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A STUDY ON H1N1 INFLUENZA IN ADULTS: CLINICAL AND LABORATORY PROFILES, AND TREATMENT OUTCOMES AT A TERTIARY CARE HOSPITAL IN SOUTHERN INDIA

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Abstract

Introduction. *The H1N1 influenza virus, a subtype of influenza A virus, is transmitted from one person another via respiratory droplets. The H1N1 influenza virus usually causes upper respiratory tract infection, leading to runny nose, chills, fever, and poor appetite. In a few cases, it may progress into lower respiratory tract infection, with severe complications including acute respiratory distress syndrome, which can result in respiratory failure and may require mechanical ventilation.*

Aim and objectives. *The study was conducted with the aim of analysing the clinical features, laboratory profile, and treatment outcome of H1N1 influenza infection in adults at a tertiary care hospital of South India. The study had following objectives: 1.) to describe the clinical profile of H1N1 influenza-affected patients, 2.) to evaluate the laboratory findings and complications among H1N1-infected patients, and 3.) to assess the response to treatment and clinical outcomes in patients with H1N1influenza.*

Materials and Methods. *This single-center, retrospective study was conducted in the Department of Internal Medicine at a tertiary care teaching hospital over a one-year period, from April 9, 2019 to April 8, 2020. It included a retrospective review of the medical records of hospitalized patients with confirmed H1N1 infection from June 2017 to December 2018. After selecting patients who met the inclusion and exclusion criteria, we analysed treatment response and clinical outcomes.*

Results. *With increasing age, the probability of complications and the risk of mortality increased significantly. Pregnant women did not show an increased risk of complications compared to non-pregnant women. Patients with abnormalities on chest radiographs had a higher risk of complications and poorer clinical outcomes.*

Conclusion. *The severity of the disease was greater in the elderly population and correlated with longer delays between symptom onset and hospital admission. The requirement of ventilatory support was associated with increased severity of the disease. In contrast, patients with a normal baseline chest X-ray were less likely to develop complications.*

Keywords: *H1N1 influenza, acute respiratory distress syndrome (ARDS), ventilator, oseltamivir.*

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INTRODUCTION

The swine influenza (H1N1) virus is a subtype of the influenza A virus. It emerged through the recombination of four distict viral genes - swine, human, avian, and Eurasian - which together formed a single H1N1 influenza strain. The virus is transmitted via respiratory droplets expelled by infected people while speaking, coughing, or sneezing. Although influenza can occur throughout the year, it is most prevalent during the winter season [*Khanna M et al., 2008; Reward S et al, 2015; Kshatriya R et al. 2018*]. Influenza epidemics typically occurs every 6 to 10 years, primarily due to antigenic shifts that introduce new strains of virus to the population [*Nogales A et al., 2009; Keenlyside J et al ., 2013*].

The H1N1 influenza virus typically causes upper respiratory tract infections, manifesting as runny nose, chills, fever, and poor appetite. In certain cases, the infection may progress to lower respiratory tract infection, leading to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Complications of swine flu include sepsis, ARDS, which may result in death.

According to the literature, risk factors for developing severe disease include obesity, underlying neurological conditions, delayed visit to the hospital, chronic lung disease, asthma, and pregnancy. As a result, the Centers for Disease Control and Prevention (CDC) recommends that all pregnant women receive the swine flue vaccination. Antiviral drugs such as oseltamivir and zanamavir (neuraminidase inhibitors) can be used to treat swine influenza and are the most effective when administered within the first two days after symptom onset [*Myers K et al.,2007; Littauer E et al., 2017; Somerville L et al., 2018*].

In 1918, the deadliest Spanish flu pandemic, caused by the H1N1 influenza virus, infected approximately one-third of the global population and resulted in an estimated 50 to 100 million deaths (3% to 5% of the world population). The H1N1 influenza pandemic began in Mexico on March 18, 2009 [*Kshatriya R et al., 2018*], and the World Health Organization (WHO) declared it a pandemic on June 11, 2009 [*Baudon E et al., 2018*]. In India, the first confirmed H1N1 case was reported on May 13, 2009 in Hyderabad, followed by a second case on June 1, 2009 in Chennai (Ministry of health and family welfare in India).

