Original Article

Clinical Profile and Outcome of Influenza (H1N1) Patients admitted in Tertiary Care Teaching Hospital in Central India

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ABSTRACT

Introduction : The onset of 2015 saw an alarming spurt in influenza A (H1N1) admissions presenting with severe upper respiratory tract infection associated with excess rate of pneumonia progressing to ARDS and respiratory failure leading to severe morbidity and mortality.

Objectives : To study the clinical profile and outcome of H1N1 positive patients hospitalized in Swine flu isolation ward.

Methods : The present study is a hospital- based observational study done at Government Medical College, Nagpur over a period of 90 days (from 14th January to 15th April 2015). The data of 156 H1N1 Positive Patients (by RT PCR) was evaluated.

Results : A total of 333 suspected H1N1 patients got hospitalized under Department of Medicine from 14th January 2015 to 15th April 2015. 156 were positive by RT PCR for H1N1and received treatment in Swine Flu Isolation Intensive Care Unit with dedicated staff. All were in 'Category C' on admission. The mean age of the patients was 42.5 + 14.75 years with 96 Females and 60 Males with a Female to Male ratio of 1.6:1. 52 (33.3%) deaths occurred in the study subjects. 86 patients were directly admitted to GMC, Nagpur; of these 65 (75.6%) Survived and 21 (24.4%) succumbed. 70 patients were referred from other hospitals. Of these 39 (55.7%) Survived and 31 (44.3%) succumbed. The Non-survivors had a poorer oxygenation status at admission as compared to Survivors (p =HS).

Conclusion : H1N1 influenza causes severe illness in young patients leading to rapid spread and life-threatening consequences like Acute Respiratory Distress Syndrome (ARDS) and Respiratory Failure that requires Mechanical Ventilation (MV) and intensive therapy (IT).

Key words : H1N1,Influenza, Clinical profile, ARDS, Swine Flu, Mechanical ventilation

Introduction -

WHO had declared the Influenza - H1N1 outbreak a public health emergency in April 2009 and announced a global pandemic in June 2009. The pandemic was declared as ended in August 2010. Low-grade seasonal infections continued during these past years[1]. However the start of 2015 saw a severe resurgence of Influenza cases in India. Antigenic Drift is responsible for new seasonal increased infections that makes necessary to detect these strains and to prepare new seasonal influenza vaccine on a yearly basis. The worst affected states have been Gujarat &Rajasthan[2,3].

Influenza - H1N1 has a tendency to affect young children with pre disposing risk factors, old age, pregnant mothers, health workers, patients with co-morbid conditions like diabetes, lung disease, heart disease, liver disease, kidney disease, blood disorders, Immuno-compromised, patients on long term steroid treatment and also sometimes young healthy adults. Prolonged winter, unseasonal rains, inadequate hygiene, crowded urban infrastructure compounds the problem.

Influenza presents with severe upper respiratory infection associated with excess rate of lower respiratory infection progressing to Acute Respiratory Distress Syndrome with rapid onset of dyspnea, hypoxemia, and bilateral infiltrates on chest radiograph.

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Early hospitalization of Category C patients and treatment with antiviral drugs along with maintenance of oxygen saturation with oxygen inhalation or ventilatory support may help in mitigating the problem. ARDS with respiratory failure is responsible for the excessive morbidity and mortality. Secondary infection and multi organ failure may add to the morbidity and mortality.[4] Deteriorating oxygenation status with bilateral lung opacities on Chest X-ray occurring within a week of acute insult defines ARDS. The oxygenation status can be assessed by the PaO2/ FiO2 or SPO2/ FiO2 ratio.

