



RISK FACTORS FOR HOSPITALIZATION AND SEVERE ILLNESS IN CHILDREN WITH H1N1 INFLUENZA

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Abstract

Introduction: Seasonal influenza is a common etiology of acute respiratory tract infection in children. H1N1 Influenza is a common etiology of morbidity and mortality in hospitalized children. This study is done to evaluate the risk factors for severe illness and outcome of children admitted with H1N1 influenza.

Methods: This was a retrospective descriptive-analytical study done at a tertiary referral care centre in South India. The study population included hospitalized children with H1N1 Influenza during the study period of 3 years. Demographic, clinical and laboratory data was collected. Risk factors for severe illness were analyzed.

Results: The study population included 88 children with H1N1 Influenza of whom 18 (20.5%) required intensive care admission. The median age of study population was 5.34years (IQR 0.6-11.4) with male: female ratio of 1.1:1. Risk factors for hospitalization included malnutrition in 28 (31.8%) children, followed by anaemia in 22 (25%), pre-existing wheeze in 12 (13.6%), pre-existing neurological illness in 9 (10.2%), congenital heart disease in 10 (11.4%), immunosuppressive state in 9 (10.2%), chronic liver disease, chronic kidney disease and kyphoscoliosis in 3 (3.4%), 2 (2.3%) and 2 (2.3%) children respectively. It was noticed that the risk of PICU admission for significantly increases in the presence of malnutrition, anaemia, NLR>2 and CRP>30 with Odds ratio of 11.5 (p<0.001), 6.53 (p<0.001), 23.8 (p<0.001) and 42.3 (p<0.001) respectively. The difference between the median levels of CRP between 2 groups was also significant (54.2 vs. 36.4, p value 0.04). Mortality was observed in 3 (3.4%) children.

Conclusion: The presence of malnutrition is a significant risk factor for hospitalization. Malnutrition, anaemia, preexisting immunosuppressive status, NLR>2 and elevated CRP>30, are risk factors severe illness.

Keywords: H1 N1 influenza; viral pneumonia; swine flu: comorbid illness

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1. Introduction

Influenza viruses are common etiology for respiratory tract infections in children. The clinical presentation of H1N1 infection varies from mild influenza like illness to severe pneumonia. In India the first pandemic of H1N1 influenza occurred in 2009. Following this the country continued to witness seasonal epidemics of H1N1 influenza in outbreaks. Seasonal H1N1 influenza is also known to be associated with increased burden of disease both in children as well as older age group¹. Various risk factors are described for hospitalization as well as for increased severity of illness. However very few paediatric studies are available in South India. The objectives of this study was to evaluate the risk factors for hospitalization in children with seasonal H1N1 influenza. Predictors of severity of illness and outcome were also studied.

2. Methods

This was a retrospective analytical study conducted at Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India. The study population included children of 1 month to 18 years of age diagnosed with H1N1 Influenza admitted to the department of Paediatrics during the study period of 3 years (August 2016 to July 2019). The diagnosis of H1N1 influenza was based on positive RT-PCR (reverse transcription polymerase chain reaction) nasopharyngeal/throat swab².

Ethical approval for study was obtained from the Institutional Ethics Committee. (IEC number 955/2019). Data were collected from the Medical Records Department and entered in the designated pro-forma. Baseline demographic, clinical and laboratory data associated with hospitalization were assessed.

Laboratory data including complete blood count, C reactive protein (CRP), renal

function tests and liver function tests were collected. Anaemia was defined as per the age specific guidelines of WHO. Leucopenia was considered if total leucocyte count (TLC) was $<4000/\text{mm}^3$ while $\text{TLC} > 11000/\text{mm}^3$ was considered as leucocytosis. A neutrophil-lymphocyte ratio (NLR) of >2 was considered significant. CRP (C reactive protein) level of $>30\text{mg/L}$ was considered as elevated.