The 2009 swine flu pandemic presented a significant challenge to the global medical community due to its rapid transmission, particularly among young and previously healthy individuals [*Chowell G et al., 2009; Michaelis M et al. 2009; Perez-Padilla R et al. 2009*]. Reports from the National Center for Disease Control in India provide comprehensive overview of the H1N1 infection trends. In India, between May 2009 and Feb 2013, a total of 2,45,239 individuals were tested for H1N1 at the National Centre for Disease Control, of whom 54,329 tested positive, and 3362 died as a result of the infection [*Singh S et al, 2023*]. Coordinated efforts by the healthcare community and government authorities successfully curbed the spread of the infection and improved the survival rates. By 2014, only 937 cases and 218 deaths were recorded. However, in 2015, India faced an unpredic surge, with nearly 43,000 confirmed cases. Since 2015 onward, the incidence has steadily declined, reaching 778 cases in 2021, even during the COVID-19 pandemic. Given the ongoing risk of sudden and unpredic increases in H1N1 incidence, we conducted a retrospective cohort study at Kasturba Medical College, Manipal, Karnataka, India, to assess recent patterns of the disease.

MATERIALS AND METHODS.

This single-center retrospective study was conducted in the Department of Internal Medicine at a tertiary care teaching hospital over a one-year period from April 9, 2019, to April 8, 2020. The sudy involved a thorough anlysis all available medical records of patients admitted to the hospital with confirmed H1N1 infection between June 2017 and December 2018.

Inclusion criteria comprised patients aged 18 years or older with features of upper and lower respiratory tract infection and complications (pneumonia and ARDS) and confirmed H1N1 influenza infection positive via RT-PCR testing of nasopharyngeal or oropharyngeal swabs. Exclusion criteria included patients who tested negative for H1N1 by RT-PCR, or RT-PCR -positive patients who were not admitted to the hospital.

Complicated cases were defined as those who develop pneumonia, ARDS, respiratory failure, or worsening of pre-existing conditions such as asth-

TABLE 1a.

Descriptive statistics (pre-clinical manifestations)

Category	n (%)
Gender	
Male	146 (45.48%)
Female	175 (54.52%)
Age group	
18 – 50 years	194(58.7%)
>50 years	127(39.7%)
Month	
May	3 (0.92%)
June	32 (9.96%)
July	102 (31.77%)
August	35 (10.90%)
September	38 (11.83%)
October	71 (22.11%)
November	31 (9.62%)
December	9 (2.80%)
Chief complaint	
Fever	296 (92.21%)
Cough	271 (84.42%)
Chills	145 (45.17%)
Sputum production	145 (45.17%)
Shortness of breath	124 (38.62%)
Runny nose	43 (13.39%)
Rigor	95 (29.59%)
Sore throat	53 (16.51%)
Headache	53 (16.51%)
Body ache	47 (14.64%)
Medical history	
Type 2 diabetes mellitus	61 (19%)
Hypertension	62 (19.31%)
Chronic Kidney Disease	17 (5.29%)
Cardiac disease	30 (9.34%)
COPD	16 (4.98%)
Asthma	13 (4.04%)
Thyroid disorder	15 (4.67%)
Immunosuppressive drug use	11 (3.42%)
Immunosuppressed state	37 (11.52%)
Chest radiograph	
Right lung infiltrates	16 (5%)
Left lung infiltrates	13 (4%)
ARDS	80 (24.9%)
Emphysema	11 (3.4 %)
Increased tracheobronchial marking	1 (0.3 %)
Pleural effusion	2 (0.62 %)
Cardiomegaly	8 (2.5 %)
Fibrosis	1 (0.3 %)
Ventilatory support	
Absent	231 (72%)
Present	90 (22 %)
Antiviral (Oseltamavir)	
Received	321 (100%)
Not Received	0

ma, chronic obstructive pulmonary disease COPD, chronic liver disease, heart failure, renal failure, or other chronic illnesses.

