Clinicolaboratory predictors of hospitalization (>7 days) in children with swine flu infection: A retrospective study from North India

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ABSTRACT

Background: High morbidity and mortality of swine flu in children result in frequent hospitalization. Clinical and laboratory parameters predicting the duration of hospitalization are important but not studied in children till date. **Aim:** This study aims to evaluate the clinical and laboratory predictors of hospitalization (>7 days) and clinicodemographics in children with swine flu infection. **Materials and Methods:** This retrospective study was done in the department of pediatrics of a tertiary care center in Delhi. The records of children between the age group of 1 and 14 years of age in the previous 3 years and having clinical symptoms and real-time polymerase chain reaction positive for H1N1 infection were included in the study. Baseline characteristics, clinical details, laboratory profile, and treatment of these patients were recorded and analyzed. The outcome parameters were compared between Group A (children hospitalized for ≤7 days) and Group B (hospitalized for >7 days) by appropriate statistical analysis. **Results:** Of 51 children analyzed, the mean age was 45.83 months and three-fourth of them were ≤5 years (50% of infants). The mean duration of hospitalization in Group A and Group B was 5.09±1.82 and 11.2±4.51 days, respectively. Patients with longer duration of breathlessness (mean difference 1.75 days, p=0.026), hypoxemia, cyanosis, and neutrophil/lymphocyte (N/L) ratio <2 after 48 h of admission were associated with prolonged hospitalization (p<0.05). Mean temperature at admission, absolute neutrophil counts, absolute lymphocyte counts, C-reactive protein levels, arterial blood gases parameters, or percentage of children with fever, altered sensorium, respiratory distress, anemia, leukocytosis, and N/L<2 at admission were comparable between the two groups (p>0.05). The most common presenting symptoms were fever (98%), cough (98%), rhinorrhea (88%), and breathing difficulty (88%) with asthma as the most common comorbid factor. **Conclusion:** The swine flu is a mild illness with highest hospitalization in children <5 years with non-specific clinical and laboratory features. Breathlessness of longer duration, hypoxemia, cyanosis, and N/L ratio <2 after 48 h of admission were risk factors for hospitalization of more 7 days.

Key words: *Acute respiratory distress syndrome, Children, H1N1, Hospitalization, Morbidity*

Swine flu is an important cause of morbidity and mortality in pediatric population. Besides, high attack rate and associated complications, panic among parents, and fear of adverse outcomes frequently necessitate hospitalization in this age group [1]. This leads to shortage of beds and pressure on hospitals and local bodies despite specific international and national guidelines on the management of patients with swine flu infection [2,3].

The previous studies have reported 5–11 days of average duration of hospitalization in children with swine flu infection [4,5]. Studies in adults have concluded persistent low PaO_2/FiO_2 ratio after admission and the presence of organ failure as risk factors for prolonged hospitalization [6,7]. Rare studies in children have reported age (5–9 years) and comorbidities as risk factors for prolonged hospitalization [8-12]. Few western reports have evaluated clinical and laboratory parameters in children and adults with swine flu infections [13,14]. As these parameters might predict duration of hospitalization, these are helpful in deciding management and discharge policies in these children. Hence, we planned this study to determine the clinicolaboratory predictors of hospitalization >7 days in children aged 1–14 years with swine flu infection, in the previous 3 years.

MATERIALS AND METHODS

It was a retrospective study conducted in the department of pediatrics in a tertiary care hospital in North India. Ethical clearance was taken from the institutional ethical committee. Records of children diagnosed of swine flu infection between 1 and 14 years of age and hospitalized in the past 3 years were evaluated. Those children who had clinical symptoms and positive real-time polymerase chain reaction (RT-PCR) (throat and nasopharyngeal swabs) were included for the final analysis. Children who were clinically symptomatic but had negative RT-PCR studies were excluded from the final analysis.

Baseline data including age, sex, presenting complaints, duration of illness, comorbidities, details of examination, laboratory parameters (hemoglobin, total leukocyte counts (TLCs) and differential leukocyte counts, platelets, serum electrolytes, blood culture, arterial blood gas parameters, serum C-reactive protein (CRP) levels, liver enzymes, blood urea, and chest X-ray), and details of treatment (duration of antibiotics, antiviral drugs, vasopressors, supplementary oxygen, and ventilator requirement) were recorded for the analysis.

We took a cutoff of hospitalization as >7 days on practical considerations as most of the viral illnesses last for an average of 7 days. All children were categorized according to the duration of hospitalization in either Group A (≤7 days) or Group B (>7 days) and were compared for any statistically significant differences in the following outcome parameters. The outcome parameters were chosen from the past studies or were theoretically thought to affect the length of stay [6,8].