Organ dysfunctions were defined as follows. Hepatic dysfunction was defined as elevation of AST (aspartate amino transferase)/ALT (alanine amino transferase) levels >2 times the normal upper limit (40IU/L). Hypotension was defined as a systolic blood pressure below the 5th percentile for the corresponding age, sex and height. Acute respiratory distress syndrome (ARDS) was defined as per Pediatric ARDS criteria. Meningoencephalitis was considered with the presence of altered sensorium or seizures with or without meningeal signs and/or along with positive CSF findings. Multiple Organ Dysfunction (MODS) - dysfunction of more than 1 organ requiring intervention to maintain homeostasis.

The study population was divided into 2 groups depending on severity of illness. Children admitted to the PICU (pediatric intensive care unit) were grouped as group1: H1N1 with complications and those not requiring PICU admission were grouped as Group 2: H1N1 without complications. The length of PICU stay and total duration of hospital stay were recorded. Outcome was defined in terms of mortality and survival.

Obtained data was analysed using the Statistical Package for Social Sciences (SPSS) V23.0. Descriptive data was expressed as frequencies and percentages. Mean and standard deviation were computed for the variables following normal distribution curve, while median and inter-quartile range were computed for non-parametric data. Fisher exact test was used to test categorical variables. Student t

test or Mann Whitney test was used to compare mean or median value of parameter between 2 groups respectively. Parameters such as age, malnutrition, anemia, thrombocytopenia, elevated CRP, leucocytosis, hypoalbuminemia were analyzed to determine their association with severity of illness. The statistical significance was considered with a p value of <0.05.

3. Results

The study population included 88 children diagnosed with H1N1 Influenza admitted during the study period. 18 (20.5%) children were admitted to the paediatric intensive care unit (PICU), while 70 (79.5%) children were admitted in the ward. The median age of study population was 5.34years (IQR 0.6-11.4) with male: female ratio of 1.1:1. 42 (47.7%) children belonged to under five age group. The median duration of symptoms prior to admission was 4.5 days (IQR 2.4-8.0).

The clinical features at admission are depicted in table 1. Fever was the most common symptom present in 86 children (96.5%) followed by cough in 76 (86.3%) and rhinorrhea in (54.5%). Fast breathing was present in 34 (38.6%). Gastrointestinal symptoms were present in approximately 1/3rd of the study population. 5 (5.7%) children presented with symptoms of central nervous system (CNS) involvement. Among the signs, congested throat was

observed in 49 (55.7%). 34 (38.6%) children had respiratory distress at admission of whom 12 (13.6%) had mild respiratory distress while moderate and severe respiratory distress was noticed in 16 (18.2%) and 6 (6.8%) children respectively. Evidence of lower respiratory tract infection (LRTI) was present in 28 (31.8%) children. 22 (40.9%) children had hypoxia at admission. Evidence of compensated shock and hypotension were present in 16 (18.2%) and 12 (13.6%) children respectively. Hepatomegaly was observed in 16 (18.2%) children while splenomegaly was present in 7 (7.9%) children.

Table 1. Signs and symptoms of H1N1 Influenza

Clinical features	n=88 (%)
Symptoms	
Fever	86 (96.5)
Cough	76 (86.3)
Rhinorrhea	48 (54.5)
Fast breathing	34 (38.6)
Sore throat	26 (29.5)
Headache	25 (28.4)
Myalgia	22 (25)
Vomiting	18 (20.5)
Abdominal pain	16 (18.2)
Diarrhoea	10 (11.4)
Seizures	5 (5.7)
Altered Sensorium	5 (5.7)
Signs	
Congested throat	49 (55.7)
Tachycardia	36 (40.9)
Respiratory distress	34 (38.6)
-Mild	12 (13.6)
-Moderate	16 (18.2)
-Severe	6 (6.8)
Rhonchi/Crackles	28 (31.8)
Rhinitis	24 (27.3)
Spo2 <90%	22 (25.0)
Poor perfusion	16 (18.2)
Hepatomegaly	16 (18.2)
Hypotension	12 (13.6)
Splenomegaly	7 (7.9)