Deterioration was defined as worsening of the clinical condition during the hospital stay. Patients who were taken to a local health facility for personal reasons and were not available for further follow-up.

Outcome was measured as either survival or death.

The study was conducted after obtaining clearance from the Institutional Ethical Committee (IEC NO.285/2019) and with permission of the medical records officer. While maintaining confidentiality, we studied outcomes, response to treatment, potential risks, and benefits.

Data were analyzed using SPSS version 20 software (IBM SPSS, Armonk, NY, USA). Continuous variables were reported as mean±Standard Deviation (SD) for normally distributed data. Categorical variables were reported as percentages ANOVA test was used to compare the mean differences of the various groups. A p-value of < 0.05 was considered statistically significant Descriptive statistics, independent samples t-test, one-way ANO-

TABLE 1a.

Descriptive statistics (continunation)

Category	n (%)
Severity of the disease	
Complicated	166 (51.7%)
Uncomplicated	155 (48.3%)
Outcome	
Improved	285 (88.8%)
Deteriorated	11 (3.4 %)
Deceased	25 (7.8%)

TABLE 1b.

Descriptive statistics
(clinical assessment of lymphopenia)

Variable	Category (Mean±SD)
Age(years)	44.17±17.409
Time from symptom onset to hospital visit(days)	4.03±2.87
Neutrophils %	71.06±14.45
Lymphocytes %	16.54±12.06
NRL	7.30±8.06
Days on INV	1.04±3.41
Days on NIV	0.62±1.88

Note: INV -Invasive ventilation , NIV -Non invasive ventilation, NRL-Neurophil-Lymphocite ratio

Table 2.

Association Between Predictive Factors and Disease Severity and Outcome

Variable	Category	Severity of disease		p	Outcome			p
		Complicated	Uncomplicated		Improved	Deteriorated	Deceased	
Pre-existing medical condition n (%)	Yes	117 (57.6%)	86 (42.4%)	0.005*	183(90.1%)	6 (3%)	14 (6.9%)	0.596[a]
	No	49 (41.5%)	69 (58.5%)		102(86.4%)	5 (4.2%)	11 (9.3%)	
Pregnancy n(%)	No	78 (54.2%)	66 (45.8%)	0.001*	127(88.2%)	7 (4.9%)	10 (6.9%)	0.129[a]
	Yes	3 (9.7%)	28 (90.3%)		31 (100%)	0	0	
Chest radiograph findings n(%)	Normal	44 (23.3%)	145 (76.7%)	0.001*	187 (98.9%)	0	2 (1.1%)	0.001*[a]
	Right lung infiltrates	15 (93.8%)	1 (6.2%)		12 (75%)	1 (6.2%)	3 (18.8%)	
	Left lung infiltrates	13 (100%)	0		8 (61.5%)	2 (15.4%)	3 (23.1%)	
	ARDS	75 (93.8%)	5 (6.2%)		57 (71.2%)	8 (10%)	15(18.8%)	
	Emphysema	8 (72.7%)	3 (27.3%)		10 (90.9%)	0	1 (9.1%)	
	Others	11 (91.7%)	1 (8.3%)		11 (91.7%)	0	1 (8.3%)	
Neutrophil-lymphocyte ratio (Mean±SD)		7.24±8.4	7.36±7.6	0.598[c]	7.14±6.8	13.36±24.5	6.4±5.8	0.922[d]
Time from symptom onset to hospital visit (Mean±SD)		4.95±2.8	3.05±2.6	<0.001*[e]	3.81±2.8 g	6.45±2.7	5.48±2.2	<0.001*[f]

Note: ** -Chi square test; a -Fisher's exact test; b -Monte Carlo method; c -Mann Whitney U test; d -Kruskal Wallis test; p≤0.05 was considered statistically significant, e -Independent samples t test; f -One way analysis of variance ; g -Subjects with improved outcome demonstrated significantly shorter symptom duration compared to the other two categories, based on in Tukey's post hoc analysis; * - denotes statistical significance; ɪ Statistics performed for only pregnant females, ARDS – Acute respiratory distress syndrome,.*

VA, Mann Whitney test, Kruskal Wallis ANOVA, Chi-square tests, Fisher's exact tests, Monte Carlo methods, and binary logistic regression analyses were performed to analyze the study data.