ARDS Berlin definition.	
The Berlin definition of acute respiratory distress syndrom	
Timing	Within 1 week of a know clinical insult or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities - not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload.
Oxygenation[b]	Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present
Mild	$200 \text{ mmHg} < PaO_2/FIO_2 \leq 300 \text{ mmHg}$ with PEEP or $CPAP \geq 5 \text{ cmH}_2O$[c]
Moderate	$100 \text{ mmHg} < PaO_2/FIO_2 \leq 200 \text{ mmHg}$ with PEEP or $CPAP \geq 5 \text{ cmH}_2O$
Severe	$PaO_2/FIO_2 \leq 100 \text{ mmHg}$ with $PEEP \geq 5 \text{ cmH}_2O$

Abbreviations : CPAP, continuous positive airway pressure; F_IO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure, [a]Chest radiograph or computed tomography scan; [b]If altitude is higher than 1,000 m, the correction factor should be calculated as follows : $[PaO_2/FIO_2$ (barometric pressure/760)]; [c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

The Sequential Organ Failure Assessment score (SOFA score) is a scoring system to determine the extent of a person's organ function or rate of failure and is based on six different system involvements. In this score the respiratory involvement sequentially is assessed by the PaO2/ FiO2 ratio. The Modified SOFA score (MSOFA) uses the ratio of SPO2/FiO2 ratio instead of PaO2 measured by arterial blood gas

analysis to monitor arterial oxygenation, as it is economical and convenient to continuously monitor patients at the bedside with this parameter.[5] This has been incorporated into triage protocols for critical care in the event of influenza pandemic and is a validated predictor of respiratory failure and mortality in critically ill patients. SPO2/FiO2 ratio as a parameter of oxygenation status was evaluated in this current study.

In view of the scarcity of regional swine flu data of disease presentation and outcome, we retrospectively evaluated the disease course and outcome of H1N1 positive patients admitted in the Swine Flu Isolation Intensive Care Unit of Government Medical College, Nagpur.

Objectives -

To study the clinical profile and outcome of H1N1 positive patients hospitalized in Swine flu isolation Intensive Care Unit of GMC, Nagpur.

Materials And Methods -

We retrospectively reviewed the medical records of patients who tested positive for RT-PCR H1N1 and were admitted from 14th January to 15th April 2015 in the Swine Flu isolation ICU of Government Medical College and Hospital, Nagpur.

All individuals seeking consultations for flu like symptoms are categorized as under:

Category-A : Patients with mild fever, cough, sore throat, body ache, headache, diarrhea and vomiting. They should confine themselves at home and avoid mixing up with public and high-risk members in the family. They do not require Oseltamivir. No testing of the patient for H1N1 is required. They are monitored for their progress over next 24-48 hours.

Category-B : In addition to all the signs and symptoms mentioned under Category-A, if the patient has high-grade fever and severe sore throat. They require home isolation and Oseltamivir. No testing for H1N1 is recommended. Patients of Category A with risk factors like pregnancy, lung diseases, heart disease, liver disease, kidney disease, blood disorders, diabetes, neurological disorders, cancer and HIV/AIDS, on long term cortisone therapy and age above 65 years are also treated with Oseltamivir

Category-C : In addition to the above signs and symptoms of Category-A and B, if the patient has breathlessness, chest pain, drowsiness, fall in blood pressure, sputum mixed with blood, bluish discoloration of nails. These patients require testing, hospitalization and treatment.

Category C patients were hospitalized. They were tested for H1N1 Influenza positive status by reverse transcriptase polymerase chain reaction (RTPCR) at Microbiology Department of Indira Gandhi Government Medical College and Hospital, Nagpur under the Indian Council of Medical Research (ICMR) project.

The RTPCR positive patients were isolated in the Swine flu isolation Intensive Care Unit. Their demographic characteristics, clinical features, risk factors, medium time delay in admission, and in hospital complications, outcome were evaluated retrospectively. The sequentially SpO2/FIO2 ratio as used in the Modified SOFA score (MSOFA) was taken as an index of oxygenation status in Survivors and Non- Survivors

Patients were managed with Oseltamivir, High flow oxygen, permissible PEEP, low tidal volume, and high respiratory rate keeping in mind the oxygenation and plateau pressure goals with noninvasive or invasive ventilation along with analgesics, sedation and paralysis as per clinical situation. Supportive therapy given keeping in view the multisystem involvement of the disease.

