ejpmr, 2017,4(6), 425-435

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

"A RETROSPECTIVE EVALUATION OF CLINICAL PROFILE AND EFFECTIVENESS OF OSELTAMIVIR IN H1N1 POSITIVE PATIENTS."

Dr. Vishnugiri Goswami*, Dr. Madhu Panjwani and Dr. Krishna Lakhani

Govt. Medical College, Bhavnagar, India.

***Corresponding Author: Dr. Vishnugiri Goswami**

Govt. Medical College, Bhavnagar, India.

Article Received on 05/04/2017 **Article Revised on 25/04/2017** **Article Accepted on 15/05/2017**

ABSTRACT

Objectives: To evaluate Clinical profile in H1N1 positive patients and effectiveness of Oseltamivir started within 48 hours and after 48 hours of onset of symptoms in H1N1 positive patients. **Materials and methods:** A retrospective study from Indoor cases of H1N1 positive patients (Total 141), were collected from the medical record section of Sir Takhatsinhji general hospital, Bhavnagar and scrutinized. H1N1 positive (category C; RT-PCR confirmed) patients admitted from June 2014 to April 2015 were included in the study. Data were collected in standard case record form like Demographic details, Duration of symptoms, Laboratory and X-ray findings, Treatment given, Various Complications after admission and Clinical outcome. **Results:** In this study total 141 patients were evaluated retrospectively among whom most of the patients were young adults like age group of 21 to 40 yrs, more residing in Urban area and gender affected was relatively equal, Total 23 patients died due to further complications and this study shows that 18 patients were with co-morbidities. Only 5 patients who died had no pre-existing history of co-morbidities. Most common symptoms were cough followed by fever, difficulties in breathing, sore throat and nasal catarrh. Other less dominant symptoms include Headache, Hemoptysis, Bodyache, Abdominal pain, Diarrheoa and Vomiting. There is significant association found between treatment (oseltamivir) given within 48 hours of symptoms onset and outcome among the swine flue patients. (p value is less than 0.05 at 1 DF and chi square value is 108.10 at 95% CI). There is significant association found between co morbidity and death among the swine flue patients. (p value is less than 0.05 at 1 DF and chi square value is 12.064 at 95% CI). **Conclusion:** In this study 141 patients were evaluated retrospectively among whom most of the patients, Most common symptoms were cough followed by fever, difficulties in breathing, sore throat and nasal catarrh. Death is more prevalent in those patients who have pre existing co-morbid conditions. Patients involved in this study have been treated with Oseltamivir and other supportive management, but patients who admitted within 48 hours of symptoms onset had better outcome and who were late after 48 hours of symptoms onset had developed complications more. And some patients died due to life threatening complications.

KEYWORDS: swine flu, oseltamivir, H1N1 influenza.

❖ *INTRODUCTION*

- Swine flu is a highly contagious respiratory disease caused by swine influenza A H1N1 virus.
- WHO declared H1N1 / Swine flu pandemic in 2009. And it was its beginning in mexico in march 2009 and in august 2010. Then after WHO declared swine flu officially over but actually it is still ongoing as of 2015.
- In late 2014 to early 2015, H1N1 swine flu outbreak created great panic in india. During that outbreak virus had a change in its amino acids sequences and Linked to enhance virulence.
- The most affected states in India were Gujarat, Rajasthan, Delhi, Maharashtra, Madhya Pradesh, Telangana, Karnataka and West Bengal. During that outbreak, Total number of cases crossed 30000 with a death of near about 2000.[4,5]
- India confirmed its first case on May 16, 2009, when a man travelling from New York via Dubai and Delhi tested positive for the H1N1 Influenza virus in Hyderabad. The second case was reported by the National Institute of Virology (NIV), Pune, in a mother and son duo from Chennai on 1 June 2009.
- From Gujarat, first H1N1 positive confirmed case was reported in June 2009.
- This study was designed to assess various clinical presentation H1N1 influenza virus infection and outcome with effectiveness of oseltamivir.

❖ *MATERIALS AND METHODS*

- **Study design:** Retrospective analysis.
- **Sample size:** Total 141 cases.
- Indoor cases of H1N1 positive patients (Total 141) will be collected from the medical record section

and scrutinized.

- H1N1 positive (category C; RT-PCR confirmed) patients admitted from June 2014 to April 2015 will be included in the study.

- ***Following data will be collected in standard case record form:***
- Demographic details
- Duration of symptoms
- Laboratory and X-ray findings
- Treatment given
- Various Complications after admission
- Clinical outcome.

❖ *RESULTS*

In the present study which involved 141 patients of Swine influenza A H1N1 positive confirmed by RT PCR assay testing, admitted at swine flu ward Sir Takhatsinhji General Hospital Bhavnagar were evaluated in relation to Age & Gender, Residence, Clinical features / Profile, Addiction like Smoking and Alcohol, Associated illness like Diabetes Mellitus, Hypertension, Renal failure, Ischemic heart disease and Respiratory illness like Chronic obstructive pulmonary disease, Bronchial Asthma, Complications by progression of the disease, X -ray Chest Findings, Laboratory investigations and its co-relation And Effectiveness of Oseltamivir, Starting (< 48 hrs and > 48 hrs. of symptoms started) of Drug as a treatment as early as symptoms were observed. It was compared with other studies too.

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). 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.

Among total number of 141 patients, 26 patients were got complicated and put on Ventilator, from which total 23 patients were died due to further complications. Most common complications were Bilateral Pneumonia which lead to Acute Respiratory Distress Syndrome (ARDS) and Hypoxic Respiratory Failure as well as some had developed Multi Organ Dysfunction Syndrome (MODS) along with ARDS.

