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Medicine

FACTORS ASSOCIATED WITH ICU ADMISSION IN H1N1 PATIENTS: A STUDY OF 2015 OUTBREAK IN NORTH INDIA

KEY WORDS:

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ABSTRACT

Introduction: The resurgence of epidemic of Influenza A (H1N1) pdm 09 was phenomenal in 2015. It was mainly due to antigenic drift and reassortment. As this disease has high mortality, many patients needed ICU care. We tried to access the prognostic factors
affecting the site of patient care and adverse outcome.

Material & Method: A study of 401 patients of Influenza A(H1N1) pdm09 confirmed with RT-PCR, hospitalized during December 2014 to March 2015 were included in the study. The patients were categorized according to requirement of ICU. We compared simple demographic data like age, sex, onset of disease & delay in treatment along with clinical presentation, co-morbidities & laboratory findings in patients requiring ICU and those treated in wards.

Result: Out of 401 patients 148(36.91) required ICU & 253(63.09) were kept in wards. ICU patients were younger (38.10±14.32 years vs 41.72±15.15 years, p <0.05). Delay in start of treatment was more in ICU patient (1.91±1.06 days vs. 0.74±0.47 days, p <0.05), category C patients needed ICU (116/192) more compared to category A (9/94).Lung involvement was higher in ICU patients (56.07±23.12 % compared to 16.69±16.20%). Pregnancy & diabetes were seen in higher number of ICU patients. CPK levels were also significantly high in ICU patients compared to Non-ICU patients (254.67±314.76 IU/L and 182.17±137.26 IU/L respectively, p <0.002). (Table no.2). Similarly, serum levels of LDH were significantly higher in ICU patients compared to non ICU patients (738.65±577.06 IU/L and 608.92±436.71 IU/L respectively, p< 0.011)

Conclusion: Influenza A (H1N1) pdm09 virus affects younger population. Delayed start of treatment causes severe infection and increased mortality. Category C patients needs ICU care. Hypoxia & >50% lung involvement on radiography were associated with ICU admission. Pregnancy and diabetes were significant co-morbid conditions associated with ICU admission with higher mortality and morbidity. CPK & LDH can be used as predictors of mortality

Introduction

Influenza A viruses are classified according to the structure of their two surface antigens: haemaglutinin (H) and neuraminidase (N). There are 16 H and 9 N types of antigens. H1N1 virus is the most common subtype. Minor changes known as antigenic drifts are associated with localized outbreaks and major reassortment changes known as antigenic shifts are associated with epidemics and pandemics of Influenza A.[1]

The current pandemic (H1N1) influenza A virus is a novel H1N1 virus which is formed after genetic reassortment and comprises of 4 distinct genetic elements namely swine, human, avian and eurasian.[1] First of all, in late march 2009, an outbreak of novel virus infection was identified in Mexico.[2] In April 2009, a novel H1N1 virus was confirmed in California. In June 2009, World Health Organization declared a global pandemic due to novel H1N1 virus[3] now labeled as "Influenza A(H1N1) pdm09".

With the starting of year 2015, there had been a sudden surge in the Influenza A(H1N1) pdm09 new cases in Rajasthan and other states of North India. Most of these patients had a mild clinical illness; however, some patients had severe disease requiring hospitalization & intensive care treatment. In literature adequate data on factors associated with severe disease are lacking and little information is available to ascertain optimal management of these patients.

This study was done to identify the factors associated with intensive care unit admission among H1N1 patients.

Material and Methods

This hospital based observational analytic study was done at a tertiary care center in North India, during December 2014 to March 2015, after taking due permission of Institutional authorities. All hospitalized, confirmed cases of Influenza A(H1N1) pdm09, above 12 years of age were included in this study. The confirmed case were defined as patients suffering from symptoms of influenza and having positive throat swab test for Influenza A(H1N1) pdm09 by real time reverse- transcriptase polymerase-chain reaction (RT-PCR) test as per CDC protocol. {REF} The patient data were collected from hospital records and analyzed retrospectively using a structured format. The patients were divided in two groups: (1) patients admitted in intensive care (ICU group) & (2) hospitalized patients other than those admitted in intensive care (non-ICU group). All the cases were clinically categorized as per guidelines of National Health & Family Welfare into category A, B and C[23]. All the patients received oral Oseltamivir and were treated with antibiotics as per need. Vasopressor support was given to those who were hemodynamically unstable. Patients with hypoxia or hemodynamic instability were given ICU care. Clinical and various laboratory parameters of all the patients were recorded.