Results -

From 14thJanuary 2015 to 15thApril 2015, a total of 316 suspected patients were tested by RTPCR for Influenza A H1N1. Of these 156 (49.3%)were found to be positive. Female admissions out numbered the male with a ratio of 1.6:1.(96F / 60M). *(Fig.1)*

Figure 1 : **Month Wise Admissions; n=156**
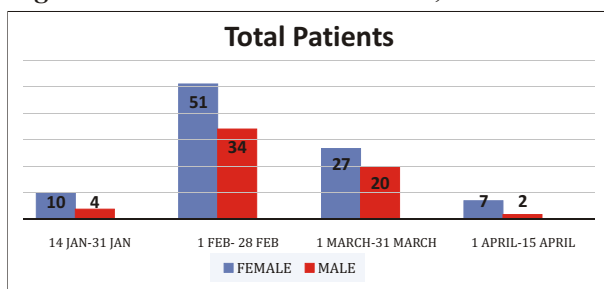
There were 14 admissions in January, 85 in February, 47 in March, and 10 admissions till 15th April 2015.

72 (46%) patients were in age groupof 21-40 years and 53 (33.9%) patients were of age group 41-60 years. The mean age of patients was 42.5 + 14.75 years. Disease found to affect adults more as compared to old patients.

114 (73.3%)patients belonged to Nagpur while the others were from surrounding areas of Vidarbha and Madhya Pradesh over a radius of around 250kms. *(Fig. 2)*

Figure 2 : **Demographic profile of the Study Subjects**

52 (33.33%)patients succumbed to their illness and 104 patients could be discharged after getting better symptomatically. There were 5 deaths in January, 22 in February, 16 in March and 7 in April.

Figure 3 : **Month Wise Deaths; n=52 (34F, 18M); Mean age = 43.53 + 13.85 yrs.**
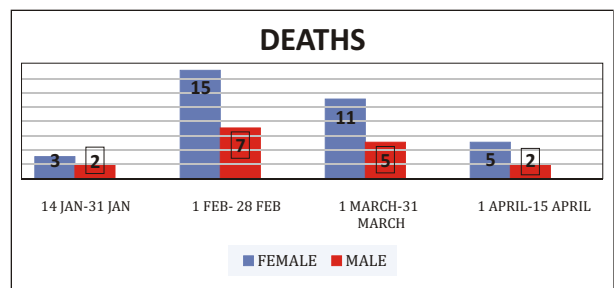
The mean age of survivors was 41.97 +15.28 years as compared to 43.66 + 13.96 years in Non-Survivors (p=0.5NS). *(Table1)*

Table 1 : **Age & Gender distribution of Survivors & Non- Survivors (n=156).**

Age in years		Males (n=60)		Female (n=96)	
		Survivors	Non-Survivors	Survivors	Non-Survivors
12-20	9	2	0	7	0
21-30	31	4	2	17	8
31-40	41	12	9	11	9
41-50	30	9	3	11	7
51-60	23	10	2	8	3
61-70	18	4	2	7	5
71-80	4	1	0	1	2
Total		42 (25.64%)	18 (11.53%)	62 (39.7%)	34 (21.7%)

18 of the 60 male admissions (30%) succumbed as compared to 34 of the 96 females admissions (35.4%). More number of females died as compared to males with a ratio of 1.88:1.

11 patients died within 24 hours of admission, 4 patients died with a stay of 1 -2 days, 17 patients died with in a stay of 2 -5 days, 20 patients died after 5 days of admission.

The mean duration of hospital stay was significantly less in Non-Survivors as compared to the Survivors. *(Table 2)*

Table 2 : **Duration of Hospital Stay in Study Subjects**

	Survivors	Non- Survivors	P value
Mean Duration of Hospital Stay(days)	7.43 ± 3.64	5.5 + 4.73	0. 014(S)

The most common presenting complaints of the patients were fever, cough and breathlessness. The mean interval between symptom onset to hospitalization was 6 days, being 4.8 days in Survivors as compared to 6.5 days in Non-Survivors. *(Fig. 4)*