The demographic and clinical risk factors associated hospitalization of children with H1N1 Influenza are summarized in table 2. History of contact with swine flu in family members was present in 18 (20.4%) children. History of influenza vaccination was present in only 10 (11.4%) children. Malnutrition was the most common risk factor present in 28 (31.8%) children, followed by anaemia 22 (25%). History of pre-existing wheeze was present in 12 (13.6%). 10 (11.4%) children were previously diagnosed with congenital heart disease (4 ventricular septal defect, 4 atrial septal defects, 2 children with

cardiomyopathy). 9 (10.2%) children had pre-existing neurological illness of whom 6 children had cerebral palsy and 3 children had neuro-metabolic disorders (methyl malonic acidemia, beta ketothiolase deficiency, hyperammonemia). 9 (10.2%) children were diagnosed with immunosuppressive state (haematological malignancy on chemotherapy in 5 children, 4 children each with oral steroid therapy). Other pre-existing systemic diseases included chronic liver disease (CLD), chronic kidney disease (CKD) and kyphoscoliosis in 3 (3.4%), 2 (2.3%) and 2 (2.3%) children respectively.

Table 2. Risk factors in children admitted with H1N1 Influenza

Risk factor	n (%)
Malnutrition	28 (31.8)
Anemia	22 (25)
Chronic wheeze	12 (13.6)
Congenital heart disease	10 (11.4)
Neurological illness	9 (10.2)
Immunosuppressive state	9 (10.2)
Chronic liver disease	3 (3.4)
Chronic kidney disease	2 (2.3)
Kyphoscoliosis	2 (2.3)

At admission, 22 (25%) children required admission to PICU. The mean duration of PICU stay was 6.2 ± 3.64 days. Hypoxia at admission was present in 22 (25%) children. 9 (10.2%) children required supplemental oxygen via LFNC (low flow nasal cannula) device. 6 (6.8%) children required HFNC (High flow nasal cannula) support, while NIV (non-invasive ventilation) and invasive mechanical ventilation was required in 3 (3.4%) and 4 (4.5%) children respectively. 3 children developed ARDS. Other complications noticed were secondary sepsis (n=8), meningoencephalitis (n=5), MODS (n=3), pleural effusion (n=2) and pneumothorax (n=1).

Oseltamivir was started as per the recommended dose in all children.

Additional antibiotic therapy was given in 22 (25%) children who were suspected to have had secondary bacterial infection. 8 (9.1%) children required fluid boluses to correct shock while 6 (6.8%) children required inotropic support. Mortality was observed in 3 children. All non-survivors presented with severe ARDS and shock at admission. 2 children succumbed secondary to MODS and renal failure. 1 child with acute lymphoblastic leukemia succumbed due to refractory septic shock secondary to pseudomonas sepsis. Table 3 depicts various clinical and laboratory parameters were compared between the 2 groups (H1N1 with complications and H1N1 without complications) as predictors of serious illness.

Table 3. Comparison of parameters between 2 groups of children with H1N1 influenza

Parameter	Severe H1N1 Illness (n=22)	Non-severe H1N1 Illness (n=66)	OR [95% CI]	P value
Median age in years (IQR)	2.24 (0.9, 6.2)	3.86 (0.8, 10.6)		##0.62
Malnutrition (n=28)	16	12	11.5 [3.45, 44.32]	*<0.001
Underlying systemic illness (n=26)	20	6	89.3 [16.3, 953.2]	*<0.001

Underlying immunosuppression (n=9)	6	3	7.63 [1.44, 52.34]	*0.006
Anaemia (n=22)	12	10	6.53 [2.00, 22.53]	*0.005
Leucopenia (n=26)	6	20	0.86 [0.24, 2.77]	*0.99
NLR>2 (n=38)	18	10	23.8 [6.23,118.2]	*<0.001
CRP >30mg/L (n=32)	20	12	42.3 [8.57, 421.20]	*<0.001
Median CRP (IQR)	54.2 (.02;182.2)	36.4 (8.64;.66.4)		##0.04

*Fisher exact test, #Independent Sample T-test, ## Mann-Whitney U test

OR [95% CI] - Odds ratio, 95% Confidence Interval

It was found that presence of malnutrition, underlying systemic illness, immunosuppressive state, anemia, NLR>2 and CRP>30 are significantly associated with severity of illness. It was noticed that the risk of PICU admission for significantly increases in the presence of malnutrition, anaemia, NLR>2 and CRP>30 with Odds ratio of 11.5 (p<0.001), 6.53 (p<0.001), 23.8 (p<0.001) and 42.3 (p<0,001) respectively. The difference between the median levels of CRP between 2 groups was also significant (54.2 vs. 36.4, p value 0.04).