Statistical analysis:

Microsoft Excel® and SPSS® 17.0 for Windows® were used for data storage and analysis. Continuous variables were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables. Statistical significance was set at P value ≤ 0.05

Results

A total of 401 patients of Influenza A (H1N1) pdm09 were included in this study. Among them, 148 (36.91%) patients were admitted to ICU during their hospital stay and 253 (63.09%) patients didn't require ICU admission. The mean age of patients was 39.44±14.71 years (range 13-84 years). Patients requiring ICU care were significantly younger than non-ICU patients (38.10±14.32 years and 41.72±15.15 years respectively, p <0.05).Time interval between symptoms onset to start of Oseltamivir was significantly longer in ICU patients (1.91±1.06 days and 0.74±0.47 days respectively, p <0.05) indicating delay in start of Oseltamivir may have resulted in serious infection. Duration of hospitalization was also prolonged in ICU patients. (Table no.1) Mean duration of ICU stay was 4.82±4.45 days. Most

of the patients (176/401, 43.9%) were in between 26-45 year age and among them 70/176 (39.77%) needed ICU care. (Fig 1)
The patients with mild infection (Category A, 75/94 patients) didn't require ICU care while most of those with serious infection (Category C, 116/192 patients) needed ICU care. (Fig 2)

Lung involvement was also significantly more in ICU patients (56.07±23.12 % compared to 16.69±16.20% of non-ICU patients). Oxygen saturation was also lower in ICU patients (74.41±18.70% compared to 94.06±8.86 % of non-ICU patients). Death rate was higher in ICU patients (70.3%). (Table no.1)

Pregnancy was the most common co-morbid condition requiring ICU care found in 47/148 (31.8%) ICU patients. Diabetes (17, 11.5%) was also seen in significantly higher number of ICU patients. CPK levels were significantly high in ICU patients compared to Non-ICU patients (254.67±314.76 IU/L and 182.17±137.26 IU/L respectively) (p 0.002). (Table no.2)

Similarly, serum levels of LDH were significantly higher in ICU patients compared to non ICU patients (738.65±577.06 IU/L and 608.92±436.71 IU/L respectively) (p 0.011)

Discussion

This study was done among 401 Influenza A(H1N1) pdm09 patients to assess factors associated with admission in ICU.

Seasonal influenza usually affects older population while 2009 Swine flu infection mainly involves comparatively younger population[5]. In our study too, comparatively younger age group was affected as most of the patients (43.9%) were between 26-45 year age which is similar to previous studies from different geographic locations.[6-9] Patients admitted in ICU were also significantly younger than non ICU patients. A possible explanation of this age variation may be acquired immunity in older persons due to exposure to other influenza A (H1N1) viruses.[10] However, there was no gender difference observed which is similar to previous Indian studies.[11-15]

This study also highlighted the importance of early treatment with Oseltamivir as delay was associated with severe infection, ICU admission and prolonged hospitalization. This observation was in accordance with previous published reports,[16-18] which have also shown reduction in morbidity and mortality on early initiation of oseltamavir[9,19-21]

Most of the patients (75/94) with mild illness (Category A) didn't need ICU care on the other hand more than half of the category C patients (116/192) needed ICU. This observation supports the triage system/referral system of health care and suggests providing high dependency or intensive care for Category C patients.[23]

The influenza A(H1N1)pdm09 virus mainly affects the respiratory system and results in pneumonia, acute lung injury & acute respiratory distress syndrome. This manifests as fever, difficulty in breathing, fall in oxygen saturation and consolidation of lung parenchyma. In our study, patients who had a significantly lower oxygen saturation and >50% lung involvement on chest radiography, required ICU care. This finding underscores the pulmonary involvement in swine flu cases and may help in deciding their site of care (ICU/Non-ICU). This finding is in echo with United Kingdom surveillance and few other reports.[22]

In our study, pregnancy (47/148, 31.8%) was the commonest co-morbid condition & diabetes (17, 11.5%) was the next common in ICU patients. Both of these conditions also led to increased mortality as reported previously from different part of the world.[5,9,13,14,17,19-22] Pregnancy is a state of compromised immunity. Fall in oncotic pressure during last trimester and diminished ability to tolerate hypoxia are some other possible explanation for vulnerable state of pregnancy.