Figure 4 : **Symptomatology of Study Subjects**
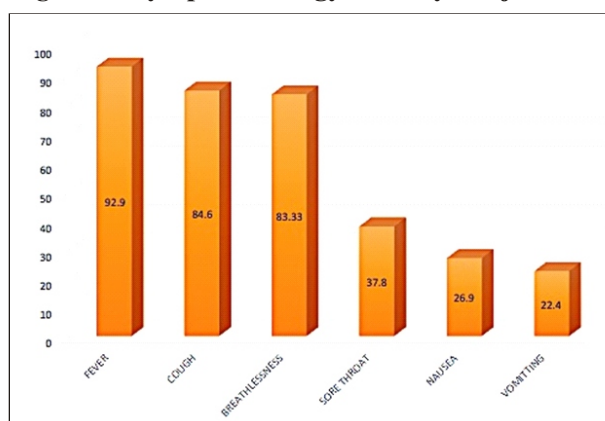
94 patients came to hospital after 48 hours of symptoms out of which 69 (73.4%) survived and 25 (26.5%) died. 58 patients presented to hospital after 5 days of symptoms out of which 33 (56.89%) survived and 25 (43.1%) died. This indicates that patients presenting after 5 days of symptom onset had a higher mortality as compared to those presenting within 5 days of symptom onset.

86 patients came directly after getting symptomatic and 70 patients were referred to GMC, Nagpur for treatment after being admitted elsewhere. The in hospital mortality of directly admitted patients was 24% as compared to 45% in the referred patients (p<0.001). Of the referred patients the mean duration of hospitalization outside was 2.05 days in Survivors as compared to 3.98 days in Non-Survivors (p=0.024S).

66.66% of the H1N1 positive patients admitted had one or more underlying medical co-morbid conditions. The common co-morbid conditions present were : hypertension & DM *(Table 3)*

Table 3 : **Logistic regression Analysis with Various Comorbid condition**

Co-Morbid Condition	No of Subjects & %	P value
Hypertension	39 (25%)	1.00 (NS)
Diabetes	34 (21%)	0.4929 (NS)
IHD	11 (7%)	0.3764 (NS)
Anemia	9 (5.7%)	0.3310 (NS)
RHD	4 (2.5%)	0.7200 (NS)
COPD/ Asthma	4 (2.5%)	0.4781 (NS)
Restrictive lung disease	2 (1.28%)	0.7200 (NS)
Hypothyroidism	3 (1.9%)	0.0641(NS)
Hyperthyroidism	1 (0.64%)	-
Carcinoma Breast	1 (0.64%)	-
Ante Natal Cases	10 (6.4%)	
Post Natal Cases	5 (3.2%)	

Of these 3 ANC patients in third trimester succumbed. Comorbid conditions were equally present in Survivors and Non-Survivors. No statistical significance was found between mortality

and comorbid conditions on logistic regression analysis. *(Table 3)*

134 patients had bilateral chest signs on admission and 22 patients had unilateral chest signs. These were seen as opacities on chest X-ray examination.

Table 4 : **Mean SPO2 / FiO2 Ratio on admission in Survivors and Non Survivors**

SPO2/ FiO2 Ratio	Total	Survivors	Non-Survivors
>400	70	68	2
316-400	45	20	25
236-315	12	4	8
150-235	15	8	7
<150	14	4	10

Mean SPO2 / FiO2 ratio on admission was 393.5+100.23 in Survivors as compared to 277.88+105.46 in Non-Survivors (p= <0.0001) *(Table 4)*

SPO2 was normal in 30 patients on admission despite their chest signs and they did not require oxygen supplementation, all these survived. Oxygen by Reservoir Face Mask was required for 49 patients for maintenance of their SPO2 above 90% and all these patients survived and were discharged.

NIPPV with oxygen was required for maintenance of oxygenation of 77 patients of these 23 got progressively better and were weaned off

successfully and discharged. The SpO2 / FIO2 ratio on admission in Survivors was significantly better than those in Non-Survivors (p=<0.0001). *(Table 5)*

Table 5 : **Oxygenation Support in Study Subjects**

|	Total (n=156)	Survivors	Non- Survivors
No O2 Supplement	30 (19.2%)	30 (19.2%)	-
O2 Bag and Mask	49 (31.4%)	49 (31.4%)	-
O2 + NIPPV	23 (14.7%)	23 (14.7%)	-
O2 + NIPPV + Invasive ventilation	34 (21.7%)	2 (1.2%)	32 (20.5%)
Invasive Ventilation	20 (12.8%)	-	20 (12.8%)

57 patients received NIPPV during their admission; 23 of these could be successfully weaned off. 34 patients did not maintain oxygenation on NIPPV and had to be put on invasive positive pressure ventilation. 20 patients were managed with invasive ventilation on admission itself. Of the 54 patients who were managed with invasive ventilation only 2 could be successfully weaned off and were discharged.