1. Age

In this study total 141 patients were evaluated retrospectively among whom most of the patients were young adults like age group of 21 to 40 yrs. (43.26%) followed by 41 to 60 yrs. (32.12%). and others groups include 1 to 20 yrs. (16.31%) and more 60 yrs. (7.8%).

Table no.1 Age distribution of patients

Age (Years)	Total Patients	Percentage (%)
1-20	23	16.31%
21-40	61	43.26%
41-60	46	32.62%
>60	11	7.8%

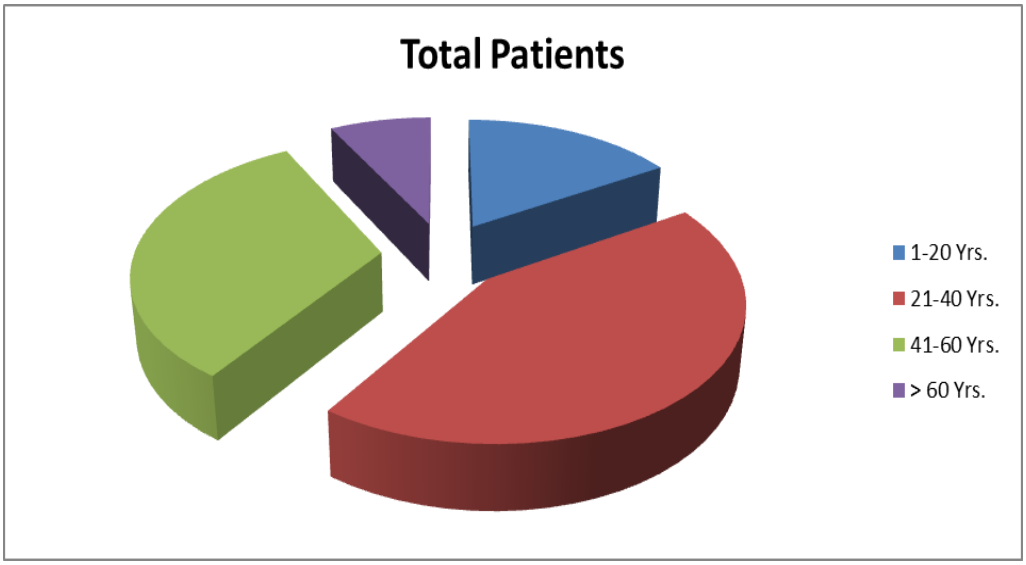

Chart no. 1 Age distribution of patients

2. Sex

In present study, Female (51.06%) were affected and Male (48.94%) were affected. F: M ratio in positive cases was around 1.04:1.

Table no.2 Sex distribution of patients

• Sex	Patients	Percentage
Male	69	48.94%
Female	72	51.06%

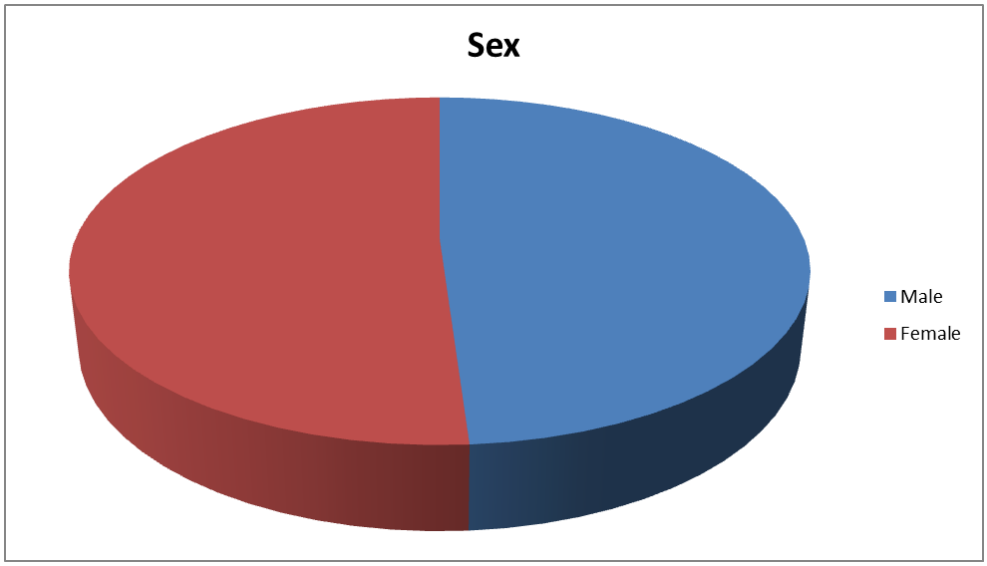

Chart no. 2 Sex distribution of patients

3. Residence

In present study, Among 141 total number of patients, 95 (67.37%) patients were residing in Urban area and rest 46 (32.63%) were residing at Rural area.