The clinical parameters assessed were age, duration of symptoms, duration of breathlessness, comorbid conditions, category of swine flu, sensorium, temperature, respiratory distress (tachypnea/chest retractions/poor efforts), hypoxemia SpO_2 <95% at room air, and cyanosis. The laboratory parameters assessed were leukopenia, leukocytosis, absolute neutrophil count, absolute lymphocyte count, neutrophil/lymphocyte (N/L) ratio at admission and after 48 h, various arterial blood gas (PaO_2, $PaCO_2$, FiO_2, and PaO_2/FiO_2) parameters, and multiorgan dysfunction.

The cutoffs for various clinical and laboratory parameters were taken as per standard age-dependent references in children [15]. The WHO growth charts were used for anthropometry [16]. Patients were further categorized into A as those with mild disease or Category B if they had mild symptoms and underlying risk factors or high-grade fever and Category C if they had red flag signs and were severely sick as per the National guidelines (3).

Statistical analysis was done by STATA version 14.1 software. Quantitative variables were represented by means and compared using Student's t-test. Qualitative variables were represented in percentage and compared by Chi-square test. Correlations were determined by applying regression analysis. $p \leq 0.05$ was considered statistically significant.

RESULTS

A total of 60 children between 1 and 14 years of age and clinical symptoms of swine flu were admitted, of whom 51 children who fulfilled the inclusion criteria were included for the final analysis and 9 children who were RT-PCR negative were excluded from the study. Most of the patients belonged to Category C (80%). All children were positive for H1N1 strain.

The mean age of enrolled children was 45.83±49.51 months (median – 20 months, range 3–168 months). Majority of the children were ≤5 years of age (76.4%, infants 37.2%) and there was male predominance (60.8%). The most common presenting symptoms were fever (98%), cough (98%), rhinorrhea (88%), breathing difficulty (88%), and decreased oral acceptance (58.8%). Other symptoms included vomiting (19.6%), diarrhea (15.7%), body ache and headache (11.7%), abdominal pain (5.9%), sore throat (3.9%), and lethargy (3.9%). The mean duration of symptoms before admission was 6.6±3.48 days (range 2–20 days). Around one-fifth of the children (n=11) had one or more comorbid conditions (asthma – 5, prematurity – 3, nephrotic syndrome – 1, global developmental delay – 2, and seizure disorder – 2).

On physical examination, fever (56.9%), tachycardia (84.3%), hypotension (10.3%), respiratory distress (90.2%), cyanosis (13.7%), hypoxemia (60.8%), and dehydration (7.8%) were commonly seen. The main systemic abnormalities were respiratory (84.3%), neurological (15.7%), hepatomegaly (11.7%), or splenomegaly (3.9%). Antibiotics were used in 49 (96%) cases with mean duration of 6±2.92 days. Most of the children (86.2%) received intravenous fluid therapy (mean duration – 3.10±2.21 days) and supplemental oxygen therapy (70.5%; mean duration – 2.62±2.36 days). Mechanical ventilation was required in four children of whom three received inotropic support. These three patients later succumbed to death and out of them, two developed multiorgan dysfunction.

Predictors of Hospitalization >7 Days

The mean duration of hospital stay was 6.7±4.11 days (range – 0.5–25 days) in all children. The mean duration of hospitalization in Group A and Group B was 5.09±1.82 and 11.2±4.51 days, respectively. The mean age, sex distribution, duration of symptoms, comorbid conditions, and categories of swine flu infection (Category B vs. Category C) had no statistically significant differences in both the groups. There was no difference in the mean temperature at admission, percentage with fever, altered sensorium, and respiratory distress between the two groups Table 1.

Anemia (two-third), abnormal TLC (one-fifth), lymphopenia (one-fourth), and thrombocytosis (one-tenth), and N/L ratio ≤2 were found in most of the children (four-fifth) (Table 2). Other common abnormalities were increased CRP levels (41.1%, mean – 4.49±3.98 mg/dL), electrolyte abnormalities (hyponatremia – 21.6% and hyperkalemia – 9.8%), raised transaminases (7.8%) and increased blood urea (11.8%), and chest X-ray abnormalities (90%; bilateral infiltrates – 26, acute respiratory distress syndrome [ARDS] – 3, and consolidation – 9). Arterial blood gases (ABG) analysis at admission revealed abnormalities in 60.8% (31/51) of children (low CO_2 – 29, CO_2 retention – n=2). The mean PaO_2 (109.78±47.84 mmHg), $PaCO_2$ (29.96±7.97 mmHg), and FiO_2 (51.08±22.74%) levels, at admission, improved after 24 h in most of the children (PaO_2, 126.73±79.23 mmHg; PCO_2, 39.2±13.22 mmHg). Percentage of children with N/L <2 was comparable in both the groups at admission, but after 48 h, statistically higher number of children was found in Group B. The