The Oxygenation status in Survivors was better than Non- Survivors on admission but it deteriorated over the first few days (p=<.001) and then improved. However in Non-Survivors the oxygenation status deteriorated further after admission and it did not improve despite treatment and ventilation. High FiO2 was required for oxygen saturation maintenance. *(Table 6) (Fig. 5)*

Table 6 : **SPO2 / FiO2 Ratio in Study Subjects**

	Survivors			Non - Survivors		
	Mean SPO2	**Mean FiO2**	**SPO2 / FiO2 Ratio**	**Mean SPO2**	**Mean FiO2**	**SPO2/ FiO2 Ratio**
Day1	91.18+9.37 (n=104)	26+12.92	394.27+100.23	67.80+16.09 (n=52)	31.63+ 25.55	277.88+105.46
Day3	96.54+ 2.55 (n=95)	41.33+22.75	312.20+151.88	85.37+8.00 (n=41)	85.24+15.93	104.7 + 26.70
Day5	95.96+ 5.99 (n=80)	33.46+17.41	352.27+134.90	82.04+12.93 (n=26)	83.62+16.86	104.06 + 33.65
Day7	96.20+ 3.26 (n=51)	29.78+15.02	377.43+118.61	85.76+12.12 (n=17)	83.24+14.28	112.66+46.77

Figure 5 : **SPO2/ FiO2 Ratio Trends in Survivors & Non-Survivors over 7 days**

SPO2 / FiO2 Ratio
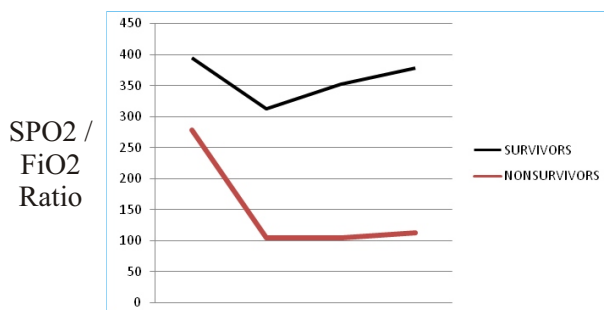
WBC count was normal in 98 (62.9%), Leucopenia on admission was found in 26 patients (16.6%) out of which 7 patients expired. However the p value was NS in survivors and non survivors. 32 patient had leukocytosis out of which 23 patients expired. It is found that patient with sepsis have 8.3 times more mortality risk when compared to patient without sepsis. (p< 0.001)

Organ dysfunction other than respiratory was found in 36 patients of which 23 succumbed. The risk of mortality was 5.5 times more in patients with MODS compaired to patients without.(p=0.001)

Discussion -

Resurgence of H1 N1 - Influenza this winter led to a situation of panic across the nation affecting the young population. It pushed the health care machinery for prompt management of the rapidly increasing number of patients, along with vaccination of the health care workers and education of the lay public at large[6].

The first spurt in admissions was seen in January that increased rapidly in the month of February with gradual decrease in admission rate as temperature increased from March to April.

156 H1N1 positive patients in Category C were hospitalised at Government Medical College Nagpur and were managed in the Swine Flu Isolation Intensive Care Unit with Dedicated Staff.

Patients in category A were confined to home and not treated with oseltamivir. Patients in category B were also home confined, but were treated with oseltamivir.More number of females were admitted and succumbed as compared to male patients.

115 (73.7%) patients were from Nagpur. 41 (26.3%) patients were from the adjoining places of Vidarbha like Wardha, Bhandara, Yavatmal, Gadchiroli, Hinganghat, Amravati, Akola and Madhya Pradesh like Betul, Chindwara, Seoni, Balaghat over a radius of 250kms.