Table no. 3 Residence

Residence	Total Patients	Percentage (%)
Urban	95	67.37 %
Rural	46	32.63 %

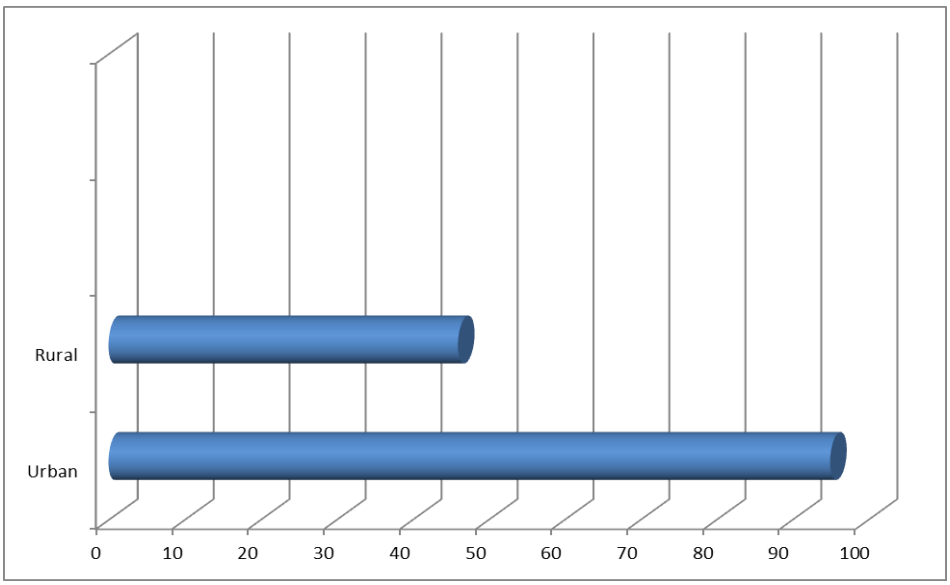

Chart No. 3 Residence

4. Addiction

Among total 141 patients, 29 (20.57%) patients were smokers, 5 (3.55%) patients were alcoholic and 107 (75.89%) patients has no history of any addiction.

Table No. 4 Addiction

Addiction	Total Patients	Percentage (%)
Smoking	29	20.57 %
Alcohol	05	3.55 %
Both	34	24.11 %
None	107	75.89 %

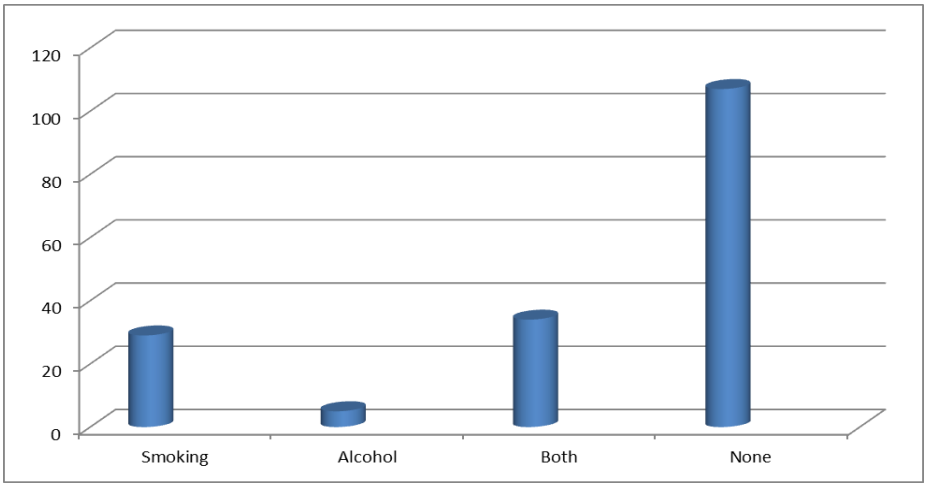

Chart no. 4 Addiction

5. Associated Illness (Co-morbid conditions)

In this study, total 141 patients were evaluated, from which 22 (15.6%) had Diabetes mellitus, 17 (12.05%) had Hypertension, 32 (22.70%) had Chronic obstructive pulmonary disease, 04 (02.84%) had Asthma, 34 (24.11%) had Ischemic heart disease, 12 (08.51%) had Reanl failure (Acute/Chronic), 07 (04.96%) were pregnant women, 08 (05.67%) had H/O Tuberculosis. Total 23 patients were died due to further developed complications and this study shows that 18 patients were with above mentioned co-morbidities. Only 5 patients were died who have no pre-existing history of any above mentioned co-morbidities.

Table no. 5 Associated Illness

Associated Illness	Total Patients	Percentage (%)
Diabetes Mellitus	22	15.6 %
Hypertension	17	12.05 %
COPD	32	22.70 %
Asthma	04	02.84 %
Ischemic Heart Disease	34	24.11 %
Renal Failure	12	08.51 %
Pregnancy	07	04.96 %
Tuberculosis	08	05.67 %

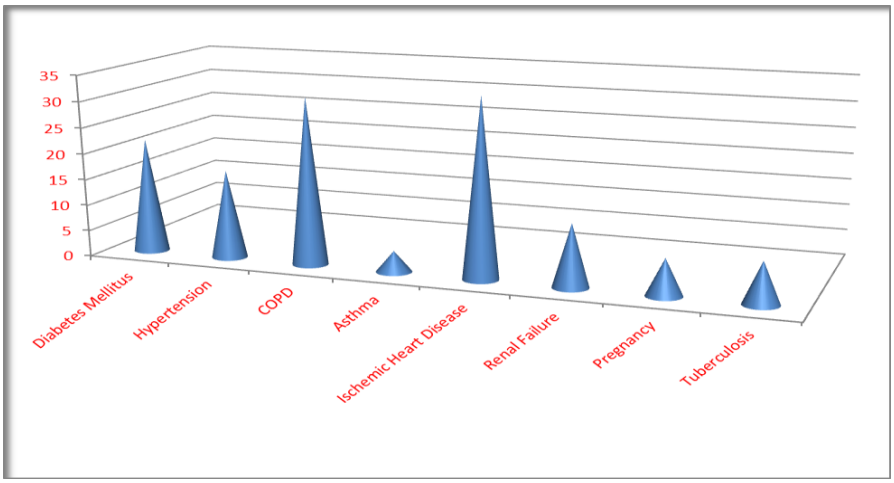

Chart No. 5 Associated Illness

6. Chest X-Ray Findings

In present study, Bilateral (B/L) consolidation (55.3%) was noticed in most number of positive cases followed by left sided (19.86%) and right sided (15.6%) consolidation, while 9.22% cases were identified without consolidation (Normal).