Mean levels of sugar, total leukocyte count, serum electrolyte levels and renal function were not significantly different in ICU and non-ICU patients but the mean levels of LDH and CPK were significantly higher in ICU patients showing their importance as markers of disease severity.[22]

Our study had some limitations. The study was conducted only among hospitalized patients at a tertiary care center and was retrospective in design so results may not represent the general population.

Conclusion

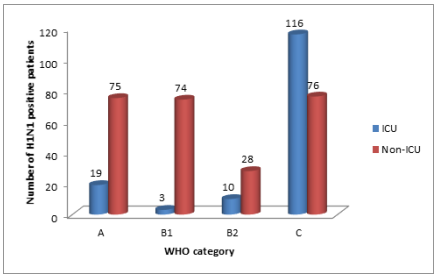
Influenza A (H1N1) pdm09 virus affects comparatively younger population. Delayed start of Oseltamivir in these cases may result in severe infection. Patients of category C should be managed with close observation in high dependency or intensive care unit. Hypoxia (low oxygen saturation) and >50% lung involvement on radiography were associated with ICU admission. Pregnancy and diabetes were significant co-morbid conditions associated with ICU admission with higher mortality and morbidity.

Table no. 1: Baseline characteristics of hospitalized patients with Novel H1N1 Infection

		Total (n= 401)	ICU (n= 148)	Non-ICU (n =253)	p	Sig
Age (years)		39.44±14.71	38.10±14.32	41.72±15.15	0.017	Sig
Sex (M:F=1:1.95)	M	136 (33.9%)	54 (36.5%)	82 (32.4%)		NS
	F	265 (66.1%)	94 (63.5%)	171 (67.6%)		
Time interval between onset of symptoms to hospitalization (days)	5.89 ± 3.60	6.18±3.54	5.72±3.63	>0.05	NS	
Time interval between onset of symptoms to start of Oseltamivir (days)	5.50±3.57	6.07±3.62	5.16±3.51	0.014	Sig	
Duration of Oseltamivir (days)	7.24±3.95	7.38±3.97	7.17±3.93	>0.05	NS	
Duration of hospitalization (days)	5.38 ± 4.06	6.83 ± 5.59	4.54 ± 2.44	0	Sig	
Severity at admission	A	94 (23.4%)	19 (12.8%)	75 (29.6%)		
	B1	77(19.2%)	3 (2%)	74 (29.2%)		
	B2	38(9.5%)	10 (6.8%)	28 (11.1%)		
	C	192(47.9%)	116 (78.4%)	76 (30.0%)		
SpO_2 (%)	86.81±16.38	74.41±18.70	94.06±8.86	0	Sig	
NIV (days)		3.2±3.33				
IMV(days)		3.34±3.89				
VENTILATOR (days)		4.02±4.39				
DEATH	116 (28.9%)	104 (70.3%)	12 (4.7%)	<0.05	Sig	

Note: insert persons with >50% lung involvement in each category!!