Category C patients were hospitalized within the isolation facility started immediately on Oseltamivir 150 mgm twice daily along with a broad-spectrum antibiotic, tested for H1N1, and supportive treatment.

The most common presenting complaints were fever, cough and breathlessness and additionally few patients had pain in abdomen with nausea, vomiting and diarrhea. The mean interval from symptom onset to hospitalization was 6 days in the study done by Regan et al,[7] the mean interval from symptom onset to hospitalization was 3 days, whereas Fajardo-Dolci et al from Mexico in 2009 reported a mean interval of 6.3 days.[8]

A high mortality of 33.33% was observed in patients. The mortality was 24% in patients who came directly and early in the course of the disease to the hospital and received bed rest and early care. However the mortality was significantly higher (45%) in patients who came after 5 days of symptom onset and after taking treatment outside. Raman Sharma et al in their study of H1N1 patients hospitalized at SMS Jaipur in January and February 2015 found a mortality of 48.6% in Category C patients[9]. However in the study by Mahendra Singh et al of H1N1 patients admitted during 2012-13 a mortality rate of 18.5% was found at Jodhpur[10]. Hence the virulence of the organism this season was more than that during the interim period.

66.66% of patients had co-morbid conditions but these were spread out equally in survivors and Non-Survivors. Other authors found comorbid condition in 64.5% of their patients who succumbed in their study at SMS Jaipur.[11, 12]

Patients not maintaining oxygen saturation were given oxygen and ventilatory support. Patients maintaining oxygen saturation were given an N95 Mask to prevent spread of infection.

The Oxygenation status at admission was significantly poorer in Non-Survivors at admission itself. 77 (49%) of hospitalized patients required ventilatory support based on the condition at the time of presentation, ABG reports and SpO2 levels.

The Survivors after showing some initial decline in their oxygenation status later improved with the given modality of treatment. However with the initial poor oxygenation status in the Non-Survivors it declined further even with ventilator support and did not improve during the course of stay. They were managed with Noninvasive and invasive ventilation with low inspiratory tidal volume, high PEEP, rapid rates, and long inspiratory time maintaining the plateau pressures below 30 mmHg.

All 52 Non-Survivors had respiratory failure and were on invasive ventilatory support. This was compounded in some with multiorgan failure and sepsis. MOF was found in 36 (23%) patients of which 23 succumbed and Sepsis was found in 32 (20.5%) of which 23 succumbed Raman et al found sepsis in 21.12% of their patients. MOF and Sepsis increased the risk of mortality by 5.5 and 8.3 times respectively.

The mean duration of hospital Stay was 5.5+4.73 days as compared to 6.79+4.12 days in survivors

Conclusions & Recommendations -

There were a significant proportion of cases that progressed rapidly and succumbed early in the disease course despite treatment in this flu season. Patients who reported late had a higher mortality rate. The main cause of mortality was respiratory failure compounded by sepsis and Multi organ failure in some.

Early referrals for Category C patients to centers equipped with facilities to handle such emergencies may help in mitigating outcome.

Early detection, home isolation / quarantine, hand hygiene, cough etiquette, maintaining safe distance from infected patients, antiviral drugs for Category B patients are recommended.

The number of visitors in Swine flu isolation is to be restricted. Medical and Nursing staff involved in Clinical Care are to be equipped with Triple layer surgical mask, along with other Personal Protective Equipment (PPE). However, if the staff is involved in any aerosol generating procedures like suction, intubation, nebulization etc. they should use N95 Respirator Mask. Health care workers and close family contacts are to be provided with antiviral prophylaxis with 75 mg of Oseltamivir till 10 days after last exposure with a maximum period of 6 weeks.

Vaccination of high-riskand pregnant females is recommended annually before the onset of flu season. Efficacy of vaccine is about 70-80% and takes about 2-3 weeks for development of immunity.

Effective communication between medical fraternity and administrative officials for provision of adequate Isolation ICU beds, Central Oxygen ports, and Mechanical Ventilators is to be done so that the treating agencies are well equipped to deal effectively with the emergency when it strikes.

Factors that contribute to rapid progression like virulence, drug resistance, or structural reformation of the virus, and host factors should form the epicenter of focus for further research and scientific development.

Acknowledgment -

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