Table no.6 Chest X-ray findings

Chest X- ray Findings	Total Patients	Percentage (%)
B/L Consolidation	*78*	*55.30 %*
Left sided Consolidation	*28*	*19.86 %*
Right sided Consolidation	*22*	*15.60 %*
Normal	*13*	*9.22 %*

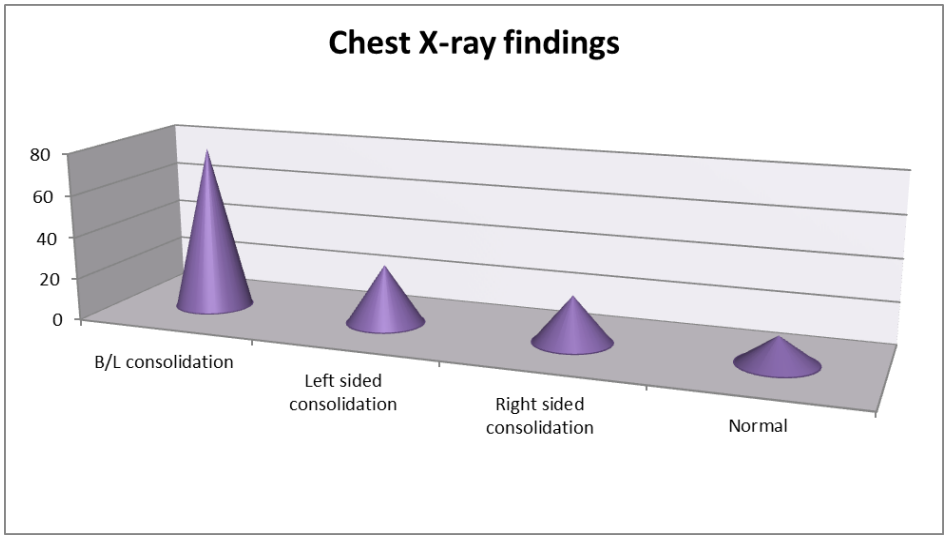

Chart no. 6 Chest X-ray findings

7. Clinical Features

In present study, predominant symptoms in confirmed cases of H1N1, Most common symptoms were cough (95.74%) followed by fever (92.20%), difficulties in breathing (90.78%), sore throat (71.63%) and nasal catarrh (44.68%). Other less dominant symptoms include Headache, Hemoptysis (4.25%), Bodyache (5.67%), Abdominal pain (6.38%), Diarrheoa (4.25%) and Vomiting (8.50%).

Table no.7 Clinical features

Clinical features	Total Patients	Percentage (%)
Cough	**135**	**95.74 %**
Fever	**130**	**92.20 %**
Breathlessness	**128**	**90.78 %**
Sore throat	**101**	**71.63 %**
Nasal catarrh	**63**	**44.68 %**
Headache	**08**	**5.67 %**
Hemoptysis	**06**	**4.25 %**
Bodyache	**08**	**5.67 %**
Abdominal Pain	**09**	**6.38 %**
Diarrheoa	**06**	**4.25 %**
Vomiting	**12**	**8.50 %**
Others	**00**	**0**

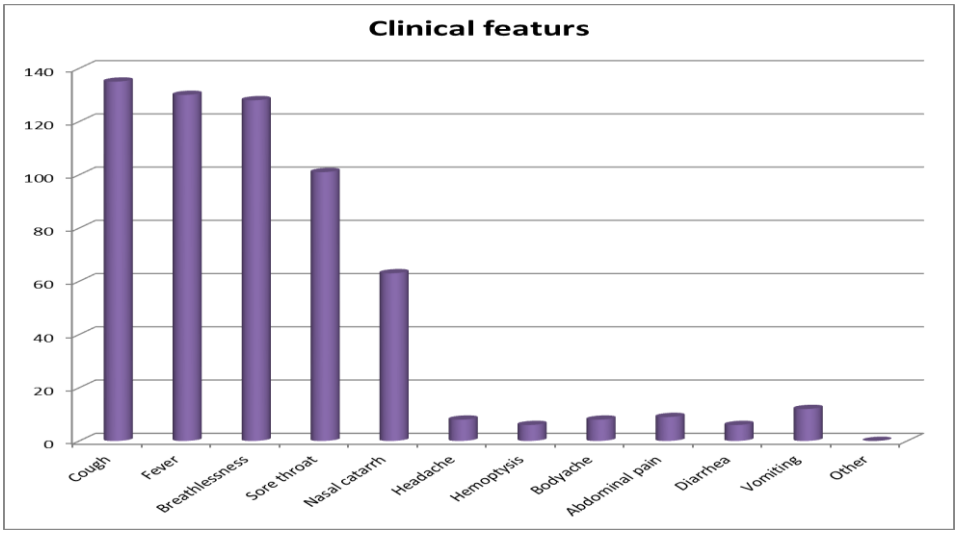

Chart no.7 Clinical features

8. Vital Signs

In present study, few important vital signs had been observed which suggest that 95.74% patients had ≥100`F Temperature, 68.79% patients had Tachycardia (Normal pulse rate 60-100 / min,), 69.50% patients had Tachypnoea (Normal Resp. Rate 16-22/min.), 24.82% patients had <95% of oxygen saturation among whom most of the patients developed complications and needed Mechanical Ventilation support and most of them were died and 79.43% patients had Abnormal Breath Sounds like Crepitations and Rhonchi.