Results.

The mean age of the study population was 44.17±17.4 years, and the median age was 43 years. Clinical characteristics prior to medical examinationare presented in **table 1a**. The majority of patients were female (54.5%) and were between 18 to 50 years of age. **The table also show**s that July recorded the highest number of cases(n=102), followed by October(n=71). Clinical investigation revealed lymphopenia observed in sixty-three percent of patients (n=196), the result are shown in **table 1b. Table 2** presents that time from onset of symptoms to visit was longer in patients with the complicated disease compared to those with uncomplicated cases (4.95+/- 2.08 vs. 3.05+/-2.63) (Mean±SD)(days). Binary regression confirmed this association (adjusted OR= 0.851 (0.75 – 0.96)) (**Table 3)**. Males demonstrated a significantly higher proportion of complicated cases than females in unadjusted analysis (n= 85 vs. 81) **(Table**

Table 3.

Adjusted Odds Ratios (95% CI) for the association between predictors and uncomplicated disease

Variable	Category	Adjusted OR (95% CI)	P value
Gender	Female	reference	
	Male	1.136 (0.548-2.354)	0.732
Age groups	<20	41.66 (3.01-575.4)	0.005*
	20-29	13.2 (2.97-58.57)	0.001*
	30-39	8.24 (1.81-37.4)	0.006*
	40-49	3.88 (0.97-15.15)	0.054
	50-59	0.93 (0.22-3.81)	0.923
	60-69	1.32 (0.34-5.07)	0.686
	≥70	reference	
Pre-existing medical condition	Yes	reference	
	No	1.327 (0.55-3.17)	0.525
Chest radiograph findings	Normal	10.42 (1.2-89.8)	0.033*
	Right lung infiltrates	0.36 (0.17-7.74)	0.52
	Left lung infiltrates	0.00 (0.00-0.00)	0.99
	ARDS	0.203 (0.019-2.16)	0.186
	Emphysema	4.17 (0.33-51.74)	0.266
	Others	reference	
Time from symptom onset to hospital visit		0.851 (0.75-0.96)	0.01*

Note: *Binary logistic regression; CI – confidence interval; * - denotes statistical significance, ARDS – Acute respiratory distress syndrome.*

TABLE 4.

Association between disease severity and requirement for ventilatory support

Variable	Disease severity	
	Complicated n(%)	Uncomplicated n(%)
Invasive ventilation		
Yes	48 (28.9%)	0
No	118 (71.1%)	155 (100%)
P	0.001*	
Non-invasive ventilation		
Yes	41(24.7%)	1 (0.6%)
No	125 (75.3)	154 (99.4%)
P	0.001*	

Note: Chi square test; p≤0.05 considered statistically significant; * - denotes statistical significance

2), but adjusted anaylsis found equivocal sex distribution. (table 3).

With increasing age, the likelihood of complications - and consiquently, deterioration or mortality increased significantly. Binary logistic regression analysis showed that patients under 40 years of age had a significantly lower odds of developing disease than subjects ≥70 years old (table 3. Table 2 shows that more than half of the complicated cases had some pre-existing condition, and it had no significant influence on the outcome (improvement vs. deterioration vs. death). Initial analysis found that pre-existing conditions were significantly more frequent in complicated cases (Table2), but binary logistic regression found no such association (adjusted OR=1.327 (0.55 – 3.17)) (table 3). In this study pregnancy was not a significant risk to the outcome (Table 2). Patients with normal chest radiographs showed a decreased risk for complications (adjusted OR=10.42 (1.2 – 89.8)) when compared with people with abnormal initial chest radiograph **table 3).** Mean neutrophil-lymphocyte ratio was similar in both complicated and uncomplicated patients, and did not significantly influence the progression of the disease. **(table 3). Table 4** shows that complicated cases had a significantly higher requirement for invasive and non-invasive ventilatory support than uncomplicated cases (p-value=0.001).