Fig 2: Distribution of H1N1 positive patients according to moh categories



	Total (401)	ICU (148)	Non-ICU (253)	P	Sig
Patients with at least one Co-morbid condition	144 (35.9%)	70 (47.3%)	74 (29.2%)	0.001	Sig
Pregnancy	55 (13.72%)	47 (31.8%)	8 (3.2%)	0.001	Sig
COPD	52 (13%)	19 (12.8%)	33 (13%)	>0.05	NS
Hemodynamic instability	39 (9.7%)	27 (18.2%)	12 (4.7%)	0.001	Sig
HTN	34 (8.5%)	16 (10.8%)	18 (7.1%)	>0.05	NS
DM	29 (7.2%)	17 (11.5%)	12 (4.7%)	0.016	Sig
Pulmonary T.B.	25 (6.2%)	13 (8.8%)	12 (4.7%)	>0.05	NS
CAD	16 (4%)	9 (6.1%)	7 (2.8%)	>0.05	NS
Hypothyroid	14 (3.5%)	4 (2.7%)	10 (4%)	>0.05	NS
Obesity BMI >35 kg/m^2	5 (1.25%)	3 (2.02%)	2 (0.79%)	>0.05	NS
Blood Sugar(mg/dl)	127.37±63.22	121.35±61.78	130.90±63.91	>0.05	NS
TLC (1000 cells/mm^3)	8.16±4.86	8.4±5.01	8.01±4.77	>0.05	NS
Nutrophils (%)	72.36±16.43	72.20±16.12	72.46±16.64	>0.05	NS
Urea (mg/dl)	41.47±44.50	38.28±44.32	43.35±44.58	>0.05	NS
Creatinine(mg/dl)	2.36±13.83	3.51±0.21	1.68±0.62	>0.05	NS
Sodium(mEq/L)	133.86±17.84	134.49±17.39	133.49±18.12	>0.05	NS
Potassium(mEq/L)	5.06±8.09	4.98±6.6	5.11±8.83	>0.05	NS
SGOT(IU/L)	75.11±5.92	89.33±2.40	66.79±7.90	>0.05	NS
SGPT(IU/L)	60.95±10.57	68.85±14.91	56.30±6.78	>0.05	NS
CPK(IU/L)	208.81±222.21	254.67±314.76	182.17±137.26	0.002	Sig
LDH(IU/L)	656.81±496.45	738.65±577.06	608.92±436.71	0.011	Sig

Fig 3: Age wise distribution of study patients

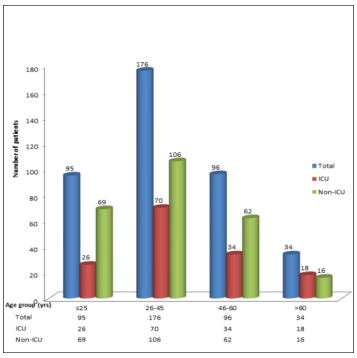
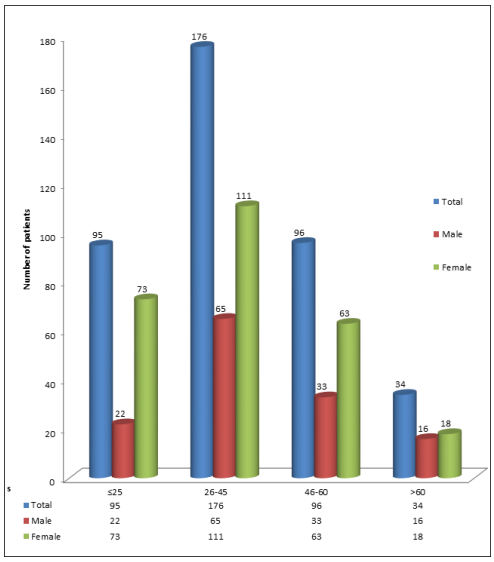