Table no. 8 Vital Signs

Vital Signs	Normal	Abnormal	Patients with Abnormal Findings	Percentage (%)
Temperature(F`)	< 100	≥100	135	95.74 %
Pulse(/min)	60-100	>100	97	68.79 %
Respiratory Rate(/min)	16-22	>22	98	69.50 %
SpO2(%)	≥95	<95	35	24.82 %
Breath Sounds	Normal	Crepitations / Rhonchi	112	79.43 %

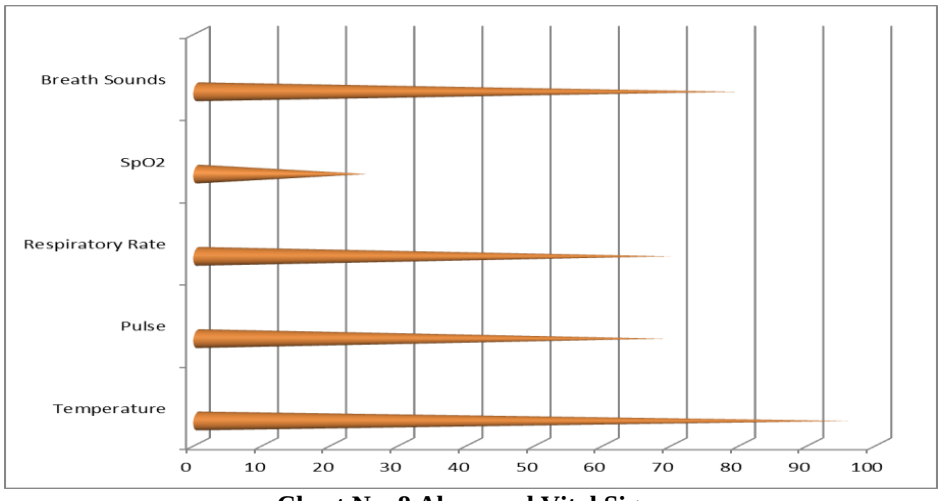

Chart No. 8 Abnormal Vital Signs

9. WBC count

In present study we have observed that most of the patients have leucopenia or near lower range of ideal white blood count. We have divided it into two parts as follows.

Table no. 9 Total leucocyte Count

WBC count	Total Patients	Percentage (%)
<6000 / cumm	103	73.05%
≥6000 / cumm	38	26.95%

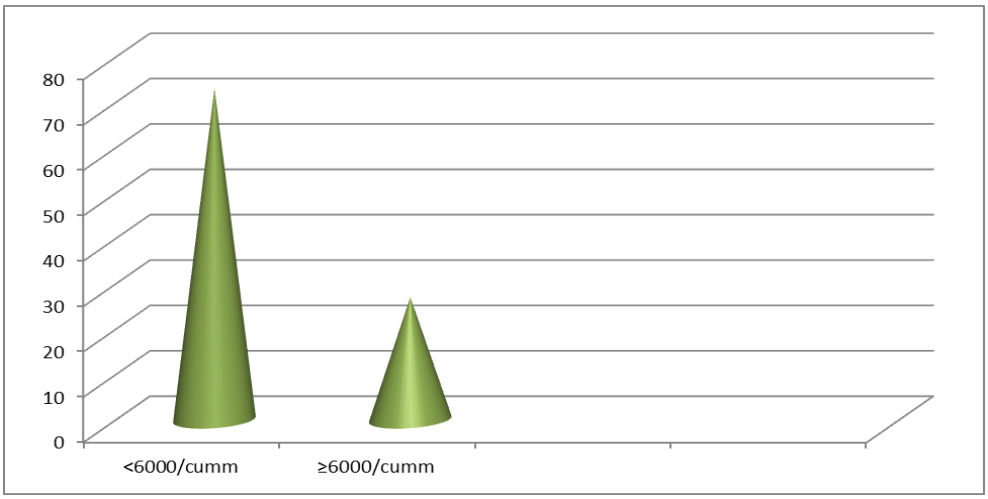

Chart No. 9 Total leucocyte Count

10. Arterial Blood Gas Analysis

In present study, All patients had been evaluated for Arterial Blood Gas Analysis and found that those had died because of further complications had Metabolic Acidosis and Respiratory Acidosis on admission.

Table No. 10 Arterial Blood Gas Analysis

ABG Report	Total Patients	Percentage (%)
Metabolic Acidosis	12	8.51%
Respiratory Acidosis	16	11.35%
Normal	113	80.14%