4. Discussion

Influenza is an acute infectious disease caused by member of ortho-myxo virus family. Influenza viruses are classified into 4 types based on antigenic structure. Influenza A viruses are further classified into subtypes based on two proteins on the surface of the virus: the haemagglutinin (H) and the neuraminidase (N): (H1 through H18 and N1 through N11 respectively). WHO declared a pandemic outbreak of H1N1 in Mexico and Southern California on 11th of June 2009 (3, 40,000 laboratory

confirmed cases and 4100 deaths worldwide)³.

The clinical presentation of H1N1 infection varies from mild influenza like illness to rapidly worsening pneumonia with ARDS. The seasonal epidemics are known to be associated with mortality and morbidity mostly in the elderly (>65 y) and in the very young (<5 y)⁴. In this study majority of children (47.7%) were in the under 5 age group.

The most common symptom among children diagnosed with H1N1 was fever (96.5%) followed by cough (86.3%). Gastrointestinal symptoms were seen in about 1/3rd of the study population. CNS involvement was present in 5.7% of children. Similar findings are reported in various studies. Congested throat (55.7%) was the most common sign followed by tachycardia (40.9%). Respiratory distress was present in 34 (38.6%) children of whom 6 children had severe respiratory distress. 28 (31.8%) had evidence of LRTI. This clinical profile is similar to that reported by RR Das et al and Ghosh U et al^{5, 6}.

Previous studies have described various risk factors for hospitalization including prematurity, congenital heart disease, reactive airway disease including asthma, malnutrition, anaemia, immunodeficiency, developmental delay, chronic kidney/liver

disease etc^{6, 7}. In our study, malnutrition was found in 28 (31.8%) children followed by anemia in 22 (25%) children. History of chronic wheeze was present in 12 (13.6%) children. 10 (11.4%) children were previously diagnosed with congenital heart disease. Immunosuppressed state group comprised children with haematological malignancy on chemotherapy and those on chronic steroid therapy.

Management includes Oseltamivir along with supportive therapy- invasive/non-invasive/invasive ventilation and broad spectrum antibiotics to prevent secondary bacterial infection. Mortality was observed in 3 (3.4%) children. Other studies have reported mortality rate of 2-5%^{8,9}. Various predictors of severe illness and mortality related to H1N1 have been reported in literature. In a study done by Kinikar AA et al, ICU admission was required for 88 (96%) children and mortality rate was 16%. Predictors of mortality included, presence of diffuse alveolar infiltrate on chest x ray (odds ratio (OR) 45, 95%CI :5.4-370; $p < 0.001$), use of corticosteroids in ARDS in children who required mechanical ventilation (OR 8.12, 95%CI: 2.44-27.05; $p = 0.001$), SpO₂ <80% on admission (OR 32.8, 95% CI: 5.8-185.5; $p < 0.001$) and presence of ARDS (OR 345.3, 95% CI :33.5-3564.1; $p < 0.001$)⁹. NLR is a novel marker of inflammation associated with adverse outcome in pneumonia¹⁰. In the current study NLR>2 was associated with severe illness. Presence of malnutrition, anaemia and leukocytosis are also common among children with severe illness and non-survivors. Pre-existing immunosuppressive state is associated with adverse outcome¹¹. In a study done by Verma N et al paediatric haemato-oncology patients had increased severity and poor outcome and associated with prolonged viral shedding¹².

Limitations: This is a retrospective descriptive study addressing the risk factors for hospitalization and severe illness in children with H1N1 influenza conducted in

a single centre. Prospective Multicentric studies are required to assess predictors of adverse outcome in paediatric age group.

5. Conclusions

Malnutrition and preexisting co-morbid illness are major risk factors for hospitalization. Presence of anaemia, immunocompromised state, NLR>2 and CRP>30 are associated with increased need for intensive care and increased risk of complications.

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Conflict of interest None declared

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6. References

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