.62
Sore throat	45	58.44
Nausea / Vomiting	19	24.68
Nasal Discharge	12	15.58
Myalgia	15	19.48
Headache	10	12.99

Regarding time of presentation, 50.65 % patient present within 48 hours of onset of symptoms. 36.36% of the patient presented 4-7 days from the onset. Remaining 12.99% patients present after 7 days of onset of illness. Initiation of antiviral treatment, even when presenting late, was associated with improvement in outcome. But late presentation was associated with increased mortality risk.

Microsoft Word and Microsoft Excel have been used to generate graphs, tables etc. Data was included in pre-structured, protected spreadsheets in Microsoft Excel.

RESULTS
Out of total 77, 65 (84.41%) belonged to urban and 12 (15.88%) belonged to rural areas; 35 (45.45%) were female and 42(54.55%) were male patients. With male to female ratio 1.2:1. In the present study, These patients were aged between 18 and 75year. Majority of the patients belong to age group 41 – 60 years (36 patients – 46.75%). However, all the age group were affected by the infection.

Most common comorbidities associated with H1N1 infection were HTN (19.48%), diabetes mellitus (15.58%), ischemic heart disease (15.58%), lung diseases like chronic obstructive pulmonary disease or old pulmonary tuberculosis (11.68%).

TABLE NO- 3 (COMORBIDITIES).

Comorbidities	No of patients (60)	Percentage of patients	Mortality in patients (17)
DM	12	15.58	7
IHD	12	15.58	6
HTN	15	19.48	4
Lung disease	9	11.69	1
CLD	2	2.60	2
CRF	1	1.30	1
Obesity	8	10.39	5

Clinical examination on admission showed that nearly 45.45% patients presented with tachycardia (pulse rate more than 90). 72.73% of patients presented with hypotension (systolic BP less than 100 mmhg). 82.62% patients present with respiratory rate 20-30/min and 13.43% patients present with respiratory rate more than 30/min on admission.

Most of the patients (66.23%) had baseline room air saturation between 81% and 100%. While 33.77% patients presented with severe desaturation. Patients presented with low room air saturation required invasive or non-invasive mechanical ventilation and more rapid progression of disease.

The most common auscultatory finding was bilateral crepitations (70.12%). Around 24.68% of cases had clear lung. A small proportion of patients (5.2%) also present with wheezing.

Haemoglobin (Hb) was normal in 40.26% patients, mildly decreased in 49.35% patients and moderate to severely decreased in 10.39% patients. Low Hb patients

are more prone to H1N1 infection. Total leukocyte count (TLC) was normal in 75.32% patients, decreased in 16.88%, increased in 7.79%. Low TLC was more suggestive of H1N1 infection in presence of appropriate clinical signs while higher TLC indicated secondary bacterial infection.

Cheat x-ray was normal in 27.27% cases on admission. However, 33.78 % of cases presented with diffuse infiltration like ARDS picture on x-ray. 19.48% cases presented with bilateral lower lobe predominant infiltrations.

Nearly 27.27% of cases did not required oxygen supplementation which mainly included patients admitted in ward. Patients admitted in ICU, however, required oxygen supplementation or ventilatory support in some form. About 27.27% of patients could be managed with non-invasive ventilation, but around 32.47% of cases required invasive ventilation. No one of these patients who required invasive ventilation tracheostomized. Most of these patients required an average 7-10 days of mechanical ventilation.

TABLE NO -4 (VENTILATOR REQUIRMENT).

Oxygen therapy	No of patients	Percentage of patients	Mortality	Percentage of mortality
Room air	21	27.27	0	0
O2 mask	10	12.99	0	0
NIV	21	27.27	0	0
Invasive	25	32.47	17	68
Total	77	100	17	

Most common complication was pneumonia 71.43%, septic shock, respiratory failure cases and sinusitis 5.19% cases. Other complications like myositis, postinfectious demyelinating encephalitis, pericarditis, GBS not found in any patient during their hospital stay.

Out of these 77 patients 10 patients referred from other private hospitals and has 100% mortality may be due to secondary complications (like extensive pneumonia, sepsis, respiratory failure) or late presentation. Of all these patients, 60 (77.92%) patients survived the disease while 17 (22.07%) patient died.

DISCUSSION
This study compares the clinical features and outcomes in relation to hospitalisation rates, hospital length of stay and comorbidities of hospitalised patients with H1N1 infection. Influenza viruses are highly unstable and capable of causing pandemics. In comparison to previous years when increased cases was observed in February – March, activity of influenza was observed in 2017 in august to October (peak in September). Only 3 patients reported in month of November and December. This similar type of time wise distribution found in V.B. Jadhav et al. study.[6] In our study 46.75% patient belongs to age group 41-60yrs followed by 18-40yrs age (32.47%) and in more than 60 years (20.78%). In our study total patients in 18-60yrs age group was 79.22%.

Sethulakshmi prasad et al. study (2017) observed majority of the patients (25%) belong to 51-60yr age group.[7] N. Thilakavithi, Shanti B. Rosyvennila study (2018) also observed majority of patients (55.34%) between 21-60 years.[8] The cases were equally distributed in both genders with slight male preponderance. Male to female ratio 1.2:1 which was comparable with previous studies. Gelotar Prakash observed 43.3% male and 56.64% male with male to female ratio 1:1.3.[9] R.M. Khatriya et al. study (2018) observed male to female ratio 1.6:1.[10] The prevalence of certain comorbidities was significantly higher among H1N1 positive patients in our study than general population. Hypertension (19.48%), diabetes mellitus (15.58%), ischemic heart disease (15.58%), lung disease (11.69%), obesity (10.39%), chronic liver disease (2.6%), chronic kidney disease (1.3%) as the most common coexisting conditions in our study. V. B. Jadhav et al in 2010 observed comorbid conditions associated are DM (8.33%) and Ischemic heart disease (8.33%).[6] Prasad et al. study (2017) observed cases with DM (21.05%), HTN (21.05%), CLD (1.32%), obesity (1.32%).[7] N. Thilakavathi and Shanti B. Rosyvennila observed 37% cases of DM, 35% with respiratory illness, HTN 25% cases, and 3% others in H1N1 infected patients.[8] Kshatriya et al. study (2016) observed 27.7% of DM cases, 36.9% cases of HTN, ischemic Heart disease in 15.4% cases.[10] Diabetes mellitus has been