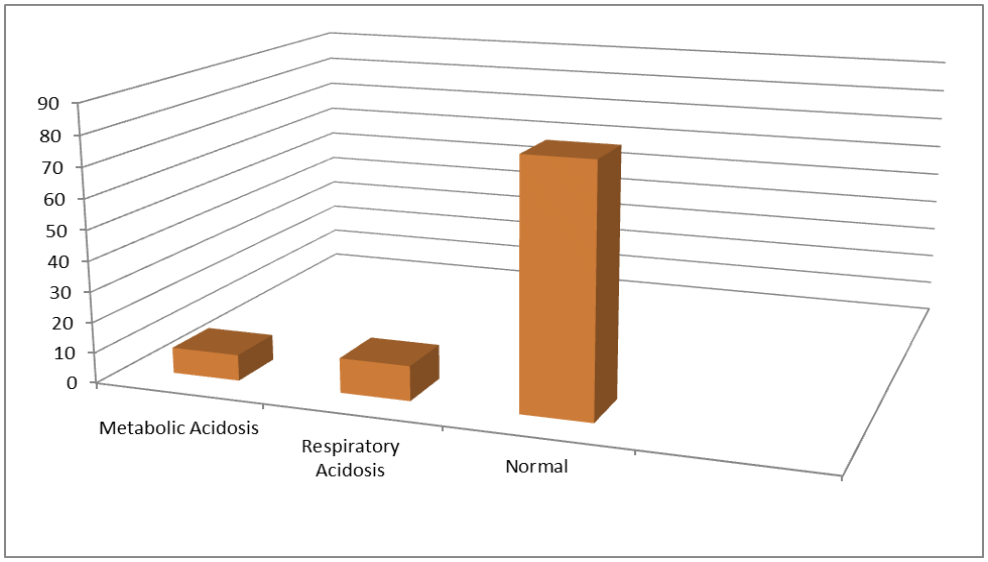

Chart no. 10 Arterial Blood Gas Analysis

11. Effectiveness of Oseltamivir

Patients involved in the study are 141 and out of them 115 patients have been treated with Oseltamivir and other supportive management within 48 hours of symptoms arised. These all patients had been well managed and less complicated. However, 26 patients who admitted late after 48 hours of symptoms arised were also treated for the same but complications developed more in later patients and most of the patient were died.

Table no. 11 Effectiveness of Oseltamivir

Effectiveness of Oseltamivir	Total Patients	Discharge	Death
Given within 48 hrs.	115	115	00
Given after 48 hrs	26	3	23

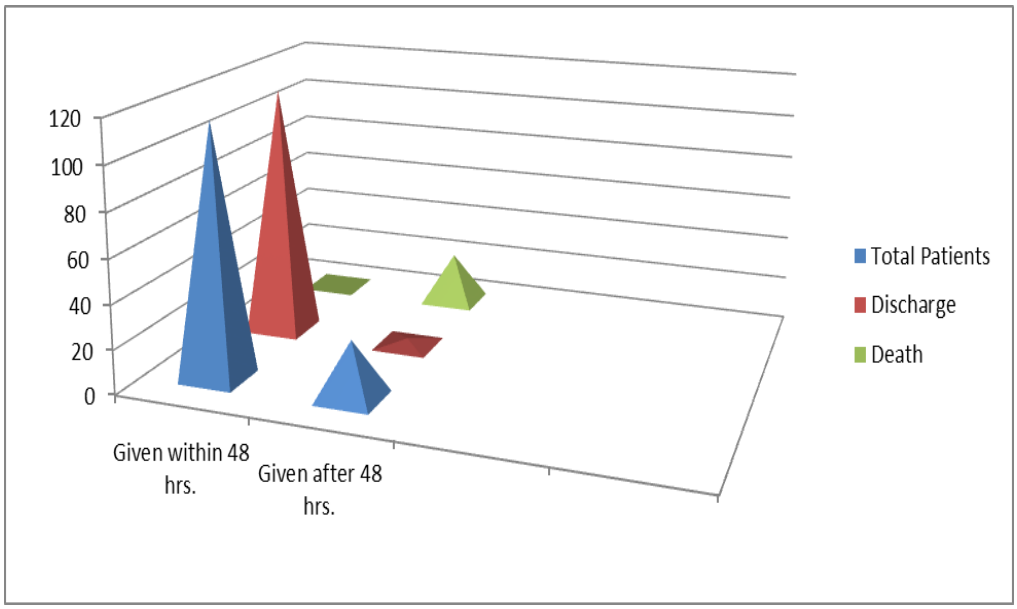

Chart no. 11 Effectiveness of Oseltamivir

❖ DISCUSSION

141 cases of swine flu Influenza H1N1 were studied retrospectively.

Statistical data of age, sex, residence, clinical features, vital parameters, laboratory investigations & effectiveness of oseltamivir in patients were studied, and compared with those published in the literature.

Table 12: Age, sex distribution compared to other studies of swine flu

Sr. No.	Authors	No of cases	M:F	Age range
1	Suendrakumar	181	1:1.13	0-70 years
2	Kadam, Borse&samgle	100	1:1.13	0-73 years
3	Shrinivasan&Rajindaran	442	1.25:1	0-65 years
4	Present study	141	1:1.04	0-80 years

The age of the patients ranged from 0 to 80 years with a mean age of 36.72years.

Swine flu were observed more in females (48.94%) than males (51.06%) with M:F ratio of 1:1.04. Age and sex distribution were comparable with other studies of swine flu.

Table 13: Clinical features compared to other studies

Clinical findings	Kadam study	Shrinivasan study	Present study
Cough	96%	95%	95.74%
Fever	95%	82.32%	92.20%
Breathlessness	83%	32.8%	90.78%
Sore throat	34%	26.7%	71.63%
Nasal catarrh	26%	-	44.68%
Headache	-	-	5.67%
Hemoptysis	9%	-	4.24%
Bodyache	15%	-	5.67%
Abdominal pain	-	-	6.28%
Diarrhea	6%	-	4.25%
Vomiting	11%	-	8.25%

The most common clinical feature in the present study was cough(95.74%), fever (92.20%), breathlessness (90.78%) and sore throat (71.63%).

The presenting symptoms were usually attributed to involvement of both upper and lower respiratory tract involvement.

Clinical features were comparable with other studies, though nasal catarrh was found in more cases in present study.

Table 14: Associated co-morbidities compared to other studies

Co-morbidities	Surendrakumar study	Kadam study	Shrinivasan study	Present study
Diabetes mellitus	5%	19.05%	6.9%	15.6%
Hypertension	6%	17.06%	7.2%	12.05%
COPD	11%	3%	-	22.7%
Asthma	-	-	-	2.84%
Ischemic heart disease	8%	4%	-	24.11%
Renal failure	1.8%	-	-	8.5%
Pregnancy	9%	13%	2.71%	4.96%
Tuberculosis	1%	-	8.8%	5.67%
Smoking	-	-	8%	20.57%
Alcohol	-	-	10.4%	3.55%

The variations in the co-morbid condition associated with swine flu is due to geographic area, immunity level and genetic difference etc.