Tablet oseltamivir was received by all patients. Some patients presented to hospital late after symptoms . But benefits of treatment with antiviral was given to all patients.

DISCUSSION

Influenza A virus caused seasonal epidemics since early 19the century . Swine flu which was the major influenza A virus started to cause epidemics of influenza since 2009 . Since then frequent epidemic and endemics of H1N1 influenza occurring throught India causing increased mortality in vulnerable population especially with chronic diseseas . Hence a retrospective study has been conducted with an aim to find out clinical profile , laboratory parameters along with outcome of patients infected with H1N1 influenza virus.

In this study , H1N1 cases distribution were nearly equal in both the sexes; this study analysis found that gender had no significant odds in the severity of the disease and its outcome (adjusted OR CI =0.548 – 2.354), which is similar to other studies [*Choudasama R et al, ;2010 , Mehta A et al., 2013, Van Kerkhove M et al.,;2011*].

In the present study, the median age of the study sample was 43 years, higher than in other studies by ten years [*Choudasama R et al, 2010; Samara T et al.;2011;Mehta A et al. 2013*], and most of the infected patients were between 18 to 50 years (59.8%), similar to the other studies. However, this study has 40 % of patients above 50 years of age, compared to 5% and 13% reported by Puvanalingam A. et al. and Mehta et al., respectively [*Puvanalingam A et al., 2011; Mehta A et al., 2013*]. Overall, this study had a similar trend of higher frequency of infection in young adults than in older individuals. One possible explanation is that the older individuals developed cross-immunity after contracting antigenically similar influenza viruses and lesser exposure to the virus due to infrequent movement in the community .

This study showed that young adults, 18 to 40 years and below, have significantly fewer complicated disease odds than elderly patients of 70 years and above, which correlated with Kerkhove et al. global pooled analysis of H1N1. This global pooled analysis found that the median age of patients increased with the severity of the disease, with the highest death per capita rate among those with ≥ 65 years of age.

In the present study, fever was the most frequent presenting symptom (92.21%). Approximately half of the patients experienced chills, and nearly one-third reported rigors. Cough was

the second most common presenting complaint (84.42%), with sputum production observed ina bout half of these cases. Shortness of breath was reported in 38.6% of patients. While the frequency of fever and cough was consistent with the findings from studies conducted during the 2009 pandemic (~90%), the proportion of patients reporting shortness of breath was 10–15% lower than those previously documented [*Puvanalingam A et al., 2011; Choudasama R, Mehta A et al., 2013*].

The most common co-morbidities in the present study were type 2 diabetes mellitus and systemic hypertension (19% each), followed by cardiac disease (9%) and kidney disease (5%). Several Indian studies have also reported diabetes as the most prevalent underlying condition [*Choudasama R et al., 2010 ; Mehta A et al., 2013*]. Acording to current literature, chronic respiratory disease, liver disease, renal disease diabetes, and pregnancy are recognized as risk factors for increased morbidity and mortality in H1N1 influenza infection [*Choudasama RK et al., 2010; Rao S et al., 2011, Samara T et al., 2011*]. However, in the present study, a pre-existing conditions were not significantly associated with complications (adjusted OR CI = 0.55 – 3.17), clinical deterioration, or mortality - findings consistent with other Indian studies [*Mehta A et al., 2013; Puvanalingam A et al., 2011*].

Pregnancy is recognized as an additional risk factor for complications in H1N1 influenza [*Siston A et al., 2010*]. Several international studies have also reported an increased risk of influenza-related morbidity among pregnant women, particularly during the third trimester [*CDC., 2009; Jamieson DJ,et al., 2009; Choudasama R et al., 2013; Van Kerkhove M et al., 2011*]. In contrast, the present study found no significant impact of pregnancy on clinical outcomes; all 31 positive pregnant patients showed improvement. Similar findings were reported by Mehta and co. [*Mehta et al.,2013*].