reported as a common coexisting condition in several previous studies. Literature showed chronic lung diseases, diabetes, chronic renal disease, chronic liver disease, and pregnancy among risk factors for H1N1 infection. However, these risk factors were not associated with increased mortality and/or need of mechanical ventilation in present study. In our study, (10.38%) were obese which was associated with increased ICU admission and mortality more in female patients. This finding correlate with those of study conducted Moser J-AS et al. study.[11]

The most common presenting symptoms in our study were fever (94.81%), cough (81.82%), breathlessness (76.62%), sore throat (58.44%). Prasad et al (2017) observed 75 (98.7%) patients with fever, 47 (61.8%) patients had dry cough, 23 (30.3%) patients had productive cough, 41 (53.9%) had breathlessness, 14 (18.4%) cases with sore throat symptom. [7] N. Thilakavathi, Shanti B. Rosyveniila observed that fever, myalgia, running nose, shortness of breath were the common symptoms in H1N1 infected patients.[8] Amravathi et al. study (2015) in their study they stated that fever in 95.45% cases followed by cough in 85.22% cases, breathlessness cases in 51.22%, and myalgia in 50% of cases affected with H1N1 infection.[12] Gelotkar Prakash (2013) observed Fever in 96.46% cases, Cough in 100% cases, sore throat in 80.53% cases, difficulty in breathing in 72.56% cases.[10] In 2016 Kshatriya et al observed symptoms like cough in 100% cases, Breathlessness in 82.10%, fever in 96.9% patients, throat pain in 96.9%cases and vomiting in (24.6%).[9] Jethani V et al. study in 2017 observed that fever was most common symptom in 83.3% cases followed by dyspnoea in 76.7% cases, cough in 70% cases, throat pain in 50%.[13] Studies during pandemic period had reported high incidence of sore throat as presenting symptom. Chudasama et al. study and Mehta et al. study reported around 54% of cases presenting with sore throat, which is approximately similar to our study (58.44%). A study done by by Jayadeva et al. also found myalgia common in their patient. Both genders were observed to be approximately equally affected in our study similar to all the previous studies.[12, 13]

In present study we observed 10.39% had < 9 mg/dl Hb level, only 2.6% patients were deranged in liver functional test, 9.09% patients had platelet count < 150000. Renal functional test deranged in 41.56% patients. Jethani V et al. study (2017) studied other lab parameters in his study he observed 33.3% patients had derangement in renal failure test followed by liver function test in 10% cases, in 13.3% cases observed hemoglobin was < 9 mg/dl. He also observed that 46.6% case had platelet count < 150000.[13]

Prasad et al. study observed that crepitation was most common auscultatory finding in 64.47% cases. Patients presented with wheezing in 6.58% cases, 3.95% patients with crepitation + wheeze, where 25% patient with normal auscultation.[7] In current study we also observed that crepitation was most common auscultation finding in 70.12%, 3.90% patients with wheeze with crypts, 1 case (1.30%) presented with wheeze and 24.68% cases had no any positive auscultation findings.

Our study showed higher incidence of bilateral than unilateral lung involvement. Diffuse bilateral involvement at presentation was associated with higher incidence of mechanical ventilation. In present study we seen 33.78% cases with diffuse infiltration followed by bilateral lower zone infiltration 19.48% and 27.27% with clear chest x-ray. Prasad et al (2017) observed that 47.37% cases had clear chest X-ray on admission.[7] There was a predilection for lower lobes and diffuse infiltration being the commonest finding on chest xray. This were similar to that observed in other Indian studies.

Furthermore, early initiation of respiratory support in the form of non-invasive ventilation was found to be helpful in preventing progression of disease and reducing requirement of invasive ventilation in most of our patients. Those patients who referred either late or present after 7- 10 days of symptoms has high mortality within 2 to 3 days despite of aggressive treatment with invasive ventilation, antiviral therapy and antibiotics. Managing severe ARDS is very difficult and associated with high mortality. Pinto and Abayadeera et al. described similar result. According to our observation most common cause of death were respiratory failure secondary to bilateral extensive pneumonia. Puvanalingam et al. also found similar most common cause of death. Overall, mortality in present study was 22.07% (17/77), that was much higher than worldwide mortality of 0.3-0.4 % (84-87). Another Indian study also reported high mortality.[14,15,16] The patients included in our study were mostly referred cases and present late at our tertiary care hospital, which would have contributed to increased mortality in present study.

CONCLUSION
Prompt initiation of treatment and management of complications seem to be the only way to reduce the disease progression and associated mortality. Patients with risk factors require additional attention as clinical course can be unpredictable. The mortality was, however, found to be higher in the older age group and in patients with comorbid conditions. Meticulous screening at the community level, health education with regard to personal hygiene, and other preventive measures for identifying the subclinical cases and isolating them will reduces the recurrence of epidemic. Patient who needed non-invasive ventilation had significantly better outcome as compared to invasive ventilation. Thus, in patients of swine flu with severe pneumonia, hypoxemia and lung injury needing invasive support chances of survival decreased significantly and which could be prevented by early utilization of healthcare resources and proper preventive measures.

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