The commonest illness were Hypertension and Diabetes mellitus reported from various studies throughout the world.

We encountered more cases of Renal failure due to in our area is costal area so having hard water.

❖ *CONCLUSION*

In the present study which involved 100 patients of Swine influenza A H1N1 positive confirmed by RT PCR assay testing, admitted at swine flu ward Sir Takhatsinhji General Hospital Bhavnagar were evaluated in relation to Age & Gender, X-ray Chest Findings, H/O Migration, Clinical Profile And Effectiveness of Oseltamivir, starting (< 48 hrs and > 48 hrs. of symptoms started) of Drug as a treatment as early as symptoms were observed. It was compared with other studies too.

In this study total 100 patients were evaluated retrospectively among whom most of the patients were young adults.

Males and females were around equally affected. Male and female were equally affected for H1N1 infection in this area may be due to outdoor work by both gender.

In present study Bilateral (B/L) consolidation was noticed in most number of positive cases followed by left sided and right sided consolidation, while cases were identified without consolidation (Normal).

We have also noticed that most of the patients involved in this study have migrated or travelled recently or attended the public gathering function.

Most common symptoms were cough followed by fever, difficulties in breathing, sore throat and nasal catarrh. Other less dominant symptoms include Headache, Hemoptysis, Bodyache, Abdominal pain, Diarrhea and Vomiting.

Patients involved in the study have treated with Oseltamivir and other supportive management within 48 hours of symptoms arised successfully but few patients who admitted late after 48 hours of symptoms arised were also treated for the same but complications developed more in later patients. And some patients died due to life threatening complications.

The data was taken only from hospitalized patients. Patients belonging to category B, treated on outpatient basis and not being tested, were not included. All diagnostic testing was clinically driven, and other investigations were not obtained in a standardized fashion. Despite the use of a standardized data collection form, not all information was collected for all patients.

Present study will help clinician to identify swine flu on clinical basis. Study highlights the identification of swine flu (Influenza A, H1N1 subtype) on clinical basis and emphasizes early initiation of antiviral treatment without waiting laboratory support, immunisation and special precautions.

❖ *REFERENCES*

1. Ministry of Health & Family Welfare, Pandemic Influenza A (H1N1), Guidelines on categorization of Influenza A H1N1 cases during screening for home isolation, testing treatment and hospitalization (Revised on 05.10.09) available from http://nvbdcpchd.gov.in/reporting%20formats/3.Categorisation%20of%20Influenza%20A%20H1N1%20cases%20screening.pdf (last accessed on 6

November, 2012). Swine influenza A (H1N1) virus infection in two children- Southern California, March-April 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 400-402.
2. Outbreak of swine-origin influenza A (H1N1) virus infection - Mexico, March-April 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 467-470.
3. Bronze MS, H1N1 influenza (swine flu). Available from http://emedicine.medscape.com/article/1807048-overview (last accessed on 18 January, 2012.
4. World Health Organization. Influenza A (H1N1) – Update 14. Geneva.2009. Available from: http://www.who.int/csr/don/2009_05_04a/en/index.html (last accessed on 2010 Feb 27).
5. Ministry of Health and Family Welfare, Government of India. Human swine influenza: A pandemic threat. CD Alert. 2009; 12: 1-8.
6. The Times of India. First swine flu case surfaces in Gujarat.18th June, 2009. Available from: http//timesofindia.indiatimes.com/city/ahmedabad/First- swine flu- case- surfaces- in-Gujarat/articleshow/4669250.cms.[Last accessed on May 01,2010].
7. The Indian Express. Saurashtra`s first confirmed swine flu case detected. 19th August, 2010. Available from: http://www.expressindia.com/latest-news/saurashtras-first-confirmed-swine-flu-case-detected-in-bhavnagar/503678/ [last accessed on 2010 Feb 27].
8. Swine influenza A (H1N1) virus infection in two children- Southern California, March-April 2009. MMWR Morb Mortal Wkly Rep 2009; 58: 400-402.
9. World Health Organization. CDC protocol of real time RTPCR for swine influenza A (H1N1). Geneva. April 28, 2009. Available from: http://www.who.int/csr/resources/publications/swine flu/CDCrealtimeRTPCRprotocol_20090428.pdf[last accessed on 2010 Jan 15].
10. Revdiwala S, Mulla S, Panwala T, Shah L, Shah A. Clinical Characterisation Of H1N1 Influenza Taqman Real Time PCR Positive Cases. National Journal of Medical Research. 2012; 2(1): 12-14s.
11. Srinivasa R, Malini J, Nandini S, Umapathy B. Profile of H1N1 infection in a tertiary care centre. Indian Journal of Pathology &Microbiology 2011; 52(2): 323-325.
12. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 2003; 163: 1667–72.
13. Gelotar PS. Epidemiological and Clinical profile of patients with swine flu (Influenza A, H1N1) attending Guru Govindsingh Government Hospital, Jamnagar, India. J Res Med Den Sci 2013; 1: 1-6.
14. Bellei NC, Cabeca TK, Carraro E, Goto JM, Cuba GT, Hidalgo SR, et al. Pandemic H1N1 illness prognosis: evidence from clinical and epidemiological data from the first pandemic wave in Sa˜o Paulo, Brazil. Clinics. 2013; 68(6): 840-845.
15. Chudasama RK, Patel UV, Verma PB, Amin CD, Shah HM, Banerjee A, Patel RR. Characteristics of Fatal Cases of Pandemic Influenza A (H1N1) from September 2009 to January 2010 in Saurashtra Region, India. *Online J Health Allied Scs.* 2010; 9(4): 9.
16. Centers for Disease Control and Prevention (CDC). Swine influenza A (H1N1) infection in two children-Southern California, March-April 2009. MMWR Morb Mortal Wkly Rep. 2009; 58: 400-2.
17. Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A (H1N1)influenza viruses circulating in humans. *Science.* 2009; 325: 197-201.
18. Khanna M, Kumar P, Choudhary K, Kumar B. Emerging influenza virus: A serious global threat. *J Biosci.* 2008; 33: 475-82.
19. A Puvanalingam, C Rajendiran, K Sivasubramanian, S Ragunanthanan, SaradaSuresh, S Gopalakrishnan. Case Series Study of the Clinical Profile of H1N1 SwineFlu Influenza. *JAPI*, 59: 2011.
20. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. *JAMA.* 2005; 294: 2188-94.
21. Custer JW, Rau RE, eds. The Harriet Lane handbook. 18th ed. Philadelphia: Elsevier Mosby, 2009.
22. Hanshaoworakul W, Simmerman JM, Narueponjirakul U, et al. Severe human influenza infections in Thailand:oseltamivir treatment and risk factors for fatal outcome. PLoS One, 2009; 4: e6051.
23. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet.* 2009; 374: 451-58.
24. Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: Systematic review and meta-analysis. BMJ 2009; 339: b5106.
25. Godlee F, Clarke M. Why don't we have all the evidence on oseltamivir? BMJ 2009; 339: b5351.
26. Doshi P. Neuraminidase inhibitors—The story behind the Cochrane review. BMJ 2009; 339: b5164.
27. Cohen D. Complications: Tracking down the data on oseltamivir. BMJ 2009; 339: b5387.
28. Smith J. Roche replies to the authors of the Cochrane review on oseltamivir. BMJ 2009; 339: b5364.
29. Smieja M. ACP Journal Club. Review: Neuraminidase inhibitors relieve influenza symptoms and reduce laboratory-confirmed influenza in healthy adults. Ann Intern Med 2010; 152: JC-211.
30. Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute

influenza—Placebo-controlled double-blind multicenter phase III trial [in Japanese]. Kansenshogaku Zasshi. [Jpn J Infect Dis] 2000; 74: 1044–61.
31. Costa-Bouzas J, Takkouche B, Cadarso-Sua´rez C, Spiegelman D. HEpiMA: A software for the identification of heterogeneity in metaanalysis. Comput Methods Programs Biomed 2001; 64: 101–7.
32. Dutkowski R, Thakrar B, Froehlich E, Suter P, Oo C, Ward P. Safety and pharmacology of oseltamivir in clinical use. Drug Saf 2003; 26: 787–801.
33. Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: A randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet 2000; 355: 1845–50.
34. Treanor JJ, Hayden FG, Vrooman PS, et al. U.S. Oral Neuraminidase Study Group. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. JAMA 2000; 283: 1016–24.
35. Taubenberger JK, Morens DM. The pathology of influenza virus infections. *Annu Rev Pathol* 2008; 3: 499–522.
36. Nobusawa E. Comparison of the mutation rates of human influenza A and B viruses. *J Virol* 2006; 80: 3675–8.
37. M atsuzaki, Y; Katsushima N, Nagai Y et al. Clinical features of influenza C virus infection in children. *J Infect Dis* 2006; 193: 1229–35.
38. Lamb RA. The gene structure and replication of influenza virus. *Annu Rev Biochem* 1983; 52: 467–506.
39. Brankston G, Gitterman L, Hirji Z et al. Transmission of influenza A in human beings. *Lancet Infect Dis* 2007; 4: 257–65.
40. S uarez, D, Spackman E, Senne D et al. The effect of various disinfectants on detection of avian influenza virus by real time RT-PCR. *Avian Dis., 47*(3 Suppl): 1091–5.
41. Influenza (Seasonal), World Health Organization, April 2009. Retrieved 2010-02-13.http://www.who.int/mediacentre/factsheets/fs211/en/.
42. R ogelio-Padilla, Daniela de La Rosa-Zamboni, Samuel Ponce de Leon et al. Pneumonia and respiratory failure from Swine-origin Influenza a (H1N1) in Mexico. *NEJM*, 2009; 361: 680-689.
43. Ghedin, Sengamalay N, Shumway M et al. Large-scale sequencing of human influenza reveals the dynamic nature of viral genome evolution. *Nature*, 2005; 437: 1162–6.
44. Wilson. Recent strategies in the search for new anti-influenza therapies. *Curr Drug Targets*, 2003; 4: 389–408.
45. Hilleman M. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. *Vaccine*, 2002; 20: 3068–87.
46. P uvanalingam A, Rajendiran C, Case series study of the clinical profile of H1N1 swine flu influenza. *J Assoc Physicians India*, 2011; 59: 14-6.
47. A nand Kumar, Ryan Zarychanski, Ruxandra Pinto et al. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. Online. *JAMA*, 12 October 2009.
48. Seema Jain, Laurie Kamimoto, Anna M et al. Hospitalised patients with 2009 H1N1 Influenza in the United States, April-June 2009. Online *N Engl J Med*, 2009; 361: 1935-44.
49. DB Kadam, SA Sangle, RT Borse et al. H1N1 Infection-largest experience from India. APIP G Medicine update. Contemporary medicine-challenges and solutions volume xxiv: Jan 2010; 373-381.
50. Bhatt KN. Study of clinical profile of novel H1N1 patients in surat district from June 2009 to March 2010. *Journal of API*, 2012; 60: 15-19.
51. R ashmi Ranjan Das, Abdus Sami, Rakesh Lodha et al. Clinical Profile and Outcome of Swine Flu in Indian Children. *Indian Pediatrics*, 2011; 48: 373-378.
52. L ouie JK, Acosta M, Winter K et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA*, 2009; 302: 1896-902.