In this study, Lymphocyte percentage (Mean±SD) was 16.54±12.06, with Lympopenia observed in 63% of cases which is similar to results in other studies [*Choudasama R et al., 2010, Mehta A et al., 2013*]. This observation can be an essential clue for targeted H1N1 testing in patients with suggestive clinical features**.** The neutrophil-to-lymphocyte ratio (NLR), which can be easily calculated from the routine blood counts, reflects the degree and possible etiology of the inflammation. Prozan L and co. compared the prognostic value of NLR in COVID-19, influenza A or B, and RSV (with H1N1 classified under influenza A) [*Prozan L et al., 2021*]. Their findings indicated that a high NLR is a poor prognostic factor in influenza A or B (AUC=0.57, n=2213). In the present study, NLR was not no significantly associated with disease severity (complicated vs. uncomplicated) or clinical outcome (improvement vs. deterioration vs. death).

Alarmingly, the most common abnormal finding on the baseline chest X-ray was ARDS, observed in 80 patients (24.9%). Other frequent findings include a right lung infiltration (5%) and a left-lung infiltration (4%). Only two patients (0.62%) had pleural effusion. According to Choudasama et al. and Mehta et al., 93% and 58% showed lung infiltrations, respectively. [*Choudasama R et al.,2010 ; Mehta A et al, 2013*]. In the present study, baseline chest X-ray findings had a significant association with the severity of the disease and the outcome; a normal chest X-ray has significantly decreased the odds of complicated disease (adjusted OR CI =1.2 – 89.8). Similarly, Mehta et al. reported an increased risk of severe disease in the presence of pneumonia (adjusted OR CI = 1.3-34.5) [*Mehta et al., 2013*], whereas Choudasama et al. did not find a significant association (adjusted OR = 0.34-1.4) [*Choudasama et al.,* 2010].

The lowest number of cases was recorded in May, while July marked the peak. Following July, there was a steady decline in August and Septmeber, with another surge in October, followed by a decline in November and December. In this geographical region, the monsoon starts in June, peaks in July, and gradually subsides but continues until November. Atmospheric temperature tends to decrease with increased rainfalls. The temporal distribution of cases in this study aligns with the well-documented seasonal pattern of increased influenza activity during the winter months [*Choudasama R et al., 2010; Reward S et al., 2015; Kshatriya R et al., 2018*].

This study has sveral strengths. While most of the existing literature depicts the scenario of the H1N1 2009 pandemic, our research reflects current trends in swine flu cases. Additionally, we examined the neutrophil-to-lymphocyte ratio, a pa-

rameter that remains insufficiently explored in the context of H1N1 infection. The recent rise in other viral diseases, including COVID-19, highlights the need for better evaluation strategies to ensure early diagnosis - especially in remote areas with limited diagnostic facilities. Early diagnosis based on clinical parameters and epidemiological evidence helps in better treatment of each viral disease succenssfully to the maximum extent.

CONCLUSION

The severity of H1N1 influenza was found to be higher in the elderly population and it tended to increase with a longer interval between the onset of symptoms and hospital visit. The need for ventilatory support was directly associated with the severity of the disease. A normal baseline chest X-ray decreased the odds of developing complicated disease. This study hold particular relevance in the context of ongoing COVID -19 pandemic. While numerous studies on H1N1 influenza were conducted during pandemic, exact data on virus-related mortality and morbidity in recent years remains known. This study provides valuable insight into the current status of H1N1 virus in the community and may also predict the potential course of COVID -19, given the similar behavior of influenza viruses..

Limitations: This retrospective study includes only hospitalized patients, excluding individuals who were not admitted or remained undiagnosed. As a result, the findings may not be generalizable to the wider community, which limits the external validity of the study at the population level.

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