Table 1: Clinical parameters predicting the duration of hospitalization in the two groups

Parameter (in Mean±SD or %)	Group A (n=33) (Admission ≤7 days)	Group B (n=15) (Admission >7 days)	Odds ratio, 95% CI	p value
Female	13 (68.42%)	6 (31.58%)	10.97, 0.28–3.39	0.97
Male	20 (68.97%)	9 (31.03%)		
Mean age	50.52±52.65	38.8±46.77	0.99, 0.98–1.01	0.46
Mean duration of symptoms	6.42±2.15	7.0±5.66	1.04, 0z.88–1.23	0.60
Presence of comorbidity	7 (21.2%)	3 (20.0%)	0.93, 0.20–4.23	0.92
Category C of swine flu	23 (69.7%)	14 (93.3%)	6.09, 0.70–52.80	0.10
Children with fever	18 (54.5%)	9 (60.0%)	1.25, 0.36–4.32	0.72
Mean temperature	37.83±0.82	37.87±0.66	52.80, 0.48–2.40	0.87
Children with respiratory distress	28 (84.8%)	15 (100%)	5.98, 0.31–115.50	0.24
Children with hypoxemia	15 (45.4%)	12 (80%)	4.80, 1.14–20.24	0.03*
Children with cyanosis	0	4 (26.7%)	26.21,1.31–525.33	0.03*
Children abnormal sensorium	3 (9%)	2 (13.3%)	1.54, 0.23–10.33	0.66
Children with organ failure	0 (0.00%)	1 (6.7%)	6.93, 0.27–180.45	0.24
Mean duration of dyspnea	1.12±1.43	2.87±3.09	1.46, 1.05–2.05	0.03*

* indicates p<0.05 significant. SD: Standard deviation, CI: Confidence interval

Table 2: Laboratory predictors of the duration of hospitalization in the two groups

Parameter (in Mean±SD or %)	Group A (n=33) (Admission ≤7 days)	Group B (n=15) (Admission >7 days)	Odds ratio, 95% CI	p value
Children anemia	18 (54.5%)	12 (80.00%)	3.33, 0.79–14.05	0.10
Children with leukocytosis	5 (15.2%)	2 (13.3%)	0.74, 0.13–4.35	0.74
Children with leukopenia	4 (12.1%)	0 (0.00%)	0.20, 0.01–4.04	0.29
Children with N/L <2 at admission	27 (81.8%)	11 (73.3%)	0.61,0.14–2.60	0.51
Children with N/L <2 after 48 h	12 (36.4%)	13 (86.7%)	11.37, 2.19–59.17	0.004*
Children with positive CRP	12 (36.4%)	9 (60.0%)	1.33, 0.75–9.19	0.13
Children with abnormal chest X-ray	27 (81.8%)	13 (86.7%)	2.41, 0.26–22.77	0.44
Children with organ failure	0 (0.00%)	1 (6.7%)	6.93, 0.27–180.45	0.24
Mean ANC	5553.39±3869.73	5097.73±3483.32	1.00, 1.00–1.00	0.69
Mean ALC	4722.12±2847.84	4979.67±3340.97	1.00, 1.00–1.00	0.78
Mean CRP	4.08±3.93	5.02±4.22	1.06, 0.85–1.33	0.58
Mean PaO_2/FiO_2	275±97.82	232.33±132.52	1.00, 0.99–1.00	0.29
Mean $PaCO_2$	28.44±4.02	33.42±9.59	1.13,0.98–1.32	0.09
Mean FiO_2	44±16.6	59.31±24.86	1.04, 0.99–1.09	0.07
PaO_2/FiO_2 after 24 h	231.2±36.51	286.5±107.57	1.01, 0.98–1.04	0.40
$PaCO_2$ after 24 h	28.67±1.15	33.45±4.22		

SD: Standard deviation, CI: Confidence interval, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, N/L: Neutrophil/lymphocyte, CRP: C-reactive protein

ABG parameters at admission and after 24 h of admission were comparable in the two groups.