Fig 4 : Age and sex wise distribution of study patients



REFERENCES

1. Trifonov V, Khiabanian H, Rabadan R. Geographic dependence, surveillance, and origins of the 2009 influenza A (H1N1) virus. N Engl J Med 2009; 361:115–9.
2. Centers for Disease Control and Prevention (CDC). Outbreak of swine-origin influenza A (H1N1) virus infection—Mexico, March-April 2009. MMWR Morb Mortal Wkly Rep. 2009;58:467–70.
3. World Health Organization. Human infection with pandemic A (H1N1) 2009 influenza virus clinical observations in hospitalized patients. July 2009 - update. and Weekly epidemiological record. 2009.
4. All the cases were categorized as per guidelines of National Health & family welfare and WHO into category A, B and C.4
5. Lone Simonsen. Preliminary Estimates of Mortality and Years of Life Lost Associated with the 2009 A/H1N1 Pandemic in the US and Comparison with Past Influenza Seasons. PLoS Curr 2010 March 20; 2: RRN1153. 10.1371/currents.RRN1153.
6. Michaelis M, Doerr H, Cinatl JJ. Novel swine – origin influenza a virus in humans: Another pandemic knocking at door. Med Microbiol Immunol. 2009;1SSSS98:175–83.
7. Choudasama RK, Patel UV, Verma PB. Hospitalizations associated with 2009 influenza A (H1N1) and seasonal influenza in Saurashtra region, India. J Infect Dev Ctries. 2010;23:834–41.
8. Chacko J, Gagan B, Ashok E, Radha M, Hemanth HV. Critically ill patients with 2009 H1N1 infection in an Indian ICU. Indian J Crit Care Med. 2010;14:77–82.
9. Talkad Chandrashekar Nagesh Kumar, Nanjangudu Subramanya Shivakumar, Telugu Sitaram Deepak et al. H1N1infected Patients in ICU and Their Clinical Outcome. N Am J Med Sci. 2012 Sep; 4(9): 394–398.
10. Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Crossreactive antibody responses to 2009 pandemic H1N1 influenza virus. N Engl J Med. 2009;361:1945–52
11. Samara T, Pawar M, Yadav A. One year experience with H1N1 infection Clinical observation from a tertiary care hospital in Northern India. Indian Journal of Community Medicine. 2011; 36:241-43.
12. Chudasama RK, Patel UV, Verma PB, Amin CD, Savaria D, Ninama R, Fichadiya N. Clinico-epidemiological features of the hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in Saurashtra region. India (September, 2009 to February, 2010). Lung India. 2011;28:11-6.
13. Rao S, Rao M, Swamy N, Umapathy B L. Profile of H1N1 infection in a tertiary care hospital. Indian Journal of Pathology and Microbiology. 2011; 54:323-25.
14. A Puvanalingam, C Rajendiran, K Sivasubramanian, S Ragunanthanan, Sarada Suresh, S Gopalakrishnan. Case Series Study of the Clinical Profile of H1N1 Swine Flu Influenza. JAPI. 2011;59:14-18.
15. AsmitaA. Mehta, V.Anil Kumar, Suresh G. Nair, Fini K Joseph et al. Clinical profile of patients admitted with swine-origin influenza A (H1N1) virus infection: an experience from a tertiary care hospital. Journal of Clinical and Diagnostic Research. 2013 Oct, Vol-7(10): 2227-2230
16. Payam Tabarsi, Ahmadreza Moradi, Majid Marjani et al. Factors associated with death or intensive care unit admission due to pandemic 2009 influenza A (H1N1) infection. Annals of Thoracic Medicine. Vol 6(2), April-June 2011, 91-95
17. Hayden FG. Clinical aspects of pandemic 2009 influenza a (H1N1) virus infection. N Engl J Med 362; 18; 1708-19.
18. WHO recommendations for Pharmacological management of Pandemic (H1N1) 2009 influenza and other influenza viruses. 2009. Aug 20, (http://www.leb.euro.who.int/h1n1_guidelines_ pharmacological_mng.pdf.)
19. Sertogullarindan B, Ozbay B, Gunini H, Sunnetcioglu A, Arisoy A, Bilgin HM, et al. Clinical and prognostic features of patients with pandemic 2009 influenza A (H1N1) virus in intensive care unit. Afr Health Sci. 2011;11:163–70.
20. Hongjie Yu, Hongjie Yu, Z. Feng, T.M. Uyeki, Q. Liao, L. Zhou, et al, Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China, Clin. Infect. Dis. 52(4) (2011) 457–465.
21. J.S. Nguyen-Van-Tam, P.J.M. Openshaw, A. Hashim, E.M. Gadd, et al, Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May–September 2009), Thorax 65 (2010) 645–651.
22. Nancy M.Abdelaty. Risk factors and prognostic criteria in 230 patients with influenza A (H1N1) infection. Egyptian Journal of Chest Diseases and Tuberculosis (2013) 62, 1–8