All the three deaths occurred ≤48 h of admission and in children <5 years of age (4.5 months, 36 and 48 months) with associated comorbid conditions (2 – malnutrition and 1 – global developmental delay). At admission, all had altered sensorium and were hemodynamically unstable. Laboratory abnormalities showed N/L<2, raised blood urea, lower pCO_2 at admission (12–42 mmHg) but later on, CO_2 retention (52–62 mmHg) leading to respiratory failure and death. Average PaO_2/FiO_2 ratio at admission (139.5) and after 12 h of admission (45.4) showed considerable fall in all three patients (94.1). Chest X-ray revealed ARDS and hyperinflated lung fields. The main cause of death was respiratory failure or refractory shock.

DISCUSSION

In our study of 51 children hospitalized of swine flu in the past 3 years, most were infants or under 5 years of age. Fever, cough, rhinorrhea, and breathing difficulty were common clinical manifestations and asthma was the most common comorbid condition (50%). Poor nutritional status, hypoxemia, tachypnea, hypotension, anemia, leukocyte abnormalities, and X-ray abnormalities were frequently present at admission. Risk factors for hospitalization >7 days included breathlessness, hypoxemia, cyanosis at admission, and persistent N/L ratio ≤2 after 24 h of admission. Anemia, leukocyte count, serum CRP levels, ABG parameters, or other comorbid conditions were not significantly associated with prolonged duration of hospitalization (p>0.05).

Similar results on demographic data including age at presentation, under-five predominance, and male predominance were reported by Das *et al.* and Chawla *et al.* [4,5,9-12]. Similarly, associated comorbidities and symptoms were comparable with previous Indian reports by Das *et al*. and Saha *et al.* [4,10]. Higher incidence of swine flu in under-five children might occur due to higher attack rates (poor immunity or higher hospitalization among them). Male predominance might be due to local bias and cultural practices of increased admission and care given to males as compared to females. The higher percentage of comorbidities in our study might be due to poor nutritional status in our local population. Our results on laboratory parameters such as leukopenia, thrombocytopenia, and elevated liver enzymes are similar to reports by Das *et al*. and Saha *et al*. [4,10].

Lymphopenia on the 2nd and 3rd days after fever and neutropenia on the 5th day is known in swine flu infection [17,18]. N/L ratio <2 in our study was little lower (78%) as compared to the previous study by Libster *et al*. in adults (92%) [14]. This might be due to late presentation in our children when lymphocyte counts start rising. Das *et al*. and Louie *et al*. have reported similar radiological abnormalities (pulmonary infiltrates and consolidation) in their studies [4,6]. Our results on ABG parameters (improvement in PaO_2 and PCO_2, 24 h after admission) were not significantly associated with length of hospitalization as compared to reports in adults possible due to small sample size. The mean duration of hospitalization in our study (6.70±4.11 days) was comparable to other reports (4–6). The previous studies have reported high requirement of oxygen, low oxygen saturation, tachycardia, presence of chest retractions, and signs of dehydration as risk factors for severe outcomes (death or admission to intensive care unit) [4,8].

Das *et al*. also found children with comorbid conditions, respiratory distress, vomiting, wheezing, diarrhea, hypotension, and infiltrates/consolidation as risk factors for hospitalization [4]. Udompornwattana *et al*. in their study on 115 children concluded age between 5 and 9 years and comorbid diseases as risk factors for prolonged hospitalization (>7 days) [9]. Similarly, the study by Coffin *et al*. assessed risk factors for prolonged hospitalization (>6 days) and found only cardiac and neurologic/neuromuscular diseases as independent risk factors for prolonged hospitalization [19]. The study in adults found persistent low PaO_2/FiO_2 ratio after admission and presence of organ failures as risk factor for hospitalization >7 days [15]. Kholy *et al*. defined prolonged hospitalization >10 days as 75th percentile of hospital stays [20] while Coffin *et al.* took it as >6 days which was median plus 2 standard deviation of the distribution of the length of stay [19]. We took a cutoff for prolonged hospitalization as >7 days on practical considerations as most of the viral illnesses last for an average of 7 days.

The major limitation of our study was its small sample size which makes the generalization of our results debatable. Hence, we suggest further studies in children assessing the above parameters.

CONCLUSION

Swine flu is a mild illness with highest hospitalization in children <5 years with non-specific clinical and laboratory features. Sequential observation of ABG, CRP, and N/L ratio before discharge might be helpful in assessing the trends and prove beneficial. Hence, simple clinical (breathlessness, hypoxemia, and cyanosis) and laboratory parameters (N/L ratio) not requiring costly or complicated test or procedures might be helpful in predicting the duration of hospitalization and recovery.

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